

White Paper Guidance for Physicians on Hormone Replacement Therapy (HRT)

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Endorsing Organizations

Academy of Anti-Aging Medicine - China
Academy of Anti-Aging Medicine - Iberia
Academy of Healthy Aging
Academy of Optimal Aging
Academy of Successful Aging
American Academy of Age Management
American Academy of Anti-Aging Medicine (A4M)
American Academy of Longevity Medicine
American College of Longevity Medicine
American Society of Longevity Medicine
Anti-Aging Medicine Specialisation
Asia-Oceania Federation of Anti-Aging Medicine (AOFAAM)
AustralAsian Academy of Anti-Aging Medicine (A5M)
Belgian Society of Anti-Aging Medicine (BELSAAM)
European Academy of Quality of Life and Longevity Medicine (EAQUALL)
European Organization of Scientific Anti-aging Medicine
European Society of Anti-Aging Medicine (ESAAM)
German Society of Anti-Aging Medicine (GSAAM)
German Society of Hemotoxicology
Hellenic Academy of Antiaging Medicine
Indonesian Society of Anti-Aging Medicine
International Academy of Anti-Aging Medicine
International Academy of Longevity Medicine
International Hormone Society (IHS)
Japan Anti-Aging Medical Spa Association (JAMSA)
Japanese Society of Clinical Anti-Aging Medicine (JSCAM)
Korea Anti-Aging Academy of Medicine (KA3M)
LatinoAmerican Federation of Anti-aging Societies
Romanian Association of Anti Aging Medicine
Sociedad de Medicina Antiejeñimiento y Longevidad de Gran Canaria
Society for Anti-Aging & Aesthetic Medicine Malaysia (SAAAMM)
South African Academy of Anti-Aging & Aesthetic Medicine (SA5M)
Spanish Society of Anti-Aging
Thai Academy of Anti-Aging Medicine
Thai Association of Anti-Aging Medicine
Anti Aging Research and Education Society, Turkey
Center for Study of Anti-Aging Medicine - UDAYANA University, Indonesia.
World Academy of Anti-Aging Medicine (WAAAM)
World Academy of Longevity Medicine
World Society of Anti-Aging Medicine (WOSAAM)

Preamble

It is the position of the American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, that the use of banned drugs or hormones for athletic enhancement constitutes inappropriate misuse. The A4M, its affiliates, and its befriended organizations (hereinafter referred to as "AM"), do not endorse or condone the use of any illicit substances for the purpose of athletic enhancement or sports cheating.

However, AM is resolute in defending the rights of the patient working in conjunction with their physician in choosing any and all justifiable therapies, drugs and interventions which can be shown to improve either the quality or duration of the human lifespan or the form and function of the individual's physiology in order to achieve greater vitality and health at every age. It is in fact the physician's duty to act as an advocate for the patient's right to obtain the full lawful measure of scientific medical therapeutics necessary for optimum health and personal freedom of choice in healthcare.

Introduction

The American Academy of Anti-Aging Medicine (A4M), its affiliates, and its befriended organizations (hereinafter referred to as "AM"), promotes the appropriate application of modern and advanced medical technologies to address the changes in chemical, hormonal, physical, and nutritional needs that occurs with aging. The scientific literature supports the benefits claimed by returning hormones to their physiological state when determined to be deficient.

Experienced anti-aging physicians have been prescribing bio-identical hormone replacement therapy (BHRT) for more than 20 years. For women, benefits may include:

- reduced osteoporosis and restoration of bone strength
- reduced hot flashes and vaginal dryness
- better maintenance of muscle mass and strength
- improved cholesterol levels
- reduced risk of endometrial and breast cancer
- reduced risk of depression
- improved sleep
- better mood, concentration and memory
- improved libido
- fewer side effects than with synthetic hormones

[Reed KD. Natural hormone replacement therapy: what it is and what consumers really want. *International Journal of Pharmaceutical Compounding*. 2001;5(5):332-335; Drusko J. Natural isomolecular hormone replacement: an evidence-based medicine approach. *International Journal of Pharmaceutical Compounding*. 2000;4(6):414-442; Boothby L, et al. Bioidentical hormone therapy: a review. *Menopause*. 2004;11(3):356-367.]

An extensive list of peer-reviewed references documenting the beneficial effects of HRT in adults is presented as Appendix A.

Recent legal actions taken against some compounding pharmacies and physicians continue to be played out in the news. Regardless of the merits or lack of merits to these allegations, these accusations should alert us to the responsibilities that each physician faces with the decision to practice hormone replacement therapy. Attempts are being made to criminalize the practice of medicine where variations to State Board-favored traditional care is undertaken. Thus we are now seeing situations where there are no injured patients and no victims being made the basis of criminal proceedings against health professionals. This is an affront to our profession and the very notion of

optimal healthcare. Errors or debate in prescribing guidelines are administrative issues: for officials to abuse their authority in recasting minor issues as criminal acts is in itself unjust and may be considered as criminal abuse of their publicly elected positions.

Unfortunately, media confusion and outright deception have muddled the reality of what has occurred in the practice of hormone replacement therapy, where doctors' legal and ethical physiological use of hormones and supplements has been misrepresented as being the inappropriate use of hormones for sports enhancement. Every time that a physician breaches the practice of good medicine by prescribing medications inappropriately under the guise of hormone replacement therapy and/or anti-aging medicine, that physician jeopardizes not only the future of our profession, but the life expectancy of us all.

Using the combined knowledge and skills of a significant and elite group of consultants regarding the medical and legal applications of hormone replacement therapy, The American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, offers the following policy positions which may help to offer general recommendations and guidelines to practitioners. However, anything offered herein should *not* be construed as legal or medical advice, and applicable state laws and regulations vary widely and should be strictly adhered to. It is recommended that any practitioner seeking specific advice of this type should contact a duly licensed and knowledgeable attorney in the state of practice and/or the medical licensing board of that state. There is no guarantee that these recommendations will fully protect a practitioner from actions taken by various state medical boards, but it is our hope that they will minimize the extent to which false accusations will be actualized.

Furthermore, the ultimate burdens for both the medical and legal issues rest with the treating physician. Therefore, it is imperative that all practitioners consult with their own State Board, the boards of any other states in which they may be deemed to practice, and legal counsel in all applicable jurisdictions regarding the content of this position paper.

Hormone Replacement Therapy

Introduction

Hormone replacement therapies with controlled substances such as testosterone and growth hormone have been used since many years. The first testosterone treatment of testosterone deficiency in adult men started around 1940 and since more than 40 years growth hormone is given to treat short stature children and since 1985 with the safer, not contaminated recombinant growth hormone, product of biotechnology. End of the 1980's, the first trial of adults with growth hormone deficiency were published, and since the beginning 1990s, growth treatment of adult patients started in private medical practice.

Testosterone and growth hormone are natural compounds made by the human body. Both hormones are controlled substances in the USA. They have been and are used in adults to correct testosterone and growth hormone deficiencies, often caused by the natural aging of the endocrine glands. Natural does not mean healthy as many studies have shown the association of various age-related diseases and possibly psychiatric disorders with low levels of these hormones, and their improvement or possibly cure with replacement therapy at small physiological doses.

Most traditional endocrinologists have had no intense training in treatment of testosterone and growth hormone deficiencies. They generally have excellent training in the treatment of diabetes, but lack of interest and expertise in how to treat testosterone and adult growth hormone deficiencies and some other hormone deficiencies that may accelerate aging. Because of this lack of knowledge, many of them have rejected these treatments and confused them with the improper use at excessive doses by

sports athletes searching to improve their performance. The American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, do not approve the improper use of these substance in sports, but do point to the right of every patient who is suffering from one of these deficiencies to get relief from their complaints by the adequate hormone treatment.

A. Selection of Patients

Historically, patients who were considered for Hormone Replacement Therapy, other than those with classical hormone deficiency syndromes (i.e., Diabetes, Hypothyroidism, Addison's disease, and Menopause, to name a few) were typically over the age of 45. This age criterion no longer applies when we take into consideration the thousands of individuals who have developed Traumatic Brain Injury-Hormone Deficiency Syndrome, which studies suggest can be treated by the use of Hormone Replacement Therapy.

Therefore, age as the single criterion for patient selection has become a moot point leaving documentation of laboratory defined hormonal deficiencies as the gold standard for any replacement strategy.

I. Recommendations for the Selection of Patients

The same concerns that exist in any other area of medicine, including screenings for contraindications, for example, apply in the field of Hormone Replacement Therapy. Additional considerations include, but are not limited to:

1. Treatment should be based upon having documented hormone deficiencies;
3. Screening should be done for participation in professional sports;
4. Screening should be done for prior hormone use and the following practice should be undertaken:
 - Copies of medical records should be requested from prior physician(s) to document any previous hormone deficiencies. Because individuals who have recently used "steroids" can transiently depress their hormone levels creating the perception that they are deficient and need hormone replacement therapy.

B. Medical Records

Proper documentation of medical treatment is important and a requirement in all areas of medicine. Illegible or incomplete medical records may subject practitioners to regulatory actions and potential misinterpretation of actual sound medical practice. Many prudent practitioners use a computer based reporting system in which the patient's visit records are recorded and transcribed. The use of a computerized menu-driven EMR (Electronic Medical Records system) can help avoid the lack of appropriate and illegible documentation.

AM does not endorse or condone the prescription or dispensation of controlled substances or any prescription drugs outside the scope of a bona fide physician-patient relationship. It is incumbent upon every practitioner to comply with the obligations imposed by federal and state laws and regulations in this area. The following subsections present examples of some of the most crucial components to practitioners' medical records that will be evaluated in determining whether a proper patient-physician relationship exists.

C. Patient History

A comprehensive medical history is essential to document rational support for ordering laboratory tests and for any subsequent treatment which may be required.

Additionally, the documentation of conditions such as Orchitis in a male to account for Hypogonadism, birth control use for prolonged periods of time, Polycystic Ovarian Disease, and a variety of medications and toxic reactions, are important to support the medical need for hormone therapy.

I. Recommendations for the Patient's History

AM recommends that a comprehensive Patient Medical History should be conducted as part of the intake procedure during a patient's initial visit. This history should include a comprehensive system review and comprehensive or interval past, family, and social history as well as a comprehensive assessment/history of prior hormone therapies and pertinent risk factors. The elements of the above history should include all those suggested by the AMA's current procedural terminology codebook.

A review of medical events in the patient's family that includes significant information about: the health status or cause of death of parents, siblings, and children; specific diseases related to problems identified in the chief complaint or history of the present illness, and/or system review; and diseases of family members that may be hereditary or place the patient at risk.

The patient's history should include a chronological description of the development of the patient's present illness from the first sign and/or symptom to the present. This includes a description of location, quality, severity, timing, context, modifying factors, and associated signs and symptoms significantly related to the presenting problem(s).

D. Laboratory Testing

Accusations of insurance fraud may occur when insurance companies believe that physicians are ordering unnecessary laboratory tests on patients. A proper medical history, as outlined above, including a review of symptoms, -- which helps define the medical problem, clarify the differential diagnosis and importantly identify needed testing -- allows for proper documentation that will help support any requested testing. Failure to obtain a proper medical history and review of symptoms can open up the physician to the potential of being investigated for improper ordering of laboratory tests, since states generally have a group of Business and Professional Codes (B&P) that defines and regulates professional conduct expected by businesses. These regulations are state driven and will vary from state to state and practitioners should check with local counsel to determine their state specific requirements. However, most professional conduct regulations encompass similar principles. As an example, in the state of California one of their regulations concerning physician prescribing is as follows:

Repeated acts of clearly excessive prescribing or administering of drugs or treatment, repeated acts of clearly excessive use of diagnostic procedures, or repeated acts of clearly excessive use of diagnostic or treatment facilities as determined by the standard of the community of licensees is unprofessional conduct for a physician and surgeon, dentist, podiatrist, psychologist, physical therapist, chiropractor, or optometrist. Any person who engages in repeated acts of clearly excessive prescribing or administering of drugs or treatment is guilty of a misdemeanor and shall be punished by a fine of not less than one hundred dollars (\$100) nor more than six hundred dollars (\$600), or by imprisonment for a term of not less than 60 days nor more than 180 days, or by both the fine and imprisonment. (California B&P section 725)

I. Recommendations for Laboratory Testing

1. Practitioners should always conduct a proper review of symptoms that will support any testing;
2. Never send in a diagnostic code (ICD-9) to justify the ordering of laboratory tests unless that code can be substantiated with proper chart documentation.
3. Never send in an insurance claim for office visits with CPT codes that cannot be substantiated and always ensure that proper documentation of any substantiation is in place. Practitioners should be scrupulous in avoiding Insurance Fraud, or even the appearance of Insurance Fraud.
4. Never prescribe a medication that the patient will receive and the pharmacy will bill to an insurance company unless the rationale for the treatment can be substantiated and proper documentation of that substantiation is in place.

E. Interpretation of Laboratory Results

If there is an area in which the practice of hormone replacement therapy is most unique, and also the most open to a Medical Board's scrutiny, it is the manner in which hormone level results are interpreted. The practice of medicine is being replaced by a financially calculating industry that decides treatment based upon numerical results. These results do not take into consideration the clinical acumen of the practice of medicine that a physician has developed over the years of his/her practice.

Mainstream medicine deals with dichotomic treatment practices on a daily basis. What is the laboratory test for depression, anxiety, bipolar disorder, and other medical conditions that fail to be quantified by a numerical test? In such cases, it becomes the medical judgment of the physician to treat a patient with medication in the absence of a measurable basis.

The use of "natural" thyroid in patients whose TSH levels for example are not yet over 5.5 has stimulated controversial cases where the treating physician has been dragged into court to explain why a thyroid supplement was administered to a patient who is not yet sick? Several, often recent, studies have now been published that show that levels of TSH within the reference range, between 2 and 5.5, in certain categories of patients have been reported to be associated with pathological abnormalities and even diseases. It is therefore no surprise that the American Association of Clinical Endocrinologists has therefore narrowed in 2002 the serum TSH reference range to 0.3-3.0 mIU/L, lowering the upper reference end to 3. The National Academy of Clinical Biochemistry, the world's most respectful organisation for editing guidelines on laboratory test interpretation, reduced the upper end of the reference range from 5.5 to 4.1 mIU per liter in 2003. The latter group also stated that "more than 95% of healthy, euthyroid subjects have a serum TSH between 0.4 - 2.5 mIU per liter" and that "patients with a serum TSH above 2.5 mIU per liter, when confirmed by repeat TSH measurement made after three to four weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected." In 2003, the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, and American Thyroid Association) recommended a target TSH range of 1.0 to 1.5 mIU per liter in patients already receiving thyroxine therapy.

The concept of Interventional Endocrinology acknowledges the fact that not everyone experiences symptoms of deficiency – relative or absolute - at the same levels. Therefore, taking a comprehensive medical history and physical can act to substantiate the application of replacement/supplementation protocols, in accordance with accepted standards of care. Clear documentation in this regard helps support the physician's approach in treating the patient.

F. Physical Examination

A “good faith” physical examination is one of the requirements of having personal knowledge of the medical status of an individual patient. Normally, this includes the standard – hands-on, examination of all systems: HEENT, Cardiovascular, Pulmonary, Gastric, Genitalia, Musculoskeletal and Neurological. This also should include the Vital Signs; Weight, Height, Blood Pressure, Pulse and Respirations.

Additional testing, where appropriate, based upon history and the initial “standard” physical examination might include but are not limited to the following: EKG, Chest x-ray, Ultra-fast CT, Bone Density, and referral for GI assessment.

I. Recommendation for the Physical Examination

1. Before dispensing any prescription medication, a complete Physical Examination should be performed in accord with applicable laws. If indicated perform additional tests to address any suspicious physical findings.

G. Treatment protocols

Treatment protocols should be based upon credible scientific literature and currently accepted practice. . The hormone therapy consensus of the International Hormone Society that are heavily referenced may serve as a model (visit www.intlhormonesociety.org for details).

H. Prescriptions

To dispense controlled substances, a professional must know the requirements for a valid prescription. A prescription is an order for medication that is dispensed to or for an ultimate user. A prescription for a controlled substance must be dated and signed on the date when issued. The practitioner is responsible for making sure that the prescription conforms in all essential respects to both federal and state laws and regulations.

A prescription order for a controlled substance may be issued only by a physician, dentist, podiatrist, veterinarian, mid-level practitioner or other registered practitioner who is: (1) authorized to prescribe controlled substances by the jurisdiction in which he/she is licensed to practice; and (2) Registered with DEA or exempted from registration (i.e., Public Health Service and Bureau of Prison physicians).

Federal regulations (21 CFR 1306.04(a)) related to prescribing contain two key operational phrases, italicized below:

(a) A prescription for a controlled substance to be effective must be issued for a *legitimate medical purpose* by an individual practitioner acting in the *usual course of his professional practice*. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

I. Recommendation for Writing Prescriptions

Generally, a prescription must include the patient's full name and address, and the practitioner's name, address, and registration number. The prescription must also include the drug name, strength, dosage form, quantity prescribed, directions for use, and number of refills. Where an oral prescription is not permitted, a prescription must be written in ink or indelible pencil or typewritten and must be manually signed by the practitioner. The practitioner is responsible for making sure that the prescription conforms to federal and all applicable state laws and regulations.

I. The Office Sale and Dispensing of Medications

Although there are general guidelines set forth by the Federal government [21 CFR 1306.04(b): "A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients."], the ability of physicians to distribute medications of all classifications from their offices is regulated by each state. Therefore, it is imperative that physicians review their own state's regulatory laws and guidelines. While state regulations will vary, record keeping and proper labeling of dispensed medications are central to most states' regulatory scheme. As an example, California mandates the following requiring physician dispensing:

A legally licensed Medical practitioner is in breach of this section of code if they: Fail to keep complete and accurate records of purchases and disposals of substances listed in the California Uniform Controlled Substances Act (Division 10 (commencing with Section 11000) of the Health and Safety Code) or controlled substances scheduled in the federal Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. Sec. 801 et seq.), or pursuant to the federal Comprehensive Drug Abuse Prevention and Control Act of 1970. A physician and surgeon shall keep records of his or her purchases and disposals of these controlled substances or dangerous drugs, including the date of purchase, the date and records of the sale or disposal of the drugs by the physician and surgeon, the name and address of the person receiving the drugs, and the reason for the disposal or the dispensing of the drugs to the person, and shall otherwise comply with all state recordkeeping requirements for controlled substances.

In the government's attempt to prevent the illegal sale and distribution of medications classified as Schedule III, laws have been enacted to make it mandatory to provide additional information about the prescriber (physician) and recipient (patient). This information is computerized and can be used to monitor both physicians and patients in terms of the number and quantity of medication that is prescribed over time.

Schedule III is added to the CURES requirement: As of January 1, 2005, all pharmacies have begun submitting Schedule III prescription information to the Controlled Utilization Review and Evaluation System (CURES) program. The CURES program compiles prescription data in a statewide database to assist state law enforcement and regulatory agencies in their efforts to reduce prescription drug diversion. This was apparently precipitated by the highly publicized prosecutions related to BALCO and allegations of athletic Steroid Abuse. This obviously impacts the sale and distribution of Testosterone and related hormones of treatment.

Prior to this change, pharmacies were required to electronically transmit only Schedule II prescription information to the CURES program. New legislation, Senate Bill 151 (Burton, Chapter 406, Statutes of 2003), requires the same information be transmitted for Schedule III prescriptions.

In addition to requiring submission of Schedule III prescription information, the bill required prescribers **dispensing** these drugs to submit prescription information to the CURES program beginning on July 1, 2004. Physicians “dispensing” from the office must comply with the mandated regulatory filings at the same level as a pharmacy.

In order to comply with the reporting regulations, pharmacies and dispensing prescribers must submit the following information for each scheduled II and III prescription filled:

- Full name, address, gender, and date of birth of the patient;
- Prescriber’s category of licensure, license number, and federal controlled substance registration number;
- Pharmacy prescription number, license number, and federal controlled substance registration number;
- NDC (National Drug Code) number of the controlled substance dispensed;
- Quantity of the controlled substance dispensed;
- ICD-9 (diagnosis code), if available;
- Date of issue of the prescription; and
- Date of dispensing of the prescription.

I. Recommendation for the Office Sale and Dispensing of Medication:

1. All states have specific requirements for the dispensing of medication. Practitioners are urged to learn about their own states requirements for dispensing all medications from the applicable state board(s).
2. In accordance with federal law, prescriptions for a controlled substance must affix to the container a label showing the pharmacy name and address, the serial number of the prescription, date of initial dispensing, the name of the patient, the name of the prescribing practitioner, and directions for use and cautionary statements, if any, contained on the prescription as required by law. FDA regulations require that the label of any drug listed as a “controlled substance” in Schedule II, III, or IV of the Controlled Substances Act must, when dispensed to or for a patient, contain the following warning: ***CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.***
3. In many cases state law is more stringent than federal law, and must be complied with in addition to federal law. Professionals dispensing controlled substances should make sure they understand their state and federal controlled substance regulations.

J. Self-Prescribing by Physicians

1. Although there isn’t a legal statute that specifically states that a physician cannot write a prescription for personal use, there are a number of Medical Board actions against physicians for the self-dispensing of narcotics and medication of abuse where the stated physician(s) lost their license to practice medicine.

K. Internet Pharmacies

The DEA has provided the following information on its Web Site (<http://www.deadiversion.usdoj.gov/faq/internetpurch.htm>):

“Federal law requires that ‘A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice’ (21 CFR 1306.04(a)). Every state separately imposes the same requirement under its laws. Under Federal and state law, for a doctor to be acting in the usual course of professional practice, there must be a bona fide doctor/ patient relationship.

For purposes of state law, many state authorities, with the endorsement of medical societies, consider the existence of the following four elements as an indication that a legitimate doctor/patient relationship has been established:

- A patient has a medical complaint;
- A medical history has been taken;
- A physical examination has been performed; and
- Some logical connection exists between the medical complaint, the medical history, the physical examination and the drug prescribed.

“A patient completing a questionnaire that is then reviewed by a physician hired by or working on behalf of an Internet pharmacy does not establish a doctor/patient relationship. A consumer can more easily provide false information in a questionnaire than in a face-to-face meeting with the physician. It is illegal to receive a prescription for a controlled substance without the establishment of a legitimate doctor/patient relationship, and it is unlikely for such a relationship to be formed through Internet correspondence alone. However, this is not intended to limit the ability of practitioners to engage in telemedicine. For purposes of this guidance document, telemedicine refers to the provision of health care using telecommunication networks to transmit and receive information including voice communications, images and patient records.

“Some Internet sites recommend to the patient that they not take a new drug before they have a complete physical performed by a doctor. These sites then ask the patient to waive the requirement for a physical and to agree to have a physical examination before taking the drug they purchase via the Internet. The physical examination does not take the place of establishing a doctor/patient relationship. The physical exam should take place before the prescription is written. These types of activities by Internet pharmacies can subject the operators of the Internet site and any pharmacies or doctors who participate in the activity to criminal, civil, or administrative actions. For DEA registrants, administrative action may include the loss of their DEA registration. Additionally, providing false material information to obtain controlled substances could be considered obtaining a controlled substance by fraud and deceit, which is subject to Federal and State penalties.”

L. Delivery of a Controlled Substance or Drug Product Containing Listed Chemicals to Persons in Another Country

Controlled substances that are dispensed pursuant to a legitimate prescription may not be delivered or shipped to individuals in another country without proper authorization. Any such delivery or shipment is an export under the CSA, and cannot be conducted unless the person sending the controlled substances:

1. Has registered with DEA as an “exporter” (see 21 CFR 1301); and
2. Has obtained the necessary permits(s), or submitted the necessary declaration(s) for export as outlined in 21 CFR 1312.

M. Compounding Pharmacy

Compounding by pharmacists has been a foundational aspect of the practice of pharmacy. While today the majority of prescription medication is mass-produced by pharmaceutical companies, many patients require custom-made preparations that are prescribed by their physician and compounded by a trained pharmacist. These custom-prepared prescription medications must originate from a physician's order and be specifically written to meet that individual patients need. Federal and state laws prohibit the compounding of medication that is not pursuant to a doctor's order.

Compounding pharmacies are strictly regulated by regulations from state boards of pharmacy. However, there have been many efforts recently to allow federal oversight of this practice. Recent legislation has been drafted that would usurp long-established state practices, concerning compounding, and turn the oversight over to the FDA.

Despite this pending legislation, courts have repeatedly upheld pharmacists' rights to compound despite repeated attempts by the FDA to challenge the activity. In May 2006, a U.S. District court judge ruled that the compounding of ingredients to create a customized medication in accordance with a valid prescription does not create a new drug subject to the FDA's approval process (see *Medical Center Pharmacy et al. v. Gonzales et al.*). Additionally, the U.S. Supreme Court has held as unconstitutional FDA's repeated attempts to regulate pharmacist compounding.

I. Recommendation for the use of a Compounding Pharmacy

The use of customized prescription medications must originate from a physician's order and be specifically written to meet an individual patient's need (i.e., a commercially available product would not meet the patient's need) and be compounded by a trained licensed pharmacist.

With regard to the availability of Human Growth Hormone (HGH) from compounding pharmacies, as of this writing there is no FDA-approved compounded HGH product, only manufactured products.

N. Appropriate Patient Monitoring

Although there are generally no state or federal guidelines for mandatory monitoring of patients receiving Testosterone or Growth Hormone, there is an implied responsibility that would follow the "Standards of treatment" for your specific medical community.

O. Off-Label Prescription Drug Prescribing

It is important for all practitioners to understand the legal basis and ability to prescribe drugs for "off-label" uses, and to adhere to all applicable limitations.

An "off-label" use of a drug or a device is simply a use for a condition or in a manner not appearing on the FDA approved label.¹ The American Medical Association reported in 1995 that approximately half of all prescriptions were written for "off-label" uses. Moreover, the General Accounting Office (GAO) has testified that 90 percent of cancer drug use, 80 percent of pediatric use, and 80-90 percent of drugs used to treat rare diseases are prescribed "off-label."² Perhaps the best known example is

¹ James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *FOOD & DRUG L.J.* 71, 71 n.2, (1998). A recent FDA presentation defined off-label drugs as medicines "use[d] for indication[s], dosage form[s], population[s] or other use parameter[s] not mentioned in the approved labeling." Janet Woodcock, *Lecture to Drug Information Association, A Shift in the Regulatory Approach*, (June 23, 1997), at www.fda.gov/cder/present/diamontreal/regappr/sld001.htm.

² *Final Report on the Activities of the House Comm. on Government and Oversight*, 104th Cong. 2d Sess. 104 H. REP. 874 (Section 2), (January 2, 1997) at 114.

aspirin. For years, physicians prescribed aspirin to reduce the risk of heart attacks. However, the FDA did not approve such usage until 1998. While some “off-label” therapies are widely accepted, and doctors could be accused of malpractice if they did not prescribe the drug, others are dangerous and are not an appropriate part of medical care.³

The FDA and various court decisions have recognized that “off-label” prescribing is a legitimate part of the practice of medicine. The FDA’s policy on “off-label” prescribing states that “a physician may, as part of the practice of medicine lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert.” This policy was affirmed by the FDA’s Policy office by William B. Schultz, Deputy Commissioner for Policy in the FDA in 1996.⁴

“Off-label” Prescribing of Human Growth Hormone

The federal hGH statute criminalizes whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition where such use has been authorized by the Secretary of Health and Human Services, and pursuant to the order of a physician [21 U.S.C. § 333(e)]. Growth hormone cannot be prescribed or dispensed for non-medical purposes. Since the natural aging process is neither a disease nor any other recognized medical condition, “anti-aging therapy” or “reversing the aging clock” is absolutely not a valid basis upon which to distribute hGH. Of course, “bodybuilding” is not a valid basis nor is improving athletic performance.

The Secretary of Health and Human Services (i.e., the Food and Drug Administration) authorizes the uses for which prescription drugs may be marketed. Pharmaceutical companies can be – and have been – sanctioned by the FDA for marketing products for “unapproved” uses. As previously described, in the case of most pharmaceuticals, the uses for which practitioners may prescribe or dispense FDA-approved drugs include “off label” uses.

The FDA has taken the language of the federal hGH statute to mean that all prescribing of hGH must be “on label” (i.e., for an “authorized use”). Although the treatment of adult growth hormone deficiency is an authorized use of hGH and it is therefore clear that a legitimate prescription for hGH replacement therapy is lawful, controversy continues. There is not yet a consensus among the medical community as to what constitutes a “deficiency” of growth hormone in an adult. Further, controversy has arisen over how to diagnose such a deficiency. For example, some staunch critics of growth hormone replacement therapy have opined that an arginine stimulation test must be administered in order to properly diagnose adult growth hormone deficiency. They point to the language on the package inserts of some commercially available brands of hGH recommending arginine stimulation tests and claim that said language makes this specific test mandatory in order to comply with the statute and avoid the commission of a federal felony. Such an interpretation of the law means that the package insert dictates to a physician not only the approved uses for the product, but in the case of growth hormone deficiency, how the diagnosis should be made. The “no off-label” interpretation held by FDA means that prescribing hGH for an authorized use such as legitimate adult growth hormone deficiency would be lawful, but prescribing for anything other than authorized uses – even to treat serious diseases where research indicates that hGH would be beneficial – would not. While a literal reading of the statute may support this interpretation, it is improbable that Congress ever intended to suppress the development and application of medical uses of HGH to treat disease. The FDA’s interpretation of the law places greater limitations on HGH prescribing than exist for

³ Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 202 n.130.

⁴ William B. Schultz, Deputy Commissioner for Policy Food and Drug Administration, Department of Health and Human Services, Before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

controlled substances such as morphine and opiates, which may be prescribed for any legitimate medical purpose. Nothing in the legislative history proves that Congress ever intended that. In fact, this interpretation of the law seems completely at odds with the intent of Congress to treat anabolic steroids more harshly than HGH, not the other way around. Ultimately, legislative or judicial clarification of these issues may be required. Meanwhile, practitioners are urged to adhere to the strictest standards of the law.

The therapeutic value of HGH was validated by a study conducted in Stockholm, Sweden. Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmacoepidemiological survey of hypopituitary adults with GHD, for 6 months before GH treatment and for 6-12 months after the start of treatment. Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (QoL) (assessed using a disease-specific questionnaire, QoL-Assessment of GHD in Adults) and satisfaction with physical activity during leisure time were also assessed. For the total group (n = 304), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly (P < 0.05) after 12 months of GH therapy. Patients also needed less assistance with daily activities, although this was significant (P < 0.01) only for the men. QoL improved after 12 months of GH treatment (P < 0.001), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months (P < 0.001). In conclusion, GH replacement therapy, in previously untreated adults with GHD, produces significant decreases in the use of healthcare resources, which are correlated with improvements in QoL. [Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP; KIMS International Board., KIMS Study Group. Pharmacia International Metabolic Database, "Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency," *J Clin Endocrinol Metab.* 2001 Nov;86(11):5277-81]

P. Insurance

Medical liability insurance carriers have recently formed a new medical specialty division for the anti-aging healthcare practitioner. Their position on underwriting coverage for hormones focuses on these specific areas: hands on training combined with your level of experience, FDA approval, and HRT must be performed by a licensed physician, NP, PA or RN. Underwriting makes a decision on whether or not to cover your specific situation. You are covered unless the procedure is specifically excluded.

Several new carriers have entered this market. Their names and contact information are available online at www.worldhealth.net.

Q. Conclusion

In addition to allowing doctors to prescribe approved drugs (other than human growth hormone) for "off-label" uses, the FDA has never sought to restrict the ability of third-parties to publish and disseminate scientific information about "off-label" uses. The FDA has repeatedly recognized the importance of "open dissemination of scientific and medical information regarding these treatments."⁵ The FDA has, however, traditionally viewed manufacturer dissemination of such materials as promotion that constitutes advertising and thus violates the FD&C Act.⁶ FDA regulation in this area has focused on "determining whether an industry-supported activity is independent and not generally subject to regulation," as opposed to manufacturer-supported and therefore regulated.⁷ It is in providing guidance on this issue that the FDA's policies have changed most dramatically in recent years, particularly in response to First Amendment criticisms.

⁵ *WLF v. Friedman*, 13 F. Supp. 2d at 56.

⁶ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64,076.

⁷ *Id.*

Disclaimer

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APPENDIX A

Growth hormone in Adults

Senescence is associated with a decline of the growth hormone (GH) axis:

Senescence is associated with lower GH and IGF-1 levels and increased somatostatin

1. Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone secretion in the adult population: relation to age and adiposity. *J Clin Invest.* 1981 May;67(5):1361-9
2. Bando H, Zhang C, Takada Y, Yamasaki R, Saito S. Impaired secretion of growth hormone-releasing hormone, growth hormone and IGF-I in elderly men. *Acta Endocrinol (Copenh).* 1991 Jan;124(1):31-3
3. Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. *J Clin Endocrinol Metab.* 1991 Nov;73(5):1081-8
4. Rudman D, Rao UMP. The hypothalamic–growth hormone–somatomedin C axis: The effect of Aging. In: *Endocrinology & Metabolism in the Elderly 1992*, Eds Morley JC & Korenman SO, Blackwell Sc Publ, Boston-USA
5. Rolandi E, Franceschini R, Marabini A, Messina V, Cataldi A, Salvemini M, Barreca T. Twenty-four-hour beta-endorphin secretory pattern in the elderly. *Acta Endocrinol (Copenh).* 1987 Aug;115(4):441-6

Senescence is associated with alterations in the circadian cycle of serum GH:

a reduced amplitude and a phase advance

6. Mazzoccoli G, Correrà M, Bianco G, De Cata A, Balzanelli M, Giuliani A, Tarquini R. Age-related changes of neuro-endocrine-immune interactions in healthy humans. *J Biol Regul Homeost Agents.* 1997 Oct-Dec;11(4):143-7

GH treatment may oppose and GH deficiency may trigger several mechanisms of senescence

Failure of repair systems: GH accelerates repair

7. Revhaug A, Mjaaland M. Growth hormone and surgery. *Horm Res.* 1993;40(1-3):99-101
8. Dahlgren LA, van der Meulen MC, Bertram JE, Starrak GS, Nixon AJ. Insulin-like growth factor-I improves cellular and molecular aspects of healing in a collagenase-induced model of flexor tendinitis. *J Orthop Res.* 2002 Sep;20(5):910-9

Immune deficiency: GH stimulates the immune system

9. Wise T, Klindt J, Macdonald GJ, Ford JJ. Effects of neonatal sexual differentiation, growth hormone and testosterone on thymic weights and thymosin-beta 4 in hypophysectomized rats. *J Reprod Immunol.* 1991 Jan;19(1):43-54
10. Knyszynski A, Adler-Kunin S, Globerson A. Effects of growth hormone on thymocyte development from progenitor cells in the bone marrow. *Brain Behav Immun.* 1992 Dec;6(4):327-40
11. Beschorner WE, Divic J, Pulido H, Yao X, Kenworthy P, Bruce G. Enhancement of thymic recovery after cyclosporine by recombinant human growth hormone and insulin-like growth factor I. *Transplantation.* 1991 Nov;52(5):879-84
12. Murphy WJ, Durum SK, Longo DL. Role of neuroendocrine hormones in murine T cell development. Growth hormone exerts thymopoietic effects in vivo. *J Immunol.* 1992 Dec 15;149(12):3851-7
13. Kappel M, Hansen MB, Diamant M, Jorgensen JO, Gyhrs A, Pedersen BK. Effects of an acute bolus growth hormone infusion on the human immune system. *Horm Metab Res.* 1993 Nov;25(11):579-85

14. Kudsk KA, Mowatt-Larssen C, Bukar J, Fabian T, Oellerich S, Dent DL, Brown R. Effect of recombinant human insulin-like growth factor I and early total parenteral nutrition on immune depression following severe head injury. *Arch Surg*. 1994 Jan;129(1):66-70
15. Takada Y, Bando H, Miyamoto Y, Kosaka M, Sano T. Effect of growth hormone on immune function in normal and hypophysectomised rats. *Nippon Naibunpi Gakkai Zasshi*. 1991 Oct 20;67(10):1162-77
16. Manfredi R, Tumietto F, Azzaroli L, Zucchini A, Chiodo F, Manfredi G. Growth hormone (GH) and the immune system: impaired phagocytic function in children with idiopathic GH deficiency is corrected by treatment with biosynthetic GH. *J Pediatr Endocrinol*. 1994 Jul-Sep;7(3):245-51
17. Jardieu P, Clark R, Mortensen D, Dorshkind K. In vivo administration of insulin-like growth factor-I stimulates primary B lymphopoiesis and enhances lymphocyte recovery after bone marrow transplantation. *J Immunol*. 1994 May 1;152(9):4320-7
18. Vara-Thorbeck R, Guerrero JA, Rosell J, Ruiz-Requena E, Capitan JM. Exogenous growth hormone: effects on the catabolic response to surgically produced acute stress and on postoperative immune function. *World J Surg*. 1993 Jul-Aug;17(4):530-7
19. Edwards CK 3rd, Ghiasuddin SM, Yunger LM, Lorence RM, Arkins S, Dantzer R, Kelley KW. In vivo administration of recombinant growth hormone or gamma interferon activities macrophages: enhanced resistance to experimental *Salmonella typhimurium* infection is correlated with generation of reactive oxygen intermediates. *Infect Immun*. 1992 Jun;60(6):2514-21
20. Huang KF, Chung DH, Herndon DN. Insulin-like growth factor 1 (IGF-1) reduces gut atrophy and bacterial translocation after severe burn injury. *Arch Surg*. 1993 Jan;128(1):47-53
21. Peake GT, Mackinnon LT, Sibbitt WL Jr, Kraner JC. Exogenous growth hormone treatment alters body composition and increases naturalkiller cell activity in women with impaired endogenous growth hormone secretion. *Metabolism*. 1987 Dec;36(12):1115-7
22. Crist DM, Kraner JC. Supplemental growth hormone increases the tumor cytotoxic activity of natural killer cells in healthy adults with normal growth hormone secretion. *Metabolism*. 1990 Dec;39(12):1320-4

Limits to healthy cell proliferation: GH/IGF-1 stimulates fibroblast proliferation and differentiation

23. Clemmons DR, Van Wyk JJ. Somatomedin-C and platelet-derived growth factor stimulate human fibroblast replication. *J Cell Physiol*. 1981 Mar;106(3):361-7
24. van Osch GJ, van der Veen SW, Verwoerd-Verhoef HL. In vitro redifferentiation of culture-expanded rabbit and human auricular chondrocytes for cartilage reconstruction. *Plast Reconstr Surg*. 2001 Feb;107(2):433-40

Poor gene polymorphism: poor GH gene polymorphisms may increase the risk of age-related diseases

25. Dennison EM, Syddall HE, Rodriguez S, Voroponov A, Day IN, Cooper C; Southampton Genetic Epidemiology Research Group. Polymorphism in the growth hormone gene, weight in infancy, and adult bone mass. *J Clin Endocrinol Metab*. 2004 Oct;89(10):4898-903

Progressive telomere shortening: GHRH may stimulate telomerase

26. Kiaris H, Schally AV. Decrease in telomerase activity in U-87MG human glioblastomas after treatment with an antagonist of growth hormone-releasing hormone. *Proc Natl Acad Sci USA*. 1999 Jan 5;96(1):226-31

GH and psychic well-being

Lower quality of life and fatigue: the association with lower GH and/or IGF-1 levels

27. Gilchrist FJ, Murray RD, Shalet SM. The effect of long-term untreated growth hormone deficiency (GHD) and 9 years of GH replacement on the quality of life (QoL) of GH-deficient adults. *Clin Endocrinol (Oxf)*. 2002 Sep;57(3):363-70
28. Abs R, Bengtsson BA, Hernberg-Stahl E, Monson JP, Tauber JP, Wilton P, Wuster C. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clin Endocrinol (Oxf)*. 1999 Jun;50(6):703-13

29. Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Shalet SM. Dose titration and patient selection increases the efficacy of GH replacement in severely GH deficient adults. *Clin Endocrinol (Oxf)*. 1999 Jun;50(6):749-57

Lower quality of life and fatigue: the effect of GH and/or IGF-1 treatment

30. Murray RD, Darzy KH, Gleeson HK, Shalet SM. GH-deficient survivors of childhood cancer: GH replacement during adult life. *J Clin Endocrinol Metab*. 2002 Jan;87(1):129-35
31. Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Smethurst LE, Shalet SM. Influences on quality of life in GH deficient adults and their effect on response to treatment. *Clin Endocrinol (Oxf)*. 1999 Nov;51(5):565-73
32. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. *Clin Endocrinol (Oxf)*. 2001 Jun;54(6):709-17
33. Davies JS, Obuobie K, Smith J, Rees DA, Furlong A, Davies N, Evans LM, Scanlon MF. A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. *Clin Endocrinol (Oxf)*. 2000 Mar;52(3):295-303
34. McGauley GA. Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. *Acta Paediatr Scand Suppl*. 1989;356:70-2
35. Cuneo RC, Judd S, Wallace JD, Perry-Keene D, Burger H, Lim-Tio S, Strauss B, Stockigt J, Topliss D, Alford F, Hew L, Bode H, Conway A, Handelsman D, Dunn S, Boyages S, Cheung NW, Hurley D. The Australian Multicenter Trial of Growth Hormone (GH) Treatment in GH-Deficient Adults. *J Clin Endocrinol Metab*. 1998 Jan;83(1):107-16
36. Li Voon Chong JS, Benbow S, Foy P, Wallymahmed ME, Wile D, MacFarlane IA. Elderly people with hypothalamic-pituitary disease and growth hormone deficiency: lipid profiles, body composition and quality of life compared with control subjects. *Clin Endocrinol (Oxf)*. 2000 Nov;53(5):551-9
37. Moorkens G, Berwaerts J, Wynants H, Abs R. Characterization of pituitary function with emphasis on GH secretion in the chronic fatigue syndrome. *Clin Endocrinol (Oxf)*. 2000 Jul;53(1):99-106
38. Wallymahmed ME, Baker GA, Humphris G, Dewey M, MacFarlane IA. The development, reliability and validity of a disease specific quality of life model for adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1996 Apr;44(4):403-11
39. Lagrou K, Xhrouet-Heinrichs D, Massa G, Vandeweghe M, Bourguignon JP, De Schepper J, de Zegher F, Ernould C, Heinrichs C, Malvaux P, Craen M. Quality of life and retrospective perception of the effect of growth hormone treatment in adult patients with childhood growth hormone deficiency. *J Pediatr Endocrinol Metab*. 2001;14 Suppl 5:1249-60
40. Stabler B. Impact of growth hormone (GH) therapy on quality of life along the lifespan of GH-treated patients. *Horm Res*. 2001;56 Suppl 1:55-8
41. Wiren L, Johannsson G, Bengtsson BA. A prospective investigation of quality of life and psychological well-being after the discontinuation of GH treatment in adolescent patients who had GH deficiency during childhood. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3494-8
42. Bjork S, Jonsson B, Westphal O, Levin JE. Quality of life of adults with growth hormone deficiency: a controlled study. *Acta Paediatr Scand Suppl*. 1989;356:55-9; discussion 60, 73-4
43. Bengtsson BA, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Stahl E, Westberg B, Wilton P, Wuster C. The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. *J Clin Endocrinol Metab*. 1999 Nov;84(11):3929-35
44. Laron Z. Consequences of not treating children with Laron syndrome (primary growth hormone insensitivity). *J Pediatr Endocrinol Metab*. 2001;14 Suppl 5:1243-8; discussion 1261-2
45. Page RC, Hammersley MS, Burke CW, Wass JA. An account of the quality of life of patients after treatment for non-functioning pituitary tumours. *Clin Endocrinol (Oxf)*. 1997 Apr;46(4):401-6

Lower quality of life and fatigue: the improvement with GH treatment

46. Wallymahmed ME, Foy P, Shaw D, Hutcheon R, Edwards RH, MacFarlane IA. Quality of life, body composition and muscle strength in adult growth hormone deficiency: the influence of growth hormone replacement therapy for up to 3 years. *Clin Endocrinol (Oxf)*. 1997 Oct;47(4):439-46
47. Kozakowski J, Adamkiewicz M, Krassowski J, Zgliczynski S. The beneficial effects of growth hormone replacement therapy on elderly men. *Pol Merkuriusz Lek*. 1999 Mar;6(33):131-4
48. Waters D, Danska J, Hardy K, Koster F, Qualls C, Nickell D, Nightingale S, Gesundheit N, Watson D, Schade D. Recombinant human growth hormone, insulin-like growth factor 1, and combination therapy in AIDS-associated wasting. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1996 Dec 1;125(11):865-72
49. Bengtsson BA, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Stahl E, Westberg B, Wilton P, Wuster C. The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. *J Clin Endocrinol Metab*. 1999 Nov;84(11):3929-35
50. Feldt-Rasmussen U, Abs R, Bengtsson BA, Bennmarker H, Bramnert M, Hernberg-Stahl E, Monson JP, Westberg B, Wilton P, Wuster C; KIMS International Study Board on behalf of KIMS Study Group. Growth hormone deficiency and replacement in hypopituitary patients previously treated for acromegaly or Cushing's disease. *Eur J Endocrinol*. 2002 Jan;146(1):67-74
51. Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP; KIMS International Board.; KIMS Study Group. Pharmacia International Metabolic Database. Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency. *J Clin Endocrinol Metab*. 2001 Nov;86(11):5277-81
52. Wiren L, Bengtsson BA, Johannsson G. Beneficial effects of long-term GH replacement therapy on quality of life in adults with GH deficiency. *Clin Endocrinol (Oxf)*. 1998 May;48(5):613-20
53. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Sacca L.A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. *N Engl J Med*. 1996 Mar 28;334(13):809-14
54. Burman P, Deijen JB. Quality of life and cognitive function in patients with pituitary insufficiency. *Psychother Psychosom*. 1998;67(3):154-67
55. Carroll PV, Littlewood R, Weissberger AJ, Bogalho P, McGauley G, Sonksen PH, Russell-Jones DL. The effects of two doses of replacement growth hormone on the biochemical, body composition and psychological profiles of growth hormone-deficient adults. *Eur J Endocrinol*. 1997 Aug;137(2):146-53
56. Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E, Karlsson FA. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. *J Clin Endocrinol Metab*. 1995 Dec;80(12):3585-90

Depression: the association with lower GH and/or IGF-1 levels

57. Jarrett DB, Miewald JM, Kupfer DJ. Recurrent depression is associated with a persistent reduction in sleep-related growth hormone secretion. *Arch Gen Psychiatry*. 1990 Feb;47(2):113-8
58. Jarrett DB, Kupfer DJ, Miewald JM, Grochocinski VJ, Franz B. Sleep-related growth hormone secretion is persistently suppressed in women with recurrent depression: a preliminary longitudinal analysis. *J Psychiatr Res*. 1994 May-Jun;28(3):211-23
59. Rubin RT, Poland RE, Lesser IM. Neuroendocrine aspects of primary endogenous depression. X: Serum growth hormone measures in patients and matched control subjects. *Biol Psychiatry*. 1990 May 15;27(10):1065-82
60. Schilkrot R, Chandra O, Osswald M, Ruther E, Baafusser B, Matussek. Growth hormone release during sleep and with thermal stimulation in depressed patients. *Neuropsychobiology*. 1975;1(2):70-9
61. Barry S, Dinan TG. Neuroendocrine challenge tests in depression: a study of growth hormone, TRH and cortisol release. *J Affect Disord*. 1990 Apr;18(4):229-34
62. Dinan TG, Barry S. Responses of growth hormone to desipramine in endogenous and non-endogenous depression. *Br J Psychiatry*. 1990 May;156:680-4

63. Voderholzer U, Laakmann G, Wittmann R, Daffner-Bujia C, Hinz A, Haag C, Baghai T. Profiles of spontaneous 24-hour and stimulated growth hormone secretion in male patients with endogenous depression. *Psychiatry Res.* 1993 Jun;47(3):215-27
64. Harro J, Rimm H, Harro M, Grauberg M, Karelson K, Viru AM. Association of depressiveness with blunted growth hormone response to maximal physical exercise in young healthy men. *Psychoneuroendocrinology.* 1999 Jul;24(5):505-17
65. Greden JF. Biological markers of melancholia and reclassification of depressive disorders. *Encephale.* 1982;8(2):193-202
66. McMillan CV, Bradley C, Gibney J, Healy ML, Russell-Jones DL, Sonksen PH. Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency. *Clin Endocrinol. (Oxf).* 2003 Oct;59(4):467-75

Depression: the improvement with GH treatment

67. Mahajan T, Crown A, Checkley S, Farmer A, Lightman S. Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone treatment on depression and quality of life. *Eur J Endocrinol.* 2004 Sep;151(3):325-32
68. Johansson JO, Larson G, Andersson M, Elmgren A, Hynsjo L, Lindahl A, Lundberg PA, Isaksson OG, Lindstedt S, Bengtsson BA. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. *Neuroendocrinology.* 1995 Jan;61(1):57-66
(*GH increases endorphins, reduces dopamine*)

Anxiety: the association with lower GH and/or IGF-1 levels

69. Tancer ME, Stein MB, Uhde TW. Growth hormone response to intravenous clonidine in social phobia: comparison to patients with panic disorder and healthy volunteers. *Biol Psychiatry.* 1993 Nov 1;34(9):591-5
70. Cameron OG, Abelson JL, Young EA. Anxious and depressive disorders and their comorbidity: effect on central nervous system noradrenergic function. *Biol Psychiatry.* 2004 Dec 1;56(11):875-83
71. Stabler B. Impact of growth hormone (GH) therapy on quality of life along the lifespan of GH-treated patients. *Horm Res.* 2001;56 Suppl 1:55-8
72. Abelson JL, Glitz D, Cameron OG, Lee MA, Bronzo M, Curtis GC. Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. *Arch Gen Psychiatry.* 1991 Feb;48(2):157-62

Anxiety: the improvement with GH treatment

73. Arwert LI, Deijen JB, Muller M, Drent ML. Long-term growth hormone treatment preserves GH-induced memory and mood improvements: a 10-year follow-up study in GH-deficient adult men. *Horm Behav.* 2005 Mar;47(3):343-9
74. Lasaitė L, Bunevicius R, Lasiene D, Lasas L. Psychological functioning after growth hormone therapy in adult growth hormone deficient patients: endocrine and body composition correlates. *Medicina (Kaunas).* 2004;40(8):740-4

Memory loss and Alzheimer's disease: the association with lower GH and/or IGF-1 levels

75. Deijen JB, de Boer H, Blok GJ, van der Veen EA. Cognitive impairments and mood disturbances in growth hormone deficient men. *Psychoneuroendocrinology.* 1996 Apr;21(3):313-22
76. Rollero A, Murialdo G, Fonzi S, Garrone S, Gianelli MV, Gazzero E, Barreca A, Polleri A. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. *Neuropsychobiology.* 1998;38(2):73-9
77. van Dam PS, de Winter CF, de Vries R, van der Grond J, Drent ML, Lijffijt M, Kenemans JL, Aleman A, de Haan EH, Koppeschaar HP. Childhood-onset growth hormone deficiency, cognitive function and brain N-acetylaspartate. *Psychoneuroendocrinology.* 2005 May;30(4):357-63
78. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, Iguchi T, Katagiri T. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. *Metabolism.* 2004 Apr;53(4):476-82

Memory loss and Alzheimer's disease: the improvement with GH treatment

79. Deijen JB, de Boer H, van der Veen EA. Cognitive changes during growth hormone replacement in adult men. *Psychoneuroendocrinology*. 1998 Jan;23(1):45-55
80. Koppeschaar HP. Growth hormone, insulin-like growth factor I and cognitive function in adults. *Growth Horm IGF Res*. 2000 Apr;10 Suppl B:S69-73

Sleep disorders: the association with lower GH and/or IGF-1 levels

81. Astrom C, Lindholm J. Growth hormone-deficient young adults have decreased deep sleep. *Neuroendocrinology*. 1990 Jan;51(1):82-4

Sleep disorders: the improvement with GH treatment

82. Astrom C, Pedersen SA, Lindholm J. The influence of growth hormone on sleep in adults with growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1990 Oct;33(4):495-500

Loss of sexual drive, sensitivity and/or potency: the association with lower GH and/or IGF-1 levels

83. Becker AJ, Uckert S, Stief CG, Scheller F, Knapp WH, Hartmann U, Brabant G, Jonas U. Serum levels of human growth hormone during different penile conditions in the cavernous and systemic blood of healthy men and patients with erectile dysfunction. *Urology*. 2002 Apr;59(4):609-14
84. Huang X, Li S, Hu L. Growth hormone deficiency and age-related erectile dysfunction. *Zhonghua Nan Ke Xue*. 2004 Nov;10(11):867

Loss of sexual potency: the improvement with GH treatment

85. Becker AJ, Uckert S, Stief CG, Truss MC, Machtens S, Scheller F, Knapp WH, Hartmann U, Jonas U. Possible role of human growth hormone in penile erection. *J Urol*. 2000 Dec;164(6):2138-42
86. Zhang XS, Wang YX, Han YF, Li Z, Xiang ZQ, Leng J, Huang XY. Effects of growth hormone supplementation on erectile function and expression of nNOS in aging rats. *Zhonghua Nan Ke Xue*. 2005 May;11(5):339-42
87. Jung GW, Spencer EM, Lue TF. Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous nerve neurotomy in rats. *J Urol*. 1998 Nov;160(5):1899-904

GH and physical appearance/body composition

Sarcopenia: the association with lower GH and/or IGF-1 levels

88. Sartorio A, Narici MV. Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. *Clin Physiol*. 1994 Sep;14(5):527-37
89. De Boer H, Blok GJ, Voerman HJ, De Vries PM, van der Veen EA. Body composition in adult growth hormone-deficient men, assessed by anthropometry and bioimpedance analysis. *J Clin Endocrinol Metab*. 1992 Sep;75(3):833-7
90. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *J Appl Physiol*. 1991 Feb;70(2):688-94

Sarcopenia: the improvement with GH treatment

91. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab.* 2000 May;85(5):1874-81
92. Butterfield GE, Marcus R, Holloway L, Butterfield G. Clinical use of growth hormone in elderly people. *J Reprod Fertil Suppl.* 1993; 46:115-8
93. Butterfield GE, Thompson J, Rennie MJ, Marcus R, Hintz RL, Hoffman AR. Effect of rhGH and rhIGF-1 treatment on protein utilization in elderly women. *Am J Physiol.* 1997 Jan; 272 (1 Pt 1): E 94-9
94. Sartorio A, Narici MV. Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. *Clin Physiol.* 1994 Sep;14(5):527-37
95. Janssen YJ, Doornbos J, Roelfsema F. Changes in muscle volume, strength, and bioenergetics during recombinant human growth hormone (GH) therapy in adults with GH deficiency. *J Clin Endocrinol Metab.* 1999 Jan;84(1):279-84
96. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet.* 1989 Jun 3;1(8649):1221-5
97. ter Maaten JC, de Boer H, Kamp O, Stuurman L, van der Veen EA. Long-term effects of growth hormone (GH) replacement in men with childhood-onset GH deficiency. *J Clin Endocrinol Metab.* 1999 Jul;84(7):2373-80
98. Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, Hadden DR. Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. *Clin Endocrinol (Oxf).* 1992 Jan;36(1):45-52
99. Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord.* 2001 Aug;25(8):1101-7

Lean body mass: the association with lower GH and/or IGF-1 levels

100. De Boer H, Blok GJ, Voerman HJ, De Vries PM, van der Veen EA. Body composition in adult growth hormone-deficient men, assessed by anthropometry and bioimpedance analysis. *J Clin Endocrinol Metab.* 1992 Sep;75(3):833-7

Lean body mass: the improvement with GH treatment

101. Bengtsson BA, Eden S, Lonn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tolli J, Sjostrom L, Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab.* 1993 Feb;76(2):309-17
102. Lombardi G, Luger A, Marek J, Russell-Jones D, Sonksen P, Attanasio AF. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. *J Clin Endocrinol Metab.* 2002 May;87(5):1974-9
103. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab.* 2000 May;85(5):1874-81
104. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. *N Engl J Med.* 1990 Jul 5;323(1):1-6
105. Davies JS, Obuobie K, Smith J, Rees DA, Furlong A, Davies N, Evans LM, Scanlon MF. A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. *Clin Endocrinol (Oxf).* 2000 Mar;52(3):295-303
106. Olsovská V, Siprova H, Beranek M, Soska V. The influence of long-term growth hormone replacement therapy on body composition, bone tissue and some metabolic parameters in adults with growth hormone deficiency. *Vnitr Lek.* 2005 Dec;51(12):1356-64

Physical appearance, body morphology improvement with GH treatment

107. Hertoghe T. Growth hormone therapy in aging adults. *Anti-aging Med Ther.* 1997;1:10-28

108. Zivicnjak M, Franke D, Ehrich JH, Filler G. Does growth hormone therapy harmonize distorted morphology and body composition in chronic renal failure? *Pediatr Nephrol.* 2000 Dec;15(3-4):229-35
109. Eiholzer U, Schlumpf M, Nordmann Y, l'Allemand D. Early manifestations of Prader-Willi syndrome: influence of growth hormone. *J Pediatr Endocrinol Metab.* 2001;14 Suppl 6:1441-4

GH and age-related diseases

Hypercholesterolemia: the association with lower GH and/or IGF-1 levels

110. Abdu TA, Neary R, Elhadd TA, Akber M, Clayton RN. Coronary risk in growth hormone deficient hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. *Clin Endocrinol (Oxf)* 2001 Aug;55(2):209-16
111. Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosen T, Lindstedt G, Lundberg PA, Bengtsson BA. Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. *Clin Endocrinol (Oxf)*. 1994 Sep;41(3):351-7
112. Sanmarti A, Lucas A, Hawkins F, Webb SM, Ulied A. Observational study in adult hypopituitary patients with untreated growth hormone deficiency (ODA study). Socio-economic impact and health status. Collaborative ODA (Observational GH Deficiency in Adults) Group. *Eur J Endocrinol.* 1999 Nov;141(5):481-9
113. Colao A, di Somma C, Pivonello R, Cuocolo A, Spinelli L, Bonaduce D, Salvatore M, Lombardi G. The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study. *J Clin Endocrinol Metab.* 2002 Mar;87(3):1088-93

Hypercholesterolemia: the improvement with GH treatment

114. Abrahamsen B, Nielsen TL, Hangaard J, Gregersen G, Vahl N, Korsholm L, Hansen TB, Andersen M, Hagen C. Dose-, IGF-I- and sex-dependent changes in lipid profile and body composition during GH replacement therapy in adult onset GH deficiency. *Eur J Endocrinol.* 2004 May;150(5):671-9
115. Elgzyri T, Castenfors J, Hagg E, Backman C, Thoren M, Bramnert M. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. *Clin Endocrinol (Oxf)*. 2004 Jul;61(1):113-22
116. Jallad RS, Liberman B, Vianna CB, Vieira ML, Ramires JA, Knoepfelmacher M. Effects of growth hormone replacement therapy on metabolic and cardiac parameters, in adult patients with childhood-onset growth hormone deficiency. *Growth Horm IGF Res.* 2003 Apr-Jun;13(2-3):81-8
117. Olsovská V, Siprova H, Beranek M, Soska V. The influence of long-term growth hormone replacement therapy on body composition, bone tissue and some metabolic parameters in adults with growth hormone deficiency. *Vnitr Lek.* 2005 Dec;51(12):1356-64 (*"a decrease of total and LDL cholesterol occurred already after a half of the year of the treatment (p < 0.05), changes were significant also in further four years. HDL cholesterol levels have had a progressive tendency, but they were not statistically significant"*)

Homocysteinemia: the improvement with GH treatment

118. Sesmilo G, Biller BM, Llevadot J, Hayden D, Hanson G, Rifai N, Klibanski A. Effects of growth hormone (GH) administration on homocyst(e)ine levels in men with GH deficiency: a randomized controlled trial. *J Clin Endocrinol Metab.* 2001 Apr;86(4):1518-24

Atherosclerosis: the association with lower GH and/or IGF-1 levels

119. Capaldo B, Patti L, Oliviero U, Longobardi S, Pardo F, Vitale F, Fazio S, Di Rella F, Biondi B, Lombardi G, Sacca L. Increased arterial intima-media thickness in childhood-onset growth hormone deficiency. *J Clin Endocrinol Metab.* 1997 May;82(5):1378-81
120. Markussis V, Beshyah SA, Fisher C, Sharp P, Nicolaides AN, Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet.* 1992;34():1188-1192.
121. Pfeifer M, Verhovec R, Zizek B, Prezelj J, Poredos P, Clayton RN. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metab.* 1999 Feb;84(2):453-7

Atherosclerosis: the improvement with GH treatment

122. Pfeifer M, Verhovec R, Zizek B, Prezelj J, Poredos P, Clayton RN. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metab.* 1999 Feb;84(2):453-7
123. Irving RJ, Carson MN, Webb DJ, Walker BR. Peripheral vascular structure and function in men with contrasting GH levels. *J Clin Endocrinol Metab.* 2002 Jul;87(7):3309-14
124. Borson-Chazot F, Serusclat A, Kalfallah Y, Ducottet X, Sassolas G, Bernard S, Labrousse F, Pastene J, Sassolas A, Roux Y, Berthezene F. Decrease in carotid intima-media thickness after one year growth hormone (GH) treatment in adults with GH deficiency. *J Clin Endocrinol Metab.* 1999 Apr;84(4):1329-33.
125. Soares DV, Spina LD, de Lima Oliveira Brasil RR, da Silva EM, Lobo PM, Salles E, Coeli CM, Conceicao FL, Vaisman M. Carotid artery intima-media thickness and lipid profile in adults with growth hormone deficiency after long-term growth hormone replacement. *Metabolism.* 2005 Mar;54(3):321

Arterial hypertension: the association with lower GH and/or IGF-1 levels

126. Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosen T, Lundstedt G, Lundberg PA, Bengtsson BA. Serum insulin-like growth factor 1 in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. *Clin Endocrinol (Oxf).* 1994 Sep;41(3):351-7

Arterial hypertension: the improvement with GH treatment

127. Caidahl K, Eden S, Bengtsson BA. Cardiovascular and renal effects of growth hormone. *Clin Endocrinol (Oxf).* 1994 Mar;40(3):393-400

Coronary heart disease: the association with lower GH and/or IGF-1 levels

128. Conti E, Andreotti F, Sciahbasi A, Riccardi P, Marra G, Menini E, Ghirlanda G, Maseri A. Markedly reduced insulin-like growth factor-1 in the acute phase of myocardial infarction. *J Am Coll Cardiol.* 2001 Jul;38(1):26-32

Coronary heart disease: the improvement with GH treatment

129. Castagnino HE, Lago N, Centrella JM, Calligaris SD, Farina S, Sarchi MI, Cardinali DP. Cytoprotection by melatonin and growth hormone in early rat myocardial infarction as revealed by Feulgen DNA staining. *Neuroendocrinol Lett;* 2002 Oct-Dec;23(5/6):391-395

Stroke and other cerebrovascular disorders: the association with GH and/or IGF-1 levels

130. Rudman D, Nagraj HS, Mattson DE, Jackson DL, Rudman IW, Boswell J, Pucci DC. Hyposomatomedinemia in the men of a Veterans Administration Nursing Home: prevalence and correlates. *Gerontology.* 1987;33(5):307-14

Obesity: the association with lower GH and/or IGF-1 levels

131. Beshyah SA, Freemantle C, Thomas E, Rutherford O, Page B, Murphy M, Johnston DG. Abnormal body composition and reduced bone mass in growth hormone deficient hypopituitary adults. *Clin Endocrinol (Oxf)* 1995 Feb;42(2):179-89
132. Attanasio AF, Bates PC, Ho KK, Webb SM, Ross RJ, Strasburger CJ, Bouillon R, Crowe B, Selander K, Valle D, Lamberts SW; Hypoptiuitary Control and Complications Study International Advisory Board. Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status--3-year results from the HypoCCS Database. *J Clin Endocrinol Metab*. 2002 Apr;87(4):1600-6
133. Stouthart PJ, de Ridder CM, Rekers-Mombarg LT, van der Waal HA. Changes in body composition during 12 months after discontinuation of growth hormone therapy in young adults with growth hormone deficiency from childhood. *J Pediatr Endocrinol Metab*. 1999 Apr;12 Suppl 1:335-8
134. Biller BM, Sesmilo G, Baum HB, Hayden D, Schoenfeld D, Klibanski A. Withdrawal of long-term physiological growth hormone (GH) administration: differential effects on bone density and body composition in men with adult-onset GH deficiency. *J Clin Endocrinol Metab*. 2000 Mar;85(3):970-6
135. Kohno H, Ueyama N, Honda S. Unfavourable impact of growth hormone (GH) discontinuation on body composition and cholesterol profiles after the completion of height growth in GH-deficient young adults. *Diabetes Obes Metab*. 1999 Sep;1(5):293-6
136. Kuromaru R, Kohno H, Ueyama N, Hassan HM, Honda S, Hara T. Long-term prospective study of body composition and lipid profiles during and after growth hormone (GH) treatment in children with GH deficiency: gender-specific metabolic effects. *J Clin Endocrinol Metab*. 1998 Nov;83(11):3890-6
137. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab*. 2000 May;85(5):1874-81
138. Norrelund H, Vahl N, Juul A, Moller N, Alberti KG, Skakkebaek NE, Christiansen JS, Jorgensen JO. Continuation of growth hormone (GH) therapy in GH-deficient patients during transition from childhood to adulthood: impact on insulin sensitivity and substrate metabolism. *J Clin Endocrinol Metab*. 2000 May;85(5):1912-7
139. Johannsson G. What happens when growth hormone is discontinued at completion of growth? Metabolic aspects. *J Pediatr Endocrinol Metab*. 2000;13 Suppl 6:1321-6

Obesity: the improvement with GH treatment

140. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE. Effects of human growth hormone in men over 60 years old. *N Engl J Med*. 1990 Jul 5;323(1):1-6
141. Rudman D, Feller AG, Cohn L, Shetty KR, Rudman IW, Draper MW. Effects of human growth hormone on body composition in elderly men. *Horm Res* 1991;36 Suppl 1:73-81
142. Bengtsson BA, Eden S, Lonn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tolli J, Sjostrom L, Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. *J Clin Endocrinol Metab*. 1993 Feb;76(2):309-17
143. Munzer T, Harman SM, Hees P, Shapiro E, Christmas C, Bellantoni MF, Stevens TE, O'Connor KG, Pabst KM, St Clair C, Sorkin JD, Blackman MR. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3604-10
144. Rodriguez-Arnan J, Jabbar A, Fulcher K, Besser GM, Ross RJ. Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. *Clin Endocrinol (Oxf)*. 1999 Jul;51(1):53-60
145. Soares CN, Musolino NR, Cunha Neto M, Caires MA, Rosenthal MC, Camargo CP, Bronstein MD. Impact of recombinant human growth hormone (RH-GH) treatment on psychiatric, neuropsychological and clinical profiles of GH deficient adults. A placebo-controlled trial. *Arq Neuropsiquiatr*. 1999 Jun;57(2A):182-9
146. Fernholm R, Brammert M, Hagg E, Hilding A, Baylink DJ, Mohan S, Thoren M. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. *J Clin Endocrinol Metab*. 2000 Nov;85(11):4104-12

147. Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA, Strasburger CJ. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. *J Clin Endocrinol Metab.* 1997 Jan;82(1):82-8
148. Beshyah SA, Freemantle C, Shahi M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R, Johnston DG. Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults *Clin Endocrinol (Oxf).* 1995 Jan;42(1):73-84
149. Moorkens G, Wynants H, Abs R. Effect of growth hormone treatment in patients with chronic fatigue syndrome: a preliminary study. *Growth Horm IGF Res.* 1998 Apr;8 Suppl B:131-3
150. Lo JC, Mulligan K, Noor MA, Schwarz JM, Halvorsen RA, Grunfeld C, Schambelan M. The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab.* 2001 Aug;86(8):3480-7
151. Christ ER, Cummings MH, Albany E, Umpleby AM, Lumb PJ, Wierzbicki AS, Naoumova RP, Boroujerdi MA, Sonksen PH, Russell-Jones DL. Effects of growth hormone (GH) replacement therapy on very low density lipoprotein apolipoprotein B100 kinetics in patients with adult GH deficiency: a stable isotope study. *J Clin Endocrinol Metab.* 1999 Jan;84(1):307-16
152. Florkowski CM, Collier GR, Zimmet PZ, Livesey JH, Espiner EA, Donald RA. Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency. *Clin Endocrinol (Oxf).* 1996 Dec;45(6):769-73
153. Ezzat S, Fear S, Gaillard RC, Gayle C, Landy H, Marcovitz S, Mattioni T, Nussey S, Rees A, Svanberg E. Gender-specific responses of lean body composition and non-gender-specific cardiac function improvement after GH replacement in GH-deficient adults. *J Clin Endocrinol Metab.* 2002 Jun;87(6):2725-33
154. Weaver JU, Monson JP, Noonan K, John WG, Edwards A, Evans KA, Cunningham J. The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. *J Clin Endocrinol Metab.* 1995 Jan;80(1):153-9
155. Vahl N, Jorgensen JO, Hansen TB, Klausen IB, Jurik AG, Hagen C, Christiansen JS. The favourable effects of growth hormone (GH) substitution on hypercholesterolaemia in GH-deficient adults are not associated with concomitant reductions in adiposity. A 12 month placebo-controlled study. *Int J Obes Relat Metab Disord.* 1998 Jun;22(6):529-36
156. Hansen TB, Gram J, Jensen PB, Kristiansen JH, Ekelund B, Christiansen JS, Pedersen FB. Influence of growth hormone on whole body and regional soft tissue composition in adult patients on hemodialysis. A double-blind, randomized, placebo-controlled study. *Clin Nephrol;* 2000 Feb;53(2):99-107
157. Fisker S, Vahl N, Hansen TB, Jorgensen JO, Hagen C, Orskov H, Christiansen JS. Growth hormone (GH) substitution for one year normalizes elevated GH-binding protein levels in GH-deficient adults secondary to a reduction in body fat. A placebo-controlled trial. *Growth Horm IGF Res.* 1998 Apr;8(2):105-12
158. Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim DS, Schoenfeld DA, Michel TH, Wittink H, Klibanski A. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Ann Intern Med.* 1996 Dec 1;125(11):883-90
159. Burman P, Johansson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *J Clin Endocrinol Metab.* 1997 Feb;82(2):550-5
160. Schambelan M, Mulligan K, Grunfeld C, Daar ES, LaMarca A, Kotler DP, Wang J, Bozzette SA, Breitmeyer JB. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Serostim Study Group. *Ann Intern Med.* 1996 Dec 1;125(11):873-82
161. Lee PD, Pivarnik JM, Bukar JG, Muurahainen N, Berry PS, Skolnik PR, Nerad JL, Kudsk KA, Jackson L, Ellis KJ, Gesundheit N. A randomized, placebo-controlled trial of combined insulin-like growth factor I and low dose growth hormone therapy for wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab.* 1996 Aug;81(8):2968-75
162. Toogood AA, Shalet SM. Growth hormone replacement therapy in the elderly with hypothalamic-pituitary disease: a dose-finding study. *J Clin Endocrinol Metab.* 1999 Jan;84(1):131-6

Diabetes: the association with lower GH and/or IGF-1 levels

163. Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord*. 2001 Aug;25(8):1101-7

Diabetes: the improvement with GH treatment

164. Gotherstrom G, Svensson J, Koranyi J, Alpsten M, Bosaeus I, Bengtsson B, Johannsson G. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab*. 2001 Oct;86(10):4657-65
165. Svensson J, Fowelin J, Landin K, Bengtsson BA, Johannsson JO. Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. *J Clin Endocrinol Metab*. 2002 May;87(5):2121-7
166. Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. *Clin Endocrinol (Oxf)*. 1994 Oct;41(4):517-24
167. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. *Clin Endocrinol (Oxf)*. 2005 Oct;63(4):428-36

Rheumatism: the association with lower GH and/or IGF-1 levels

168. Neidel J. Changes in systemic levels of insulin-like growth factors and their binding proteins in patients with rheumatoid arthritis. *Clin Exp Rheumatol*. 2001 Jan-Feb;19(1):81-4
169. Leal-Cerro A, Povedano J, Astorga R, Gonzalez M, Silva H, Garcia-Pesquera F, Casanueva FF, Dieguez C. The growth hormone (GH)-releasing hormone-GH-insulin-like growth factor-1 axis in patients with fibromyalgia syndrome. *J Clin Endocrinol Metab*. 1999 Sep;84(9):3378-81
170. Bagge E, Bengtsson BA, Carlsson L, Carlsson J. Low growth hormone secretion in patients with fibromyalgia--a preliminary report on 10 patients and 10 controls. *J Rheumatol*. 1998 Jan;25(1):145-8

Rheumatism: the improvement with GH treatment

171. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med*. 1998 Mar;104(3):227-31
172. Bennett R. Growth hormone in musculoskeletal pain states. *Curr Pain Headache Rep*. 2005 Oct;9(5):331-8

Osteoporosis: the association with lower GH and/or IGF-1 levels

173. Foldes J, Lakatos P, Zsadyani J, Horvath C. Decreased serum IGF-I and dehydroepiandrosterone sulphate may be risk factors for the development of reduced bone mass in postmenopausal women with endogenous subclinical hyperthyroidism. *Eur J Endocrinol*. 1997 Mar;136(3):277-81
174. Monson JP, Abs R, Bengtsson BA, Bennmarker H, Feldt-Rasmussen U, Hernberg-Stahl E, Thoren M, Westberg B, Wilton P, Wuster C. Growth hormone deficiency and replacement in elderly hypopituitary adults. KIMS Study Group and the KIMS International Board. Pharmacia and Upjohn International Metabolic Database. *Clin Endocrinol (Oxf)*. 2000 Sep;53(3):281-9
175. Longobardi S, Di Rella F, Pivonello R, Di Somma C, Klain M, Maurelli L, Scarpa R, Colao A, Merola B, Lombardi G. Effects of two years of growth hormone (GH) replacement therapy on bone metabolism and mineral density in childhood and adulthood onset GH deficient patients. *J Endocrinol Invest*. 1999 May;22(5):333-9
176. Beckers V, Milet J, Legros JJ. Prolonged treatment with recombinant growth hormone improves bone measures: study of body composition in 21 deficient adults on treatment. *Ann Endocrinol (Paris)*. 2001 Dec;62(6):507-15
177. Gomez JM, Gomez N, Fiter J, Soler J. Effects of long-term treatment with GH in the bone mineral density of adults with hypopituitarism and GH deficiency and after discontinuation of GH replacement. *Horm Metab Res*. 2000 Feb;32(2):66-70

178. Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M. Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. *J Clin Endocrinol Metab.* 1992 Jan;74(1):118-23
179. Calo L, Castrignano R, Davis PA, Carraro G, Pagnin E, Giannini S, Semplicini A, D'Angelo A. Role of insulin-like growth factor-I in primary osteoporosis: a correlative study. *J Endocrinol Invest.* 2000 Apr;23(4):223-7
180. Colao A, Di Somma C, Pivonello R, Loche S, Aimaretti G, Cerbone G, Faggiano A, Corneli G, Ghigo E, Lombardi G. Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. *J Clin Endocrinol Metab.* 1999 Jun;84(6):1919-24
181. Nakaoka D, Sugimoto T, Kaji H, Kanzawa M, Yano S, Yamauchi M, Sugishita T, Chihara K. Determinants of bone mineral density and spinal fracture risk in postmenopausal Japanese women. *Osteoporos Int.* 2001;12(7):548-54
182. Rico H, Del Rio A, Vila T, Patino R, Carrera F, Espinos D. The role of growth hormone in the pathogenesis of postmenopausal osteoporosis. *Arch Intern Med.* 1979 Nov;139(11):1263-5
183. Ljunghall S, Johansson AG, Burman P, Kampe O, Lindh E, Karlsson FA. Low plasma levels of insulin-like growth factor 1 (IGF-1) in male patients with idiopathic osteoporosis. *J Intern Med.* 1992 Jul;232(1):59-64

Osteoporosis: the improvement with GH treatment

184. ter Maaten JC, de Boer H, Kamp O, Stuurman L, van der Veen EA. Long-term effects of growth hormone (GH) replacement in men with childhood-onset GH deficiency. *J Clin Endocrinol Metab.* 1999 Jul;84(7):2373-80
185. Gomez JM, Gomez N, Fiter J, Soler J. Effects of long-term treatment with GH in the bone mineral density of adults with hypopituitarism and GH deficiency and after discontinuation of GH replacement. *Horm Metab Res.* 2000 Feb;32(2):66-70
186. Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim DS, Schoenfeld DA, Michel TH, Wittink H, Klibanski A. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. *Ann Intern Med.* 1996 Dec 1;125(11):883-90
187. Valimaki MJ, Salmela PI, Salmi J, Viikari J, Kataja M, Turunen H, Soppi E. Effects of 42 months of GH treatment on bone mineral density and bone turnover in GH-deficient adults. *Eur J Endocrinol* 1999 Jun;140(6):545-54
188. Vandeweghe M, Taelman P, Kaufman JM. Short and long-term effects of growth hormone treatment on bone turnover and bone mineral content in adult growth hormone-deficient males. *Clin Endocrinol (Oxf).* 1993 Oct;39(4):409-15
189. Clagnet C, Seck T, Hinke V, Wuster C, Ziegler R, Pfeilschifter J. Effects of 6 years of growth hormone (GH) treatment on bone mineral density in GH-deficient adults. *Clin Endocrinol (Oxf).* 2001 Jul;55(1):93-9
190. Beshyah SA, Thomas E, Kyd P, Sharp P, Fairney A, Johnston DG. The effect of growth hormone replacement therapy in hypopituitary adults on calcium and bone metabolism. *Clin Endocrinol (Oxf).* 1994 Mar;40(3):383-91
191. Biller BM, Sesmilo G, Baum HB, Hayden D, Schoenfeld D, Klibanski A. Withdrawal of long-term physiological growth hormone (GH) administration: differential effects on bone density and body composition in men with adult-onset GH deficiency. *J Clin Endocrinol Metab* 2000 Mar;85(3):970-6
192. Benbassat CA, Wasserman M, Laron Z. Changes in bone mineral density after discontinuation and early reinstatement of growth hormone (GH) in patients with childhood-onset GH deficiency. *Growth Horm IGF Res.* 1999 Oct;9(5):290-5
193. Sartorio A, Ortolani S, Galbiati E, Conte G, Vangeli V, Arosio M, Porretti S, Faglia. Effects of 12-month GH treatment on bone metabolism and bone mineral density in adults with adult-onset GH deficiency. *J Endocrinol Invest.* 2001 Apr;24(4):224-30
194. Finkenstedt G, Gasser RW, Hofle G, Watfah C, Fridrich L. Effects of growth hormone (GH) replacement on bone metabolism and mineral density in adult onset of GH deficiency: results of a double-blind placebo-controlled study with open follow-up. *Eur J Endocrinol.* 1997 Mar;136(3):282-9
195. Erdtsieck RJ, Pols HA, Valk NK, Van OBM, Lamberts SW, Mulder P, Birkenhager JC. Treatment of post-menopausal osteoporosis with a combination of growth hormone and pamidronate: a placebo controlled trial. *Clin Endocrinol (Oxf).* 1995;43:557-565

Cancer: the association with lower GH and/or IGF-1 levels

196. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum IGF-1: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. *Cancer Res.* 2003 Jul 15;63(14):3991-4
197. Baffa R, Reiss K, El-Gabry EA, Sedor J, Moy ML, Shupp-Byrne D, Strup SE, Hauck WW, Baserga R, Gomella LG. Low serum insulin-like growth factor 1 (IGF-1): a significant association with prostate cancer. *Tech Urol.* 2000 Sep;6(3):236-9
198. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. *J Clin Endocrinol Metab.* 2000 Aug;85(8):2744-7
199. Chokkalingam AP, Pollak M, Fillmore CM, Gao YT, Stanczyk FZ, Deng J, Sesterhenn IA, Mostofi FK, Fears TR, Madigan MP, Ziegler RG, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev.* 2001 May;10(5):421-7
200. Colombo F, Iannotta F, Fachinetti A, Giuliani F, Cornaggia M, Finzi G, Mantero G, Fraschini F, Malesci A, Bersani M, et al. [Changes in hormonal and biochemical parameters in gastric adenocarcinoma] *Minerva Endocrinol.* 1991 Jul-Sep;16(3):127-39

Cancer: improvement with GH treatment?

201. Torosian MH. Growth hormone and prostate cancer growth and metastasis in tumor-bearing animals. *J Pediatr Endocrinol.* 1993 Jan-Mar;6(1):93-7
202. Ng EH, Rock CS, Lazarus DD, Stiaino-Coico L, Moldawer LL, Lowry SF. Insulin-like growth factor I preserves host lean tissue mass in cancer cachexia. *Am J Physiol.* 1992 Mar;262(3 Pt 2):R426-31
203. Bartlett DL, Charland S, Torosian MH. Growth hormone, insulin, and somatostatin therapy of cancer cachexia. *Cancer.* 1994 Mar 1;73(5):1499-504

Longevity: the association with GH and/or IGF-1 levels

204. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet.* 1990 Aug 4;336(8710):285-8
205. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS, Mullis PE.. Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab.* 2003 Aug;88(8):3664-7
206. Bates AS, Van't Hoff W, Jones PJ, Clayton RN. The effect of hypopituitarism on life expectancy. *J Clin Endocrinol Metab.* 1996;81(3):1169-72

Longevity: the improvement with GH treatment

207. Khansari DN, Gustad T. Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. *Mech Ageing Dev.* 1991 Jan;57(1):87-100
208. Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease, modifies age-related pathology, and increases life span. *Endocrinology.* 2005;146(7):2920-32
209. Bengtsson BA, Koppeschaar HP, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP, Feldt-Rasmussen U, Wuster C. Growth hormone replacement therapy is not associated with any increase in mortality. KIMS Study Group. *J Clin Endocrinol Metab.* 1999;84(11):4291-2

GH diagnosis

210. Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KKY. Diagnosis of growth-hormone deficiency in adults. *Lancet* 1994;343:1064-8

Biochemical and clinical differences between childhood and adulthood-onset GH deficiency

211. Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA, Strasburger CJ. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. *J Clin Endocrinol Metab.* 1997 Jan;82(1):82-8

GH clinical evaluation

212. Cuneo RC, Salomon F, McGauley GA, Sonksen PH. The growth hormone deficiency syndrome in adults. *Clin Endocrinol (Oxf).* 1992;37:387-97
213. Christ ER, Carroll PV, Russell JDL, Sonksen PH. The consequences of growth hormone deficiency in adulthood, and the effects of growth hormone replacement. *Schweiz Med Wochenschr.* 1997; 127:1440-9
214. Labram EK, Wilkin TJ. Growth hormone deficiency in adults and its response to growth hormone replacement. *QJM.* 1995;88:391-9
215. Rosen T, Johannsson G, Johannsson JO, Bengtsson BA. Consequences of growth hormone deficiency in adults and the benefits and risks of recombinant human growth hormone treatment. *Horm Res.* 1995;43:93-9
216. Jorgensen JO, Muller J, Moller J, Wolthers T, Vahl N, Juul A, Skakkebaek NE, Christiansen JS. Adult growth hormone deficiency. *Horm Res.* 1994;42:235-241
217. Lieberman SA, Hoffman AR. Growth hormone deficiency in adults: characteristics and response to growth hormone replacement. *J Pediatr.* 1996;128:S58-S60.

Serum GH tests

Serum IGF-1

218. Breier BH, Gallaher BW, Gluckman PD. Radioimmunoassay for insulin-like growth factor-I: solutions to some potential problems and pitfalls. *J Endocrinol.* 1991 Mar;128(3):347-57
219. Ivan D, Brabant G, Kann PH; German KIMS Board. Applicability of recently established reference values for serum insulin-like growth factor 1: A comparison of two assays--an (automated) chemiluminescence immunoassay and an enzyme-linked immunosorbent assay. *Clin Lab.* 2005;51(7-8):381-7

Low serum IGF-1 for diagnosis of GH deficiency

220. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ; HypoCCS Advisory Board; U.S. HypoCCS Study Group. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab.* 2002 Feb;87(2):477-85
221. Granada ML, Murillo J, Lucas A, Salinas I, Llopis MA, Castells I, Foz M, Sanmarti A. Diagnostic efficiency of serum IGF-I, IGF-binding protein-3 (IGFBP-3), IGF-I/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. *Eur J Endocrinol.* 2000 Mar;142(3):243-53
222. Hilding A, Hall K, Wivall-Helleryd IL, Saaf M, Melin AL, Thoren M. Serum levels of insulin-like growth factor I in 152 patients with growth hormone deficiency, aged 19-82 years, in relation to those in healthy subjects. *J Clin Endocrinol Metab.* 1999 Jun;84(6):2013-9
223. Milani D, Carmichael JD, Welkowitz J, Ferris S, Reitz RE, Danoff A, Kleinberg DL. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. *J Clin Endocrinol Metab.* 2004 May;89(5):2271-4

Serum IGF-1 and IGF-BP-3

224. Schutt BS, Weber K, Elmlinger MW, Ranke MB. Measuring IGF-I, IGFBP-2 and IGFBP-3 from dried blood spots on filter paper is not only practical but also reliable. *Growth Horm IGF Res.* 2003 Apr-Jun;13(2-3):75-80
225. Blum WF, Albertsson-Wikland K, Rosberg S, Ranke MB. Serum levels of insulin-like growth factor I (IGF-I) and IGF binding protein 3 reflect spontaneous growth hormone secretion. *J Clin Endocrinol Metab.* 1993 Jun;76(6):1610-6

Arginine with GHRH test as good a test as the insulin stimulation test for evaluation of GH secretion in adults, but safer, excellent alternative

226. Donaubaue J, Kiess W, Kratzsch J, Nowak T, Steinkamp H, Willgerodt H, Keller E. Re-assessment of growth hormone secretion in young adult patients with childhood-onset growth hormone deficiency. *Clin Endocrinol (Oxf)*. 2003 Apr;58(4):456-63
227. Ghigo E, Goffi S, Nicolosi M, Arvat E, Valente F, Mazza E, Ghigo MC, Camanni F. Growth hormone (GH) responsiveness to combined administration of arginine and GH-releasing hormone does not vary with age in man. *J Clin Endocrinol Metab*. 1990 Dec;71(6):1481-5
229. Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, Stavrou S, Kleinberg DL, Chipman JJ, Hartman ML. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab*. 2002 May;87(5):2067-79

Insulin stimulation test

230. Pfeifer M, Kanc K, Verhovec R, Kocijancic A. Reproducibility of the insulin tolerance test (ITT) for assessment of growth hormone and cortisol secretion in normal and hypopituitary adult men. *Clin Endocrinol (Oxf)*. 2001 Jan;54(1):17-22 ("a single ITT could misclassify some hypopituitary patients with partial GH or ACTH deficiency")

How many lab tests

231. Lissett CA, Thompson EG, Rahim A, Brennan BM, Shalet SM. How many tests are required to diagnose growth hormone (GH) deficiency in adults? *Clin Endocrinol (Oxf)*. 1999 Nov;51(5):551-7

24-hour urine GH tests

Urinary Growth Hormone

232. Hourd P, Edwards R. Current methods for the measurement of growth hormone in urine. *Clin Endocrinol (Oxf)*. 1994 Feb;40(2):155-70
233. Girard J. Apparent growth hormone levels in plasma and urine. Methodological "artefacts". *Nucl Med Biol*. 1994 Apr;21(3):381-92
234. Bullen H, Wilkin TJ. An enzyme-linked immunosorbent assay (ELISA) for urinary growth hormone suitable for use in the routine laboratory. The Wessex Growth Study. *J Immunol Methods*. 1989 Jul 26;121(2):247-52
235. Haffner D, Schaefer F, Girard J, Ritz E, Mehls O. Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. *J Clin Invest*. 1994 Mar;93(3):1163-71
236. Okuno A, Yano K, Itoh Y, Hashida S, Ishikawa E, Mohri Z, Murakami Y. Urine growth hormone determinations compared with other methods in the assessment of growth hormone secretion. *Acta Paediatr Scand Suppl*. 1987;337:74-81
237. Sukegawa I, Hizuka N, Takano K, Asakawa K, Horikawa R, Hashida S, Ishikawa E, Mohri Z, Murakami Y, Shizume K. Urinary growth hormone (GH) measurements are useful for evaluating endogenous GH secretion. *J Clin Endocrinol Metab*. 1988 Jun;66(6):1119-23
238. McConway MG, Smith KA, Beastall GH. Development and evaluation of a direct immunofluorimetric assay for urinary growth hormone. *Ann Clin Biochem*. 1999 Sep;36 (Pt 5):649-54
239. Kohno H, Murakami Y, Kodaira T. Urinary human growth hormone measurement using a highly sensitive sandwich enzyme immunoassay: diagnostic and therapeutic uses in patients with growth hormone deficiency. *J Clin Endocrinol Metab*. 1990 Dec;71(6):1496-500
240. Braschi S, Faivre A, Charbonnel B. Normal values of growth hormone assay in urine in adults, established with a commercial kit. *Pathol Biol (Paris)*. 1994 Jun;42(6):621-4
241. Hizuka N, Takano K, Asakawa K, Sukegawa I, Horikawa R, Yoshizawa Y, Saito S, Shizume K. Urinary IGF-I measurement and its clinical application. *Acta Paediatr Scand Suppl*. 1988;347:127-33
242. Albini CH, Quattrin T, Vandlen RL, MacGillivray MH. Quantitation of urinary growth hormone in children with normal and abnormal growth. *Pediatr Res*. 1988 Jan;23(1):89-92

243. Sukegawa I, Hizuka N, Takano K, Asakawa K, Horikawa R, Hashida S, Ishikawa E, Mohri Z, Murakami Y, Shizume K. Measurement of nocturnal urinary growth hormone values. *Acta Endocrinol (Copenh)*. 1989 Aug;121(2):290-6
244. Granada ML, Murillo J, Lucas A, Salinas I, Llopis MA, Castells I, Foz M, Sanmarti A. Diagnostic efficiency of serum IGF-I, IGF-binding protein-3 (IGFBP-3), IGF-I/IGFBP-3 molar ratio and urinary GH measurements in the diagnosis of adult GH deficiency: importance of an appropriate reference population. *Eur J Endocrinol*. 2000 Mar;142(3):243-53
245. Hattori N, Shimatsu A, Kato Y, Koshiyama H, Ishikawa Y, Tanoh T, Assadian H, Imura H. Urinary excretion of human growth hormone: daily variation and relationship with albumin and alpha 1-microglobulin in urine. *Acta Endocrinol (Copenh)*. 1989 Oct;121(4):533-7
246. Hattori N, Shimatsu A, Yamanaka C, Momoi T, Imura H. Nocturnal urinary growth hormone excretion in children with short stature. *Acta Endocrinol (Copenh)*. 1988 Sep;119(1):113-7
247. Weissberger AJ, Ho KY, Stuart MC. Quantification of urinary growth hormone (GH) excretion by centrifugal ultrafiltration and radioimmunoassay: appraisal of the relationship between 24 h urinary GH and mean 24 h serum GH levels in normal and abnormal states of GH secretion. *Clin Endocrinol (Oxf)*. 1989 Jun;30(6):687-98
248. Girard J, Fischer-Wasels T. Measurement of urinary growth hormone. A noninvasive method to assess the 'growth hormone status. *Horm Res*. 1990;33 Suppl 4:12-8
249. Nukada O, Moriwake T, Kanzaki S, Katayama M, Higuchi J, Kimoto H. Age-related changes in urinary growth hormone level and its clinical application. *Acta Paediatr Jpn*. 1990 Feb;32(1):32-8
250. Quade A, Rahn M, Schweikert HU, Bidlingmaier F, Klingmuller D. Urinary excretion of GH in healthy individuals and patients with acromegaly, hypopituitarism and dwarfism. *Acta Endocrinol (Copenh)*. 1993 Jan;128(1):24-8
251. Bates AS, Evans AJ, Jones P, Clayton RN. Assessment of GH status in adults with GH deficiency using serum growth hormone, serum insulin-like growth factor-I and urinary growth hormone excretion. *Clin Endocrinol (Oxf)*. 1995 Apr;42(4):425-30
252. Lin MH, Lin DY. Measurements of urinary growth hormone in the assessment of its secretory status. *J Formos Med Assoc*. 1993 Sep;92(9):807-11
253. Main KM, Jarden M, Angelo L, Dinesen B, Hertel NT, Juul A, Muller J, Skakkebaek NE. The impact of gender and puberty on reference values for urinary growth hormone excretion: a study of 3 morning urine samples in 517 healthy children and adults. *J Clin Endocrinol Metab*. 1994 Sep;79(3):865-71
254. Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkebaek NE. The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. *Clin Endocrinol (Oxf)*. 1994 Jul;41(1):85-93
255. Juul A, Scheike T, Pedersen AT, Main KM, Andersson AM, Pedersen LM, Skakkebaek NE. Changes in serum concentrations of growth hormone, insulin, insulin-like growth factor and insulin-like growth factor-binding proteins 1 and 3 and urinary growth hormone excretion during the menstrual cycle. *Hum Reprod*. 1997 Oct;12(10):2123-8
256. Flanagan DE, Moore VM, Godsland IF, Cockington RA, Robinson JS, Phillips DI. Reduced foetal growth and growth hormone secretion in adult life. *Clin Endocrinol (Oxf)*. 1999 Jun;50(6):735-40
257. Flanagan DE, Taylor MC, Parfitt V, Mardell R, Wood PJ, Leatherdale BA. Urinary growth hormone following exercise to assess growth hormone production in adults. *Clin Endocrinol (Oxf)*. 1997 Apr;46(4):425-9
258. Saugy M, Cardis C, Schweizer C, Veuthey JL, Rivier L. Detection of human growth hormone doping in urine: out of competition tests are necessary. *J Chromatogr B Biomed Appl*. 1996 Dec 6;687(1):201-11
259. Main KM, Jansson C, Skakkebak N, Albertsson-Wikland K. Influence of gender on the correlation between plasma growth hormone profiles and urinary growth hormone excretion. *Horm Res*. 1997;48(1):16-22
260. Thalange NK, Gill MS, Gill L, Whatmore AJ, Addison GM, Price DA, Clayton PE. Infradian rhythms in urinary growth hormone excretion. *J Clin Endocrinol Metab*. 1996 Jan;81(1):100-6
261. Glander L, Karlberg JP, Larsson LA, Rosberg S, Albertsson-Wikland K. Overnight urinary growth hormone in normally growing prepubertal children: effect of urine volume. The one-year growth study. *Horm Res*. 1998;49(1):8-16

262. Fall CH, Clark PM, Hindmarsh PC, Clayton PE, Shiell AW, Law CM. Urinary GH and IGF-I excretion in nine year-old children: relation to sex, current size and size at birth. *Clin Endocrinol (Oxf)*. 2000 Jul;53(1):69-76
263. Edge JA, Hourd P, Edwards R, Dunger DB. Urinary growth hormone during puberty in normal and diabetic children. *Clin Endocrinol (Oxf)*. 1989 Apr;30(4):413-20
264. Phillip M, Chalew SA, Stene MA, Kowarski AA. The value of urinary growth hormone determination for assessment of growth hormone deficiency and compliance with growth hormone therapy. *Am J Dis Child*. 1993 May;147(5):553-7
265. Sanmarti A, Lucas A, Granada ML, Salinas I, Reverter JL, Cuatrecasas JM, Foz M, Audi L. Effect of chronic clonidine treatment on urinary growth hormone excretion and linear growth in children with short stature. *Horm Res*. 1990;34(5-6):193-6
266. Quattrin T, Albin CH, Mills BJ, MacGillivray MH. Comparison of urinary growth hormone and IGF-I excretion in small- and appropriate-for-gestational-age infants and healthy children. *Pediatr Res*. 1990 Sep;28(3):209-12
267. Walker JM, Wood PJ, Williamson S, Betts PR, Evans AJ. Urinary growth hormone excretion as a screening test for growth hormone deficiency. *Arch Dis Child*. 1990 Jan;65(1):89-92
268. Tanaka T, Yoshizawa A, Miki Y, Ito J, Tanaka M, Tanae A, Yokoya S, Hibi I. Clinical usefulness of urinary growth hormone measurement in short children. *Acta Paediatr Scand Suppl*. 1990;366:155-8
269. Butt DA, Sochett EB. Urinary growth hormone: a screening test for growth hormone sufficiency. *Clin Endocrinol (Oxf)*. 1997 Oct;47(4):447-54
270. Price DA, Addison GM, Herbert ED. Increase in urinary growth hormone excretion in puberty. *Arch Dis Child*. 1990 Nov;65(11):1203-4
271. Crowne EC, Wallace WH, Shalet SM, Addison GM, Price DA. Relationship between urinary and serum growth hormone and pubertal status. *Arch Dis Child*. 1992 Jan;67(1):91-5
272. Skinner AM, Price DA, Addison GM, Clayton PE, Mackay RI, Soo A, Mui CY. The influence of age, size, pubertal status and renal factors on urinary growth hormone excretion in normal children and adolescents. *Growth Regul*. 1992 Dec;2(4):156-60
273. Skinner AM, Clayton PE, Price DA, Addison GM, Mui CY. Variability in the urinary excretion of growth hormone in children: a comparison with other urinary proteins. *J Endocrinol*. 1993 Aug;138(2):337-43
274. Fortes ES, Chacra AR, Kunii HS, Vieira JG, Russo EM. Nocturnal urinary growth hormone excretion as a criterion for growth hormone deficiency. *Braz J Med Biol Res*. 1995 Apr;28(4):433-8
275. Skinner AM, Clayton PE, Addison GM, Price DA. Nocturnal urinary growth hormone excretion in growth hormone-deficient children on and off growth hormone treatment. *Horm Res*. 1995;44(4):147-51
276. Braegger CP, Torresani T, Murch SH, Savage MO, Walker-Smith JA, MacDonald TT. Urinary growth hormone in growth-impaired children with chronic inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 1993 Jan;16(1):49-52
277. Tomita H, Ogawa M, Kamijo T, Mori O, Ishikawa E, Mohri Z, Murakami Y. A highly sensitive sandwich enzyme immunoassay of urinary growth hormone in children with short stature, Turner's syndrome, and simple obesity. *Acta Endocrinol (Copenh)*. 1989 Oct;121(4):513-9
278. Quattrin T, Albin CH, Cara JF, Vandlen RL, Mills BJ, MacGillivray MH. Quantitation of urinary somatomedin-C and growth hormone in preterm and fullterm infants and normal children. *J Clin Endocrinol Metab*. 1988 Apr;66(4):792-7
279. Jacobsen S, Main K, Danneskiold-Samsoe B, Skakkebaek NE. A controlled study on serum insulin-like growth factor-I and urinary excretion of growth hormone in fibromyalgia. *J Rheumatol*. 1995 Jun;22(6):1138-40
280. Murao K, Takahara J, Sato M, Tamaki M, Niimi M, Ishida T. Relationship between thyroid functions and urinary growth hormone secretion in patients with hyper- and hypothyroidism. *Endocr J*. 1994 Oct;41(5):517-22
281. Umezawa S. Urinary hGH, albumin, alpha 1 MG and beta 2 MG in normal and diabetic children. *Nippon Naibunpi Gakkai Zasshi*. 1989 Jan 20;65(1):55-65
282. Suzuki K, Miyata H, Suzuki T, Kajinuma H. Evaluation and clinical applications of measurement of urinary growth hormone in diabetic subjects. *Diabetes*. 1989 Dec;38(12):1567-72

283. Pan FP, Stevenson JL, Donaldson DL, Levy J, Wiegmann T, Moore WV. Correlation of urinary albumin and beta-2-microglobulin and growth hormone excretion in patients with diabetes mellitus and short stature. *J Clin Endocrinol Metab.* 1990 Sep;71(3):611-7
284. Hattori N, Kato Y, Murakami Y, Hashida S, Ishikawa E, Mohri Z, Imura H. Urinary growth hormone levels measured by ultrasensitive enzyme immunoassay in patients with renal insufficiency. *J Clin Endocrinol Metab* 1988 Apr;66(4):727-32
285. Matsuura M, Kitagawa T, Hashida S, Murakami Y. High urinary levels of human growth hormone in children with renal tubular dysfunction. *Nephron.* 1989;51(4):561-2
286. Perrone L, Sinisi AA, Criscuolo T, Manzo T, Maresca G, Bellastella A, del Gado R. Plasma and urinary growth hormone and insulin-like growth factor I in children with chronic renal insufficiency. *Child Nephrol Urol.* 1990;10(2):72-5
287. Mauri M, Pico AM, Alfayate R, Dominguez JR, Camara R, Miralles C. Usefulness of urinary growth hormone (GH) measurement for evaluating endogenous GH secretion in acromegaly. *Horm Res.* 1993;39(1-2):13-8
288. Pholsena M, Le Bouc Y, Rousseau E, Christol R, Birman P, Perin L, Girard F. Evaluation of acromegaly by measurement of 24-hourly urinary growth hormone excretion. *Acta Endocrinol (Copenh).* 1993 Jan;128(1):9-14
289. Main KM, Lindholm J, Vandeweghe M, Skakkebaek NE. Urinary growth hormone excretion in acromegaly: diagnostic value in mild disease activity. *Acta Endocrinol (Copenh).* 1993 Nov;129(5):409-13
290. Bates AS, Evans AJ, Jones P, Clayton RN. Assessment of GH status in acromegaly using serum growth hormone, serum insulin-like growth factor-1 and urinary growth hormone excretion. *Clin Endocrinol (Oxf).* 1995 Apr;42(4):417-23
291. Evans AJ, Willis DS, Wood PJ. The assay of urinary growth hormone in normal and acromegalic adults. *Clin Endocrinol (Oxf).* 1991 Nov;35(5):413-8
292. Lunt H, Tucker AJ, Bullen H, Gibbs C, Wilkin TJ. Overnight urinary growth hormone measurement in the diagnosis of acromegaly. *Clin Endocrinol (Oxf).* 1990 Aug;33(2):205-12
293. Winer LM, Shaw MA, Baumann G. Urinary growth hormone excretion rates in normal and acromegalic man: a critical appraisal of its potential clinical utility. *J Endocrinol Invest.* 1989 Jul-Aug;12(7):461-7
294. Albini CH, Sotos J, Sherman B, Johanson A, Celniker A, Hopwood N, Quattrin T, Mills BJ, MacGillivray MH. Diagnostic significance of urinary growth hormone measurements in children with growth failure: correlation between serum and urine growth hormone. *Pediatr Res.* 1991 Jun;29(6):619-22
295. Gill MS, Toogood AA, O'Neill PA, Thorner MO, Shalet SM, Clayton PE. Urinary growth hormone (GH), insulin-like growth factor I (IGF-I), and IGF-binding protein-3 measurements in the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab.* 1998 Jul;83(7):2562-5
296. Aman J, Jones I. Urinary growth hormone determination in prepubertal children using a modification of a commercial kit designed for determination of growth hormone in serum. *Scand J Clin Lab Invest* 1994 May;54(3):227-33
297. Audi L, Antonia Llopis M, Luisa Granada M, Hermoso F, del Valle J, Dolores Rodriguez-Arno M, Bel J, Luzuriaga C, Gallego E, Marin F; Grupo Espanol de Estudio de la Talla Baja. Low sensitivity of IGF-I, IGFBP-3 and urinary GH in the diagnosis of growth hormone insufficiency in slowly-growing short-statured boys. *Grupo Espanol de Estudio de la Talla Baja Med Clin (Barc).* 2001 Jan 13;116(1):6-11

Corrective GH Therapy

298. Hertoghe T. Growth hormone therapy in aging adults. *Anti-Aging Medical Therapeutics* (Eds Klatz RM & Goldman R) 1997;1:10-28

GH Medications

GH subcutaneous injections

299. Jorgensen JO. Human growth hormone replacement therapy: pharmacological and clinical aspects. *Endocr Rev.* 1991;12:189-207.

300. Beshyah SA, Freemantle C, Shah M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R, Johnston DG. Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. *Clin Endocrinol*. 1995;42:73-84
301. Kehely A, Bates PC, Frewer P, Birkett M, Blum WF, Mamessier P, Ezzat S, Ho KK, Lombardi G, Luger A, Marek J, Russell-Jones D, Sonksen P, Attanasio AF. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. *J Clin Endocrinol Metab*. 2002 May;87(5):1974-9
302. Jostel A, Mukherjee A, Alenfall J, Smethurst L, Shalet SM. A new sustained-release preparation of human growth hormone and its pharmacokinetic, pharmacodynamic and safety profile. *Clin Endocrinol (Oxf)*. 2005 May;62(5):623-7

Intranasal GH

303. Hedin L, Olsson B, Diczfalusy M, Flyg C, Petersson AS, Rosberg S, Albertsson-Wikland K. Intranasal administration of human growth hormone (hGH) in combination with amembrane permeation enhancer in patients with GH deficiency: a pharmacokinetic study. *J Clin Endocrinol Metab*. 1993 Apr;76(4):962-7

GH treatment: dosage

304. MacGillivray MH, Baptista J, Johanson A. Outcome of a four-year randomized study of daily versus three times weekly somatotropin treatment in prepubertal naive growth hormone-deficient children. *J Clin Endocrinol Metabol*. 1996;81:1806-9
305. de Boer H, Blok GJ, Popp-Snijders C, Stuurman L, Baxter RC, van der Veen E. Monitoring of growth hormone replacement therapy in adults, based on measurement of serum markers. *J Clin Endocrinol Metabol*. 1996;81:1371-7
306. de Boer H, Blok GJ, Voerman B, de Vries P, Popp-Snijders C, van der Veen E. The optimal growth hormone replacement dose in adults, derived from bioimpedance analysis. *J Clin Endocrinol Metab*. 1995 Jul;80(7):2069-76.
307. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab*. 1998;83:379-81
308. Burman P, Johansson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone deficient men are more responsive to GH replacement therapy than women. *J Clin Endocrinol Metab*. 1997;82:550-5
309. Drake WM, Coyte D, Camacho-Hubner, Jivanji NM, Kaltsas G, Wood DF, Trainer PJ, Grossman AB, Besser GM, Monson JP. Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. *J Clin Endocrinol Metab*. 1998;83:9313-9
310. Weksler ME. Hormone replacement therapy for men: has the time come? *Geriatrics*. 1995;50:52-4
311. Underwood LE, Attie KM, Baptista J; Genentech Collaborative Study Group. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: a two-year, multicenter, multiple-dose, placebo-controlled study. *J Clin Endocrinol Metab*. 2003 Nov;88(11):5273-80
312. Chihara K, Koledova E, Shimatsu A, Kato Y, Kohno H, Tanaka T, Teramoto A, Bates PC, Attanasio AF. An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency. *Eur J Endocrinol*. 2005 Jul;153(1):57-65 (*"The incidence of oedema and cases with a high IGF-I level were less frequent under the IGF-I controlled regimen compared with those during the fixed-dose titration method"*)

GH treatment: interferences or associations

313. Bellantoni MF, Vittone J, Campfield AT, Bass KM, Harman SM, Blackman MR. Effects of oral vs. transdermal estrogen on the growth hormone-insulin-like growth factor I axis in younger and older postmenopausal women. *J Clin Endocrinol Metab*. 1996;81:2848-53

314. Liu L, Merriam GR, Sherins RJ. Chronic sex steroid exposure increases mean plasma GH concentration and pulse amplitude in men with isolated hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 1987;64:651-6
315. Moe KE, Prinz PN, Larsen LH, Vitiello MV, Reed SO, Merriam GR. Growth hormone in postmenopausal women after long-term oral estrogen replacement therapy. *J Gerontol A Biol Sci Med Sci.* 1998 Mar;53(2):B117-24
316. Guidice LC. Insulin-like growth factors and ovarian follicular development. *Endocrine Reviews.* 1992;13: 641-69

GH treatment: safety, side effects, complications

317. Monson JP. Long-term experience with GH replacement therapy: efficacy and safety. *Eur J Endocrinol.* 2003 Apr;148 Suppl 2:S9-14
318. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. *Clin Endocrinol Oxf.* 1993 ;39:417-25
319. Daughaday WH. The possible autocrine/paracrine and endocrine roles of insulin-like growth factors of human tumors. *Endocrinology.* 1990; 127:1-4
320. Ezzat S, Melmed S. Clinical review 18: Are patients with acromegaly at increased risk for neoplasia? *J Clin Endocrinol Metab.* 1991;72:245-9
321. Brunner JE, Johnson CC, Zafar S, Peterson EL, Brunner JF, Mellinger RC. Colon cancer and polyps in acromegaly: increased risk associated with family history of colon cancer. *Clin Endocrinol (Oxf).* 1990;32:65-71
322. Bengtsson BA, Ed'en S, Ernest I, Od'en A, Sjogren B. Epidemiology and long-term survival in acromegaly: a study of 166 cases diagnosed between 1955 and 1984. *Acta Med Scand.* 1988; 223:327-35
323. Massa G, Vanderschueren-Lodeweyckx M, Bouillon R. Five-year follow-up of growth hormone antibodies in growth hormone deficient children treated with recombinant human growth hormone. *Clin Endocrinol.* 1993;38:137-42
324. Kaplan SL, August GP, Blethen SL, Brown DR, Hintz RL, Johansen A, Plotnick LP, Underwood LE, Bell JJ, Blizzard RM, Foley TP, Hopwood NJ, Kirkland RT, Rosenfeld RG, Van Wyk JJ. Clinical studies with recombinant-DNA-derived methionyl human growth hormone in growth hormone deficient children. *Lancet.* 1986;I:697-700
325. Milner RDG, Barnes ND, Buckler JMH, Carson DJ, Hadden DR, Hughes IA, Johnston DI, Parkin JM, Price DA, Rayner PH, Savage DCL, Savage MO, Smith CS, Swift PG
326. Pirazzoli P, Cacciari E, Mandini M, Cicognani A, Zucchini S, Sganga T, Capelli M. Follow-up anti-bodies to growth hormone in 210 growth hormone-deficient children treated with different commercial products. *Acta Paediatr.* 1995 ;84:1233-6
327. Malozowski S, Tanner LA, Wysowski D, Fleming GA. Growth hormone, insulin-like growth factor I, and benign intracranial hypertension. *N Engl J Med.* 1993;329:665-6
328. Blethen SL, Alien DB, Graves D, August G, Moshang T, Rosenfeld R. Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study experience. *J Clin Endocrinol Metab.* 1996;81:1704-10

GH secretagogues

329. Borges JL, Blizzard RM, Evans WS, Furlanetto R, Rogol AD, Kaiser DL, Rivier J, Vale W, Thorner MO. Stimulation of growth hormone and somatomedin C in idiopathic GH-deficient subjects by intermittent pulsatile administration of human pancreatic tumor GH-releasing factor. *J Clin Endocrinol Metab.* 1984;59:1-6
330. Corpas E, Harman SM, Pineyro MA, Roberson R, Blackman MR. Growth hormone (GH)-releasing hormone-(1-29) twice daily reverses the decreased GH and insulin-like growth factor-I levels in old men. *J Clin Endocrinol Metab.* 1992;75:530-5
331. Vittone J, Blackman MR, Busby-Whitehead J, Tsiao C, Stewart KJ, Tobin J, Stevens T, Bellantoni MF, Rogers MA, Baumann G, Roth J, Harman SM, Spencer RG. Effects of single

- nightly injections of growth hormone-releasing hormone GHRH 1-29 in healthy elderly men. *Metabolism*. 1997;46:89-96
332. Khorram O, Laughlin GA, Yen SSC. Endocrine and metabolic effects of long-term administration of [Nle²⁷] growth hormone-releasing hormone (1-29)NH₂ in age-advanced men and women. *J Clin Endocrinol Metab*. 1997;82:1472-9
 333. Chapman IM, Bach MA, van Cauter E, Farmer M, Krupa D, Taylor AM, Schilling AM, Cole KY, Skiles EH, Pczzoli SS. Stimulation of the growth hormone (GH)-insulin-like growth factor I axis by daily oral administration of a GH secretagogue MK-677 in healthy elderly subjects. *J Clin Endocrinol Metab*. 1996;81:4249-57
 334. Mericq VG, Salazar T, Avila A, Iniguez G, Bowers CY, Cassoria FG, Merriam GR. Effects of eight months treatment with graded doses of growth hormone-releasing peptide in growth hormone-deficient children. *J Clin Endocrinol Metab* 1998;83:2355-60
 335. Smith RG. Development of growth hormone secretagogues. *Endocr Rev*. 2005 May;26(3):346-60

TOPICS OF DISCUSSION

GH TREATMENT'S INFLUENCE ON GH ENDOGENOUS SECRETION: normally no adverse influence when used at physiological doses

Normal doses of GH do not change the endogenous GH secretion

1. Wu RH, St Louis Y, DiMartino-Nardi J, Wesoly S, Sobel EH, Sherman B, Saenger P. Preservation of physiological growth hormone (GH) secretion in idiopathic short stature after recombinant GH therapy. *J Clin Endocrinol Metab.* 1990 Jun;70(6):1612-5 (*data show that exogenous GH therapy does not interfere with the maintenance of endogenous pulsatile secretion of GH: pre- and (48 hours after stopping) posttreatment GH secretory profiles were comparable with respect to the number of peaks, mean concentrations, peak amplitude, and secretory rate, even after 12 months of GH treatment*)

Pharmacological doses of GH mildly and temporarily reduce the GH-response to GRF in healthy and diabetics with insulin secretion, but does not influence it in diabetics without insulin secretion

2. Wurzbürger MI, Prelevic GM, Sonksen PH, Balint-Peric LA, Wheeler M. The effect of recombinant human growth hormone on regulation of growth hormone secretion and blood glucose in insulin-dependent diabetes. *J Clin Endocrinol Metab.* 1993 Jul;77(1):267-72 (*The response of GH to GRF in diabetics without residual beta-cell activity (C peptide negative) was almost unchanged after 7 days of high dose 4 IU/day of GH treatment, whereas it became lowered in diabetics with endogenous pancreatic beta-cell activity (C peptide positive) and controls*)

EXERCISE AS AN ALTERNATIVE TO GH TREATMENT

Claim: It is enough to let elderly patients regularly exercise to increase their IGF-1 back to youthful levels, GH therapy is not necessary for them.

Fact: Exercise does generally not significantly increase GH and IGF-1 in elderly persons, and certainly not to youthful levels.

Arguments contra GH therapy

Exercise may increase GH, but more rarely IGF-1 levels, in young adults persons to satisfying levels

1. Kraemer WJ, Aguilera BA, Terada M, Newton RU, Lynch JM, Rosendaal G, McBride JM, Gordon SE, Hakkinen K. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise. *J Appl Physiol.* 1995 Oct;79(4):1310-5.
2. Nemet D, Connolly PH, Pontello-Pescatello AM, Rose-Gottron C, Larson JK, Galassetti P, Cooper DM. Negative energy balance plays a major role in the IGF-I response to exercise training. *J Appl Physiol.* 2004 Jan;96(1):276-82

Exercise causes a significant GH response in elderly men, but not in elderly women (>70 yr)

3. Hakkinen K, Pakarinen A, Kraemer WJ, Newton RU, Alen M. Basal concentrations and acute responses of serum hormones and strength development during heavy resistance training in middle-aged and elderly men and women. *J Gerontol A Biol Sci Med Sci.* 2000 Feb;55(2):B95-105

Twice a week heavy exercise for 24 weeks in elderly men and women causes a significant GH response, but less than in young men

4. Hakkinen K, Pakarinen A, Hannonen P, Hakkinen A, Airaksinen O, Valkeinen H, Alen M. Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. *J Rheumatol.* 2002 Jun;29(6):1287-95

5. Hakkinen K, Pakarinen A, Newton RU, Kraemer WJ. Acute hormone responses to heavy resistance lower and upper extremity exercise in young versus old men. *Eur J Appl Physiol Occup Physiol.* 1998 Mar;77(4):312-9

16 weeks of training causes a significant GH response after acute exercise in elderly men (60 yrs), but does not change the serum IGF-1

6. Nicklas BJ, Ryan AJ, Treuth MM, Harman SM, Blackman MR, Hurley BF, Rogers MA. Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55-70 years. *Int J Sports Med.* 1995 Oct;16(7):445-50

Conclusion: Only heavy (unhealthy?) exercise acutely increases GH secretion in some studies with elderly persons, but not as much as in young people and it does not increase GH metabolic activity, reflected by serum IGF-1.

Arguments pro GH therapy: Exercise alone does not really help to correct low GH and IGF-1 levels in elderly persons who are usually the ones who need most Gh supplementation

No significant (0 to + 3 %) GH response to exercise in elderly persons

7. Pyka G, Wiswell RA, Marcus R. Age-dependent effect of resistance exercise on growth hormone secretion in people. *J Clin Endocrinol Metab.* 1992 Aug;75(2):404-7
8. Craig BW, Brown R, Everhart J. Effects of progressive resistance training on growth hormone and testosterone levels in young and elderly subjects. *Mech Ageing Dev.* 1989 Aug;49(2):159-69
9. Hakkinen K, Pakarinen A. Acute hormonal responses to heavy resistance exercise in men and women at different ages. *Int J Sports Med.* 1995 Nov;16(8):507-13
10. Figueroa A, Going SB, Milliken LA, Blew RM, Sharp S, Teixeira PJ, Lohman TG. Effects of exercise training and hormone replacement therapy on lean and fat mass in postmenopausal women. *J Gerontol A Biol Sci Med Sci.* 2003 Mar;58(3):266-70
11. Hakkinen K, Pakarinen A, Kraemer WJ, Hakkinen A, Valkeinen H, Alen M. Selective muscle hypertrophy, changes in EMG and force, and serum hormones during strength training in older women. *J Appl Physiol.* 2001 Aug;91(2):569-80
12. Kiilavuori K, Naveri H, Leinonen H, Harkonen M. The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure. *Eur Heart J.* 1999 Mar;20(6):456-64
13. Kostka T, Patricot MC, Mathian B, Lacour JR, Bonnefoy M. Anabolic and catabolic hormonal responses to experimental two-set low-volume resistance exercise in sedentary and active elderly people. *Aging Clin Exp Res.* 2003 Apr;15(2):123-30

GH TREATMENT AND MUSCLE STRENGTH

Claim: GH treatment does not increase muscle strength in adults, so it is not useful for them.

Fact: GH treatment has been reported to help elderly adults increase their muscle strength.

Welle S, Thornton C, Statt M, McHenry B. Growth hormone increases muscle mass and strength but does not rejuvenate myofibrillar protein synthesis in healthy subjects over 60 years old. *J Clin Endocrinol Metab.* 1996 Sep;81(9):3239-43

GH TREATMENT AND FUNCTIONAL CAPACITIES

Claim: GH treatment does not increase functional capacities.

Fact: It does: breathing capacity in patients with chronic bronchitis for example.

1. Pape GS, Friedman M, Underwood LE, Clemmons DR. The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. *Chest*. 1991 Jun;99(6):1495-500

GH TREATMENT AND METABOLIC RATE

Claim: GH treatment does not increase resting metabolic rate.

Fact: On the contrary, it does.

An association between GH production and resting metabolic rate has been found, at least in young adults

1. Jorgensen JO, Vahl N, Dall R, Christiansen JS. Resting metabolic rate in healthy adults: relation to growth hormone status and leptin levels. *Metabolism*. 1998 Sep;47(9):1134-9 (*"in the young subgroup, GH production rate was a positive determinant of resting metabolic rate/lean body mass"*)
2. Medical Department M (Endocrinology and Diabetes), Aarhus University Hospital, Denmark.

GH therapy increases resting metabolic rate

3. Snel YE, Doerga ME, Brummer RJ, Zelissen PM, Zonderland ML, Koppeschaar HP. Resting metabolic rate, body composition and related hormonal parameters in growth hormone-deficient adults before and after growth hormone replacement therapy. *Eur J Endocrinol*. 1995 Oct;133(4):445-50

GH TREATMENT AND ADVERSE EFFECTS

Claim: GH treatment has substantial adverse effects such as edema, etc.

Fact: Substantial adverse effects only appear at overdoses such as is the case for any other medical treatment, it is sufficient to reduce the dose to avoid them.

1. Wuster C, Melchinger U, Eversmann T, Hensen J, Kann P, von zur Muhlen A, Ranke MB, Schmeil H, Steinkamp H, Tuschy U. Reduced incidence of side-effects of growth hormone substitution in 404 patients with hypophyseal insufficiency. Results of a multicenter indications Study. *Med Klin*. 1998 Oct 15;93(10):585-91
2. Amato G, Izzo G, La Montagna G, Bellastella A. Low dose recombinant human growth hormone normalizes bone metabolism and cortical bone density and improves trabecular bone density in growth hormone deficient adults without causing adverse effects. *Clin Endocrinol (Oxf)*. 1996 Jul;45(1):27-32 (*no adverse effects with doses of 10µg/kg/day or a mean of 500-800 µg /day*)
3. Chihara K, Koledova E, Shimatsu A, Kato Y, Kohno H, Tanaka T, Teramoto A, Bates PC, Attanasio AF. An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency. *Eur J Endocrinol*. 2005 Jul;153(1):57-65 (*"The incidence of oedema and cases with high IGF-I level were less frequent under the IGF-I controlled regimen compared with those during the fixed-dose titration method"*)

GH TREATMENT AND THE DIABETES CONTROVERSY

Suspicion: Can GH at physiological doses cause diabetes?

Facts: GH's role is to prevent hypoglycaemia by elevating the low serum glucose levels of GH deficient subjects back to normal. It does not at physiological doses cause diabetes.

Arguments contra GH use

GH is a hyperglycemic hormone

1. Ward PS, Savage DC. Growth hormone responses to sleep, insulin hypoglycaemia and arginine infusion. *Horm Res.* 1985;22(1-2):7-11

Treatment of GH-deficient children: higher incidence of diabetes

2. Cutfield WS, Wilton P, Bennmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA . Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. : *Lancet.* 2000 Feb 19;355(9204):610-3 (*"GH treatment did not affect the incidence of type 1 diabetes mellitus in any age group. ... the higher than expected incidence of type 2 diabetes mellitus with GH treatment may be an acceleration of the disorder in predisposed individuals. Type 2 diabetes did not resolve after GH therapy was stopped."; critics: very high GH doses are used in children; no increased incidence of type 2 diabetes has been seen in adults taking GH*)

Serum GH levels are higher in diabetes patients (*critics: yes, two times higher serum GH, but -50% lower serum IGF-1, which reflects GH activity; insulin treatment of diabetes significantly increases serum IGF-1 and lower GH*)

3. Shishko PI, Sadykova RE, Kovalev PA, Goncharov BV. Insulin-like growth factor I in patients with newly detected insulin-dependent diabetes mellitus. *Probl Endocrinol (Mosk).* 1992 Jan-Feb;38(1):17-9

Acromegaly is associated with an increased incidence of diabetes

4. Mercado M, Espinosa de los Monteros AL, Sosa E, Cheng S, Mendoza V, Hernandez I, Sandoval C, Guinto G, Molina M. Clinical-biochemical correlations in acromegaly at diagnosis and the real prevalence of biochemically discordant disease. *Horm Res.* 2004;62(6):293-9.
5. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M, Gilibert M. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). *Eur J Endocrinol.* 2004 Oct;151(4):439-46
6. Fukuda I, Hizuka N, Murakami Y, Itoh E, Yasumoto K, Sata A, Takano K. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. *Intern Med.* 2001 Oct;40(10):987-92

Arguments pro GH use:

Insulin secretion: the tonic secretion of insulin from the beta-cells depends on IGF-1

7. Kulkarni RN, Holzenberger M, Shih DQ, Ozcan U, Stoffel M, Magnuson MA, Kahn CR. Beta-cell-specific deletion of the IGF1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. *Nat Genet.* 2002 May;31(1):111-5

GH is an anti-hypoglycemic hormone: it neutralizes hypoglycaemia

8. Ward PS, Savage DC. Growth hormone responses to sleep, insulin hypoglycaemia and arginine infusion. *Horm Res.* 1985;22(1-2):7-11
9. West TE, Sonksen PH. Is the growth-hormone response to insulin due to hypoglycaemia, hyperinsulinaemia or a fall in plasma free fatty acids? *Clin Endocrinol (Oxf).* 1977 Oct;7(4):283-8 (*hypoglycaemia per se was the important stimulus to GH secretion and not hyperinsulinaemia or a lowering of plasma free fatty acids*)
10. Khaleeli A, Perumainar M, Spedding AV, Teale JD, Marks V. Treatment of tumour-induced hypoglycaemia with human growth hormone. *J R Soc Med.* 1992 May;85(5):303

IGF-1 therapy has insulin-like effects: it reduces glycemia and serum insulin in controls and type 2 diabetic patients

11. Moses AC, Young SC, Morrow LA, O'Brien M, Clemmons DR. Recombinant human insulin-like growth factor I increases insulin sensitivity and improves glycemic control in type II diabetes. *Diabetes*. 1996 Jan;45(1):91-100

Diabetes: the association with lower GH and/or IGF-1 levels

12. Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. *Int J Obes Relat Metab Disord*. 2001 Aug;25(8):1101-7

Diabetes patients have high GH, but low IGF-1, marker of GH metabolic activity: a lower IGF-1 in insulin-dependent diabetes pubers is associated with a higher serum glycosylated hemoglobine HbA1C)

13. Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. *Clin Endocrinol (Oxf)*. 1994 Oct;41(4):517-24

Acromegaly: GH production in acromegaly is 10 to 100 times the normal production; 10 to 300 times the doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a **polyhormonal deficit**: hypothyroidism, hypogonadism, hypocorticism, ..., endocrine conditions that increase the risk of glucose intolerance and diabetes. These conditions are not found in corrective GH treatment of GH deficiency.

14. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. *J Clin Endocrinol Metab*. 1994 Dec;79(6):1706-15 (*"Patients with active acromegaly ...secretion rate per 24 h was 25 times greater in female acromegalics and 100 times greater in male acromegalics than that in the controls"*)
15. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. *J Clin Endocrinol Metab*. 1983 Nov;12(3):509-34 (*"The possibility of deficiencies of the other pituitary hormones should then be addressed in patients with secretory tumours. In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order. Basal thyroid function tests, serum oestradiol or testosterone, and basal gonodotrophins should be routinely obtained in patients with macroadenomas. Additionally, the integrity of the pituitary-adrenal axis should be determined and an overnight water deprivation test for assessment of neurohypophyseal function is also recommended."*)
16. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. *J Clin Endocrinol Metab*. 1979 Feb;48(2):309-14
17. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. *Am J Med*. 1982 Jun;72(6):861-73

GH therapy increases first, then reduces glycemia when given to HIV-infected patients with fat accumulation:

18. Lo JC, Mulligan K, Noor MA, Schwarz JM, Halvorsen RA, Grunfeld C, Schambelan M. The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3480-7

GH therapy at physiological doses to type 1 diabetics: no effect on glycemia

19. Bright GM, Melton RW, Rogol AD, Clarke WL. The effect of exogenous growth hormone on insulin requirements during closed loop insulin delivery in insulin-dependent diabetes mellitus. *Horm Metab Res*. 1984 Jun;16(6):286-9

GH therapy to type 1 diabetics: increased insulin requirements, but improved the control of hypoglycaemic attacks

20. Christ ER, Simpson HL, Breen L, Sonksen PH, Russell-Jones DL, Kohner EM. The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency. *Clin Endocrinol (Oxf)*. 2003 Mar;58(3):309-15

Low dose GH therapy (0.10 mg/day) improves insulin sensitivity in young healthy adults

21. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. *Clin Endocrinol (Oxf)*. 2005 Oct;63(4):428-36 (*"The low GH dose (0.10 mg/day) decreased fasting glucose levels ($P < 0.01$) and enhanced insulin sensitivity ($P < 0.02$), the standard GH (mean dose 0.48 mg/day) did not modify insulin sensitivity"*)

Diabetes: the improvement with GH treatment

22. Gotherstrom G, Svensson J, Koranyi J, Alpsten M, Bosaeus I, Bengtsson B, Johannsson G. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab*. 2001 Oct;86(10):4657-65
23. Svensson J, Fowelin J, Landin K, Bengtsson BA, Johannsson JO. Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. *J Clin Endocrinol Metab*. 2002 May;87(5):2121-7
24. Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. *Clin Endocrinol (Oxf)*. 1994 Oct;41(4):517-24
25. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. *Clin Endocrinol (Oxf)*. 2005 Oct;63(4):428-36

GH AND CARDIOVASCULAR SYSTEM

Claim: GH treatment has adverse effects on the cardiovascular system.

Facts: Most studies are reports of beneficial effects of GH on the heart and blood vessels.

Arguments contra GH use: mainly based on studies of excess GH LEVELS and their correction

Acromegalic patients have an increased heart disease mortality (*critics: acromegaly is a disease with GH and IGF-1 levels several times those obtained with a safe corrective GH treatment, with a Gh production that is 25 to 100 times the normal daily production; the acromegalic heart has myocardial hypertrophy with proliferation of the myocardial fibrous tissue, resulting in impaired ventricular relaxation, and eventually heart failure, a condition that is not found in GH deficient adults treated with correct doses of GH*)

1. Erfurth EM, Hagmar L. Cerebrovascular disease in patients with pituitary tumors. Trends Endocrinol Metab. 2005 Sep;16(7):334-42
2. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4

Critics: in acromegaly is the GH production 10 to 100 times the normal production, 10 to 300 times the doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a **polyhormonal deficit:** hypothyroidism, hypogonadism, hypocorticism, endocrine conditions that increase the risk of glucose intolerance and diabetes. These conditions are not found in corrective GH treatment of GH deficiency.

3. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 (*"Patients with active acromegaly ...secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls"*)
4. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. Clin Endocrinol Metab. 1983 Nov;12(3):509-34 (*"In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order"*)
5. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab. 1979 Feb;48(2):309-14
6. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. Am J Med. 1982 Jun;72(6):861-73

Octreotide therapy of acromegaly suppresses GH production and reverses the heart disease

7. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. Endocr Rev. 1994 Oct;15(5):555-73
8. Merola B, Cittadini A, Colao A, Ferone D, Fazio S, Sabatini D, Biondi B, Sacca L, Lombardi G. Chronic treatment with the somatostatin analog octreotide improves cardiac abnormalities in acromegaly. J Clin Endocrinol Metab. 1993 Sep;77(3):790-3

Arguments pro GH use: GH treatment improves the failing GH heart of GH deficient persons

GH improves the heart function

9. Cittadini A, Berggren A, Longobardi S, Ehrnborg C, Napoli R, Rosen T, Fazio S, Caidahl K, Bengtsson BA, Sacca L. Supraphysiological doses of GH induce rapid changes in cardiac morphology and function. J Clin Endocrinol Metab. 2002 Apr;87(4):1654-9
10. Napoli R, Guardasole V, Matarazzo M, Palmieri EA, Oliviero U, Fazio S, Sacca L. Growth hormone corrects vascular dysfunction in patients with chronic heart failure. J Am Coll Cardiol. 2002 Jan 2;39(1):90-5
11. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Sacca L. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med. 1996 Mar 28;334(13):809-14

GH deficient patients have a higher rate of myocardial infarction risk and mortality

12. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

The premature mortality in hypopituitarism (and thus GH deficiency) is due to cardiovascular disease

13. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet.* 1990 Aug 4;336(8710):285-8

Coronary heart disease: the association with lower GH and/or IGF-1 levels

14. Conti E, Andreotti F, Sciahbasi A, Riccardi P, Marra G, Menini E, Ghirlanda G, Maseri A. Markedly reduced insulin-like growth factor-1 in the acute phase of myocardial infarction. *J Am Coll Cardiol.* 2001 Jul;38(1):26-32

Hypopituitarism increases the cerebrovascular mortality

15. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf).* 1997 Jan;46(1):75-81

GH deficient patients have a higher incidence of cerebrovascular events

16. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12
17. Cittadini A, Cuocolo A, Merola B, Fazio S, Sabatini D, Nicolai E, Colao A, Longobardi S, Lombardi G, Sacca L. Impaired cardiac performance in GH-deficient adults and its improvement after GH replacement. *Am J Physiol.* 1994 Aug;267(2 Pt 1):E219-25

GH TREATMENT

GH therapy to GH deficient patients: normalizes the (excessive) rate of myocardial infarction and its mortality

18. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

GH treatment may improve coronary heart disease

19. 121. Castagnino HE, Lago N, Centrella JM, Calligaris SD, Farina S, Sarchi MI, Cardinali DP. Cytoprotection by melatonin and growth hormone in early rat myocardial infarction as revealed by Feulgen DNA staining. *Neuroendocrinol Lett* 2002 Oct-Dec;23(5/6):391-395

GH therapy partially normalizes the higher incidence of cerebrovascular events found in GH deficient patients

20. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12
21. Cittadini A, Cuocolo A, Merola B, Fazio S, Sabatini D, Nicolai E, Colao A, Longobardi S, Lombardi G, Sacca L. Impaired cardiac performance in GH-deficient adults and its improvement after GH replacement. *Am J Physiol.* 1994 Aug;267(2 Pt 1):E219-25

GH AND CANCER

Claim: GH increases the risk of cancer

Facts: The epidemiological studies, which indicate an association between serum IGF-I and cancer risk, have not established causality. An increased cancer risk with GH therapy has not been proven in humans.

Arguments contra GH use:

GH LEVELS: Studies where positive associations between higher serum GH and/or IGF-1 levels and an increased risk of prostate or breast cancer

Studies where a higher serum IGF-1 and/or high IGF-I to IGFBP-3 molar ratio was found associated with an increased risk of prostate cancer (*critics: the increased IGF-1 may be due to local production of IGF-1 by the tumour and may thus be a marker, and not a cause of cancer, or a bias due to nutritional factors - see further*)

1. Peng L, Tang S, Xie J, Luo T, Dai B. Quantitative analysis of IGF-1 and its application in the diagnosis of prostate cancer. *Hua Xi Yi Ke Da Xue Xue Bao.* 2002 Jan;33(1):137
2. Li L, Yu H, Schumacher F, Casey G, Witte JS. Relation of serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 to risk of prostate cancer (United States). *Cancer Causes Control.* 2003 Oct;14(8):721-6
3. Chokkalingam AP, Pollak M, Fillmore CM, Gao YT, Stanczyk FZ, Deng J, Sesterhenn IA, Mostofi FK, Fears TR, Madigan MP, Ziegler RG, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev.* 2001 May;10(5):421-7
4. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. *J Clin Endocrinol Metab.* 2000 Nov;85(11):4258-65

Studies where a higher serum GH was found associated with an increased risk of breast cancer (*critic: based on the measurement of the daytime serum GH level, which is not representative of GH 24-hour secretion*)

5. Emerman JT, Leahy M, Gout PW, Bruchovsky N. Elevated growth hormone levels in sera from breast cancer patients. *Horm Metab Res.* 1985 Aug;17(8):421-4

Studies where a higher serum IGF-1 or IGF-1/IGF-BP-3 ratio is found associated with an increased risk of breast cancer, in particular in women with ≥ 19 CA repeats in IGF-1 gene

6. Yu H, Li BD, Smith M, Shi R, Berkel HJ, Kato I. Polymorphic CA repeats in the IGF-I gene and breast cancer. *Breast Cancer Res Treat.* 2001 Nov;70(2):117-22
7. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. *Oncology.* 1999 Nov;57(4):330-40 (*up to 7x greater breast cancer incidence in women in the highest quintile of serum IGF-1: serum IGFBP-3 ratio compared to women in the lowest quintile*)

A study where a lower serum IGF-BP-3 was found in breast cancer patients

8. Bruning PF, Van Doorn J, Bonfrer JM, Van Noord PA, Korse CM, Linders TC, Hart AA. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. *Int J Cancer.* 1995 Jul 28;62(3):266-70

A study where a higher serum IGF-1 / IGF-BP-3 was found associated with an increased colon cancer risk (the colon cancer risk was 4 times increased only for subjects in the upper tertile of IGF-1 and lower tertile of IGF-BP-3; for other tertiles or a combination of tertiles there was: no significant association)

9. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospective study of colorectal cancer risk in men and plasma levels of IGF-1 and IGF-BP-3. *J Natl Cancer Inst.* 1999; 91: 620-5

In acromegaly, the incidence of and/or mortality from digestive cancer is increased

10. Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. *Cancer.* 1991 Oct 15;68(8):1673-7 (but no increase in overall cancer incidence)
11. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab.* 1998 Aug;83(8):2730-4 (but decreased overall incidence of cancer in acromegaly, and no increased overall cancer mortality)

Critics: in acromegaly the GH production is 10 to 100 times the normal production, 10 to 300 times the daily doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a **polyhormonal deficit**: hypothyroidism, hypogonadism, hypocorticism, ..., endocrine conditions that increase the risk of glucose intolerance and diabetes These conditions are not found in corrective GH treatment of GH deficiency.

12. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. *J Clin Endocrinol Metab.* 1994 Dec;79(6):1706-15 (*"Patients with active acromegaly ...secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls"*)
13. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. *Clin Endocrinol Metab.* 1983 Nov;12(3):509-34 (*"In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order"*)
14. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. *J Clin Endocrinol Metab.* 1979 Feb;48(2):309-14
15. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. *Am J Med.* 1982 Jun;72(6):861-73

GH TREATMENT WITH HUMAN PITUITARY GH HORMONE

A study where the use of human pituitary GH as therapy to GH-deficient patients treated during childhood and early adulthood up to 1985 was associated with an increased risk of colon cancer and overall cancer mortality (critics: the data are based on patients having taken GH extracted from human cadavers, now only biosynthetic growth hormone is used; moreover, the doses used in childhood are extremely high – at least seven times those used in treatment of GH-deficiency in adults)

16. Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. *Lancet.* 2002 Jul 27;360(9329):273-7

Neutral information and alternative explanations on a possible GH and cancer relation

Possible bias in the studies with increased prostate and breast cancer risk:

Bias 1: The diagnosis of cancer may be more rapidly made in patients with high IGF-1 because they may undergo more intensive scrutiny: *As raised IGF-1 may cause tissue hyperplasia, including increase in size of prostate and breast tissue, the existence of these bigger tissues and possibly of the symptoms they may cause, may lead to more intensive scrutiny, from increased rate of PSA, CEA or C1.25 measurements, to ultrasound and RX examinations, prostate or breast biopsies, and thus an increased rate of detection of very slow, asymptomatic prostate or breast cancers that would have remained undiagnosed or diagnosed much later in patients with low IGF-1. Such higher rate of cancer detection may be particularly the case for prostate cancer, where the number of detected prostate cancer cases is very low compared to the total number of cases found at autopsy, and premenopausal breast cancer patients who were diagnosed within the 2 years after the first blood sample.*

17. Cohen P, Clemmons DR, Rosenfeld RG. Does the GH-IGF axis play a role in cancer pathogenesis? *Growth Horm IGF Res.* 2000 Dec;10(6):297-305

Higher levels of IGF-1 or GH or acromegaly have been associated with benign prostatic hyperplasia, but not necessarily with prostate cancer

18. Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Sesterhenn IA, Mostofi FK, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and risk of benign prostatic hyperplasia. *Prostate.* 2002 Jul 1;52(2):98-105.
19. Colao A, Marzullo P, Ferone D, Spiezia S, Cerbone G, Marino V, Di Sarno A, Merola B, Lombardi G. Prostatic hyperplasia: an unknown feature of acromegaly. *J Clin Endocrinol Metab.* 1998 Mar;83(3):775-9

GH and IGF-1 treatment of primates can increase breast hyperplasia, not specifically breast cancer

20. Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. *Nat Med.* 1997 Oct;3(10):1141-4

Bias 2: After adjustment for prostate volume, no longer significant associations between serum IGF-I and prostate cancer risk may persist (Serum IGF-I is not useful for diagnosis of prostate cancer, but a marker of benign prostatic hyperplasia and enlargement)

21. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. *J Clin Endocrinol Metab.* 2000 Aug;85(8):2744-77

Bias 3: Serum IGF-I may actually be a surrogate marker of nutritional factors that may increase the cancer risk such as meat and milk intake (persons who eat a lot of protein, especially red meat, have higher IGF-1 levels and an increased cancer risk)

22. Dai Q, Xiao-ou Shu, Fan Jin, Yu-Tang Gao, Zhi-Xian Ruan, Zheng W. Consumption of Animal Foods, Cooking Methods, and Risk of Breast Cancer. *Cancer Epidemiol Biom Prev.* 2002;11:801-8

Link between meat, milk and/or protein intake, and prostate or breast cancer

23. Zheng W, Deitz AC, Campbell DR, Wen WQ, Cerhan JR, Sellers TA, Folsom AR, Hein DW. N-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 1999 Mar;8(3):233-9
24. Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. *J Nat Cancer Inst.* 1999; 91 (23):2038-44
25. Sinha R, Chow WH, Kulldorff M, Denobile J, Butler J, Garcia-Closas M, Weil R, Hoover RN, Rothman N. Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res.* 1999;59(17):4320-4

26. Butler LM, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD, Ammerman AS, Sandler RS. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am J Epidemiol.* 2003;157(5):434-45
27. Wolk A. Diet, lifestyle and risk of prostate cancer. *Acta Oncol.* 2005;44(3):277-81
28. Grant WB. An ecologic study of dietary links to prostate cancer. *Altern Med Review* 1999; 4(3): 162-9 (*in more than 14 European countries*)
29. Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, Willett WC. Premenopausal fat intake and risk of breast cancer. *J Natl Cancer Inst.* 2003 Jul 16;95(14):1079-85

Red meat and milk intake is correlated with high IGF-1

30. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. *J Clin Oncol.* 1999 Oct;17(10):3291-8
31. Larsson SC, Wolk K, Brismar K, Wolk A. Association of diet with serum insulin-like growth factor I in middle-aged and elderly men. *Am J Clin Nutr.* 2005 May;81(5):1163-7
32. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev.* 2002 Nov;11(11):1441-8
33. Hoppe C, Molgaard C, Juul A, Michaelsen KF. High intakes of skimmed milk, but not meat, increase serum IGF-I and IGFBP-3 in eight-year-old boys. *Eur J Clin Nutr.* 2004 Sep;58(9):1211-6

Bias 4: The increases of serum IGF-1 may be produced by the malignant tumour and constitute a consequence and not a cause as suggested in some animal studies.

34. DiGiovanni J, Kiguchi K, Frijhoff A, Wilker E, Bol DK, Beltran L, Moats S, Ramirez A, Jorcano J, Conti C. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. *Proc Natl Acad Sci USA.* 2000 Mar 28;97(7):3455-60
35. Kaplan PJ, Mohan S, Cohen P, Foster BA, Greenberg NM. The insulin-like growth factor axis and prostate cancer: lessons from the transgenic adenocarcinoma of mouse prostate (TRAMP) model. *Cancer Res.* 1999 May 1;59(9):2203-9

Bias 5: the variability of serum IGF-1 makes that if two weeks after the initial blood test another measurement of IGF-1 was done, the results of the studies would have been different (about 40° % of participants of the study would have switched from one quartile to the other)

36. Milani D, Carmichael JD, Welkowitz J, Ferris S, Reitz RE, Danoff A, Kleinberg DL. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. *J Clin Endocrinol Metab.* 2004 May;89(5):2271-4 (*"If fasting serum IGF-1 is measured twice, two weeks apart, individually differences range from -36.25 to +38.24%, while the mean value for the group of 84 shows high correlation between the two IGF-Is (r=0.922; p<0.0001) and varies much less (mean 120 at first visit) versus 115; p=0.03) in normal volunteers between the ages of 50 and 90 years. When considered in quartiles, IGF-I changed from one quartile to another in 34/84 (40.5%) of the volunteers. When the group was divided in halves, tertiles, quartiles, or quintiles there was an increasing number of subjects who changed from one subdivision to another as the number of gradations increased. These results suggest that the predictive outcomes of earlier studies that used single IGF-I samples for analysis of risk ratios according to tertiles, quartiles, or quintiles could have been different if a second IGF-I was used to establish the risk ratio."*)

No significant associations of serum levels and prostate cancer risk

No difference in plasma GH or IGF-1 between prostate cancer patients and controls

37. Yu H, Nicar MR, Shi R, Berkel HJ, Nam R, Trachtenberg J, Diamandis EP. Levels of IGF-I and IGF BP- 2 and -3 in serial postoperative serum samples and risk of prostate cancer recurrence. *Urology*. 2001 Mar;57(3):471-5.
38. Hill M, Bilek R, Safarik L, Starka L. Analysis of relations between serum levels of epitestosterone, estradiol, testosterone, IGF-1 and prostatic specific antigen in men with benign prostatic hyperplasia and carcinoma of the prostate. *Physiol Res*. 2000;49 Suppl 1:S113-8
39. Kurek R, Tunn UW, Eckart O, Aumuller G, Wong J, Renneberg H. The significance of serum levels of insulin-like growth factor-1 in patients with prostate cancer. *BJU Int*. 2000 Jan;85(1):125-9
40. Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalgleish AG, Kirby RS. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. *BJU Int*. 1999 Jun;83(9):996-9
41. Ismail HA, Pollak M, Behloui H, Tanguay S, Begin LR, Aprikian AG. Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples. *BJU Int*. 2003 Nov;92(7):699-702
42. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. *Cancer Res*. 2003 Jul 15;63(14):3991-4
43. Ismail A H, Pollak M, Behloui H, Tanguay S, Begin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. *J Urol*. 2002 Dec;168(6):2426-30
44. Bublely GJ, Balk SP, Regan MM, Duggan S, Morrissey ME, Dewolf WC, Salgami E, Mantzoros C. Serum levels of insulin-like growth factor-1 and insulin-like growth factor-1 binding proteins after radical prostatectomy. *J Urol*. 2002 Nov;168(5):2249-52
45. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. *Cancer Epidemiol Biomarkers Prev*. 2004 Sep;13(9):1444-51.

In acromegaly, the incidence of cancer, other than possibly colon cancer, does not appear to be significantly increased; in one study it was even significantly reduced by -14 %. Overall mortality is normal for patients with low posttreatment GH, but increased for patients with high posttreatment GH.

46. J. Svensson, B.-Å. Bengtsson, T. Rosén, Odén A, Johannsson G. Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without GH Replacement Therapy . *J Clin Endocrinol Metab*. 2004 Jul;89(7):3306-12
47. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab*. 1998 Aug;83(8):2730-4 (*"The overall cancer incidence rate was 24 % lower than that in the general population of the U.K.; the overall cancer mortality rate was not increased, but the colon cancer mortality rate was increased."*)

No difference in serum IGF-1 between breast cancer patients and controls

48. Li BD, Khosravi MJ, Berkel HJ, Diamandi A, Dayton MA, Smith M, Yu H. Free insulin-like growth factor-I and breast cancer risk. *Int J Cancer*. 2001 Mar 1;91(5):736-9
49. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. *Cancer Epidemiol Biomarkers Prev*. 2004 Sep;13(9):1444-51.

GH transgenic mice with high serum IGF-1 do not develop breast, prostate, or colonic malignancies

50. Wennbo H, Gebre-Medhin M, Gritli-Linde A, Ohlsson C, Isaksson OG, Tornell J. Activation of the prolactin receptor but not the growth hormone receptor is important for induction of mammary tumors in transgenic mice. *J Clin Invest*. 1997 Dec 1;100(11):2744-51
51. Wennbo H, Tornell J. The role of prolactin and GH in breast cancer. *Octogene*. 2000;19:1072-6

Arguments pro GH use:

Inverse (protective) associations of serum GH/IGF-1 levels and overall cancer risk

Untreated GH deficient patients have an increased overall cancer incidence (2x the normal incidence) and cancer mortality (4x)

52. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

A high serum IGF-1 is found associated with a lower risk of prostate cancer

53. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. *J Clin Endocrinol Metab.* 2000 Aug;85(8):2744-7

54. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum IGF-1: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. *Cancer Res.* 2003;15;63(14):3991-4 (- 48 % for men in the highest quartile of serum IGF-1)

55. Baffa R, Reiss K, El-Gabry EA, Sedor J, Moy ML, Shupp-Byrne D, Strup SE, Hauck WW, Baserga R, Gomella LG. Low serum insulin-like growth factor 1 (IGF-1): a significant association with prostate cancer. *Urol.* 2000 Sep;6(3):236-9

No significant association between serum IGF-1 and prostate cancer:

GH therapy increases serum IGF-BP-3, which may protect against cancer: IGF-BP-3 causes apoptosis of cancer cells and inhibits IGF action on cancer cells in vitro => Serum IGF-BP-3 is in general negatively correlated with the cancer risk cancer: the higher IGF-BP-3, the lower the cancer risk

56. Wollmann HA, Schonau E, Blum WF, Meyer F, Kruse K, Ranke MB. Dose-dependent responses in insulin-like growth factors, insulin-like growth factor-binding protein-3 and parameters of bone metabolism to growth hormone therapy in young adults with growth hormone deficiency. *Horm Res.* 1995;43(6):249-56

57. Grimberg A, Cohen P. GH & prostate cancer: guilty by association? *J Endocrinol Invest.* 1999;22(5 Suppl):64-73

A high serum IGF-BP-3 is associated with a reduced prostate cancer risk (-30%), and/or prostate cancer recurrence

58. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. *J Clin Endocrinol Metab.* 2000 Nov;85(11):4258-65

Studies where GH therapy given to cancer patients reduced the cancer recurrence, and reduces the cancer mortality or increases survival time

59. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WD, Brada M, Hayward RD, Brook CG, Hindmarsh PC, Shalet SM. Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab.* 2000 Dec;85(12):4444-9

60. Tacke J, Bolder U, Herrmann A, Berger G, Jauch KW. Long-term risk of gastrointestinal tumor recurrence after postoperative treatment with recombinant human growth hormone. *J Parenter Enteral Nutr.* 2000 May-Jun;24(3):140-4

Long-term GH replacement (60 months) reduced the increased cancer risk and mortality of GH deficient patients by half

61. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

GH or IGF-1 therapy to animals with cancer: may reduce the tumour incidence and/or progression

Combined GH- insulin therapy reduced the development of mammary carcinoma in female rats

62. Bartlett DL, Charland S, Torosian MH. Growth hormone, insulin, and somatostatin therapy of cancer cachexia. *Cancer.* 1994 Mar 1;73(5):1499-504

GH-therapy reduced the development of lung metastases in rats with prostate cancer

63. Torosian MH. Growth hormone and prostate cancer growth and metastasis in tumor-bearing animals. *J Pediatr Endocrinol.* 1993 Jan-Mar;6(1):93-7

A lower serum GH level is found in gastric cancer patients

64. Colombo F, Iannotta F, Fachinetti A, Giuliani F, Cornaggia M, Finzi G, Mantero G, Fraschini F, Malesci A, Bersani M, et al. [Changes in hormonal and biochemical parameters in gastric adenocarcinoma] *Minerva Endocrinol.* 1991 Jul-Sep;16(3):127-39

GH-therapy inhibits the development of liver cancer due to carcinogens (aflatoxin B1 or N-OH-acetyl- aminofluoren) in male rats

65. Liao D, Porsch-Hallstrom I, Gustafsson JA, Blanck A. Sex differences at the initiation stage of rat liver carcinogenesis—influence of growth hormone. *Carcinogenesis.* 1993 Oct;14(10):2045-9

IGF-1-therapy preserved lean mass in rats with sarcoma and cachexia

66. Ng EH, Rock CS, Lazarus DD, Stiaino-Coico L, Moldawer LL, Lowry SF. Insulin-like growth factor I preserves host lean tissue mass in cancer cachexia. *Am J Physiol.* 1992 Mar;262(3 Pt 2):R426-31

Conclusion on the cancer studies and GH

- **GH therapy raises both the levels of both IGF-I and IGFBP-3.** IGF-BP-3 is a potent inhibitor of IGF action in breast and prostate tissues.
- **Autocrine production of IGF's and GH,** have been identified in **cancer cells and tissues.** Thus, serum IGF-I may actually be a confounding variable, serving as a marker for local prostatic IGF-I production.
- Since GH-deficient patients often have a subnormal IGF-I serum level, which normalizes on therapy, the cancer risk on **GH therapy does probably not substantially increase above that of the normal population.** On the contrary, the evidence points to a normalization of the risk.
- It seems prudent that when we treat adult GH deficiency, we should aim to maintain serum IGF-1 in the normal range.

GH AND LIFE SPAN

Claim: GH may have adverse effects on life span

Facts: GH treatment appears to reduce mortality, except for special mice species and humans put in extreme conditions.

Arguments contra GH use

Studies where higher GH and/or IGF-1 levels were found associated with premature death

A high serum GH was associated with premature death in humans (*critics: an old fashioned technique, which lacked assay precision, was used to measure GH; the daytime serum GH were measured, which is not accurate except for acromegaly patients; serum GH does not reflect GH activity, serum IGF-1 does it, but up to a certain degree; an increased serum GH may possibly reflect increased binding of GH to increased serum GHBP and thus inactivation of GH, but the serum GHBP level was not checked in the study*)

1. Maison P, Balkau B, Simon D, Chanson P, Rosselin G, Eschwege E. Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study. *BMJ*. 1998 Apr 11;316(7138):1132-3

Acromegaly adults have premature death only when they keep high posttreatment GH and thus a probably continuing active growth hormone-secreting tumor that crushes down all the other pituitary cells, overall mortality is normal for patients with low posttreatment GH,

2. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab*. 1998 Aug;83(8):2730-4.

Mice models of genetic pituitary failure with multiple hormone deficiency (Ames and Snell mice) and GH receptor knockout mice (primary IGF1-deficiency) may have a significant higher longevity (*critics: the heterozygous IGF-1 receptor knock-out mutants are special mice species, as are Ames and Snell mice . They react in a completely different way to GH than normal mice species. They have a 50 % decrease in IGF-1 receptors, but a 32% higher serum IGF-1; they have more glucose intolerance; are slightly smaller; the lifespan was only significantly longer in female mice (+33%), not in male mice (+16%); the results based on a shortliving species (mice) may not be necessarily true for species with a long life such as humans*)

3. Liang H, Masoro EJ, Nelson JF, Strong R, McMahan CA, Richardson A. Genetic mouse models of extended lifespan. *Exp Gerontol*. 2003 Nov-Dec;38(11-12):1353-64
4. Holzenberger M. The GH/IGF-I axis and longevity. *Eur J Endocrinol*. 2004 Aug;151 Suppl 1:S23-7
5. Kulkarni RN, Holzenberger M, Shih DQ, Ozcan U, Stoffel M, Magnuson MA, Kahn CR. beta-cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. *Nat Genet*. 2002 May;31(1):111-5 (*lack IGF-1 receptors on beta-cells => glucose interance and less beta-cells*)
6. Hauck SJ, Aaron JM, Wright C, Kopchick JJ, Bartke A. Antioxidant enzymes, free-radical damage, and response to paraquat in liver and kidney of long-living growth hormone receptor/binding protein gene-disrupted mice. *Horm Metab Res*. 2002 Sep;34(9):481-6

Can GH therapy increases mortality?

GH therapy to critically ill patients: doubles the mortality rate

7. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999 Sep 9;341(11):785-92 (*Critics on the study: the doses used were too high doses: 10 to 70 times the normal dose in very weak persons; the control group had an abnormally lower mortality rate than predicted; combined to the high mortality rates of the treatment group, the average mortality rate was very similar to that of a historical cohort; GH treatment lowers cortisol levels, which are crucial to critically ill patients*)

8. Freeman BD, Danner RL, Banks SM, Natanson C. Safeguarding patients in clinical trials with high mortality rates. *Am J Respir Crit Care Med.* 2001 Jul 15;164(2):190-2

BUT: Studies where GH therapy lowered the levels of cortisol and its metabolites by 20 to 40 %, which is dangerous for critically-ill patients who desperately need cortisol for their survival

9. Vierhapper H, Nowotny P, Waldhausl W. Treatment with growth hormone suppresses cortisol production in man. *Metabolism* 1998 Nov;47(11):1376-8 ;
10. Rodriguez-Arno J, Perry L, Besser GM, Ross RJ. Growth hormone treatment in hypopituitary GH deficient adults reduces circulating cortisol levels during hydrocortisone replacement therapy. *Clin Endocrinol (Oxf).* 1996 Jul;45(1):33-7
11. Weaver JU, Thaventhiran L, Noonan K, Burrin JM, Taylor NF, Norman MR, Monson JP. The effect of growth hormone replacement on cortisol metabolism and glucocorticoid sensitivity in hypopituitary adults. *Clin Endocrinol (Oxf).* 1994 Nov;41(5):639-48

...and a study where patients who have poor responsive adrenals (poorly able to increase their cortisol production) and are in septic shock, die easier

12. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet.* 1991 Mar 9;337(8741):582-3

.. and studies where glucocorticoid treatments considerably increased survival of critically-ill patients

survival of HIV patient from pneumonia

13. Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. *N Engl J Med.* 1990 Nov 22;323(21):1444-50

survival from typhus

14. Hoffman SL, Punjabi NH, Kumala S, Moechtar MA, Pulungsih SP, Rivai AR, Rockhill RC, Woodward TE, Loedin AA. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. *N Engl J Med.* 1984 Jan 12;310(2):82-8

NEUTRAL information on GH and longevity

No increased mortality in acromegaly if levels of GH are less than 2.5 ng/ml

15. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab.* 1998 Aug;83(8):2730-4

Arguments pro GH use

GH/IGF-1 LEVELS: Higher serum GH and IGF-1 levels are associated with a higher survival

Persistent GH deficiency (without GH therapy) in humans, is associated with a shorter life expectancy: increased overall and cardiovascular mortality

16. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet.* 1990 Aug 4;336(8710):285-8
17. AS Bates, W Van't Hoff, PJ Jones and RN Clayton. The effect of hypopituitarism on life expectancy. *J Clin Endocrin Metab.* 1996 Mar;81(3):1169-72

Higher mortality in GH deficient women

18. Svensson J, Bengtsson BA, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

Higher mortality in 11 GH deficient adults suffering from a genetic defect (6.7-kb spanning deletion of genomic DNA of the GH-1 gene) that causes isolated GH deficiency (hereditary

dwarfism), untreated men lost 21 years of life (-25% compared to the unaffected brothers) and women 34 years less (-44% versus unaffected sisters)

19. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS, Mullis PE. Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab.* 2003;88(8):3664-7

Patients with hypopituitarism have increased overall and cardiovascular mortality; the increased mortality from cerebrovascular disease (esp. in women) was the main contributor to the increased cardiovascular mortality

20. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf).* 1997 Jan;46(1):75-81
21. Bengtsson BA, Koppeschaar HP, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP, Feldt-Rasmussen U, Wuster C. Growth hormone replacement therapy is not associated with any increase in mortality. KIMS Study Group. *J Clin Endocrinol Metab.* 1999 Nov;84(11):4291-2

GH TREATMENT: Corrective GH hormone treatment increases survival

GH replacement therapy of GH deficient adults lowers the excessive mortality back to normal

22. Bengtsson BA, Koppeschaar HP, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP, Feldt-Rasmussen U, Wuster C. Growth hormone replacement therapy is not associated with any increase in mortality. KIMS Study Group. *J Clin Endocrinol Metab.* 1999 Nov;84(11):4291-2
23. Svensson J, Bengtsson BA, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3306-12

GH treatment of normal elderly mice, extended the mean and maximal life span⁸⁻⁹.

24. Khansari DN, Gustad T. Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. *Mech Ageing Dev.* 1991 Jan;57(1):87-100

GH treatment of GH deficient mice extended life span, but lifespan of (non GH treated) mice was similar to that of normal mice.

25. Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease modifies age-related pathology, and increases life span. *Endocrinology.* 2005 Jul;146(7):2920-32

Conclusion: Persistent GH deficiency reduces the life expectancy, while GH treatment of GH-deficient patients improves it. Caution should be applied when using GH treatment in critically-ill patients.

Thyroid Hormone

DISCUSSIONS ON THYROID DIAGNOSIS

SERUM TSH: IS THE TSH SERUM MEASUREMENT ALONE SUFFICIENT FOR DIAGNOSIS AND FOLLOW-UP OF THYROID DEFICIENCY?

Claim: TSH is the first line test to do. It is sufficient to diagnose all forms of eu-, hypo- and hyperthyroidism. No other test is necessary for the diagnosis.

Facts: TSH is often insufficient on its own to diagnose between eu-, hypo- and hyperthyroidism, particularly to diagnose milder, borderline states of hypothyroidism. Other tests are necessary, as is a complete clinical evaluation (medical history, actual complaints, physical examination) of the patient.

Article defending the serum TSH test as the first line approach to diagnose thyroid dysfunction

1. Nunez S, Leclere J. Diagnosis of hypothyroidism in the adult. *Rev Prat.* 1998; 48(18): 1993-8.

Doubts on the usefulness of the serum TSH test alone for diagnosis

Overreliance on laboratory tests without clinical evaluation may lead to considerable diagnostic errors

2. Nicoloff JT, Spencer CA. The use and misuse of the sensitive thyrotropin assay. *J Clin Endocrinol Metab.* 1990;71:553-8.
3. De Los Santos ET, Mazzaferri EL. Sensitive thyroid-stimulating hormone assays: Clinical applications and limitations. *Compr Ther.* 1988; 14(9): 26-33.
4. Becker DV, Bigos ST, Gaitan E, Morris JCrd, rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. Optimal use of blood tests for assessment of thyroid function. *JAMA* 1993 Jun 2; 269: 273 ("the decision to initiate therapy should be based on both clinical and laboratory findings and not solely on the results of a single laboratory test")
5. Rippere V. Biochemical victims: False negative diagnosis through overreliance on laboratory results—a personal report. *Med Hypotheses.* 1983; 10(2): 113.

Discussions and controversy in medical associations and journals on the TSH reference range

6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA.* 2004;291:228–38 (*conclusions of a consensus panel of the Endocrine Society, the American Thyroid Association, and American Association of Clinical Endocrinology. Although the panel concluded that there was good data that patients with slight elevations of TSH above 4.5 may progress to overt hypothyroidism, and that levothyroxine therapy would prevent symptoms, they did not agree that early treatment provided any benefit!*)
7. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. *Thyroid.* 2005 Sep;15(9):1035-9
8. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab.* 2005 Sep;90(9):5483-8 (*remarkable article of which a lot of the following information is extracted*)
9. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *J Clin Endocrinol Metab.* 2005;90:581–5
10. Surks MI. Commentary: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *J Clin Endocrinol Metab.* 2005;90:586–7
11. Ringel MD, Mazzaferri EL. Editorial: subclinical thyroid dysfunction: can there be a consensus about the consensus? *J Clin Endocrinol Metab.* 2005;90:588–90
12. Pinchera A. Subclinical thyroid disease: to treat or not to treat? *Thyroid.* 2005;15:1–2

Studies that show that the serum TSH reference range of 0.1-5.1 mU/liter for a POPULATION is too large

Studies indicating a population mean value of 1.5 mU/liter for an iodine-sufficient population

13. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55–68
14. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002; 87:489–99
15. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab*. 2002;87:1068–72
16. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf)*. 2003;58:138–40
17. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid*. 2003 Jan;13(1):3-126

A longitudinal study in diabetics where a baseline TSH levels above the 1.53 mU/liter predicted subsequent thyroid dysfunction, whereas no thyroid dysfunction if TSH levels < 1.53 mU/liter, the reference range for diabetics should then be 0.4-1.52 mU/liter

18. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. *Thyroid*. 2004;14:853–7

If the serum TSH reference range would be **based upon a cohort of truly normal individuals with no personal or family history of thyroid dysfunction, no visible or palpable goiter, not taking any medication, who are seronegative for thyroid peroxidase antibodies, and whose blood samples are drawn fasting in the morning hours (06–10 h), the TSH reference range would become 0.4–2.5 mU/L** (Demers & co, Baloch & co.)

19. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf)*. 2003;58:138–40
20. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002; 87:489–99
21. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid*. 2003 Jan;13(1):3-126

When data for subjects with positive TPOAb or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mU/liter. This tighter reference range may certainly be more applicable to African-Americans, who have a lower mean TSH

22. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002; 87:489–99
23. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf)*. 2003;58:138–40

Publications with data to support a more narrow reference range for serum TSH that would be obtained when persons with diffuse hypoechogenicity of the thyroid on ultrasound, a condition that precedes thyroid peroxidase antibody positivity in autoimmune thyroid disease, would be excluded

24. Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. *Thyroid*. 2000;10:251–9

For the American Association of Clinical Endocrinologists the revised reference TSH range is 0.3–3.0 mU/L

25. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457–69

Ethnic differences: the mean TSH level in African-Americans is 1.18 mU/liter, in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites (12.3%) than in blacks (4.3%), which may have unjustifiedly skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range should therefore be lower than in whites

26. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–9

A study, which suggests that the serum TSH cut-off point between hypo- and euthyroidism is 2, not 4 or 5.5

27. Michalopoulou G, Alevizaki M, Pipingos G, Mitsibounas D, Mantzos E, Adampoulos P, Koutras DA. High serum cholesterol levels in persons with 'high-normal' TSH levels: Should one extend the definition of subclinical hypothyroidism? *Eur J Endocrinol*. 1998 Feb;138(2):141-5 (*Treating TPO antibody-positive hypercholesterolemic patients with TSH levels between 2-4 mU/L with low dose levothyroxine normalizes TSH levels and improves the lipid profile*)

In 2003, the National Academy of Clinical Biochemistry (NACB) has reduced the upper limit of the reference range from 5.5 to 4.1 mU/L, but stating also that "**greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4 - 2.5 mU/L**". "**.. patients with a serum TSH >2.5 mU/L, when confirmed by repeat TSH measurement made after 3 to 4 weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected**"

28. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid*. 2003 Jan;13(1):3-126

Supporters of the recommendations of the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, American Thyroid Association) promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy

29. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid*. 2003 Jan;13(1):3-126

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies

30. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid*. 2003 Jan;13(1):3-126
31. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf)*. 1991;34:77-83
32. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. *Thyroid*. 2004;14:853–7

33. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:526–34
34. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med.* 1991;151:165–8
35. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT. Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. *J Am Geriatr Soc.* 1993;41:823–8
36. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet.* 2001;358:861–5

The TSH reference range for an INDIVIDUAL is narrower than the reference range for a population

The value of a population-based reference range is limited when the individual patient-based reference range (*i.e.* his personal reference range) is narrow

37. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. *Crit Rev Clin Lab Sci.* 1989;27:409–37
38. Harris EK. Effects of intra- and interindividual variation on the appropriate use of normal ranges. *Clin Chem.* 1974;20:1535–42

The individual TSH reference ranges are remarkably narrow within a relatively small segment of the population reference range, *i.e.* confined to only 25% of a range of 0.3–5.0 mU/liter.

A shift in the TSH value of the individual outside of his or her individual reference range, but still within the population reference range, would not be normal for that individual. For example, an individual (as in Anderson's series) with a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005)

39. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab.* 2002;87:1068–72

Studies of twins have data to support that each of us has a genetically determined optimal free T4 (FT4)-TSH set point or relationship

40. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf).* 2003;58:138–40
41. Meikle AW, Stringham JD, Woodward MG, Nelson JC. Hereditary and environmental influences on the variation of thyroid hormones in normal male twins. *J Clin Endocrinol Metab.* 1988 ; 66:588–92

A measured TSH difference of 0.75 mU/liter can already be significant in a patient. The NACB guideline 8 states that "the magnitude of difference in ...TSH values that would be clinically significant when monitoring a patient's response to therapy... is 0.75 mU/liter." Greater TSH fluctuations in a specific patient may mean that s/he becomes hypothyroid or hyperthyroid.

42. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid.* 2003 Jan;13(1):3-126

A serum TSH that rises in a given individual from a set point of 1.0 to 3.5 is likely to be abnormally elevated and imply early thyroid failure. A minor change in serum free T4 results in an amplified change in TSH to outside of the usual population-based reference range, although the free T4 is still within its own population-based reference range, because of the the log-linear relationship between TSH and free T4. In the case of **subclinical hypothyroidism**, for example, a slight drop in free T4 results in an amplified and inverse response in TSH secretion (as explained by Wartofsky 2005)

43. Cooper DS. Subclinical hypothyroidism. *N Engl J Med.* 2001;345:260–5

44. Ayala A, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. *Endocrinologist*. 1997;7:44–50

There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml)

89. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B,
45. Feistner H, Hesch RD, von zur Muhlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. *J Clin Endocrinol Metab*. 1990 Feb;70(2):403-9

Conclusion: TSH reference range is too large => need for narrower ranges

46. Pain RW. Simple modifications of three routine in vitro tests of thyroid function. *Clin Chem*. 1976; 22(10): 1715-8.
47. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. *Thyroid*. 2005 Sep;15(9):1035-9
48. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab*. 2005 Sep;90(9):5483-8

Other arguments that may explain why the TSH test alone is not the only test

The TSH test is insufficient to diagnose all forms of hypothyroidism, including the borderline forms.

The frequency of abnormal TSH values

49. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526–34
50. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. *Thyroid*. 2004;14:853–7

Longitudinal studies indicating a rate of progression of mild thyroid failure into overt hypothyroidism of about 5% per year (50% or more in 10 years!): they have to be treated

51. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995; 43:55–68
52. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf)*. 1991;34:77–83
53. Huber G, Staub J-J, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab*. 2002;87:3221–6
54. Kabadi UM. 'Subclinical hypothyroidism:' natural course of the syndrome during a prolonged follow-up study. *Arch Intern Med*. 1993;153:957-61

The pituitary 5'-deiodinase type 2 that converts thyroxine into triiodothyronine (T3), is different than the liver and kidney 5'-deiodinase type 1 that provides the T3 for the rest of the body. This difference may explain why TSH secretion and thus serum TSH secreted by the pituitary gland may be normal, while the rest of the body may be in a thyroid deficient state.

55. Koenig RJ, Leonard JL, Senator D, Rappaport N, Watson A, Larsen PR. Regulation of thyroxine 5'-deiodinase activity by 3,5,3'-triiodothyronine in cultured anterior pituitary cells. *Endocrinology*. 1984 Jul;115(1):324-9.

In fasting, hypothyroidism or selenium deficiency for example, the 5'-deiodinase of the pituitary gland increases or remains unchanged, while that of the liver decreases.

56. Suda AK, Pittman CS, Shimizu T, Cambers JB. The production and metabolism of 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine in normal and fasting subjects. *J Clin Endocrinol Metab*. 1978 Dec;47(6):1311-9

57. Larsen PR, Silva JE, Kaplan MM. Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. *Endocr Rev.* 1981 Winter;2(1):87-102.
58. Chanoine JP, Safran M, Farwell AP, Tranter P, Ekenbarger DM, Dubord S, Arthur JR, Beckett GJ, Braverman LE, Dubord S, Alex S, Arthur JR, Beckett GJ, Braverman LE, Leonard JLI. Selenium deficiency and type II 5'-deiodinase regulation in the euthyroid and hypothyroid rat: evidence of a direct effect of thyroxine. *Endocrinology.* 1992 Jul;131(1):479-84

A normal or low serum TSH may reflect in elderly persons hypothyroidism in peripheral tissues, and not anymore eu- or hyperthyroidism, because the pituitary gland has aged. Progressively with increasing age, the serum TSH test becomes less reliable as a diagnostic test.

59. Urban RJ. Neuroendocrinology of aging in the male and female. *Endocrinol Metab Clin North Am.* 1992;21(4): 921-31.

Necessity for other tests than the TSH to diagnosis thyroid dysfunction, e.g. the serum free T4

60. Ladenson PW. Diagnosis of hypothyroidism. In Werner and Ingbar's *The Thyroid*, 7th edition, Braverman LE and Utiger RE, Lippincott-Raven Publishers, Philadelphia. 1996; 878-82
61. Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A. Serum free thyroid hormones in subclinical hypothyroidism. *J Endocrinol Invest.* 1986 Aug;9(4):315-9
62. Surks MI, Chopra IJ, Mariosh CN, Nicoloff JT, Salomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. *JAMA.* 1990 Mar 16;263(11):1529-32
63. Davis JR, Black EG, Sheppard MC. Evaluation of a sensitive chemiluminescent assay for TSH in the follow-up of treated thyrotoxicosis. *Clin Endocrinol Oxf.* 1987; 27(5): 563-70

Serum thyroid hormone levels may not reflect the cellular thyroid status

64. Escobar del Rey F, Ruiz de Ona C, Bernal J, Obregon MJ, Morreale de Escobar G. Generalized deficiency of 3, 5, 3'-triiodothyronine in tissues from rats on a low iodine intake, despite normal circulating T3 levels. *Acta Endocrinol (Copenh)* 1989; 120: 490-8

Need to analyse valuable indicators of peripheral activity such as the serum levels of plasma binding proteins SHBG, TBG, CBG, or of thyroid-dependent enzymes such as alkaline phosphatase, osteocalcin

65. Smallridge RC. Metabolic, physiologic, and clinical indexes of thyroid function. In Werner and Ingbar's *The Thyroid*, 7th edition, Braverman LE and Utiger RP, Lippincott-Raven Publishers, Philadelphia, 1996
66. Foldes J, Tarjan G, Banos C, Nemeth J, Varga F, Buki B. Biologic markers in blood reflecting thyroid hormone effect at peripheral tissue level in patients receiving levothyroxine replacement for hypothyroidism. *Exp Clin Endocrinol.* 1992; 99(3): 129-33

Conditions or factors that DEPRESS the serum TSH

Aging

67. Urban RJ. Neuroendocrinology of aging in the male and female. *Endocrinol Metab Clin North Am.* 1992;21(4): 921-31
68. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med.* 1991; 151(1): 165-8

Fasting

69. Croxson MS, Hall TD, Kletzky OA, Jaramillo JE, Nicoloff OA. Decreased serum thyrotropin induced by fasting. *J Clin Endocrinol Metab.* 1977; 45: 560
70. Borst GC, Osburne RC, O'Brian JT, Georges LP, Burman KD. Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: A potential cause of misinterpretation of thyroid function tests in the critically ill. *J Clin Endocrinol Metab.* 1983 Aug;57(2):380-3
71. Campbell GA, Kurcz M, Marshall S, Meites J. Effects of starvation in rats on serum levels of follicle stimulating hormone, luteinizing hormone, thyrotropin, growth hormone and prolactin; response to LH-releasing hormone and thyrotropin-releasing hormone. *Endocrinology.* 1977; 100(2): 580-7
72. Opstad PK. The thyroid function in young men during prolonged physical stress and the effect of energy and sleep deprivation. *Clin Endocrinol.* 1984; 20: 657-69.

Strenuous physical exercise

73. Scanlon MF, Toft AD. Regulation of thyrotropin secretion. In Werner and Ingbar's *The Thyroid*, 7th edition

Pregnancy (first trimester)

74. Braverman LE and Utiger RE, Lippincott-Raven Publishers, Philadelphia. 1996; 220-40.

Depression and anxiety disorders

75. Bartalena L, Placidi GF, Martino E, Falcone M, Pellegrini L, Dell'Osso L, Pacchiarotti A, Pinchera A. Nocturnal serum thyrotropin (TSH) surge and the TSH response to TSH-releasing hormone: dissociated behavior in untreated depressives. *Clin Endocrinol Metab.* 1990 Sep;71(3):650-5.
76. Rupprecht R, Rupprecht C, Rupprecht M, Noder M, Mahlstedt J. Triiodothyronine, thyroxine, and TSH response to dexamethasone in depressed patients and normal controls. *Biol Psychiatry.* 1989;25(1): 22-32.
77. Maeda K, Yoshimoto Y, Yamadori A. Blunted TSH and unaltered PRL responses to TRH following repeated administration of TRH in neurological patients: A replication of neuroendocrine features of major depression. *Biol Psychiatry.* 1993; 33(4): 277-83.
78. Duval F, Macher JP, Mokrani MC. Difference between evening and morning thyrotropin responses to protirelin in major depressive episode. *Arch Gen Psychiatry.* 1990; 47(5): 443-8.
79. Loosen PT, Prange AJ Jr. Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: A review. *Am J Psychiatry* 1982; 139(4): 405-16.

Non-thyroidal diseases: diabetes mellitus, Cushing's syndrome, renal failure, cancer, myocardial infarction, AIDS, post-traumatic syndromes, chronic alcoholic liver disease, other illnesses

80. Devos P. Rationele keuze van schildklierfunctie tests. *Tijdschr Geneesk.* 1990; 46(8): 591-9
81. Alexander CM, Kaptein EM, Lum SMC, Spencer CA, Kumar K, Nicoloff JT. Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus. *J Clin Endocrinol Metab.* 1982; 54: 362-366
82. Andrade SF, Kanitz-MI, Povoas H Jr. Study of thyrotropic reserve in diabetics of adult type. *Acta Biol Mod Ger* 1977; 36(10): 1479-81
83. Gonzalez C, Montoya-E, Jolin T. Effect of streptozotocin diabetes on the hypothalamic pituitary thyroid axis in the rat. *Endocrinology* 1980; 107(6): 2099-103

84. Rossi GL, Bestetti GE, Tontis DK, Varini M. Reverse hemolytic plaque assay study of luteinizing and follicle-stimulating hormone and thyrotropin secretion in diabetic rat pituitary glands. *Diabetes* 1989; 38(10): 1301-6
85. Adriaanse R, Brabant G, Endert E, Wiersinga W. Pulsatile thyrotropin secretion in patients with Cushing's syndrome. *Metabolism*. 1994 Jun;43(6):782-6
86. Beyer HK-, Schuster P, Pressler H. Studies on hypothalamic pituitary thyroid regulation in hemodialysis patients. *Nuklearmedizin* 1981;20(1):19-24
87. Kokei S, Inoue T, Iino S. Serum free thyroid hormones and response of TSH to TRH in nonthyroidal illnesses. *Nippon Naibunpi Gakkai Zasshi*. 1986; 62(11): 1231-43
88. De Marinis L, Mancini A, Masala R, Torlontano M, Sandric S, Barbarino A. Evaluation of pituitary-thyroid axis response to acute myocardial infarct. *J Endocrinol Invest*. 1985; 8(6): 519-22
89. Rondanelli M, Solerte SG, Fioravanti M, Scevola K, et al. Circadian secretory pattern of growth hormone, insulin-like growth factor type I, cortisol, adrenocorticotrophic hormone, thyroid-stimulating hormone, and prolactin during HIV infection. *AIDS Res Hum Retroviruses*. 1997; 13(14): 1243-9.
90. Wintemitz WW, Dzur JA. Pituitary failure secondary to head trauma. Case report. *J Neurosurg*. 1976; 44(4): 504-5
91. Dzur JA, Wintemitz WW. Posttraumatic hypopituitarism: Anterior pituitary insufficiency secondary to head trauma. *South Med J*. 1976; 69(10): 1377-9
92. Modigliani E, Periac P, Perret G, Hugues JN, Coste T. TRH response in 53 patients with chronic alcoholism. *Ann Med Interne Paris*. 1979; 130(5):297-302
93. Ekman AC, Vakkuri O, Ekman M, Leppalusto J, Ruckonen A, Knip M. Ethanol decreases nocturnal plasma levels of thyrotropin and growth hormone but not those of thyroid hormones or protection in man. *J Clin Endocrinol Metab*. 1996; 81(7):2627-32
94. Bacci V, Schussler GC, Kaplan TB. The relationship between serum triiodothyronine and thyrotropin during systemic illness. *J Clin Endocrinol Metab*. 1982; 54:1229-35
95. Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV, Topliss DJ, Stockigt JR. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. *J Clin Endocrinol Metab*. 1986 Apr;62(4):717-22
96. Bermudez F, Sucks MI, Opperheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. *J Clin Endocrinol Metab*. 1975; 41: 27-40.

Medications: *thyroid therapy, estroprogestative birth control pills, progestogens, anti-inflammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptics, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF-1, somatostatin, etc.*

97. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. *J Clin Endocrinol Metab*. 1994;78(6):1368-71
98. Gow SM, Caldwell G, Toft AD, Seth J, Hussey AJ, Sweeting VM, Beckett GJ. Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. *J Clin Endocrinol Metab*. 1987;64(2):364-70
99. Custro N, Scafidi V, Costanzo G, Corsello FP. Variations in the serum levels of thyroid hormones and TSH after intake of a dose of L-thyroxine in euthyroid subjects and in adequately treated hypothyroid patients. *Bull Soc Ital Biol Sper*. 1989; 65(11):1045-52
100. England ML, Hershman JM. Serum TSH concentration as an aid to monitoring compliance with thyroid hormone therapy in hypothyroidism. *Am J Med Sci*. 1986 Nov;292(5):264-6
101. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. *Endocrinology*. 1978; 103(2): 393-402
102. Fraser WD, Biggart EM, O'Reilly DS, Gray HW, McKillop JH, Thomson JA. Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement? *Br Med J (Clin Res Ed)*. 1986 Sep 27;293(6550): 293-808

103. Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab.* 1981 Dec;53(6):1238-42
104. Saberi M, Utiger RD. Serum thyroid hormone and thyrotropin concentrations during thyroxine and triiodothyronine therapy. *J Clin Endocrinol Metabol.* 1974;39:923-7
105. Rey Stocker I, Zufferey MM, Lemarchand MT, Rais M. The sensibility of the hypophysis, the gonads and the thyroid before and after the administration of oral contraceptives. A resume. *Pediatr Ann.* 1981;10(12):15-20.
106. Lemarchand-Beraud T. Influence of estrogens on pituitary responsiveness to LHRH and TRH in human. Reymond M, Berthier C. *Ann Endocrinol Paris.* 1977; 38(6): 379-82.
107. El-Etreby MF, Graf KJ, Gunzel P, Neumann F. Evaluation of effects of sexual steroids on the hypothalamic-pituitary system of animals and man. *Arch Toxicol Suppl.* 1979;2:11-39
108. Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von Zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathological conditions. *Horm Metab Res Suppl.* 1990; 23:12-7
78. 59.Re RN, Kourides IA, Ridgeway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. *J Clin Endocrinol Metab.* 1976; 43:338-46.
109. Atterwill CK, Catto LC, Heal DJ, Holland CW, Dickens TA, Jones CA. The effects of desipramine (DMI) and electroconvulsive shock (ECS) on the function of the hypothalamo-pituitary-thyroid axis in the rat. *Psychoneuroendocrinology.* 1989;14(5):339-46
110. Kaptein EM, Kletzsky OA, Spencer CA, Nicoloff JT. Effects of prolonged dopamine infusion on anterior pituitary function in normal males. *J Clin Endocrinol Metab* 1980; 51:488-91
111. Samuels MH, Kramer P, Wilson D, Sexton F. Effect of naloxone infusions on pulsatile thyrotropin secretion. *J Clin Endocrinol Metab.* 1994;78(5):129-32.
112. Burger A, Nicod DP, Lemarchand-Beraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxine and thyrotropin. *J Clin Invest* 1976; 58: 255-9
113. Davis PJ, Davis FB, Utiger RD, Kulaga SF Jr. Changes in serum thyrotropin (TSH) in man during halofenate administration. *J Clin Endocrinol Metab* 1976; 43(4): 873-81
114. Trainer PI, Holly 1, Medbak S, Rais LH, Besser GM. The effect of recombinant IGF-1 on anterior pituitary function in healthy volunteers. *Clin Endocrinol (Chif)* 1994; 41(6): 801-7.

Toxic foods: *MSG, alcohol*

115. Bakke JL, Lawrence N, Bennett J, Robinson S, Bowers CY. Late endocrine effects of administering monosodium glutamate to neonatal rats. *Neuroendocrinology* 1978; 26(4): 220-8.
116. Greeley GH Jr, Nicholson GF, Kizer JS. A delayed LH/FSH rise after gonadectomy and a delayed serum TSH rise after thyroidectomy in monosodium-L-glutamate (MSG)-treated rats. *Brain Res* 1980; 195(1):111-22
117. Modigliani E, Periac P, Perret G, Hugues JN, Coste T. TRH response in 53 patients with chronic alcoholism. *Ann Med Interne Paris.* 1979; 130(5): 297-302

Thyroid diseases: *hyperthyroidism, Graves-Basedow disease, nodular goiter, thyroiditis, secondary or tertiary hypothyroidism, congenital hypothyroidism*

118. Spencer CA, Lai-Rosenfeld AO, Guttler RB, LoPresti J, Marcus AO, Nimalasuriya A, Eigen A, Doss RC, Green BJ, Nicoloff JT. Thyrotropin secretion in thyrotoxic and thyroxine-treated patients: assessment by a sensitive immunoenzymometric assay. *J Clin Endocrinol Metab.* 1986 Aug;63(2):349-55
119. Yeo PP, Loh KC. Subclinical thyrotoxicosis. *Adv Intern Med.* 1998; 43: 501-32
120. Chanson P. Insuffisance thyrotropic. *Rev Prat.* 1998 15; 48(18): 2023-6
121. Petersen PH, Rosleff, Rasmussen J, Hobolth N. Studies on the required analytical quality of TSH measurements in screening for congenital hypothyroidism. *Scand J Clin Lab Invest Suppl.* 1980;155: 5-93.
122. Fofanova OV, Takamura N, Kinoshita E, Yoshimoto M, Tsuji Y, Peterkova VA, Evgrafov OV, Dedov II, Goncharov NP, Yamashita S. Rarity of PIT1 involvement in children from Russia with combined pituitary hormone deficiency. *Am J Med Genet* 1998; 77(5): 360-5.

FACTORS that ELEVATE the serum TSH

Neonatus, stress - emotional arousal, cold exposure, sleep deprivation, adrenal insufficiency, recovery from severe illness, congenital malformations

123. Hashimoto H, Sato F, Kubo M, Ohki T. Maturation of the pituitary-thyroid axis during the perinatal period. *Endocrinol Jpn* 1991;38(2):151-7
124. Gendrel D, Feinstein MC, Grenier J, Roger M, Ingrand J, Chaussain JL, Canlorbe P, Job JC. Falsely elevated serum thyrotropin (TSH) in newborn infants: Transfer from mothers to infants of a factor interfering in the TSH radioimmunoassay. *J Clin Endocrinol Metab* 1981;52(1):62-5.
125. Armario A, Lopez Calderon A, Jolin T, Castellanos JM. Sensitivity of anterior pituitary hormones to graded levels of psychological stress. *Life Sci* 1986; 39(5): 471-5
126. Reed HL, Silverman ED, Shakir KM, Dons R, Burman KD, O'Brian JT. Changes in serum triiodothyronine (T₃) kinetics after prolonged Antarctic residence: The polar T₃ syndrome. *J Clin Endocrinol Metab*. 1990; 70(4): 965-74
127. Sadamatsu M, Kato N, Iida H, Takahashi S, Sakaue K, Takahashi K, Hashida S, Ishikawa E. The 24-hour rhythms in plasma growth hormone, prolactin and thyroid stimulating hormone: effect of sleep deprivation. *J Neuroendocrinol*. 1995 Aug;7(8):597-606
128. Sjoberg S, Wemer S. Increased level of TSH can be a sign of adrenal cortex failures: Not necessarily of thyroid gland disease. *Lakartidningen* 1999; 96(5):464-5
129. De Nayer P, Dozin B, Vandeput Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyronine and its nuclear receptors in absence of cortisol: A proposed mechanism for increased thyrotropin secretion in corticoid deficiency states. *Eur J Clin Invest*. 1987 Apr;17(2):106-8
130. Oakley GA, Muir T, Ray M, Girdwood RW, Kennedy R, Donaldson MD. Increased incidence of congenital malformations in children with transient thyroid-stimulating hormonal elevation on neonatal screening. *J Pediatr*. 1998; 132(4): 573-4

Medications: iodine, antithyroidea, , lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sulfapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestographic agents, etc.

131. Devos P. Rationele keuze van schildklierfunctie tests. *Tijdschr Geneesk*. 1990;46(8):591-9
132. Kleinmann RE, Vagenakis AG, Braverman LE. The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. *J Clin Endocrinol Metab*. 1980;51(2): 399-403
133. Mc Caven KC, Garber JR, Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med*. 1997; 337(14):1010-1
134. Brown CG, Harland RE, Major IR, Atterwill CK. Effects of toxic doses of a novel histamine (H₂) antagonist on the rat thyroid gland. *Food Chem Toxicol*. 1987; 25(10):787-94

Auto-immune thyroiditis and hypothyroidism: primary, iodine-deficient, thyroid hormone resistance

135. Devos P. Rationele keuze van schildklierfunctie tests. *Tijdschr Geneesk*. 1990;46(8): 591-9
136. Missler U, Gutekunst R, Wood WG. Thyroglobulin is a more sensitive indicator of iodine deficiency than thyrotropin: Development and evaluation of dry blood spot assays for thyrotropin and thyroglobulin in iodine- deficient geographical areas. *Eur J Clin Chem Clin Biochem* 1994; 32(3): 137-43
87. Volpe R. Subacute (de Quervain's) thyroiditis. *J Clin Endocrinol Metab*. 1979 Mar;8(1):81-95
88. Massoudi MS, Meilahn EN, Orchard TJ, Foley TP Jr, Kuller LH, Costantino JP, Buhari AM. Thyroid function and perimenopausal lipid and weight changes: the Thyroid Study in Healthy Women (TSH-W). *J Womens Health*. 1997 Oct;6(5):553-8
89. Smallridge RC, Parker RA, Wiggs EA, Rajagopal KR, Fein HG. Thyroid hormone resistance in a large kindred: physiologic, biochemical, pharmacologic, and neuropsychologic studies. *Am J Med*. 1989 Mar;86(3):289-96

TSH-secreting tumors (rare)

90. Smallridge RC. Thyrotropin-secreting pituitary tumors, *Endocrinol Metab Clin North Am* 1987 Sep;16(3):765-92

FACTORS that ELEVATE or DEPRESS serum TSH

Physiological serum TSH fluctuations

91. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B, Feistner H, Hesch RD, von zur Muhlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. *J Clin Endocrinol Metab.* 1990 Feb;70(2):403-9
92. Brabant G, Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathophysiological conditions. *Horm Metab Res Suppl.* 1990;23:12-7
93. Goichot B, Brandenberger G, Schlienger JL. Secretion of thyrotropin during states of wakefulness and sleep. Physiological data and clinical applications. *Presse Med.* 1996;25(21):980-4
94. Rao ML, Gross G, Strebel B, Halaris A, Huber G, Braunig P, Marler M. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. *Biol Psychiatry.* 1994;1:35(3): 151-63
95. Rose SR, Nisula BC. Circadian variation of thyrotropin in childhood. *J Clin Endocrinol Metab.* 1989; 68(6):1086-90
96. Scanlon MF, Weetman AP, Lewis M, Pourmand M, Rodriguez Arnao MD, Weightman DR, Hall R. Dopaminergic modulation of circadian thyrotropin rhythms and thyroid hormone levels in euthyroid subjects. *J Clin Endocrinol Metab.* 1980 Dec;51(6):1251-6
97. Rom Bugoslavskaja ES, Shcherbakova VS. Seasonal characteristics of the effect of melatonin on thyroid function. *Bull Eksp Biol Med.* 1986;101(3):268-9

Variations in the biological activity of TSH

98. Beck-Peccoz P, Persani L. Variable biological activity of thyroid stimulating hormone. *Eur J Endocrinol.* 1994 Oct;131(4):331-40
99. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, De Meyer F, Scharpe S. Components of biological variation of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. *Clin Endocrinol (Oxf).* 1997 May;46(5):587-98
100. Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'-triiodo-thyronine response to TSH and in vitro bioactivity of TSH. *J Clin Endocrinol Metab.* 1995 Apr;80(4):1124-8

TSH test kit imperfections

101. Rasmussen AK, Hilsted L, Perrild H, Christiansen E, Siersbaek-Nielsen K, Feldt-Rasmussen U. Discrepancies between thyrotropin (TSH) measurement by four sensitive immunometric assays. *Clin Chim Acta*. 1997 Mar 18;259(1-2):117-28
102. Libeer JC, Simonet L, Gillet R. Analytical evaluation of twenty assays for determination of thyrotropin (TSH). *Ann Biol Clin Paris*. 1989; 47(1): 1-11
103. Spencer CA, Takeuchi M, Kazarosyan M, MacKenzie F, Beckett GJ, Wilkinson E. Interlaboratory/intermethod differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. *Clin Chem*. 1995 Mar;41(3):367-74
104. Faber J, Gam A, Siersbaek Nielsen K. Improved sensitivity of serum thyrotropin measurements: Studies on serum sex hormone-binding globulin in patients with reduced serum thyrotropin. *Acta Endocrinol Copenh* 1990; 123(5): 535-40
105. Laurberg P. Persistent problems with the specificity of immunometric TSH assays. *Thyroid*. 1993 Winter;3(4):279-83
106. Schlienger JL, Sapin R, Grunenberger F, Gasser F, Pradignac A. Thyrotropin assay by chemiluminescence in the diagnosis of dysthyroidism with low thyrotropin and normal thyroid hormones levels. *Pathol Biol Paris*. 1993; 41(5): 463-8
107. Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem*. 1987 Aug;33(8):1391-6
108. Spencer CA, Challand GS. Interference in a radioimmunoassay for human thyrotropin. *Clin Chem* 1977;23(3): 584-8
109. Kahn BB, Weintraub BD, Csako G, Zweig MH. Factitious elevation of thyrotropin in a new ultra-sensitive assay: Implications for the use of monoclonal antibodies in 'sandwich' immuno-assay. *J Clin Endocrinol Metab*. 1988 Mar;66(3):526-33
110. Kourides IA, Weintraub BD, Martorana MAL, Maloof F. Alpha subunit contamination of human albumin preparations: Interference in radioimmunoassay. *J Clin Endocrinol Metab*. 1976; 43(4): 919-23
111. Bartlett WA, Browning MC, Jung RT. Artefactual increase in serum thyrotropin concentration caused by heterophilic antibodies with specificity for IgG of the family Bouidea. *Clin Chem*. 1986; 32(12): 22(4-9)
112. Csako G, Weintraub BD, Zweig MH. The potency of immunoglobulin antibodies in a monoclonal immunoradiometric assay for thyrotropin. *Clin Chem*. 1988 Jul;34(7):1481-3
113. Seghers J, Schruers F, De Nayer P, Beckers C. Interference in thyrotropin (TSH) determination: Falsely elevated TSH values in a transplanted patient. *Eur J Nucl Med*. 1989; 15(4): 194-6
114. Spencer C, Eigen A, Shen D, Duda M, Quails S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem*. 1987;33(8):1391-6
115. Ealey PA, Marshall NJ, Ekins RP. Time-related thyroid stimulation by thyrotropin and thyroid-stimulating antibodies, as measured by the cytochemical section bioassay. *J Clin Endocrinol Metab*. 1981;52(3): 483-7

Doubts on the adequateness of measuring the serum TSH as a help to monitor a thyroid treatment (follow-up)

The serum TSH test for follow-up: The risk of misinterpretation increases when monitoring the treatment of hyper- or hypothyroidism

116. Talbot JN, Duron F, Feron R, Aubert P, Milhaud G. Thyroglobulin, thyrotropin and thyrotropin binding inhibiting immunoglobulins assayed at the withdrawal of antithyroid drug therapy as predictors of relapse of Graves' disease within one year. *J Endocrinol Invest.* 1989; 12(9): 589-95

In 36-47 % of cinically euthyroid patients receiving adequate long-term thyroid therapy for hypothyroidism, an undetectable serum TSH is found

117. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. *J Clin Endocrinol Metab* 1994; 78(6): 1368-71
118. Gow SM, Caldwell G, Toft AD, Seth J, Hussey AJ, Sweeting VM, Beckett GJ. Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. *J Clin Endocrinol Metab.* 1987; 64(2): 364-70

After intake of thyroidhormones, the serum TSH is transitorily depressed within 60 minutes and remains low for up to 9 hours after intake

119. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3',5'-triiodothyronine (rT3), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. *Endocrinology.* 1978;103(2):393-402

Some patents who exhibit reversion of an initially high TSH level back into the reference range, are found to subsequently develop mild thyroid failure

120. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trichitta V, Tassi V, Sava L, Vigneri R. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. *J Clin Endocrinol Metab.* 2002;87:3209–14

Supporters of the recommendations of the consensus panel promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy, whereas they refuse to accept TSH levels of 3–10 mU/liter as abnormal in patients not receiving T4 therapy.

121. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid.* 2003 Jan;13(1):3-126

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies

122. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. *Thyroid.* 2003 Jan;13(1):3-126
123. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf).* 1991;34:77-83
124. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. *Thyroid.* 2004;14:853–7
125. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:526–34

126. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991;151:165–8
127. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT. Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8
128. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5

Other tests : urinary T3 as a complementary test

129. Baisier W, Hertoghe J, Eeckhaut W. Thyroid insufficiency Is TSH measurement the only diagnostic tool? J Nutr Environm Med. 2000; 10(3): 109-113

Testosterone in men

Senescence is associated with a decline of the pituitary-testosterone axis in men

Senescence in men is associated with a decline in testosterone levels

1. Deslypere JP, Vermeulen A. Influence of age on steroid concentrations in skin and striated muscle in women and in cardiac muscle and lung tissue in men. *J Clin Endocrinol Metab.* 1985 Oct;61(4):648-53
2. Deslypere JP, Vermeulen A. Leydig cell function in normal men: effect of age, life-style, residence, diet, and activity. *J Clin Endocrinol Metab.* 1984 Nov;59(5):955-62
3. Morer-Fargas F, Nowakowski H. The urinary excretion of testosterone in males. *Acta endocrinol (Copenh).* 1965 Jul;49:443-52
4. Gapstur SM, Gann PH, Kopp P, Colangelo L, Longcope C, Liu K. Serum androgen concentrations in young men: a longitudinal analysis of associations with age, obesity, and race. The CARDIA male hormone study. *Cancer Epidemiol Biomarkers Prev.* 2002 Oct;11(10 Pt 1):1041-7
5. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab.* 2001 Feb;86(2):724-31 (*the incidence of (overt) hypogonadal testosterone levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 yr of age, and even greater percentages when free T index criteria were employed*)
6. Drafta D, Schindler AE, Stroe E, Neacsu E. Age-related changes of plasma steroids in normal adult males. *J Steroid Biochem.* 1982 Dec;17(6):683-7

The speed of age-related decline of serum testosterone in men

7. Vermeulen A. Plasma levels and secretion rate of steroids with anabolic activity in man. *Environ Qual Saf Suppl.* 1976;(5):171-80

Senescence in men is associated with a decline in metabolic clearance of testosterone

8. Wang C, Catlin DH, Starcevic B, Leung A, DiStefano E, Lucas G, Hull L, Swerdloff RS. Testosterone metabolic clearance and production rates determined by stable isotope dilution/tandem mass spectrometry in normal men: influence of ethnicity and age. *J Clin Endocrinol Metab.* 2004 Jun;89(6):2936-41
9. Baker HW, Burger HG, de Kretser DM, Hudson B, O'Connor S, Wang C, Mirovics A, Court J, Dunlop M, Rennie GC. Changes in the pituitary-testicular system with age. *Clin Endocrinol (Oxf).* 1976 Jul;5(4):349-72

Senescence in men is associated with alterations of the circadian cycle of serum testosterone levels: reduced amplitude and desynchronisation of its circadian rhythm

10. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab.* 1983 Jun;56(6):1278-81

The age-related decline of serum testosterone starts in middle age in men

11. Luboshitzky R, Shen-Orr Z, Herer P. Middle-aged men secrete less testosterone at night than young healthy men. *J Clin Endocrinol Metab.* 2003 Jul;88(7):3160-6

Senescence in men is associated with a loss of the circadian rhythm of serum testosterone

12. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadianrhythmicity in blood testosterone levels withme
13. aging in normal men. *J Clin Endocrinol Metab.* 1983;56:1278-81

Senescence in men is associated with an increased peripheral conversion of androgens into estrogens: the increased estrogen level in aging males may inhibit the androgen production

14. Drafta D, Schindler AE, Stroe E, Neacsu E. Age-related changes of plasma steroids in normal adult males. *J Steroid Biochem.* 1982 Dec;17(6):683-7 (*"The age related changes of plasma steroids in elderly men, were suggestive of decreased testicular function with increased*

peripheral conversion of androgens into estrogens. ... The negative correlation between estrone and 17-OH-P (precursor of testosterone) found in elderly men, suggested that increased estrogen level in aging males may be considered able to inhibit the testicular androgen production")

Testosterone treatment may oppose and testosterone deficiency may trigger several mechanisms of senescence in men

Excessive free radical formation: Testosterone has antioxidant activity

Testosterone and estrogens

15. Tam NN, Ghatak S, Ho SM. Sex hormone-induced alterations in the activities of antioxidant enzymes and lipid peroxidation status in the prostate of Noble rats. *Prostate*. 2003 Apr 1;55(1):1-8
16. Ahlbom E, Prins GS, Ceccatelli S. Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. *Brain Res*. 2001 Feb 23;892(2):255-62

Testosterone

17. Klinger W, Lupp A, Karge E, Baumbach H, Eichhorn F, Feix A, Fuldner F, Gernhardt S, Knels L, Kost B, Mertens G, Werner F, Oettel M, Romer W, Schwarz S, Elger W, Schneider B. Estradiol, testosterone, dehydroepiandrosterone and androstenedione: novel derivatives and enantiomers. Interactions with rat liver microsomal cytochrome P450 and antioxidant/radical scavenger activities in vitro. *Toxicol Lett*. 2002 Mar 10;128(1-3):129-44
18. Juliet PA, Hayashi T, Daigo S, Matsui-Hirai H, Miyazaki A, Fukatsu A, Funami J, Iguchi A, Ignarro LJ. Combined effect of testosterone and apocynin on nitric oxide and superoxide production in PMA-differentiated THP-1 cells. *Biochim Biophys Acta*. 2004 Sep 17;1693(3):185-91
19. Tam NN, Gao Y, Leung YK, Ho SM. Androgenic regulation of oxidative stress in the rat prostate: involvement of NAD(P)H oxidases and antioxidant defense machinery during prostatic involution and regrowth. *Am J Pathol*. 2003 Dec;163(6):2513-22

Glycation: Anabolic steroids exert a protective against advanced glycation end-products

20. Celec P, Jani P, Smrekova L, Mrljan A, Kudela M, Hodosy J, Boor P, Kristova V, Jakubovsky J, Jezova D, Halcak L, Bozek P, Slamova J, Ulicna O, Hojsik D, Jurkovicova I. Effects of anabolic steroids and antioxidant vitamins on ethanol-induced tissue injury. *Life Sci*. 2003 Dec 12;74(4):419-34

Imbalanced apoptosis: Testosterone enhances the apoptosis of cancer cells induced by an antioxidant

21. Gunawardena K, Murray DK, Meikle AW. Testosterone is a potential augmentor of antioxidant-induced apoptosis in human prostate cancer cells. *Cancer Detect Prev*. 2002;26(2):105-13

Immune deficiency: Testosterone and dihydrotestosterone may improve the immune resistance in certain conditions

Testosterone

30. Alevizaki M, Cimponeriu AT, Garofallaki M, Sarika HL, Alevizaki CC, Papamichael C, Philippou G, Anastasiou EA, Lekakis JP, Mavrikakis M. The androgen receptor gene CAG polymorphism is associated with the severity of coronary artery disease in men. *Clin Endocrinol (Oxf)*. 2003 Dec;59(6):749-55
22. Jung-Testas I, Baulieu EE. Effects of steroid hormones and antihormones in cultured cells. *Exp Clin Endocrinol*. 1985 Dec;86(2):151-64

Dihydrotestosterone

23. Coletta RD, Reynolds MA, Martelli-Junior H, Graner E, Almeida OP, Sauk JJ. Testosterone stimulates proliferation and inhibits interleukin-6 production of normal and hereditary gingival fibromatosis fibroblasts. *Oral Microbiol Immunol*. 2002 Jun;17(3):186-92

Testosterone and psychic well-being in men

Quality of life and fatigue in men: the association with lower testosterone

24. Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L, Callegari C, Swerdloff RS. Testosterone replacement therapy improves mood in hypogonadal men - a clinical research center study. *J Clin Endocrinol Metab.* 1996 Oct;81(10):3578-83
25. Seidman SN, Araujo AB, Roose SP, Devanand DP, Xie S, Cooper TB, McKinlay JB. Low testosterone levels in elderly men with dysthymic disorder. *Am J Psychiatry.* 2002 Mar;159(3):456-9
26. Salminen E, Portin R, Korpela J, Backman H, Parvinen LM, Helenius H, Nurmi M. Androgen deprivation and cognition in prostate cancer. *Br J Cancer.* 2003 Sep 15;89(6):971-6
27. van Andel G, Kurth KH. The impact of androgen deprivation therapy on health related quality of life in asymptomatic men with lymph node positive prostate cancer. *Eur Urol.* 2003 Aug;44(2):209-14
28. Pether M, Goldenberg SL, Bhagirath K, Gleave M. Intermittent androgen suppression in prostate cancer: an update of the Vancouver experience. *Can J Urol.* 2003 Apr;10(2):1809-14
29. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, Venner PM, Quinney HA, Jones LW, D'Angelo ME, Wells GA. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 2003 May 1;21(9):1653-9
30. Potosky AL, Reeve BB, Clegg LX, Hoffman RM, Stephenson RA, Albertsen PC, Gilliland FD, Stanford JL. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. *J Natl Cancer Inst.* 2002 Mar 20;94(6):430-7
31. Fowler FJ Jr, McNaughton Collins M, Walker Corkery E, Elliott DB, Barry MJ. The impact of androgen deprivation on quality of life after radical prostatectomy for prostate carcinoma. *Cancer.* 2002 Jul 15;95(2):287-95
32. Lubeck DP, Grossfeld GD, Carroll PR. The effect of androgen deprivation therapy on health-related quality of life in men with prostate cancer. *Urology.* 2001 Aug;58(2 Suppl 1):94-100
33. Herr HW, O'Sullivan M. Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol.* 2000 Jun;163(6):1743-6
34. van Kemenade JF, Cohen-Kettenis PT, Cohen L, Gooren LJ. Effects of the pure antiandrogen RU 23.903 (anandron) on sexuality, aggression, and mood in male-to-female transsexuals. *Arch Sex Behav.* 1989 Jun;18(3):217-28
35. Novak A, Brod M, Elbers J. Andropause and quality of life: findings from patient focus groups and clinical experts. *Maturitas.* 2002 Dec 10;43(4):231-7

Lower quality of life and fatigue in men: the improvement with testosterone treatment

36. Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clin Endocrinol (Oxf)* 1997 Dec;47(6):727-37
37. Park NC, Yan BQ, Chung JM, Lee KM. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. *Aging Male.* 2003 Jun;6(2):86-93
38. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation.* 2000 Oct 17;102(16):1906-11
39. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry.* 2000 Feb;57(2):141-7
40. Rabkin JG, Wagner GJ, Rabkin R. Testosterone therapy for human immunodeficiency virus-positive men with and without hypogonadism. *J Clin Psychopharmacol.* 1999 Feb;19(1):19-27
41. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. *J Clin Psychopharmacol.* 2004 Aug;24(4):379-85
42. O'Connor DB, Archer J, Hair WM, Wu FC. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. *Physiol Behav.* 2002 Apr 1;75(4):557-66

43. Rozenek R, Rahe CH, Kohl HH, Marple DN, Wilson GD, Stone MH. Physiological responses to resistance-exercise in athletes self-administering anabolic steroids. *J Sports Med Phys Fitness*. 1990 Dec;30(4):354-60.
44. Wagner GJ, Rabkin JG, Rabkin R. Testosterone as a treatment for fatigue in HIV+ men. *Gen Hosp Psychiatry*. 1998 Jul;20(4):209-13
45. Wagner G, Rabkin J, Rabkin R. Exercise as a mediator of psychological and nutritional effects of testosterone therapy in HIV+ men. *Med Sci Sports Exerc*. 1998 Jun;30(6):811-7
46. Okun MS, McDonald WM, DeLong MR. Refractory nonmotor symptoms in male patients with Parkinson disease due to testosterone deficiency: a common unrecognized comorbidity. *Arch Neurol*. 2002 May;59(5):807-11
47. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab*. 2003 Jul;88(7):3167-76
48. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parلمان K, Anderson E, Basgoz N, Klibanski A. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998 Jul 1;129(1):18-26
49. Howell SJ, Radford JA, Adams JE, Smets EM, Warburton R, Shalet SM. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. *Clin Endocrinol (Oxf)*. 2001 Sep;55(3):315-24
50. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc*. 2003 Jan;51(1):101-15
51. van Basten JP, van Driel MF, Jonker-Pool G, Sleijfer DT, Schraffordt Koops H, van de Wiel HB, Hoekstra HJ. Sexual functioning in testosterone-supplemented patients treated for bilateral testicular cancer. *Br J Urol*. 1997 Mar;79(3):461-7

Depression in men: the association with lower testosterone levels

52. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 1999 Feb;84(2):573-7
53. Werner AA. The male climacteric *JAMA*. 1946; 132 (4):188-94
54. Steiger A, von Bardeleben U, Wiedemann K, Holsboer F. Sleep EEG and nocturnal secretion of testosterone and cortisol in patients with major endogenous depression during acute phase and after remission. *J Psychiatr Res*. 1991;25(4):169-77
55. 3Unden F, Ljunggren JG, Beck-Friis J, Kjellman BF, Wetterberg L. Hypothalamic-pituitary-gonadal axis in major depressive disorders. *Acta Psychiatr Scand* 1988 Aug;78(2):138-46
56. Shores MM, MD; Sloan KL, Matsumoto AM, Mocerri VM, Felker B, Kivlahan D. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry*. 2004;61:162-7
57. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab*. 2000 Jan;85(1):60-5

Depression in men: the improvement with testosterone treatment

58. Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003 Jan;160(1):105-11
59. Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry*. 2000 Feb;57(2):141-7
60. Grinspoon S, Corcoran C, Stanley T, Baaj A, Basgoz N, Klibanski A. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. *J Clin Endocrinol Metab*. 2000 Jan;85(1):60-5
61. Schmitz G. Erfahrungen mit dem neuen synthetischen testes-hormon-preparat "Perandren." *Deutsche Medizinische Wochenschrift*. 1937; 63:230–1
62. Davidoff E, Goodstone GL. Use of testosterone propionate in treatment of involuntal psychosis in the male. *Arch Neurol Psychiatry*. 1942; 48:811–7
63. Altschule MD, Tillotson KJ. The use of testosterone in the treatment of depression. *N Engl J Med*. 1948; 239:1036–8
64. Lamar CP. Clinical endocrinology of the male: with special reference to the male climacteric. *J Fla Med Assoc*. 1940; 26:398–404
65. O'Carroll R, Shapiro C, Bancroft J. Androgens, behavior and nocturnal erection in hypogonadal men: the effects of varying the replacement dose. *Clin Endocrinol*. 1985; 23:527–538
66. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double-blind controlled study. *Clin Endocrinol*. 1981; 14:49–61
67. Rabkin JG, Rabkin R, Wagner G: Testosterone replacement therapy in HIV illness. *Gen Hosp Psychiatry* 1995;17:37–47
68. Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, Channer KS. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*. 2004 Aug;90(8):871-6.

Anxiety in men: the association with lower testosterone levels

69. Werner AA. The male climacteric *JAMA*. 1946;132(4):188-94
70. Diamond P, Brisson GR, Candas B, Peronnet F. Trait anxiety, submaximal physical exercise and blood androgens. *Eur J Appl Physiol Occup Physiol*. 1989;58(7):699-704

Anxiety in men: the improvement with testosterone treatment

71. Cooper MA, Ritchie EC. Testosterone replacement therapy for anxiety. *Am J Psychiatry*. 2000 Nov;157(11):1884
72. Aikey JL, Nyby JG, Anmuth DM, James PJ. Testosterone rapidly reduces anxiety in male house mice (*Mus musculus*). *Horm Behav*. 2002 Dec;42(4):448-60

Memory loss and Alzheimer's disease levels in men: the association with lower testosterone

73. Tan RS. Memory loss as a reported symptom of andropause. *Arch Androl* 2001 Nov-Dec;47(3):185-9
74. Tan RS, Pu SJ. The andropause and memory loss: is there a link between androgen decline and dementia in the aging male? *Asian J Androl*. 2001 Sep;3(3):169-74
75. Alexander GM, Swerdloff RS, Wang C, Davidson T, McDonald V, Steiner B, Hines M. Androgen-behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Horm Behav*. 1998 Apr;33(2):85-94
76. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004 Sep;29(8):1071-81
77. Morley JE, Kaiser F, Raum WJ, Perry HM 3rd, Flood JF, Jensen J, Silver AJ, Roberts E. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci U S A*. 1997 Jul 8;94(14):7537-42
78. Hogervorst E, Williams J, Budge M, Barnetson L, Combrinck M, Smith AD. Serum total testosterone is lower in men with Alzheimer's disease. *Neuro Endocrinol Lett*. 2001 Jun;22(3):163-8

79. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, Iguchi T, Katagiri T. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. *Metabolism*. 2004 Apr;53(4):476-82
80. Gouchie C, Kimura D: The relationship between testosterone levels and cognitive ability patterns. *Psychoneuroendocrinology* 1991; 16:323–34

Memory loss and Alzheimer's disease in men: the improvement with testosterone treatment

81. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, Raskind MA, Brodtkin K, Bremner W, Petrova A, LaTendresse S, Craft S. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001 Jul 10;57(1):80-8
82. Janowsky JS, Oviatt SK, Orwoll ES: Testosterone influences spatial cognition in older men. *Behav Neurosci* 1994; 108:325–32

Sleep disorder in men: the improvement with testosterone treatment

83. Davis A, Gilbert K, Misiowiec P, Riegel B. Perceived effects of testosterone replacement therapy in perimenopausal and postmenopausal women: an internet pilot study. *Health Care Women Int*. 2003 Nov;24(9):831-48

Loss of sexual drive, sensitivity and/or potency in men: the association with lower testosterone levels

84. Jannini EA, Scroponi E, Carosa E, Pepe M, Lo Giudice F, Trimarchi F, Benvenega S. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *Int J Androl*. 1999 Dec;22(6):385-92
85. Rakic Z, Starcevic V, Starcevic VP, Marinkovic J. Testosterone treatment in men with erectile disorder and low levels of total testosterone in serum. *Arch Sex Behav*. 1997 Oct;26(5):495-504
86. Guay AT. Decreased testosterone in regularly menstruating women with decreased libido: a clinical observation. *J Sex Marital Ther*. 2001;27(5):513-9
87. Persky H, Lief HI, Strauss D, Miller WR, O'Brien CP. Plasma testosterone level and sexual behavior of couples. *Arch Sex Behav*. 1978 May;7(3):157-73
88. Aversa A, Isidori AM, De Martino MU, Caprio M, Fabbri E, Rocchietti-March M, Frajese G, Fabbri A. Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. *Clin Endocrinol (Oxf)*. 2000 Oct;53(4):517-22
89. Younes AK. Low plasma testosterone in varicocele patients with impotence and male infertility. *Arch Androl*. 2000 Nov-Dec;45(3):187-95
90. Hirshkowitz M, Moore CA, O'Connor S, Bellamy M, Cunningham GR. Androgen and sleep-related erections. *J Psychosom Res*. 1997 Jun;42(6):541-6
91. Hwang TI, Yang CR, Chang CL, Chang CH, Wu HC, Hwang YF. Hormonal screening in impotent patients. *J Formos Med Assoc*. 1991 Jun;90(6):560-4

Loss of sexual drive, sensitivity and/or potency in men: the improvement with testosterone treatment

92. Wang C, Swedloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab*. 2000 Aug;85(8):2839-53
93. Matsumoto AM, Weber T, Berman N. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab*. 2000 Aug;85(8):2839-53
94. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000 Aug;164(2):371-5
95. McClellan KJ, Goa KL. Transdermal testosterone. *Drugs* 1998 Feb;55(2):253-8
96. Hwang TI, Yang CR, Chang CL, Chang CH, Wu HC, Hwang YF. Hormonal screening in impotent patients. *J Formos Med Assoc*. 1991 Jun;90(6):560-4

Fertility:

Loss of fertility in men: the improvement with androgen treatment

97. Ros A. Our experience with mesterolone therapy. Evaluation of 22 hormonal steroids constituting the gas chromatographic picture in the total neutral urinary fraction. The effectiveness of mesterolone in the therapy of oligoasthenospermias. *Attual Ostet Ginecol.* 1969;15:37-53

Testosterone and physical appearance/body composition

Sarcopenia in men: the association with low testosterone levels

98. Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard J, Katznelson L, Walsh M, Guccione A, Cannan J, Heller H, Basgoz N, Klibanski A. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab.* 1996 Nov;81(11):4051-8

Reduced muscle strength development with exercise in men: the association with low testosterone levels

99. Hansen L, Bangsbo J, Twisk J, Klausen K.. Development of muscle strength in relation to training level and testosterone in young male soccer players. *J Appl Physiol.* 1999 Sep;87(3):1141-7

Sarcopenia in men: the improvement with testosterone treatment

100. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men--a clinical research center study. *J Clin Endocrinol Metab.* 1996 Oct;81(10):3469-75
101. Zachwieja JJ, Smith SR, Lovejoy JC, Rood JC, Windhauser MM, Bray GA. Testosterone administration preserves protein balance but not muscle strength during 28 days of bed rest. *J Clin Endocrinol Metab.* 1999 Jan;84(1):207-12
102. Urban RJ, Bodenbun YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol.* 1995 Nov;269(5 Pt 1):E820-6
103. Griggs RC, Kingston W, Jozefowicz RF, Herr BE, Forbes G, Halliday D. Effect of testosterone on muscle mass and muscle protein synthesis. *J Appl Physiol.* 1989 Jan;66(1):498-503
104. Griggs RC, Halliday D, Kingston W, Moxley RT 3rd. Effect of testosterone on muscle protein synthesis in myotonic dystrophy. *Ann Neurol.* 1986 Nov;20(5):590-6
105. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, Lee WP, Bunnell TJ, Casaburi R. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J Clin Endocrinol Metab.* 1997 Feb;82(2):407-13.

Lean body mass in men: the association with lower testosterone levels

106. Mauras N, Hayes V, Welch S, Rini A, Helgeson K, Dokler M, Veldhuis JD, Urban RJ. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab.* 1998 Jun;83(6):1886-92
107. Bhasin S, Tenover JS. Age-associated sarcopenia--issues in the use of testosterone as an anabolic agent in older men. *J Clin Endocrinol Metab.* 1997 Jun;82(6):1659-60.

Lean body mass in men: the improvement with testosterone treatment

108. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men - a clinical research center study. *J Clin Endocrinol Metab.* 1996 Oct;81(10):3469-75
109. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab.* 2001 Dec;281(6):E1172-81
110. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N; Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab.* 2000 Aug;85(8):2839-53

111. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab.* 2004 May;89(5):2085-98
112. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, Lee WP, Bunnell TJ, Casaburi R. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J Clin Endocrinol Metab.* 1997 Feb;82(2):407-13.
113. Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, Shen R, Arver S, Beall G. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab.* 1998 Sep;83(9):3155-62

Testosterone and age-related diseases in men

Hypercholesterolemia in men: the association with lower testosterone levels

114. Barrett-Connor E. Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. *Ann Intern Med.* 1992 Nov 15;117(10):807-11
115. Gutai J, LaPorte R, Kuller L, Dai W, Falvo-Gerard L, Caggiula A. Plasma testosterone, high density lipoprotein cholesterol and other lipoprotein fractions. *Am J Cardiol.* 1981 Nov;48(5):897-902
116. Khaw KT, Barrett-Connor E. Endogenous sex hormones, high density lipoprotein cholesterol, and other lipoprotein fractions in men. *Arterioscler Thromb.* 1991;11(3):489-94
117. Freedman DS, O'Brien TR, Flanders WD, DeStefano F, Barboriak JJ. Relation of serum testosterone levels to high density lipoprotein cholesterol and other characteristics in men. *Arterioscler Thromb.* 1991 Mar-Apr;11(2):307-15
118. Hamalainen E, Tikkanen H, Harkonen M, Naveri H, Adlercreutz H. Serum lipoproteins, sex hormones and sex hormone binding globulin in middle-aged men of different physical fitness and risk of coronary heart disease. *Atherosclerosis.* 1987 Oct;67(2-3):155-62

Hypercholesterolemia in men: the improvement with testosterone treatment

119. Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med.* 2001 Sep;111(4):261-9
120. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 1992 Oct;75(4):1092-8
121. Wu S, Weng X. Therapeutic effect of andriol on serum lipids and apolipoproteins in elderly male coronary heart disease patients. *Chin Med Sci J.* 1992 Sep;7(3):137-41

Atherosclerosis in men: the association with lower testosterone levels

122. Winkler UH. Effects of androgens on haemostasis. *Maturitas*. 1996 Jul;24(3):147-55
123. Glueck CJ, Glueck HI, Stroop D, Speirs J, Hamer T, Tracy T. Endogenous testosterone, fibrinolysis, and coronary heart disease risk in hyperlipidemic men. *J Lab Clin Med*. 1993 Oct;122(4):412-20
124. Bonithon-Kopp C, Scarabin PY, Bara L, Castanier M, Jacqueson A, Roger M. Relationship between sex hormones and haemostatic factors in healthy middle-aged men. *Atherosclerosis*. 1988 May;71(1):71-6
125. Bennet A, Caron P, Sie P, Louvet JP, Bazex J. Post-phlebotic leg ulcers and XYY karyotype: fibrinolysis and androgenic function tests. Apropos of 3 cases. *Ann Dermatol Venereol*. 1987;114(9):1097-101
126. Dockery F, Bulpitt CJ, Donaldson M, Fernandez S, Rajkumar C. The relationship between androgens and arterial stiffness in older men. *J Am Geriatr Soc*. 2003 Nov;51(11):1627-32.

Atherosclerosis in men: the improvement with testosterone treatment

127. Walker ID, Davidson JF, Young P, Conkie JA. Effect of anabolic steroids on plasma antithrombin III, alpha2 macroglobulin and alpha1 antitrypsin levels. *Thromb Diath Haemorrh*. 1975 Sep 30;34(1):106-14
128. Walker ID, Davidson JF, Young P, Conkie JA. Plasma fibrinolytic activity following oral anabolic steroid therapy. *Thromb Diath Haemorrh*. 1975 Sep 30;34(1):236-45
129. Klocking HP, Markwardt F, Hoffmann A. Animal experiments on the enhancement of fibrinolytic potential by anabolic steroids. *Biomed Biochim Acta*. 1984;43(4):501-7
130. Kluft C, Preston FE, Malia RG, Bertina RM, Wijngaards G, Greaves M, Verheijen JH, Dooijewaard G. Stanozolol-induced changes in fibrinolysis and coagulation in healthy adults. *Thromb Haemost*. 1984;51:157-64
131. Preston FE, Burakowski BK, Porter NR, Malia RG. The fibrinolytic response to stanozolol in normal subjects. *Thrombos Res*. 1981; 22 :543-57
132. Bhasin S. Effects of testosterone administration on fat distribution, insulin sensitivity, and atherosclerosis progression. *Clin Infect Dis*. 2003;37 Suppl 2:S142-9

Arterial hypertension in men: the association with lower testosterone levels

133. Hughes GS, Ringer TV, Watts KC, DeLoof MJ, Francom SF, Spillers CR. Fish oil produces an atherogenic lipid profile in hypertensive men. *Atherosclerosis*. 1990 Oct;84(2-3):229-37
134. Tuev AV, Lunegova NV. Several indicators of hormonal homeostasis (hypophysis - gonads) in patients with hypertension. *Russ Med Zh*. 1992;(3):10-3
135. Phillips GB, Jing TY, Resnick LM, Barbagallo M, Laragh JH, Sealey JE. Sex hormones and hemostatic risk factors for coronary heart disease in men with hypertension. *J Hypertens*. 1993 Jul;11(7):699-702

Arterial hypertension in men: the improvement with testosterone treatment

136. Shapiro J, Christiana J, Frishman WH. Testosterone and other anabolic steroids as cardiovascular drugs. *Am J Ther*. 1999 May;6(3):167-74

Coronary heart disease in men: the association with lower testosterone levels

137. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis*. 1996 Aug 23;125(1):1-13
138. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb*. 1994 May;14(5):701-6
139. Chearskul S, Charoenlarp K, Thongtang V, Nitiyanant W. Study of plasma hormones and lipids in healthy elderly Thais compared to patients with chronic diseases: diabetes mellitus, essential hypertension and coronary heart disease. *J Med Assoc Thai*. 2000 Mar;83(3):266-77

Coronary heart disease in men: the improvement with testosterone treatment

140. Wu SZ, Weng XZ. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chin Med J (Engl)*. 1993 Jun;106(6):415-8
141. Rosano GM, Leonardo F, Pagnotta P, Pelliccia F, Panina G, Cerquetani E, della Monica PL, Bonfigli B, Volpe M, Chierchia SL. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*. 1999 Apr 6;99(13):1666-70
142. Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, Channer KS. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*. 2004 Aug;90(8):871-6
143. Sigler LH, Tulgan J. Treatment of angina pectoris by testosterone propionate. *NY State J Med*. 1943;43:1424-8
144. Walker TC. The use of testosterone propionate and estrogenic substance in the treatment of essential hypertension, angina pectoris and peripheral vascular disease. *J Clin Endocrinol*. 1942;2:560-8
145. Hamm L. Testosterone propionate in the treatment of angina pectoris. *J Clin Endocrinol*. 1942;2:325-8
146. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. *J Clin Endocrinol*. 1946;6:549-57

Peripheral vascular disease (including intermittent claudication) in men: the improvement with testosterone treatment

147. Edwards E, Hamilton J, Duntley S. Testosterone propionate as a therapeutic agent in patients with organic disease of peripheral vessels. *N Engl J Med*. 1939;220:865-9
148. Levine S, Likoff W. The therapeutic value of testosterone propionate in angina pectoris. *N Engl J Med*. 1943;228:770-2

Stroke in men: the association with lower testosterone levels

149. Jeppesen LL, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS, Winther K. Decreased serum testosterone in men with acute ischemic stroke. *Arterioscler Thromb Vasc Biol*. 1996 Jun;16(6):749-54
150. Elwan O, Abdallah M, Issa I, Taher Y, el-Tamawy M. Hormonal changes in cerebral infarction in the young and elderly. *J Neurol Sci*. 1990 Sep;98(2-3):235-43
151. Dash RJ, Sethi BK, Nalini K, Singh S. Circulating testosterone in pure motor stroke. *Funct Neurol*. 1991 Jan-Mar;6(1):29-34

Stroke in men: the improvement with testosterone treatment

152. Pan Y, Zhang H, Acharya AB, Patrick PH, Oliver D, Morley JE. Effect of testosterone on functional recovery in a castrate male rat stroke model. *Brain Res*. 2005 May 10;1043(1-2):195-204
153. Department of Neurology, Saint Louis University Hospital, Saint Louis, MO 63110, USA. pany@slu.edu

Obesity in men: the association with lower testosterone levels

154. Tibblin G, Adlerberth A, Lindstedt G, Bjorntorp P. The pituitary-gonadal axis and health in elderly men: a study of men born in 1913. *Diabetes*. 1996 Nov;45(11):1605-9
155. [Abate N](#), [Haffner SM](#), [Garg A](#), [Peshock RM](#), [Grundy SM](#). Sex steroid hormones, upper body obesity, and insulin resistance. *J Clin Endocrinol Metab*. 2002 Oct;87(10):4522-7
156. Penotti M, Sironi L, Cannata L, Vigano P, Casini A, Gabrielli L, Vignali M. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. *Fertil Steril*. 2001 Aug;76(2):235-40

Obesity in men: the improvement with testosterone treatment

157. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male*. 2003 Mar;6(1):1-7
158. Marin P. Testosterone and regional fat distribution. *Obes Res*. 1995 Nov;3 Suppl 4:609S-12S
159. Rebuffe-Scrive M, Marin P, Bjorntorp P. Effect of testosterone on abdominal adipose tissue in men. *Int J Obes*. 1991;15(11):791-5

Diabetes in men: the association with lower testosterone levels

160. Andersson B, Marin P, Lissner L, Vermeulen A, Bjorntorp P. Testosterone concentrations in women and men with NIDDM. *Diabetes Care*. 1994 May;17(5):405-11
161. Goodman-Gruen D, Barrett-Connor E. Sex differences in the association of endogenous sex hormone levels and glucose tolerance status in older men and women. *Diabetes Care*. 2000 Jul;23(7):912-8
162. Corrales JJ, Burgo RM, Garca-Berrocá B, Almeida M, Alberca I, Gonzalez-Buitrago JM, Orfao A, Miralles JM. Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycemic control. *Metabolism*. 2004 May;53(5):666-72
163. Jansson PA, Eliasson B, Lindmark S, Eriksson JW. Endocrine abnormalities in healthy first-degree relatives of type 2 diabetes patients--potential role of steroid hormones and leptin in the development of insulin resistance. *Eur J Clin Invest*. 2002 Mar;32(3):172-8
- Pei D, Sheu WH, Jeng CY, Liao WK, Fuh MM. Insulin resistance in patients with Klinefelter's syndrome and idiopathic gonadotropin deficiency. *J Formos Med Assoc*. 1998 Aug;97(8):534-40

Diabetes in men: the improvement with testosterone treatment

164. Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, Lindstedt G, Bjorntorp P. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord*. 1992 Dec;16(12):991-7
165. Marin P, Krotkiewski M, Bjorntorp P. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. *Eur J Med* 1992 Oct;1(6):329-36
166. Simon JA, Mazer NA, Wekselman K. Safety profile: transdermal testosterone treatment of women after oophorectomy. *Obstet Gynecol*. 2001 Apr;97(4 Suppl 1):S10-S11

Rheumatism in men: the association with lower testosterone levels

167. Stafford L, Bleasel J, Giles A, Handelsman D. Androgen deficiency and bone mineral density in men with rheumatoid arthritis. *J Rheumatol*. 2000 Dec;27(12):2786-90
168. Tengstrand B, Carlstrom K, Hafstrom I. Bioavailable testosterone in men with rheumatoid arthritis-high frequency of hypogonadism. *Rheumatology (Oxford)*. 2002 Mar;41(3):285-9
169. Gordon D, Beastall GH, Thomson JA, Sturrock RD. Androgenic status and sexual function in males with rheumatoid arthritis and ankylosing spondylitis. *Q J Med*. 1986;60:671-9
170. Cutolo M, Balleari E, Giusti M, Monachesi M, Accardo S. Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. *Arthritis Rheum*. 1988;31:1314-7
171. Spector DT, Perry LA, Tubb G, Silman AJ, Huskisson EC. Low free testosterone levels in rheumatoid arthritis. *Ann Rheum Dis*. 1988;47:65-8
172. Spector TD, Ollier W, Perry LA, Silman AJ, Thomson PW, Edwards A. Free and serum testosterone levels in 276 males: A comparative study of rheumatoid arthritis, ankylosing spondylitis and healthy controls. *Clin Rheumatol* 1989;8:37-41
173. Cutolo M, Masi AT. Do androgens influence the pathophysiology of rheumatoid arthritis? Facts and hypothesis. Editorial. *J Rheumatol*. 1998;25:1041-7
174. Masi AT. Incidence of rheumatoid arthritis: do the observed age-sex interaction patterns support a role of androgen-anabolic steroid deficiency in its pathogenesis? *Br J Rheumatol*. 1994;33:697-70
175. Gordon D, Beastall GH, Thomson JA, Sturrock RD. Prolonged hypogonadism in male patients with rheumatoid arthritis during flares in disease activity. *Br J Rheumatol*. 1988;27:440-4
176. Hedman M, Nilsson E, de la Torre B. Low blood and synovial fluid levels of sulpho-conjugated steroids in rheumatoid arthritis. *Clin Exp Rheumatol*. 1992 Jan-Feb;10(1):25-30

Rheumatism in men: the improvement with testosterone treatment

177. Cutolo M, Balleari E, Giusti M, Intra E, Accardo S. Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum.* 1991 Jan;34(1):1-5

Osteoporosis in men: the association with

Lower estrogens and androgen levels

178. Deutsch S, Benjamin F, Seltzer V, Tafreshi M, Kocheril G, Frank A. The correlation of serum estrogens and androgens with bone density in the late postmenopause. *Int J Gynaecol Obstet.* 1987 Jun;25(3):217-22
179. Garnerio P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *J Bone Miner Res.* 2000 Aug;15(8):1526-36
180. Lau EM, Suriwongpaisal P, Lee JK, Das De S, Festin MR, Saw SM, Khir A, Torralba T, Sham A, Sambrook P. Risk factors for hip fracture in Asian men and women: the Asian osteoporosis study. *J Bone Miner Res.* 2001 Mar;16(3):572-80
181. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab.* 2000 Sep;85(9):3276-82

Lower testosterone levels

182. Foresta C, Zanatta GP, Busnardo B, Scanelli G, Scandellari C. Testosterone and calcitonin plasma levels in hypogonadal osteoporotic young men. *J Endocrinol Invest.* 1985 Aug;8(4):377-9
183. Jassal SK, Barrett-Connor E, Edelstein SL. Low bioavailable testosterone levels predict future height loss in postmenopausal women. *J Bone Miner Res.* 1995 Apr;10(4):650-4

Osteoporosis in men: the improvement with testosterone treatment

184. Anderson FH, Francis RM, Faulkner K. Androgen supplementation in eugonadal men with osteoporosis-effects of 6 months of treatment on bone mineral density and cardiovascular risk factors. *Bone.* 1996 Feb;18(2):11-7
185. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab.* 1996 Dec;81(12):4358-65
186. Isaia G, Mussetta M, Pecchio F, Sciolla A, di Stefano M, Molinatti GM. Effect of testosterone on bone in hypogonadal males. *Maturitas.* 1992 Aug;15(1):47-51
187. Salamano G, Isaia GC, Pecchio F, Appendino S, Mussetta M, Molinatti GM. Effect on phosphocalcium metabolism of testosterone administration in hypogonadal males. *Arch Ital Urol Nefrol Androl.* 1990 Mar;62(1):149-53
188. Diamond T, Stiel D, Posen S. Effects of testosterone and venesection on spinal and peripheral bone mineral in six hypogonadal men with hemochromatosis. *J Bone Miner Res.* 1991 Jan;6(1):39-43
189. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci.* 2001 May;56(5):M266-72
190. Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab.* 2000 Aug;85(8):2670-7
191. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG Jr, Strom BL. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab.* 1999 Jun;84(6):1966-72

Hip fractures in men: the association with lower testosterone levels

192. Leifke E, Wichers C, Gorenai V, Lucke P, von zur Muhlen A, Brabant G. Low serum levels of testosterone in men with minimal traumatic hip fractures. *Exp Clin Endocrinol Diabetes*. 2005 Apr;113(4):208-13

Cancer in men: the association with lower testosterone levels

193. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab* 1982 Jun;54(6):1104-8
194. Turkes AO, Turkes A, Read GF, Fahmy DR. A sensitive fluorometric enzyme immunoassay for testosterone in plasma and saliva [proceedings] *J Endocrinol*. 1979 Oct;83(1):31P.
195. *Vestsi Akademii Medicina Navuk USSR* 1980; 3: 72-7 (mentioned in *The natural prostate cure* (Proger Mason 2000 ISBN 1-884820-61-1)^o
196. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. *J Surg Oncol*. 1990 Jun;44(2):122-8
197. *Progress in Clinical Biological Research* 1975; 6: 143-58 (mentioned in *The natural prostate cure* (Proger Mason 2000 ISBN 1-884820-61-1))
198. *Zhonghua Yixue Zazhi* 1993; 73: 489-90 (mentioned in *The natural prostate cure* (Proger Mason 2000 ISBN 1-884820-61-1))
199. Hulka BS, Hammond JE, DiFerdinando G, Mickey DD, Fried FA, Checkoway H, Stumpf WE, Beckman WC Jr, Clark TD. Serum hormone levels among patients with prostatic carcinoma or benign prostatic hyperplasia and clinic controls. *Prostate* 1987;11(2):171-82
200. Ortega E, Ruiz E, Mendoza MC, Martin-Andres A, Osorio C. Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men. *Experientia*. 1979 Jun 15;35(6):844-5
201. Wright F, Poizat, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 1985; 60 (2) 294-8
202. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev*. 1995 Oct-Nov;4(7):735-41
203. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate* 1982;3(6):579-88
204. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). *Cancer Causes Control* 1997 Jul;8(4):632-6
205. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol*. 1996 Mar;77(3):433-40
206. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res* 1988 Jun 15;48(12):3515-7
207. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol* 2000 Mar;163(3):824-7
208. Wynder EL, Laakso K, Sotarauta M, Rose DP. Metabolic epidemiology of prostatic cancer. *Prostate* 1984;5(1):47-53

Cancer mortality in men: increased risk if low testosterone levels

209. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. *Am J Clin Oncol*. 1997 Dec;20(6):605-8
210. [Iversen P, Rasmussen F, Christensen IJ](#). Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. *Scand J Urol Nephrol Suppl*. 1994; 157: 41-7
211. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. *Prostate*. 1988;12(4):325-32

Cancer in men: the protection with testosterone or dihydrotestosterone treatment?

212. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause*. 2004 Sep-Oct;11(5):531-535
213. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. *Can Med Assoc J*. 1971;105(1):71-2
214. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer*. 1967 Nov;20(11):1871-8
215. Joly-Pharaboz MO, Soave MC, Nicolas B, Mebarki F, Renaud M, Foury O, Morel Y, Andre JG. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. *J Steroid Biochem Mol Biol* 1995 Oct;55(1):67-76
216. [Wolf DA](#), [Schulz P](#), [Fittler F](#). Synthetic androgens suppress the trans- formed phenotype in human prostate carcinoma cell line LNCaP. *Br J Cancer*. 1991 Jul; 64 (1): 47-53
217. Andrews P, Krygier S, Djakiew D. Dihydrotestosterone (DHT) modulates the ability of NSAIDs to induce apoptosis of prostate cancer cells. *Cancer Chemother Pharmacol* 2002 Mar;49(3):179-86

Longevity in men: the association with testosterone levels

218. Suzuki M. Centenarians in Japan. *Nakayamshoten Tokyo (Japan)*, 1995: 64-78
219. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. *Prostate*. 1988;12(4):325-32

Longevity in men: improvement of survival with testosterone treatment

220. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. *Can Med Assoc J*. 1971;105(1):71-2
221. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer*. 1967 Nov;20(11):1871-8

Testosterone diagnosis

222. Nachtigall LB, Boepple PA, Pralong FP, Crowley WF, Jr. Adult-onset idiopathic hypogonadotropic hypogonadism—a treatable form of male infertility. *N Engl J Med*. 1997;336:410-5.
223. Schubert M, Jockenhovel F. Late-onset hypogonadism in the aging male (LOH): definition, diagnostic and clinical aspects. *J Endocrinol Invest*. 2005;28(3 Suppl):23-7
224. Vermeulen A, Kaufman JM. Diagnosis of hypogonadism in the aging male. *Aging Male*. 2002 Sep;5(3):170-6 (*"The diagnosis of hypoandrogenism in elderly males requires both the presence of clinical symptoms and reduced (free) testosterone levels."*)

Clinical testosterone evaluation in men

225. Tenover JL: Testosterone and the aging male. *J Androl*. 1997; 18:103–6
226. Schow DA, Redmon B, Pryor JL: Male menopause: how to define it, how to treat it. *Postgrad Med*. 1997; 101:62–79
227. Vermeulen A: The male climacterium. *Ann Med*. 1993; 25:531–534
228. Morley JE, Kaiser FE, Sih R, Hajjar R, Perry HM III: Testosterone and frailty. *Clin Geriatr Med* 1997;13:685–95
229. Swerdloff RS, Wang C. Androgen deficiency and aging in men. *West J Med* 1993; 159:579–85
230. Burns-Cox N, Gingell C. The andropause: fact or fiction? *Postgrad Med J* 1997; 73:553–6
231. Vermeulen A, Kaufman JM. Ageing of the hypothalamic-pituitary-testicular axis in men. *Horm Res* 1995;43:25–8
232. Werner AA. The male climacteric. *JAMA*. 1946;132(4):188-94
233. Mahmoud AM, Goemaere S, El-Garem Y, Van Pottelbergh I, Comhaire FH, Kaufman Ersoz H, Onde ME, Terekci H, Kurtoglu S, Tor H. Causes of gynaecomastia in young adult males and factors associated with idiopathic gynaecomastia. *Int J Androl*. 2002 Oct;25(5):312-6
234. Mahmoud AM, Goemaere S, El-Garem Y, Van Pottelbergh I, Comhaire FH, Kaufman JM. Testicular volume in relation to hormonal indices of gonadal function in community-dwelling elderly men. *J Clin Endocrinol Metab*. 2003 Jan;88(1):179-84

235. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? *BJU Int.* 2004 Nov;94(7):1066-70
236. Tancredi A, Reginster JY, Schleich F, Pire G, Maassen P, Luyckx F, Legros JJ. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. *Eur J Endocrinol.* 2004 Sep;151(3):355-60
237. Tsujimura A, Matsumiya K, Matsuoka Y, Takahashi T, Koga M, Iwasa A, Takeyama M, Okuyama A. Bioavailable testosterone with age and erectile dysfunction. *J Urol.* 2003 Dec;170(6 Pt 1):2345-7

Frequency of overt hypogonadism in men

238. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab.* 2001 Feb;86(2):724-31 (*"the incidence of (overt) hypogonadal testosterone levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 yr of age, and even greater percentages when free T index criteria were employed"*)

Serum androgen tests in men

239. Fears TR, Ziegler RG, Donaldson JL, Falk RT, Hoover RN, Stanczyk FZ, Vaught JB, Gail MH. Reproducibility studies and interlaboratory concordance for androgen assays of male plasma hormone levels. *Cancer Epidemiol Biomarkers Prev.* 2002 Aug;11(8):785-9

Serum FSH in men

240. Odink RJ, Schoemaker J, Schoute E, Herdes E, Delemarre-van de Waal HA. Predictive value of serum follicle-stimulating hormone levels in the differentiation between hypogonadotropic hypogonadism and constitutional delay of puberty. *Horm Res.* 1998;49(6):279-87

Serum testosterone in men

241. Elmlinger MW, Kuhnel W, Wormstall H, Doller PC. Reference intervals for testosterone, androstenedione and SHBG levels in healthy females and males from birth until old age. *Clin Lab.* 2005;51(11-12):625-32
242. Hwang TI, Yang CR, Chang CL, Chang CH, Wu HC, Hwang YF. Hormonal screening in impotent patients. *J Formos Med Assoc.* 1991 Jun;90(6):560-4
243. Morley JE, Patrick P, Perry HM 3rd. Evaluation of assays available to measure free testosterone. *Metabolism.* 2002 May;51(5):554-9
244. Murray MAF, Corker CS. Levels of testosterone and luteinizing hormone in plasma samples taken at 10 minute intervals in normal men. *J Clin Endocrinol Metab.* 1973; 56: 157
245. Goncharov N, Katsya G, Dobracheva A, Nizhnik A, Kolesnikova G, Todua T, Lunenfeld B. Serum testosterone measurement in men: evaluation of modern immunoassay technologies. *Aging Male.* 2005 Sep-Dec;8(3):194-202

Serum dihydrotestosterone and androstanediol glucuronide in men

246. Toscano V, Horton R. Circulating dihydrotestosterone may not reflect peripheral formation. *J Clin Invest.* 1987 Jun;79(6):1653-8
247. Morimoto I, Edmiston A, Hawks D, Horton R. Studies on the origin of androstanediol and androstanediol glucuronide in young and elderly men. *J Clin Endocrinol Metab.* 1981 Apr;52(4):772-8
248. Ertel NH, Akgun S, Samojlik E, Kirschner MA, Imperato-McGinley J. Decreased 3 alpha-androstanediol glucuronide levels in plasma and random urines in male pseudohermaphroditism caused by 5 alpha-reductase deficiency. *Metabolism.* 1989 Sep;38(9):817-21
249. Rittmaster RS, Thompson DL, Listwak S, Loriaux DL. Androstanediol glucuronide isomers in normal men and women and in men infused with labeled dihydrotestosterone. *J Clin Endocrinol Metab.* 1988 Jan;66(1):212-6
250. Andre M, Valsamis J. Reference values for androstanediol glucuronide. *Clin Chem.* 1994 Jan;40(1):162

Serum PSA in men

251. Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. *JAMA.* 2000 Sep 20;284(11):1399-405
252. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. *JAMA.* 1997 May 14;277(18):1456-60
253. Thiel R, Pearson JD, Epstein JI, Walsh PC, Carter HB. Role of prostate-specific antigen velocity in prediction of final pathologic stage in men with localized prostate cancer. *Urology.* 1997 May;49(5):716-20.
254. Carter HB, Pearson JD. Prostate-specific antigen velocity and repeated measures of prostate-specific antigen. *Urol Clin North Am.* 1997 May;24(2):333-8
255. Carter HB, Partin AW, Luderer AA, Metter EJ, Landis P, Chan DW, Fozard JL, Pearson JD. Percentage of free prostate-specific antigen in sera predicts aggressiveness of prostate cancer a decade before diagnosis. *Urology.* 1997 Mar;49(3):379-84
256. Pearson JD, Luderer AA, Metter EJ, Partin AW, Chan DW, Fozard JL, Carter HB. Longitudinal analysis of serial measurements of free and total PSA among men with and without prostatic cancer. *Urology.* 1996 Dec;48(6A Suppl):4-9

24-hour urine androgen tests in men

Urinary testosterone in men

257. Ooi LS, Panesar NS, Masarei JR. Within- and between-subject variation in, and associations between, serum concentrations and urinary excretion of testosterone and estradiol in Chinese men. *Clin Chim Acta.* 1995 Apr 30;236(1):87-92
258. Borts DJ, Bowers LD. Direct measurement of urinary testosterone and epitestosterone conjugates using high-performance liquid chromatography/tandem mass spectrometry. *J Mass Spectrom.* 2000 Jan;35(1):50-61
259. Choi MH, Kim KR, Chung BC. Simultaneous determination of urinary androgen glucuronides by high temperature gas chromatography-mass spectrometry with selected ion monitoring. *Steroids.* 2000 Jan;65(1):54-9
260. Makino H, Kobegawa A. Radioimmunoassay of urinary testosterone. *Horumon To Rinsho.* 1974 Jul;22(7):893-6
261. Bezverkhaia TP. Method of determining urinary testosterone levels. *Lab Delo.* 1981;(5):285-8
262. Osada H, Osawa K, Makino T, Kandogawa A. Proceedings: Determination of urinary testosterone by radioimmunoassay. *Nippon Naibunpi Gakkai Zasshi.* 1974 Feb 20;50(2):190
263. Tresguerres JA, Tamm J. Urinary and plasma testosterone glucosiduronate measurement by a simple RIA method. *J Steroid Biochem.* 1979 Jul;11(1A):143-6
264. Sayo H, Hosokawa M. Spin immunoassay of urinary testosterone. *Yakugaku Zasshi.* 1980 Jan;100(1):56-60

265. Rudd BT, Rosenfield RL, Bongiovanni AM, Eberlein WR. The measurement of urinary testosterone glucuronide by competitive protein binding and validation by a double isotope derivative assay. *Steroids*. 1969 Feb;13(2):227-45
266. Futterweit W, Eng Y, Griboff SI. Gas chromatographic determination of urinary testosterone and epitestosterone glucuronide. *Mt Sinai J Med*. 1971 May-Jun;38(3):281-3
267. Venturelli E, Cavalleri A, Secreto G. Methods for urinary testosterone analysis. *J Chromatogr B Biomed Appl*. 1995; 671 (1-2): 363-80
268. Vermeulen A. A study of the urinary excretion of testosterone. *Verh K Vlaam Acad Geneeskld Belg*. 1966;28(5):461-519
269. Doberne Y, New MI. Urinary androstanediol and testosterone in adults. *J Clin Endocrinol Metab*. 1976 Jan;42(1):152-4
270. Andino N, James VH, Parker V, Rippon AE. Excretion of non-conjugated androstenedione and testosterone in human urine. *Steroids*. 1976 Dec;28(6):837-46
271. Callow, Nancy H. The isolation of two transformation products of testosterone from urine. *Biochem J*. 1939;33:559-64
272. Wilkins RB, Carlson L. Qualitative studies of neutral 17-ketosteroids in normal subjects. *J Clin Endocrinol Met*. 1952; 12: 647-3
273. Vestergaard P, Raabo E, Vedso S. Determination of urinary testosterone in men, women and children. *Clin Chim Acta*. 1966 Oct;14(4):540-52
274. Krawczynska H, Zachmann M, Prader A. Urinary testosterone glucuronide and sulphate in newborns and young infants. *Acta Endocrinol (Copenh)*. 1976 Aug;82(4):842-50
275. Yamaguchi T, Konno K, Kawabe K, Yasuda K, Mori H, Suzuki T, Yanaihara T, Nakayama T. Simultaneous determination of five androgens in early neonatal urine by selected ion monitoring GC-MS using 19-d3 steroids as internal standards. *Endocrinol Jpn*. 1985;32(2):279-85
276. Raynaud E, Audran M, Pages JC, Fedou C, Brun JF, Chanal JL, Orsetti A. Determination of urinary testosterone and epitestosterone during pubertal development: a cross-sectional study in 141 normal male subjects. *Clin Endocrinol (Oxf)*. 1993 Apr;38(4):353-9
277. Raynaud E, Audran M, Pages JC, Brun JF, Fedou C, Chanal JL, Orsetti A. Study of urinary excretion of testosterone and epitestosterone glucuronides in children and adolescents *Pathol Biol (Paris)*. 1993 Feb;41(2):159-63
278. Dehennin L, Delgado A, Peres G. Urinary profile of androgen metabolites at different stages of pubertal development in a population of sporting male subjects. *Eur J Endocrinol*. 1994 Jan;130(1):53-9
279. Gleispach H, Fauster R, Borkenstein M, Wendler H. Urinary testosterone excretion in boys in relation to other parameters of somatic maturity (a longitudinal study). *Wien Klin Wochenschr*. 1981 Feb 6;93(3):89-93
280. Popa M, Ciocirdia C, Florea I, Tache A, Dimitriu V. Clinical assessment of cryptorchid boys by determination of urinary testosterone glucuronide following large doses of human chorionic gonadotropin (hCG). *Endocrinologie*. 1976 Oct-Dec;14(4):313-7
281. Mauvais-Jarvis P, Charransol G, Bobas-Masson F. Simultaneous determination of urinary androstanediol and testosterone as an evaluation of human androgenicity. *J Clin Endocrinol Metab*. 1973 Mar;36(3):452-9
282. Demichenko AN, Serdechnaia LI. Excretion of testosterone in men with various forms of hypogonadism. *Probl Endokrinol (Mosk)*. 1975 Jul-Aug;21(4):31-4
283. Demchenko AN, Serdechnaia LI. Urinary excretion of testosterone and androstenedione in hypogonadism in men. *Probl Endokrinol (Mosk)* 1977 Mar-Apr;23(2):43-7
284. Marenich LP. Excretion of testosterone, epitestosterone, androstenedione and 7-ketodehydroepiandrosterone in healthy men of different ages. *Probl Endokrinol (Mosk)*. 1979 Jul-Aug;25(4):28-31
285. Deslypere JP, Wiers PW, Sayed A, Vermeulen A. Urinary excretion of androgen metabolites, comparison with excretion of radioactive metabolites after injection of [4-14C]testosterone. Influence of age. *Acta Endocrinol (Copenh)*. 1981 Feb;96(2):265-72
286. Favino A, Cavalleri A, Tilli M. Relations between urinary excretion of 17-ketosteroids, androsterone, etiocholanolone, testosterone and epitestosterone in adult and aged male subjects. *Folia Endocrinol* 1967 Jun;20(3):331-44
287. Wright F, Poizat R, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5 alpha-androstane-3 alpha,17 beta-diol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 1985 Feb;60(2):294-8

288. Niermann H, Lenau H, Ayi-Bonte G, Schulz H. Excretion of urinary testosterone in Klinefelter's syndrome. *Humangenetik*. 1975;26(1):61-70
289. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatitis. *Andrologia*. 1977 Jan-Mar;9(1):89-94
290. Pedersen-Bjergaard K, Tonnesen M. Sex hormone analyses. II. The excretion of sexual hormones by normal men, impotent males, polyarthritics and prostatics. *Acta Med Scand*. 1948; 213: 284-97
291. Oka M, Nakashima K. Endocrine therapy and serum and urinary testosterone levels, as a monitoring, in patients with carcinoma of the prostate *Nippon Gan Chiryō Gakkai Shi*. 1977 Sep 20;12(3):336-42
292. Kisliakova ND, Luntovskaia VA. Testosterone, epitestosterone and total estrogen excretion in men with cancer of certain localizations] *Vopr Onkol*. 1979;25(5):12-4
293. Zumoff B, Rosenfeld RS, Friedman M, Byers SO, Rosenman RH, Hellman L. Elevated daytime urinary excretion of testosterone glucuronide in men with the type A behavior pattern. *Psychosom Med*. 1984 May-Jun;46(3):223-5
294. Guillard JC, Moreau D, Malval M, Morville R, Klepping J. Evaluation of sympathoadrenal activity, adrenocortical function and androgenic status in five men during a Himalayan mountaineering expedition (ascent of Mt Pabil, 7,102 m, 23,294 ft). *Eur J Appl Physiol Occup Physiol*. 1984;52(2):156-62
295. Yap BK, Kazlauskas R, Elghazi K, Johnston GA, Weatherby RP. Profiling of urinary testosterone and luteinizing hormone in exercise-stressed male athletes, using gas chromatography-mass spectrometry and enzyme immunoassay techniques. *J Chromatogr B Biomed Appl*. 1996 Dec 6;687(1):117-25
296. Bandelow B, Sengos G, Wedekind D, Huether G, Pilz J, Broocks A, Hajak G, Ruther E. Urinary excretion of cortisol, norepinephrine, testosterone, and melatonin in panic disorder. *Pharmacopsychiatry*. 1997 Jul;30(4):113-7
297. Gode JD, Singh RH, Settiwar RM, Gode KD, Udupa KN. Increased urinary excretion of testosterone following a course of yoga in normal young volunteers. *Indian J Med Sci*. 1974 Apr-May;28(4-5):212-5
298. Yamamoto A, Ito M. Sebaceous gland activity and urinary androgen levels in children. *J Dermatol Sci*. 1992 Sep;4(2):98-104
299. Loewit K, Schwarz S, Hussl B, Richter E. Urinary androgen- and estrogen excretion in men with pachydermia laryngis and cancer of the larynx. *Endokrinologie*. 1979 Apr;73(2):151-6
300. Tokar' VI, Gurovich AA. Mechanism of a decrease in urinary testosterone excretion in chronic fluoride poisoning. *Gig Tr Prof Zabol*. 1979;(1):37-9
301. Shackleton CH, Phillips A, Chang T, Li Y. Confirming testosterone administration by isotope ratio mass spectrometric analysis of urinary androstane diols. *Steroids*. 1997 Apr;62(4):379-87
302. Borts DJ, Bowers LD. Direct measurement of urinary testosterone and epitestosterone conjugates using high-performance liquid chromatography/tandem mass spectrometry. *J Mass Spectrom*. 2000 Jan;35(1):50-61
303. Dehennin L. Detection of simultaneous self-administration of testosterone and epitestosterone in healthy men. *Clin Chem*. 1994 Jan;40(1):106-9
304. Carlstrom K, Palonek E, Garle M, Oftebro H, Stanghelle J, Bjorkhem I. Detection of testosterone administration by increased ratio between serum concentrations of testosterone and 17 alpha-hydroxyprogesterone. *Clin Chem*. 1992 Sep;38(9):1779-84
305. Southan GJ, Brooks RV, Cowan DA, Kicman AT, Unnadkat N, Walker CJ. Possible indices for the detection of the administration of dihydrotestosterone to athletes. *J Steroid Biochem Mol Biol*. 1992 Mar;42(1):87-94
306. Dehennin L, Scholler R. Detection of self-administration of testosterone as anabolic by determination of the ratio of urinary testosterone to urinary epitestosterone in adolescents. *Pathol Biol (Paris)*. 1990 Nov;38(9):920-2
307. Aguilera R, Catlin DH, Becchi M, Phillips A, Wang C, Swerdloff RS, Pope HG, Hatton CK. Screening urine for exogenous testosterone by isotope ratio mass spectrometric analysis of one pregnane diol and two androstane diols. *J Chromatogr B Biomed Sci Appl*. 1999 Apr 30;727(1-2):95-105
308. Bosy TZ, Moore KA, Poklis A. The effect of oral dehydroepiandrosterone (DHEA) on the urine testosterone/epitestosterone (T/E) ratio in human male volunteers. *J Anal Toxicol*. 1998 Oct;22(6):455-9

309. Babar A, Kaachy A, Cutie AJ, Plakogiannis FM. Gas chromatographic method for simultaneous analysis of urinary testosterone, androsterone and etiocholanolone. Determinations after a single dose of testosterone. *Pharm Acta Helv.* 1988;63(9-10):278-81
310. Aguilera R, Becchi M, Casabianca H, Hatton CK, Catlin DH, Starcevic B, Pope HG Jr. Improved method of detection of testosterone abuse by gas chromatography/combustion/isotope ratio mass spectrometry analysis of urinary steroids. *J Mass Spectrom.* 1996 Feb;31(2):169-76
311. Aguilera R, Becchi M, Grenot C, Casabianca H, Hatton CK. Detection of testosterone misuse: comparison of two chromatographic sample preparation methods for gas chromatographic-combustion/isotope ratio mass spectrometric analysis. *J Chromatogr B Biomed Appl.* 1996 Dec 6;687(1):43-53
312. Becchi M, Aguilera R, Farizon Y, Flament MM, Casabianca H, James P. Gas chromatography/combustion/isotope-ratio mass spectrometry analysis of urinary steroids to detect misuse of testosterone in sport. *Rapid Commun Mass Spectrom.* 1994 Apr;8(4):304-8
313. Dehennin L, Peres G. Plasma and urinary markers of oral testosterone misuse by healthy men in presence of masking epitestosterone administration. *Int J Sports Med.* 1996 Jul;17(5):315-9
314. Uralets VP, Gillette PA. Over-the-counter anabolic steroids 4-androsten-3,17-dione; 4-androsten-3beta,17beta-diol; and 19-nor-4-androsten-3,17-dione: excretion studies in men. *J Anal Toxicol* 1999 Sep;23(5):357-66
315. van de Kerkhof DH, de Boer D, Thijssen JH, Maes RA. Evaluation of testosterone/epitestosterone ratio influential factors as determined in doping analysis. *J Anal Toxicol.* 2000 Mar;24(2):102-15

Urinary 7-ketosteroids in men

316. Hamilton JB, Bunch LD, Mestler GE. Urinary 17-ketosteroids in castrated vs. noncastrated men. *J Clin Endocrinol Metab.* 1959 Dec;19:1680-2
317. Furman RH, Howard RP. Urinary 17-ketosteroid excretion in castrated and intact men. *J Clin Endocrinol Metab.* 1959 Nov;19:1510-2
318. Dorfman RI, Hamilton JB. Concerning the metabolism of testosterone to androsterone. *J Biol Chem.* 1940;133:753-60
319. Callow, Nancy H. The isolation of two transformation products of testosterone from urine. *Biochem J.* 1939; 33: 559-64
320. Dehennin L, Matsumoto AM. Long-term administration of testosterone enanthate to normal men: alterations of the urinary profile of androgen metabolites potentially useful for detection of testosterone misuse in sport. *J Steroid Biochem Mol Biol.* 1993;44 (2):179-89
321. Harrison LM, Martin D, Gotlin RW, Fenessey PV. Effect of extended use of single anabolic steroids on urinary steroid excretion and metabolism. *J Chromatogr.* 1989;489(1):121-6
322. Motta E, Rosciszewska D, Buntner B, Sliwa P. Total serum testosterone levels and urinary 17-ketosteroids of men with epilepsy and decreased sexual activity. *Psychiatr Pol.* 1987;21(3):251-5
323. Maroulis GB, Manlimos FS, Abraham E. Comparison between urinary 17-ketosteroids and serum androgens in hirsute patients. *Obstet Gynecol* 1977;49:454-8
324. Maynar M, Caballero MJ, Mena P, Rodriguez C, Cortes R, Maynar JI. Urine excretion of androgen hormones in professional racing cyclists. *Eur J Appl Physiol.* 1994; 68(3):200-4
325. Robinson A. The excretion of 17-ketosteroids in men of different age groups, with special reference to prostatic cancer. *Brit J Cancer.* 1948;2:13-6
326. Kirk E. The urinary excretion of neutral 17-ketosteroids in the middle-aged and old men. *J Gerontol.* 1949;5:222-6
327. Pincus G, Romanoff L, Carlo J. Excretion of urinary steroids by men and women of various ages. *J Gerontol.* 1954;9:113-32

Corrective testosterone/androgen therapy for men

328. Cantrill J, Dewis P, Large D, Newman M, Anderson D. Which testosterone replacement therapy? *Clin Endocrinol (Oxf).* 1984;21:97-107

329. Nieschlag E, Behre H. Pharmacology and clinical uses of testosterone. In: Nieschlag E, Behre H eds, Testosterone action, deficiency, substitution. Berlin, Heidelberg, New York: Springer-Verlag.

Various testosterone/androgen medications for men

330. Nieschlag E, Cuppers H, Wiegelmann W, Wickings E. Bioavailability and LH-suppressing effect of different testosterone preparations in-normal and hypogonadal men. *Horm Res.* 1976;7:138-45

Transdermal testosterone for men

331. Hameed A, Brothwood T, Bouloux P. Delivery of testosterone replacement therapy. *Curr Opin Investig Drugs.* 2003 Oct;4(10):1213-9
332. Ahmed SR, Boucher AE, Manni A, Santen RJ, Bartholomew M, Demers LM. Transdermal testosterone therapy in the treatment of male hypogonadism. *J Clin Endocrinol Metab.* 1988;66:546-51.
333. Bals-Pratsch M, Knuth UA, Yoon YD, Nieschlag E. Transdermal testosterone substitution therapy for male hypogonadism. *Lancet.* 1986;2:943-6.
334. Cunningham GR, Cordero E, Thornby JI. Testosterone replacement with transdermal therapeutic systems. Physiological serum testosterone and elevated dihydrotestosterone levels. *JAMA.* 1989;261:2525-30.
335. Findlay JC, Place V, Snyder PJ. Treatment of primary hypogonadism in men by the transdermal administration of testosterone. *J Clin Endocrinol Metab.* 1989;68:369-373.
336. Carey PO, Howards SS, Vance ML. Transdermal testosterone treatment of hypogonadal men *J Urol.* 1988;140:76-79.
337. Findlay JC, Place VA, Snyder PJ. Transdermal delivery of testosterone. *J Clin Endocrinol Metab.* 1987;64:266-8
338. Meikle AW, Mazer NA, Moellmer JF, Stringham JD, Tolman KG, Sanders SW, Odell WD. Enhanced transdermal delivery of testosterone across non-scrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. *J Clin Endocrinol Metab.* 1992;74:623-8
339. Meikle A, Arver.S, Dobs, AS, Sanders, SW, Mazer, NA. Androderm: a permeation enhanced non-scrotal testosterone transdermal system for the treatment of male hypogonadism. In: Bhasin S, Gabelnick HL, Spieler JM, Swerdloff RS, Wang C, eds. *Pharmacol, Biol Clin Appl Androgens.* Wiley-Liss, Inc, New-York, 1966
340. Mazer N, Bell D, Wu J, Fischer J, Cosgrove M, Eilers B; BS, RN,. Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. *J Sex Med.* 2005 Mar;2(2):213-26
341. Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab.* 2000 Dec;85(12):4500-10
342. Wang C, Berman N, Longstreth JA, Chuapoco B, Hull L, Steiner B, Faulkner S, Dudley RE, Swerdloff RS. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. *J Clin Endocrinol Metab.* 2000 Mar;85(3):964-9.
343. Rolf C, Kemper S, Lemnitz G, Eickenberg U, Nieschlag E. Pharmacokinetics of a new transdermal testosterone gel in gonadotrophin-suppressed normal men. *Eur J Endocrinol.* 2002 May;146(5):673-9

Oral testosterone for men

344. Daggett P, Wheeler M, Nabarro J. Oral testosterone: a reappraisal. *Horm Res.* 1978;9(3):121-9
(*The absorption is not sufficiently reliable for routine use. The large doses required to achieve therapeutic levels, make oral administration of free testosterone impractical*)
345. Johnsen S, Bennett E, Jensen V. Therapeutic effectiveness of oral testosterone. *Lancet.* 1974 Dec 21; 2:1473-5

Oral mesterolone for men

346. Ros A. Our experience with mesterolone therapy. Evaluation of 22 hormonal steroids constituting the gas chromatographic picture in the total neutral urinary fraction. The effectiveness of mesterolone in the therapy of oligoasthenospermias. *Acta Obstet Gynecol.* 1969;15:37-53
347. Gerhards E, Nieuweboer B, Richter E. On the alkyl-substituted steroids. V. Testosterone excretion in man after oral administration of alpha-methyl-5alpha-androstane-17beta-ol-3-one (mesterolone) and 17-alpha-methyl-androst-4-en-17beta-ol-3-one (17alpha-methyltestosterone). *Arzneimittelforschung.* 1969;19:765-6
348. Komatsu Y, Tomoyoshi T, Okada K. Clinical experiences with mesterolone, an orally administered androgen, in male urology. *Hinyokika Kiyo.* 1969;15:663-9
349. Aakvaag A, Stromme S. The effect of mesterolone administration to normal men on the pituitary-testicular function. *Acta Endocrinol (Copenh).* 1974;77:380-6

Oral testosterone undecanoate for men

350. Schurmeyer T, Wickings E, Freischlag C, Nieschlag E. Saliva and serum testosterone following oral testosterone administration in normal and hypogonadal men. *Acta Endocrinol (Copenh).* 1983;102:456-62
351. Tauber U, Schroder K, Dusterberg B, Matthes H. Absolute bioavailability of testosterone after oral administration of testosterone-undecanoate and testosterone. *Eur J Drug Metab Pharmacokinet.* 1986;11:145-9
352. Luisi M, Franchi F. Double-blind group comparative study of testosterone undecanoate and mesterolone in hypogonadal male patients. *J Endocrinol Invest.* 1980;3:305-8
353. Maisey N, Bingham J, Marks V, English J, Chakraborty J. Clinical efficacy of testosterone undecanoate in male hypogonadism. *Clin Endocrinol (Oxf).* 1981;14:625-9
354. Tax L. Absolute bioavailability of testosterone after oral administration of testosterone undecanoate and testosterone [letter]. *Eur J Drug Metab Pharmacokinet.* 1987;12:225-6
355. Coert A, Geelen J, de Visser J, van der Vies J. The pharmacology and metabolism of testosterone undecanoate (TU), a new orally active androgen. *Acta Endocrinol (Copenh).* 1975;79:789-800
356. Skakkebaek N, Bancroft J, Davidson D, Wamer P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol (Oxf).* 1981;14:49-61

Sublingual testosterone for men

357. Salehian B, Wang C, Alexander G, Davidson T, McDonald V, Berman N, Dudley RE, Ziel F, Swerdloff RS. Pharmacokinetics, bioefficacy, and safety of sublingual testosterone cyclodextrin in hypogonadal men: comparison to testosterone enanthate- a clinical research center study. *J Clin Endocrinol Metab* 1995;80:3567-75
358. Stuenkel CA, Dudley RE, Yen SS. Sublingual administration of testosterone-hydroxypropyl-beta-cyclodextrin inclusion complex simulates episodic androgen release in hypogonadal men *J Clin Endocrinol Metab.* 1991 ;72:1054-9
359. Wang C, Eyre DR, Dark R, et al. Sublingual testosterone replacement improves muscle mass and strength, decreases bone resorption, and increases bone formation markers in hypogonadal men- a clinical research center study. *J Clin Endocrinol Metab.* 1996;81:3654-62
360. Salehian B, Wang C, Alexander G, et al. Pharmacokinetics, bioefficacy, and safety of sublingual testosterone cyclodextrin in hypogonadal men: comparison to testosterone enanthate- a clinical research center study. *J Clin Endocrinol Metab.* 1995;80:3567-75

Intramuscular injections of testosterone enanthate or cypionate for men

361. Schulte-Beerbuhl M, Nieschlag E. Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone in serum after injection of testosterone enanthate or testosterone cypionate. *Fertil Steril* 1980;33:201-3
362. Schurmeyer T, Nieschlag E. Comparative pharmacokinetics of testosterone enanthate and testosterone cyclohexanecarboxylate as assessed by serum and salivary testosterone levels in normal men *Int J Androl* 1984;7:181-7
363. Nankin H. Hormone kinetics after intramuscular testosterone cypionate. *Fertil Steril* 1987;47:1004-9

364. Snyder PJ, Lawrence DA. Treatment of male hypogonadism with testosterone enanthate. *J Clin Endocrinol Metab.* 1980;51:1335-9
365. Demisch K, Nickelsen T. Distribution of testosterone in plasma proteins during replacement therapy with testosterone enanthate in patients suffering from hypogonadism. *Andrologia.* 1983; 15 Spec No:536-41
366. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab.* 1999 Oct;84(10):3469-78
367. Kenny AM, Prestwood KM, Raisz LG. Short-term effects of intramuscular and transdermal testosterone on bone turnover, prostate symptoms, cholesterol, and hematocrit in men over age 70 with low testosterone levels. *Endocr Res.* 2000 May;26(2):153-68

Intramuscular injections of nandrolone decanoate for men

368. Strawford A, Barbieri T, Neese R, Van Loan M, Christiansen M, Hoh R, Sathyan G, Skowronski R, King J, Hellerstein M. Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999 Feb 1;20(2):137-46 (*"It is reasonable to expand the criteria for androgen treatment in AIDS wasting syndrome to include at least patients in the lowest quartile of serum testosterone"*)
369. Flicker L, Hopper JL, Larkins RG, Lichtenstein M, Buirski G, Wark JD. Nandrolone decanoate and intranasal calcitonin as therapy in established osteoporosis. *Osteoporos Int.* 1997;7(1):29-35

Intramuscular injections of testosterone undecanoate for men

370. Harle L, Basaria S, Dobs AS. Nebido: a long-acting injectable testosterone for the treatment of male hypogonadism. *Expert Opin Pharmacother.* 2005 Aug;6(10):1751-9
371. Schubert M, Minnemann T, Hubler D, Rouskova D, Christoph A, Oettel M, Ernst M, Mellinger U, Krone W, Jockenhovel F. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab.* 2004 Nov;89(11):5429-34
372. von Eckardstein S, Nieschlag E. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. *J Androl.* 2002 May-Jun;23(3):419-25.
373. Behre HM, Abshagen K, Oettel M, Hubler D, Nieschlag E. Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. *Eur J Endocrinol.* 1999 May;140(5):414-9

Testosterone pellets for men

374. Handelsman D, Conway A, Boylan L. Suppression of human spermatogenesis by testosterone implants. *J Clin Endocrinol Metab.* 1992;75:1326-32
375. Handelsman D, Conway A, Boylan L. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab.* 1990;71:216-22

Transdermal dihydrotestosterone for men

376. Choi S, Kirn D, de Lingnieres B. Transdermal dihydrotestosterone therapy and its effects on patients with microphallus. *J Urol* 1993; 150:657-60
377. Chemana D, Morville R, Fiet J, Villette JM, Tabuteau F, Brerault JL, Passa P. Percutaneous absorption of 5-alpha-dihydrotestosterone in man. II. Percutaneous administration of 5 alpha-dihydrotestosterone in hypogonadal men with idiopathic haemochromatosis; clinical, metabolic and hormonal effectiveness. *Int J Androl* 1982;5:595-606
378. Kuhn J, Laudat M, Roca R, Dugue M, Luton J, Bricaire H. Gynecomastia: effect of prolonged treatment with dihydrotestosterone by the percutaneous route. *Presse Med* 1983;12:21-5
379. Schaison G, Nahoul K, Couzinet, B. Percutaneous dihydrotestosterone (DHT) treatment. In: Nieschlag E, Behre HM, ed. *Testosterone-action, deficiency, substitution.* Springer-Verlag, Berlin, Heidelberg, New York, 1990, p. 155-64

380. De Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause'. *Annals Med.* 1993;25:235-41

Importance of reducing excessive levels of estradiol in men

381. Leder BZ, Rohrer JL, Rubin SD, Gallo J, Longcope C. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. *J Clin Endocrinol Metab.* 2004 Mar;89(3):1174-80
382. Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. *Metabolism.* 2003 Sep;52(9):1126-8.
383. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol.* 2002 Feb;167(2 Pt 1):624-9
384. Chearskul S, Charoenlarp K, Thongtang V, Nitiyanant W. Study of plasma hormones and lipids in healthy elderly Thais compared to patients with chronic diseases: diabetes mellitus, essential hypertension and coronary heart disease. *J Med Assoc Thai.* 2000 Mar;83(3):266-77 (*"Hypertensive men had the highest plasma estradiol levels"*)
385. Cengiz K, Alvur M, Dindar U. Serum creatine phosphokinase, lactic dehydrogenase, estradiol, progesterone and testosterone levels in male patients with acute myocardial infarction and unstable angina pectoris. *Mater Med Pol.* 1991 Jul-Sep;23(3):195-8 (*"Serum estradiol levels in the patient groups were significantly higher than the control group (p < 0.001). There was a positively good correlation between the serum CPK and LDH levels in acute myocardial infarction and the serum estradiol levels. .. These results suggest that hyper estrogenemia may be a risk factor for myocardial infarct in middle-aged men."*)

..... and the Importance of avoiding too low levels of estradiol in men: risk of osteoporosis

386. Carlsen CG, Soerensen TH, Eriksen EF. Prevalence of low serum estradiol levels in male osteoporosis. *Osteoporos Int.* 2000;11(8):697-701

Treatment of borderline androgen deficiencies in men

387. Strawford A, Barbieri T, Neese R, Van Loan M, Christiansen M, Hoh R, Sathyan G, Skowronski R, King J, Hellerstein M. Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999 Feb 1;20(2):137-46

Use of youthful (young adult) male reference values

388. Vermeulen A, Kaufman JM. Diagnosis of hypogonadism in the aging male. *Aging Male.* 2002 Sep;5(3):170-6 (*"In the absence of convincing arguments for altered requirements with age, we consider that the normal range of (free) testosterone levels in young adults is also valid for elderly"*)

Testosterone/androgen treatment in men: dosages

389. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab.* 2001 Dec;281(6):E1172-81

Testosterone/androgen treatment in men: safety, adverse effects, complications

390. Gooren L. Long-term safety of the oral androgen testosterone undecanoate. *Int J Androl.* 1986-9-21-6
391. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab.* 1997 Nov;82(11):3793-6.

392. Matsumoto A. Clinical use and abuse of androgens and antiandrogens. In: Becker K, ed Principles and Practice of Endocrinology and Metabolism. 2nd ed. J.B. Lippincott, Philadelphia 1995-1110-22
393. Westaby D, Ogle S, Paradinas F, Randell J, Murray-Lyon I. Liver damage from long-term methyltestosterone. Lancet. 1977;2:262-3

Testosterone/androgen treatment in men: interferences – associations

394. Isidori AM, Lenzi A. Risk factors for androgen decline in older males: lifestyle, chronic diseases and drugs. J Endocrinol Invest. 2005;28(3 Suppl):14-22
395. Wortsman J, Rosner W, Dufau M. Abnormal testicular function in men with primary hypothyroidism. Am J Med. 1987;82:207-12.

Follow-up of testosterone/androgen treatment in men: judging the efficacy of the androgen replacement by monitoring the patient's clinical and laboratory test responses

396. Santen RJ. Male Hypogonadism. In: Yen SSC, Jaffe RB, eds. Reproductive Endocrinology, 3rd ed. Saunders, Philadelphia, 1991, pp. 739-94
397. Griffin JE, Wilson JD. Disorders of the Testes and Male Reproductive Tract. In: Wilson JD, Foster DW, eds. William's Textbook of Endocrinology, 8th ed. Saunders, Philadelphia, 1992:799-852
398. Nieschlag E, Mauss J, Coert A, Kicovic P. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. Acta Endocrinol (Copenh). 1975;79:366-74
399. Ebert T, Jockenhovel F, Morales A, Shabsigh R. The current status of therapy for symptomatic late-onset hypogonadism with transdermal testosterone gel. Eur Urol. 2005 Feb;47(2):137-46
400. Babar A, Kaachy A, Cutie AJ, Plakogiannis FM. Gas chromatographic method for simultaneous analysis of urinary testosterone, androsterone and etiocholanolone. Determinations after a single dose of testosterone. Pharm Acta Helv. 1988;63(9-10):278-81

TOPICS OF DISCUSSION:

TESTOSTERONE TREATMENT AND TESTICULAR SUPPRESSION

Full recovery of testosterone (endogenous) secretion and serum levels after stopping high dose testosterone–progestogen treatment for contraception

1. Fogh M, Corker CS, McLean H, Hunter WM, Petersen IB, Philip J, Schou G, Skakkebaek NE. Clinical trial with levo-norgestrel and testosterone oenanthate for male fertility control. Acta Endocrin. (Copenh). 1980 Oct;95(2):251-7
2. Foegh M, Damgaard-Pedersen F, Gormsen J, Knudsen JB, Schou G. Oral levo-norgestrel - testosterone effects on spermatogenesis, hormone levels, coagulation factors and lipoproteins in normal men. Contraception. 1980 Apr;21(4):381-91

Full recovery of testosterone production to youthful (young adult) levels in old animals after long-term suppression of endogenous testosterone secretion by high doses of exogenous testosterone (Leydig cell aging was prevented by the high doses of testosterone treatment)

3. Chen H, Zirkin BR. Long-term suppression of Leydig cell steroidogenesis prevents Leydig cell aging. Proc Natl Acad Sci U S A. 1999;96(26):14877-81

Up to 14.5 weeks for recovery of normal sperm production after treatment with high doses of testosterone-progestogen used for contraception (sperm suppression)

4. Ly LP, Liu PY, Handelsman DJ. Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. Hum Reprod. 2005 Jun;20(6):1733-40

TESTOSTERONE TREATMENT AND PROSTATE CANCER

Prostate cancer: epidemiology

On the important annual incidence of (detected) prostate cancer in men who are alive in the United States

1. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: Cancer statistics review 1973-1986. Bethesda, MD: NIH;1989;III.45

On the very high incidence of prostate cancer when biopsies are made in men aged 62 or over, even with low serum PSA

2. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab. 1982 Jun;54(6):1104-8 (*Among the 2950 men (age range, 62 to 91 years), prostate cancer was diagnosed in 15.2 %; 14.9 % of the prostate cancers had a Gleason score of 7 or higher. The prevalence of prostate cancer was 6.6 % among men with a PSA level of up to 0.5 ng/ml, 10.1 % among those with values of 0.6 to 1.0 ng/ml,, 17.0 % among those with values of 1.1 to 2.0 ng/ml, 23.9 % among those with values of 2.1 to 3.0 ng/ml, and 26.9 % among those with values of 3.1 to 4.0 ng/ml. The prevalence of high-grade cancers increased from 12.5 % of cancers associated with a PSA level of 0.5 ng/ml, or less to 25.0 % of cancers associated with a PSA level of 3.1 to 4.0 ng/ml. Conclusions: biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.*)

On the real incidence of prostate cancer: much higher prevalence rate of prostate cancer are found at post-mortem

3. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. Cancer Epidemiol Biomarkers Prev. 1992 Mar-Apr;1(3):189-93 (*"3.6% of men in life were diagnosed with prostate cancer, whereas 27% of autopsied Hawaii Japanese men who died after 50 years of age had prostate cancer, reaching a frequency of 63% among men over 80 years of age. The volume of 48(60%) of these cancers was less than 150 mm³. These small tumors would probably not have been discovered in a screening program. Tumors larger than 1000 mm³ would probably be discovered using modern diagnostic procedures but were found in only 13 (4.4%) of the autopsied men*)
4. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. Cancer Surv. 1995;23:267-80 (*"The vast majority of cases of prostate cancer remain undetected during life, the prevalence of prostate cancer detected at autopsy being 2800 times that of lethal cancer in Japanese in Japan, 570 times in whites in the USA and 470 times in blacks in the USA. A case-control study of prostate cancer carried out in Japan and the Netherlands revealed a number of statistically significant risk factors, including ... no morning erections, , episodes of sexually transmitted disease, lower plasma testosterone and dihydrotestosterone concentrations."*)
5. Sanchez-Chapado M, Olmedilla G, Cabeza M, Donat E, Ruiz A. Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. Prostate. 2003 Feb 15;54(3):238-47(*"The prevalence of prostate cancer (CaP) is 3.58, 8.82, 14.28, 23.80, 31.7, and 33.33% in the 3rd, 4th, 5th, 6th, 7th, and 8th decades, respectively. The rates of high-grade prostatic intraepithelial neoplasia (HGPIN) were 7.14, 11.75, 35.71, 38.06, 45.40, and 48.15% at the 3rd, 4th, 5th, and 8th decades of life....in 21/27 cases (77.7%), an association between CaP and HGPIN was found. The prevalence of both lesions in Caucasian Mediterranean males is significantly lower than in Caucasian American and Afro-American males in all the age groups evaluated."*)
6. Rich AR. J Urol. 1935; 33: 215-33
7. Baron E et al. Arch Path. 1941;32:787-93
8. Dixon RJ et al. Atlas of Tumor Pathology. 1952, p.197

Prostate cancer patients have a low risk of dying from cancer

9. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. *Cancer Epidemiol Biomarkers Prev.* 1992 Mar-Apr;1(3):189-93. (*"Prostate cancer was diagnosed in life among 274 of 8006 (3.6%) members of a cohort of Japanese men in Hawaii between 1965 and 1990. Only 55 (20%) of the 274 diagnosed cases died with prostate cancer, and they accounted for only 2% of the 2893 deaths that occurred among the men during this period."*)
10. Quinn M. Cancer Trends in the USA - A View From Europe. *J Nat Cancer Inst.* 2003;95(17):1258-61

Prostate cancer, esp. non-metasized is rarely a cause of death in men

11. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. *Cancer Surv.* 1995;23:267-80
12. Oefelein MG, Ricchiuti VS, Conrad PW, Goldman H, Bodner D, Resnick MI, Seftel A. Clinical predictors of androgen-independent prostate cancer and survival in the prostate-specific antigen era. *Urology.* 2002 Jul;60(1):120-4

Side effects of testosterone/androgen deprivation therapy of prostate cancer

Androgen deprivation therapy may severely impair the quality of life

13. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. *J Am Geriatr Soc.* 2006 Jan;54(1):85-90 (*"Participants receiving androgen deprivation therapy (ADT) reported significantly poorer quality of life in the areas of physical function (P<.001), general health (P<.001), and physical health component summary (P<.001) than men not receiving ADT; After controlling for comorbidity, total testosterone level rather than ADT accounted for a small yet statistically significant percentage of the total variance of the physical health .."*)
14. Chen AC, Petrylak DP. Complications of androgen-deprivation therapy in men with prostate cancer. *Curr Urol Rep.* 2005 May;6(3):210-6 (*"Androgen-deprivation therapy (ADT) is indicated for the treatment of metastatic prostate cancer and locally advanced disease. In addition to sexual side effects, long-term ADT results in several other changes, including hot flashes; gynecomastia; changes in body composition, metabolism, and the cardiovascular system; osteoporosis; anemia; psychiatric and cognitive problems; and fatigue and diminished quality of life"*)

Androgen deprivation causes anemia

15. Choo R, Chander S, Danjoux C, Morton G, Pearce A, Deboer G, Szumacher E, Loblaw A, Cheung P, Woo T. How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients? *Can J Urol.* 2005 Feb;12(1):2547-52 (*"The decline and recovery of hemoglobine was closely related to that of testosterone."*)

Androgen deprivation causes impotence

16. Basaria S, Lieb J 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M, Dobs AS. Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol (Oxf).* 2002 Jun;56(6):779-86
17. Potosky AL, Knopf K, Clegg LX, Albertsen PC, Stanford JL, Hamilton AS, Gilliland FD, Eley JW, Stephenson RA, Hoffman RM. Quality-of-life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. *J Clin Oncol.* 2001 Sep 1;19(17):3750-7
18. Fowler FJ, McNaughton Collins M, Walker Corkery E, Elliott DB, Barry MJ. The impact of androgen deprivation on quality of life after radical prostatectomy for prostate carcinoma. *Cancer.* 2002 Jul 15;95(2):287-95

Androgen deprivation therapy may cause urinary incontinence

19. Miller NL, Bissonette EA, Bahnson R, Wilson J, Theodorescu D. Impact of a novel neoadjuvant and adjuvant hormone-deprivation approach on quality of life, voiding function, and sexual function after prostate brachytherapy. *Cancer.* 2003 Mar 1;97(5):1203-10

Androgen deprivation therapy generates a greater rate of bone loss in men with prostate cancer

20. Preston DM, Torrens JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis.* 2002;5(4):304-10

Testosterone deprivation therapy increases arterial stiffness in men with prostate cancer

21. Dockery F, Bulpitt CJ, Agarwal S, Rajkumar C. Testosterone suppression in men with prostate cancer is associated with increased arterial stiffness. *Aging Male.* 2002 Dec;5(4):216-22

Dihydrotestosterone deprivation therapy increases the risk of aggressive prostate cancer

22. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003 Jul 17;349(3):215-24

Arguments against population-based PSA screening for prostate cancer and against treatment of prostate cancer:

1. High prevalence rates of prostate cancer at postmortem
 2. Increasing biopsy rates leads to overdiagnosis and overtreatment
 3. Despite widespread use of such tests in the USA, and apparent incidence rates of detected prostate cancer almost 3 times higher than in the U.K., the mortality in the USA has for many years been almost the same as in the U.K. and other European countries
 4. 1/3 of screen-detected cases are incurable
 5. No clear benefit of treatment
 6. Side effects of prostatectomy include impotence in a large proportion of cases and incontinence in a smaller proportion
 7. Screening and follow-up of treatment (much of which may be unnecessary) is expensive (high costs)
 8. Few years of life to gain in many elderly patients
 9. No consequent reduction in mortality has yet been demonstrated in a randomized controlled trial
23. Quinn M. Cancer Trends in the USA-A View From Europe. *J Nat Cancer Inst.* 2003; 95 (17): 1258-61

ARGUMENTS PRO TESTOSTERONE THERAPIES

HUMAN STUDIES:

Studies where low testosterone apparently increases the risk of prostate cancer

The urinary free testosterone decreases with aging, while the incidence of prostate cancer increases

24. Morer-Fargas F, Nowakowski H. Die Testosteronausscheidung im Harn bei Männlichen Individuen. *Acta Endocrinol.* 1965; 49: 443-52
25. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: *Cancer statistics review 1973-1986.* Bethesda, MD: NIH;1989;III.45

Low serum testosterone is associated with an increased prostate cancer risk

26. Chen C, Weiss NS, Stanczyk FZ, Lewis SK, DiTommaso D, Etzioni R, Barnett MJ, Goodman GE. Endogenous sex hormones & prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. *Cancer Epidemiol Biomarkers Prev.* 2003;12(12):1410-6
27. Stattin P, Lumme S, Tenkanen L, Alfthan H, Jellum E, Hallmans G, Thoresen S, Hakulinen T, Luostarinen T, Lehtinen M, Dillner J, Stenman UH, Hakama M. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. *Int J Cancer.* 2004 Jan 20;108(3):418-24

Low serum testosterone levels have been found in prostate cancer patients

28. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab* 1982 Jun;54(6):1104-8
29. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate*. 1982;3(6):579-88 (*Low testosterone in prostate cancer patients less than 65 years*)
30. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. *J Surg Oncol*. 1990 Jun;44(2):122-8
31. Turkes AO, Turkes A, Read GF, Fahmy DR. A sensitive fluorometric enzyme immunoassay for testosterone in plasma and saliva [proceedings] *J Endocrinol*. 1979 Oct;83(1):31P
32. *Vestsi Akademii Medicina Navuk USSR* 1980; 3: 72-7 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)°
33. *Revista Experimental Fisiology* 1990; 46:63-8 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)
34. *Revista Experimental Fisiology* 1991; 47: 161-6 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)
35. *Progress in Clinical Biological Research* 1975; 6: 143-58 (*mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)*)
36. *Zhonghua Yi Xue Za Zhi* 1993; 73: 489-90 (*mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)*)

Close to statistical significance lower testosterone levels in prostate cancer patients

37. Hulka BS, Hammond JE, DiFerdinando G, Mickey DD, Fried FA, Checkoway H, Stumpf WE, Beckman WC Jr, Clark TD. Serum hormone levels among patients with prostatic carcinoma or benign prostatic hyperplasia and clinic controls. *Prostate*. 1987;11(2):171-82
38. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol*. 1996 Mar;77(3):433-40
39. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res*. 1988 Jun 15;48(12):3515-7

Low testosterone levels are found in prostate cancer patients and in their (not yet affected) relatives with familial predisposition to prostate cancer

40. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab*. 1982 Jun;54(6):1104-8

A high serum SHBG (and thus less bioavailable testosterone) is found in men with family history of prostate cancer

41. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev.* 1995 Oct-Nov;4(7):735-41

A high incidence of prostate cancer is found in patients with low testosterone and normal digital rectal examination and normal PSA (≤ 4 ng/ml)

42. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. *JAMA.* 1996 Dec 18;276(23):1904-6.

Low serum levels of total and bio-available testosterone are found in populations with a higher risk of prostate cancer (such as African-Americans and whites)

43. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev.* 1995 Oct-Nov;4(7):735-41 (*Asian-Americans had higher total and bioavailable testosterone compared to African-Americans and whites*)

Studies where a low serum dihydrotestosterone (DHT) was found in prostate cancer patients

44. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate.* 1982;3(6):579-88 (*Low in prostate cancer patients less than 65 years*)
45. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Laggiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). *Cancer Causes Control.* 1997 Jul;8(4):632-6

A study where DHT is inversely, significantly, and strongly associated with the risk of prostate cancer

46. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Laggiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). *Cancer Causes Control.* 1997 Jul;8(4):632-6

Studies where close to statistical significance lower DHT levels were found in prostate cancer patients

47. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol.* 1996 Mar;77(3):433-40
48. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res.* 1988 Jun 15;48(12):3515-7

High grade prostate cancers are associated with low testosterone levels

49. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. (editorial note *A Bohle*). Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *Int Braz J Urol.* 2005 Nov-Dec;31(6):609
50. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *J Urol.* 2005 Dec;174(6):2178-80.
51. Schatzl G, Madersbacher S, Haitel A, Gsur A, Preyer M, Haidinger G, Gassner C, Ochsner M, Marberger M. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. *J Urol.* 2003 Apr;169(4):1312-5

52. Schatzl G, Madersbacher S, Thurnidl T, Waldmuller J, Kramer G, Haitel A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate*. 2001 Apr;47(1):52-8
53. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol*. 2000 Mar;163(3):824-7

Gene polymorphisms with increased risk of high grade prostate cancer are associated with low testosterone levels

54. Schatzl G, Marberger M, Remzi M, Grosser P, Unterlechner J, Haidinger G, Zidek T, Preyer M, Micksche M, Gsur A. Polymorphism in ARE-I region of prostate-specific antigen gene associated with low serum testosterone level and high-grade prostate cancer. *Urology*. 2005 Jun;65(6):1141-5

Metastatic prostate cancer (PC) is associated with a low serum testosterone compared to localized PC

55. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, Ueda T, Shiraishi T, Ichikawa T. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. *Eur Urol*. 2005 Mar;47(3):308-12

A low serum testosterone level in patients with metastatic prostate cancer predicts a worse response to androgen withdrawal therapy (progression to androgen-independent prostate cancer)

56. Furuya Y, Nozaki T, Nagakawa O, Fuse H. Low serum testosterone level predicts worse response to endocrine therapy in Japanese patients with metastatic prostate cancer. *Endocr J*. 2002 Feb;49(1):85-90
57. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. *Endocr J*. 2001 Oct;48(5):573-8

Lower prostate tissue levels of DHT (but similar levels of testosterone) **are found in men with recurrent prostate cancer compared to men with benign prostate hypertrophy**

58. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. *Clin Cancer Res*. 2004 Jan 15;10(2):440-8

Low testosterone levels are associated with an increased prostate cancer mortality in prostate cancer patients

59. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. *Am J Clin Oncol* 1997 Dec;20(6):605-8
60. [Iversen P, Rasmussen F, Christensen IJ](#). Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. *Scand J Urol Nephrol Suppl*. 1994; 157: 41-7
61. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. *Prostate*. 1988;12(4):325-32
62. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. *Am J Clin Oncol*. 1997 Dec;20(6):605-8.

A study where low testosterone levels are found in men with benign prostate hypertrophy

63. Ortega E, Ruiz E, Mendoza MC, Martin-Andres A, Osorio C. Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men. *Experientia*. 1979 Jun 15;35(6):844-5

A study where a low androstanediol glucuronide level was found in patients with benign prostate hypertrophy

64. Wright F, Poizat, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 1985; 60 (2) 294-8

Men with chronic prostatitis have often low testosterone

65. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatitis. *Andrologia*. 1977 Jan-Mar;9(1):89-94 (*In 73.1% of patients considerable reduction of testosterone excretion was revealed. Reduction of testicular endocrine function is in direct correlative dependence on severity of clinical symptoms, duration of disease and form of chronic prostatitis.*)

A history of prostatitis is positively associated with a history of benign prostatic hyperplasia and cancer

66. Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC; Osteoporotic Fractures in Men (MrOS) Research Group. Correlates and prevalence of prostatitis in a large community-based cohort of older men. *Urology*. 2005 Nov;66(5):964-70 (*"We found positive associations for a history of prostatitis with a history of benign prostatic hyperplasia (odds ratio 8.0, 95% confidence interval 6.8 to 9.5) and a history of prostate cancer (odds ratio 5.4, 95% CI: 4.4 to 6.6)"*)

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone

67. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. *Cancer Res*. 1978 Nov;38(11 Pt 2):4126-34.
68. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat prostate in organ culture. *C R Acad Sci Hebd Seances Acad Sci D*. 1977 Oct 31;285(11):1119-22

Studies where testosterone treatment appears to protect against prostate cancer

Studies where testosterone/androgen treatment of patients with advanced prostate cancer increased their survival time and quality of life

69. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. *Can Med Assoc J*. 1971;105(1):71-2
70. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer*. 1967 Nov;20(11):1871-8

Studies where testosterone /androgen treatment inhibits the proliferation of human prostate cancer cells or induces their apoptosis in vitro

71. Joly-Pharaboz MO, Soave MC, Nicolas B, Mebarki F, Renaud M, Foury O, Morel Y, Andre JG. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. *J Steroid Biochem Mol Biol* 1995 Oct;55(1):67-76
72. [Wolf DA, Schulz P, Fittler F](#). Synthetic androgens suppress the transformed phenotype in human prostate carcinoma cell line LNCaP. *Br J Cancer*. 1991 Jul; 64 (1): 47-53
73. Andrews P, Krygier S, Djakiew D. Dihydrotestosterone (DHT) modulates the ability of NSAIDs to induce apoptosis of prostate cancer cells. *Cancer Chemother Pharmacol*. 2002 Mar;49(3):179-86

Studies where testosterone treatment reduces prostate dysfunction complaints (dysuria, nocturia)

74. Flamm J, Kiesswetter H, Englisch M. An urodynamic study of patients with benign prostatic hypertrophy treated conservatively with phytotherapy or testosterone. *Wien Klin Wochenschr* 1979 Sep 28;91(18):622-7
75. Kearns WM. Testosterone in the treatment of testicular deficiency and prostatic enlargement. *Wisconsin Med J*. 1941; 40:927 (*testosterone propionate therapy did not reduce the size of the prostate, but reduced the dysuria*)
76. Meltzer M. Male hormone therapy of prostatic hypertrophy. *Lancet*. 1939; 59: 279
77. Trasoff A. The treatment of benign prostatic hypertrophy with testosterone propionate. *J Lab Clin Med*. 1940; 25: 377
78. Markham MJ. The clinical use of peroral methyltestosterone in benign prostatic hypertrophy. *Urol Cutan Rev*. 1942; 46: 225
79. Markham MJ. The clinical use of testosterone propionate in benign prostatic hypertrophy. *Urol Cutan Rev*. 1941; 45: 35

80. Laqueur E. Behandlung der Prostathypertropie mit männlichen Hormone (Hombreol) une experimentell Begründung dieser Therapie. Schweiz Med Wochenschr. 1934; 64: 1116
81. South Med J, 1939, 32: 154

Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)

82. South Med J, 1939, 32: 154

Studies where dihydrotestosterone treatment reduced the prostate volume (-15 to -20% after 1 year treatment)

83. de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause. Ann Med 1993 Jun;25(3):235-41
84. Swerdloff RS, Wang C. Dihydrotestosterone: a rationale for its use as a non-aromatizable androgen replacement therapeutic agent. Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):501-6
85. Sitruk-Ware R. Contraception, 1989, 39: 1-191

ANIMAL STUDIES:

Studies where androgen deprivation stimulates the progression of hormone-sensitive mouse prostate cancer cells to hormone insensitive in vitro

86. Sato N, Watabe Y, Suzuki H, Shimazaki J. Progression of androgen-sensitive mouse tumor (Shionogi carcinoma 115) to androgen-insensitive tumor after long-term removal of testosterone. Jpn J Cancer Res. 1993 Dec;84(12):1300-8

Studies where antiandrogens (which cause androgen deficiency) may promote DMAB-induced prostate cancer incidence or increase its malignancy

87. Akaza H, Tsukamoto S, Morita T, Yamauchi A, Onozawa M, Shimazui T, Ideyama Y, Shirai T. Promoting effects of antiandrogenic agents on rat ventral prostate carcinogenesis induced by 3,2'-dimethyl-4-aminobiphenyl (DMAB). Prostate Cancer Prostatic Dis. 2000 Aug;3(2):115-9
88. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349(3):215-24

A study where significantly lower testosterone (and androstenedione) levels are found in mice with prostate inflammation. This means that testosterone (and androstenedione) may be necessary to counter prostate inflammation.

89. Bondarenko LA, Breslavskii AS, Vartapetov BA, Gladkova AI. Secretion of testicular androgens under conditions of chronic experimental inflammation of the prostate gland. Probl Endocrinol (Mosk). 1977 Jul-Aug;23(4):111-5

A study where testosterone treatment may prevent benign prostate hypertrophy by inhibiting stromal proliferation-induced by estradiol and by keeping prostate glandular cells health, preventing their atrophy in vitro

90. Feyel-Cabanès T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.

A study where testosterone treatment reduces the proliferation of mouse prostate cancer cells in vitro

91. Suzuki H, Nihei N, Sato N, Ichikawa T, Mizokami A, Shimazaki J. Inhibition of growth and increase of acid phosphatase by testosterone on androgen-independent murine prostatic cancer cells transfected with androgen receptor cDNA. Prostate. 1994 Dec;25(6):310-9

A study where testosterone treatment reduces the proliferation of guinea pig prostate stroma cells in vitro

92. Ricciardelli C, Horsfall DJ, Sykes PJ, Marshall VR, Tilley WD. Effects of oestradiol-17 beta and 5 alpha-dihydrotestosterone on guinea- pig prostate smooth muscle cell proliferation and steroid receptor expression in vitro. *J Endocrinol.* 1994 Mar;140(3):373-83

A study where testosterone treatment at high doses does not increase the incidence of prostate cancer cells in mice

93. Mainwaring WI. The effect of testosterone on the age-associated changes in the ventral prostate gland of the mouse. *Testosterone and ageing of the prostate. Gerontologia.* 1968;14(1):133-41

A study where testosterone, DHT and progesterone protects the prostate glandular epithelium against metaplasia and excessive stroma proliferation induced by estrogens in castrated male mice

94. Burrows H. *Nature (London).* 1936, 138: 164

A study where testosterone treatment of certain species of mice can inhibit prostate cancer growth

95. Umekita Y, Hiipakka RA, Kokontis JM, Liao S. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. *Proc Natl Acad Sci U S A* 1996 Oct 15;93(21):11802-7

Studies where dihydrotestosterone treatment of certain species of rats can inhibit prostate cancer growth

96. Pollard M. Dihydrotestosterone prevents spontaneous adenocarcinomas in the prostate-seminal vesicle in aging L-W rats. *Prostate* 1998 Aug 1;36(3):168-71
97. Pollard M, Luckert PH, Snyder D. Prevention and treatment of experimental prostate cancer in Lobund-Wistar rats. I. Effects of estradiol, dihydrotestosterone, and castration. *Prostate* 1989;15(2):95-103

A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells

98. Bruckheimer EM, Kyprianou N. Dihydrotestosterone enhances transforming growth factor-beta-induced apoptosis in hormone-sensitive prostate cancer cells. *Endocrinology.* 2001 Jun;142(6):2419-26

Breast Cancer in women: protection with testosterone or dihydrotestosterone treatment?

99. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause.* 2004 Sep-Oct;11(5):531-535

NEUTRAL EFFECTS OF TESTOSTERONE THERAPIES

REVIEW STUDIES where the authors did not find an adverse effect of testosterone levels or treatment on the prostate cancer risk

Review studies with conclusions that there is no data to support the view that testosterone treatment could increase the risk of prostate cancer, making e.g. a prostate cancer progress from a preclinical to a clinical stage

100. Rolf C, Nieschlag E. Potential adverse effects of long-term testosterone therapy. *Baillieres Clin Endocrinol Metab.* 1998 Oct;12(3):521-34.
101. Wirth MP, Hakenberg OW Testosterone and the prostate. *Urologe A* 2000 Sep;39(5):418-20
102. Morley JE. Testosterone replacement and the physiologic aspects of aging in men. *Mayo Clin Proc.* 2000 Jan;75 Suppl:S83-7 (*"There is no clinical evidence that the risk of either prostate cancer or benign prostate hypertrophy increases with testosterone treatment"*)
103. Rhoden NEJM 2004 (*"No compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time of a man's life when testosterone levels decline."*)
104. Basaria S, Wahlstrom JT, Dobs AS. Anabolic-Androgenic Steroid Therapy in the Treatment of Chronic Diseases. *J Clin Endocrinol Metab.* 2001Nov;86(11):5108-17(*"...recent reviews suggest that the incidence of prostate cancer is not increased by testosterone administration"*)
105. Morales A. Androgen replacement therapy and prostate safety. *Eur Urol* 2002 Feb;41(2):113-20 (*"To date there is no evidence that exogenous androgens promote development of prostate cancer"*)
106. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. *Cancer Res.* 1999 Sep 1;59(17):4161-4 (*"... contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and ;.. androgen supplementation would probably lower the incidence of the disease. ... consider the possibility that the growth of androgen-independent prostate cancers might be reduced by the administration of androgens"*)

STUDIES with no association between serum androgen levels and prostate disease, including cancer

Studies with no significant difference in plasma testosterone and/or DHT and/or androstanediol glucuronide between prostate cancer patients and controls

107. Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. *Cancer.* 1999 Jul 15;86(2):312-5
108. Carter HB, Pearson JD, Metter EJ, Chan DW, Andres R, Fozard JL, Rosner W, Walsh PC. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate.* 1995 Jul;27(1):25-31
109. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1996 Aug;5(8):621-5
110. Habib FK, Lee IR, Stinch SR, Smith PH. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. *J Endocrinol* 1976 OCT;71(1):99-107
111. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. *Cancer Epidemiol Biomarkers Prev* 1997 Nov;6(11):967-9
112. Wright F, Poizat R, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab.* 1985; 60 (2) 294-8

Studies with no correlation between serum testosterone and serum PSA

113. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. *Urology* 1995 Jul;46(1):58-61
114. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. *Urology* 1995 Jul;46(1):62-4
115. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. *Prostate* 2000;44(3):219-24
116. Vijayakumar S, Quadri SF, Dong L, Ignacio L, Kathuria IN, Sutton H, Halpern H. Results of a study to correlate serum prostate specific antigen and reproductive hormone levels in patients with localized prostate cancer. *J Natl Med Assoc* 1995 Nov;87(11):813-9

A study with no correlation between serum testosterone and prostate tumour volume, weight or Gleason score

117. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. *Urology*. 1995 Jul;46(1):62-4

A study where therapeutic androgen deprivation (blockade) has no beneficial effect on the evolution of the prostate cancer

118. Young HH 2nd, Kent JR. Plasma testosterone levels in patients with prostatic carcinoma before and after treatment. *J Urol*. 1968 Jun;99(6):788-92

A study with no significant association of serum testosterone with benign prostate hyperplasia

119. Lagiou P, Mantzoros CS, Tzonou A, Signorello LB, Lipworth L, Trichopoulos D. Serum steroids in relation to benign prostatic hyperplasia. *Oncology*. 1997 Nov-Dec;54(6):497-501

STUDIES where testosterone/androgen treatments had no adverse effect on the risk of prostate disease, including the risk of prostate cancer

Small clinical studies, performed before the days of PSA, where androgen treatment, usually with small dosages of androgen, did not stimulate the growth of many prostatic tumors and in some cases the tumours were even inhibited by the treatment; the responses were extremely variable

120. Prout GRJ, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer (Phila.)*. 1967;20:1871-8
121. Trunnell JD, Duffy BJ Jr. The influence of certain steroids on the behavior of human prostate cancer. *Trans. NY Acad Sci*. 1950;11:238-41
122. Brendler H, Lowry O, Brock M. Further investigation of hormonal relationships. *Arch Surg*. 1950;61:433-40
123. Pearson OH. Discussion of Dr. Huggins' paper: "Control of cancers of man by endocrinological methods." *Cancer Res*. 1957;17:473-9
124. Morales A, Connolly J, Burr R, Bruce A. The use of radioactive phosphorus to treat bone pain in metastatic carcinoma of the prostate. *Can Med Assoc J*. 1970;103: 372-3

Studies where testosterone treatment had no significant effect on PSA and/or prostate volume

125. Cooper CS, Perry PJ, Sparks AE, MacIndoe JH, Yates WR, Williams RD. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol*. 1998 Feb;159(2):441-3
126. Cooper CS, MacIndoe JH, Perry PJ, Yates WR, Williams RD. The effect of exogenous testosterone on total and free prostate specific antigen levels in healthy young men. *J Urol*. 1996 Aug;156(2 Pt 1):438-41
127. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf)*. 1994 Mar;40(3):341-9
128. Douglas TH, Connelly RR, McLeod DG, Erickson SJ, Barren R 3rd, Murphy GP. Effect of exogenous testosterone replacement on prostate-specific antigen and prostate-specific membrane antigen levels in hypogonadal men. *J Surg Oncol*. 1995 Aug;59(4):246-50

129. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab.* 1997 Jun;82(6):1661-7
130. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab.* 1997 Nov;82(11):3793-6
131. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. *Int J Impot Res.* 2005 Sep 22 (*No statistical increase: average = 0.31 ng/ml after 1 year of treatment of hypogonadal men*)
132. Shibasaki T, Sasagawa I, Suzuki Y, Yazawa H, Ichiyanagi O, Matsuki S, Miura M, Nakada T. Effect of testosterone replacement therapy on serum PSA in patients with Klinefelter syndrome. *Arch Androl.* 2001 Nov-Dec;47(3):173-6

A study where dihydrotestosterone treatment had no significant effect on serum PSA

133. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab.* 2002 Apr;87(4):1467-72

Studies where testosterone treatment increases the serum PSA but normalizes it in patients with initial atrophic prostate bringing it up to normal levels without any excessive increase

134. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf).* 1994 Mar;40(3):341-9.
135. Behre HM, Nieschlag E. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. *J Clin Endocrinol Metab.* 1992 Nov;75(5):1204-10
136. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. *Endocr Pract.* 2000 Mar-Apr;6(2):132-8
137. McClellan KJ, Goa KL. Transdermal testosterone. *Drugs* 1998 Feb;55(2):253-8; discussion 259
138. Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clin Endocrinol (Oxf).* 1997 Dec;47(6):727-37
139. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 1992 Oct;75(4):1092-8

Testosterone treatment does not increase the incidence of prostate disease

140. Hartnell J, 72nd Endocrine Soc. Meeting, 1990, A 428

A study where previous testosterone propionate treatment (terminated 1 to 7 years before the study) did not increase the risk of prostate hypertrophy or palpable prostate irregularities in men over 45 years, whatever the treatment length or dose

141. Lesser MA, Vose SN, Dixey GM. Effect of testosterone propionate on the prostate gland of patients over 45. *J Clin Endocrinol Metab.* 1955 Mar;15(3):297-300

Studies where DHT treatment had no effect on the prostate volume

142. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab.* 2002 Apr;87(4):1467-72.
143. Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. *J Clin Endocrinol Metab.* 2001 Sep;86(9):4078-88

ARGUMENTS CONTRA TESTOSTERONE THERAPIES:

Studies that suggest that testosterone may increase the prostate cancer risk

Prostate cancer: the association with high free testosterone levels

144. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev.* 2005 Sep;14(9):2257-60(*critics: a potential bias may come from nutritional factors: individuals who eat a lot of food related to a higher cancer risk such as meat, particularly if cooked well-done, and/or milk, have also higher levels of testosterone as well as of other hormones associated with a higher cancer risk. Moreover, there is no information in this study on estradiol levels. This is important as the simultaneous presence of high levels of testosterone and estradiol may, following certain reports, increase the prostate cancer (PC) risk, not testosterone levels alone; heavy alcohol drinking, another risk factor for PC, that is in some countries of the world frequent can considerably increase both the estradiol levels and the PC risk in consumers. Other possible bias: data were not adjusted for other PC risk factors such as smoking, nutritional deficiencies, etc.*)
145. Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the prostate. *Prostate Cancer Prostatic Dis.* 2001;4(2):101-105 (*critics: no dietary factors were taken into account, only high BMI as a risk factor, none was serum SHBG analysed: dehydrated persons have usually high SHBG, and thus higher total testosterone, which is bound to it, but generally low active, bioavailable and free testosterone levels*)
146. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst.* 1996 Aug 21;88(16):1118-26 (*critics: study did not consider dietary or BMI PC risk factors*)
147. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. *Exp Clin Endocrinol.* 1992;99(2):68-70 (*critic: no estrogen levels, nor dietary factors checked*)

Note: on the importance to check dietary factors:

Studies where the consumption of high amounts of protein and saturated fat such as milk products and meat increased testosterone levels

148. Sharpe RM, Martin B, Morris K, Greig I, McKinnell C, McNeilly AS, Walker M. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. *Hum Reprod.* 2002 Jul;17(7):1692-703
149. Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, Clevidence BA, Campbell WS, Nair PP, Franz C, Kahle L, Taylor PR. Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. *Am J Clin Nutr.* 1996 Dec;64(6):850-5
150. Hamalainen E, Adlercreutz H, Puska P, Pietinen P. Diet and serum sex hormones in healthy men. *J Steroid Biochem.* 1984 Jan;20(1):459-64
151. Volek JS, Kraemer WJ, Bush JA, Incledon T, Boetes M. Testosterone and cortisol in relationship to dietary nutrients and resistance exercise. *J Appl Physiol.* 1997 Jan;82(1):49-54

Milk or meat intake may increase the risk of prostate (in fact the increased risk may disappear if the vegetable intake which is lower in meat eaters is taken into account)

Link between meat, milk and/or protein intake, and prostate cancer

152. Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. *J Nat Cancer Inst.* 1999; 91(23):2038-44
153. Wolk A. Diet, lifestyle and risk of prostate cancer. *Acta Oncol.* 2005;44(3):277-81
154. Grant WB. An ecologic study of dietary links to prostate cancer. *Altern Med Review* 1999; 4(3):162-9 (study in 14 European countries)

A study where higher levels of testosterone were found in patients who are in the advanced D-stage of PC, compared to the levels found in patients in the more moderate B and C-stages of prostate cancer

155. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. *Endocr J.* 2001 Oct;48(5):573-8 (*note: but those in*

D-stage that had the highest testosterone had the best prognosis, including longer cancer-free survival time)

A study where a higher rate of metastasis (-relapse) is found in prostate cancer patients with testosterone > 500 ng/dl that have been locally irradiated (*critic: the irradiation may change the risk*)

156. Zagars GK, Pollack A, von Eschenbach AC. Serum testosterone - a significant determinant of metastatic relapse for irradiated localized prostate cancer. *Urology*. 1997 Mar;49(3):327-34

A study where testosterone treatment increases the growth of prostate cancer: in vitro

157. Tymchuk CN, Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. *Nutr Cancer*. 2002;42(1):112-6.

ESTROGENS AND PROSTATE CANCER RISK

Studies that suggest that it is the simultaneous presence of high testosterone levels with high estradiol levels (and with possibly a low DHEA levels) **that may promote prostate cancer**

1. Christov KT, Moon RC, Lantvit DD, Boone CW, Kelloff GJ, Steele VE, Lubet RA, Pezzuto JM. Prostate intraepithelial neoplasia in Noble rats, a potential intermediate endpoint for chemoprevention studies. *Eur J Cancer*. 2004 Jun;40(9):1404-11
2. Suzuki K, Takezawa Y, Suzuki T, Honma S, Yamanaka H. Synergistic effects of estrogen with androgen on the prostate--effects of estrogen on the prostate of androgen-administered rats and 5-alpha-reductase activity. *Prostate*. 1994 Oct;25(4):169-76

A study where estrogens inflamed prostate tissues in the presence of testosterone

3. Ho E, Boileau TW, Bray TM. Dietary influences on endocrine-inflammatory interactions in prostate cancer development. *Arch Biochem Biophys*. 2004 Aug 1;428(1):109-17

Studies that suggest that high estrogen levels alone may promote prostate cancer

A study where a high estrone level was found in men with prostate cancer

4. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate*. 1982;3(6):579-88

A study where increased urinary 16-alpha-OH- estrone and lower 2-OH-estrone metabolites are found in prostate cancer patients (*results nearly reached statistical significance*)

5. Muti P, Westerlind K, Wu T, Grimaldi T, De Berry J 3rd, Schunemann H, Freudenheim JL, Hill H, Carruba G, Bradlow L. Urinary estrogen metabolites and prostate cancer: a case-control study in the United States. *Cancer Causes Control*. 2002 ;13(10):947-55 State University of New York

A study where higher estradiol and estrone levels and very low testosterone concentrations were found in prostatic fluid than in serum of prostate cancer patients

6. Wynder EL, Laakso K, Sotarauta M, Rose DP. Metabolic epidemiology of prostatic cancer. *Prostate* 1984;5(1):47-53

Studies where high urinary estrogens are associated with an increased rate of prostate stromal hyperplasia

7. Seppelt U. Correlation among prostate stroma, plasma estrogen levels, and urinary estrogen excretion in patients with benign prostatic hypertrophy. *J Clin Endocrinol Metab*. 1978 Dec;47(6):1230-5
8. Seppelt U, Buhl K, Drews M. Histologic components of benign prostatic hypertrophy (bph) in relation to the androgen-estrogen status. *Urologe A*. 1978 Mar;17(2):117-9

A study where estrogen treatment of castrated mice caused metaplasia of prostate glandular cells

9. Burrows H, *Nature (London)*, 1936, 138: 164

A study where anti-estrogen treatment blocked the growth of prostate cancer in mice, although it increased testosterone levels

10. Raghov S, Hooshdaran MZ, Katiyar S, Steiner MS. Toremifene prevents prostate cancer in the transgenic adenocarcinoma of mouse prostate model. *Cancer Res*. 2002 Mar 1;62(5):1370-6

A study where estrogen treatment stimulate prostate stromal hyperplasia

11. Nakada T, Kubota Y, Sasagawa I, Suzuki H, Watanabe M, Suzuki Y. The effect of oestradiol-17 beta on connective tissue protein in rat prostate. *Int Urol Nephrol.* 1994;26(3):327-35

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone

12. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. *Cancer Res.* 1978 Nov;38(11 Pt 2):4126-34.
13. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat prostate in organ culture. *C R Acad Sci Hebd Seances Acad Sci D.* 1977 Oct 31;285(11):1119-22

Testosterone in women

Senescence is associated with a decline of the adrenal- and ovarian-testosterone axes:

Senescence is associated with a reduction of the serum testosterone level in women

1. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab.* 1995 Apr;80(4):1429-30

Testosterone derives in women for more than 90% from the much quicker declining serum DHEA

2. Labrie F, Belanger A, Luu-The V, Labrie C, Simard J, Cusan L, Gomez JL, Candas B., DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging. *Steroids*, 1998;63(5-6):322-8

Testosterone treatment may oppose and testosterone deficiency may trigger some mechanisms of senescence in women

Immune deficiency: testosterone may improve the immune resistance in certain conditions

3. Dalal M, Kim S, Voskuhl RR. Testosterone therapy ameliorates experimental autoimmune encephalomyelitis and induces a T helper 2 bias in the autoantigen-specific T lymphocyte response. *J Immunol.* 1997 Jul 1;159(1):3-6
4. Buggage RR, Matteson DM, Shen de F, Sun B, Tuaille N, Chan CC. Effect of sex hormones on experimental autoimmune uveoretinitis (EAU). *Immunol Invest.* 2003 Nov;32(4):259-73
5. Nakazawa M, Fantappie MR, Freeman GL Jr, Eloi-Santos S, Olsen NJ, Kovacs WJ, Secor WE, Colley DG. *Schistosoma mansoni*: susceptibility differences between male and female mice can be mediated by testosterone during early infection. *Exp Parasitol.* 1997 Mar;85(3):233-40

Testosterone and psychic well-being in women

Lower quality of life and fatigue in women: the association with lower testosterone levels

6. 323. Abrahamsson L, Hackl H, Lindstrom B, Sogn J. Long-term treatment of virilized women with cyproterone acetate. *Wien Klin Wochenschr.* 1981 Sep 18;93(17):552-6

Quality of life in women: the improvement with testosterone treatment

7. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause.* 2003 Sep-Oct;10(5):390-8

Vasomotor symptoms in women: the improvement with testosterone treatment

8. Simon J, Klaiber E, Wiita B, Bowen A, Yang HM. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. *Menopause.* 1999 Summer;6(2):138-46

Depression in women: the association with lower testosterone levels

9. Rohr UD. The impact of testosterone imbalance on depression and women's health. *Maturitas.* 2002 Apr 15;41 Suppl 1:S25-46

Depression in women: the improvement with testosterone treatment

10. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. *J Affect Disord.* 1988 Mar-Apr;14(2):177-87

Negative symptoms in women: the association with lower serum testosterone levels

11. Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels *Ann N Y Acad Sci.* 2004 Dec;1032:291-4

Anxiety in women: the association with lower testosterone levels

12. Landen M, Baghaei F, Rosmond R, Holm G, Bjorntorp P, Eriksson E. Dyslipidemia and high waist-hip ratio in women with self-reported social anxiety. *Psychoneuroendocrinology*. 2004 Sep;29(8):1037-46 (*Serum levels of total testosterone (1.6+/-0.8 vs. 2.2+/-1.1, P=0.013) and free thyroxin (14+/-2 vs. 16+/-4, P=0.04) were lower in subjects confirming social anxiety*)

Anxiety in women: the improvement with testosterone treatment

13. Montgomery JC, Appleby L, Brincat M, Versi E, Tapp A, Fenwick PB, Studd JW. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *Lancet*. 1987 Feb 7;1(8528):297-9
14. van Honk J, Peper JS, Schutter DJ. Testosterone reduces unconscious fear but not consciously experienced anxiety: implications for the disorders of fear and anxiety. *Biol Psychiatry*. 2005 Aug 1;58(3):218-25

Memory loss and Alzheimer's disease in women: the association with lower testosterone levels

15. Simpson E, Davis S. Why do the clinical sequelae of estrogen deficiency affect women more than men? *J Clin Endocrinol Metab*. 1998 Jun;83(6):2214

Memory in women: the improvement with testosterone treatment

16. Wisniewski AB, Nguyen TT, Dobs AS. Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. *Horm Res*. 2002;58(3):150-5

Love in women: the association with higher testosterone in women

17. Marazziti D, Canale D. Hormonal changes when falling in love. *Psychoneuroendocrinology*. 2004 Aug;29(7):931-6

Loss of sexual drive, sexual gratification, intercourse frequency in women: the association with lower testosterone levels

18. Persky H, Lief HI, Miller WR, O'Brien CP. Plasma testosterone level and sexual behavior of couples. *Arch Sex Behav*. 1978 May; 7(3):157-73

Sexuality decline in women: the improvement with testosterone treatment

19. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas*. 1995 Apr;21(3):227-36
20. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause*. 2003 Sep-Oct;10(5):390-8
21. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. *J Reprod Med*. 1998 Oct;43(10):847-56
22. Sarrel PM. Psychosexual effects of menopause: role of androgens. *Am J Obstet Gynecol*. 1999 Mar;180(3 Pt 2):S319-24
23. Penotti M, Sironi L, Cannata L, Vigano P, Casini A, Gabrielli L, Vignali M. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. *Fertil Steril*. 2001 Aug;76(2):235-40
24. Tuiten A, Laan E, Panhuysen G, Everaerd W, de Haan E, Koppeschaar H, Vroon P. Discrepancies between genital responses and subjective sexual function during testosterone substitution in women with hypothalamic amenorrhea. *Psychosom Med*. 1996 May-Jun;58(3):234-41
25. Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R. Time course of effects of testosterone administration on sexual arousal in women. *Arch Gen Psychiatry*. 2000 Feb;57(2):149-53
26. Shifren JL. The role of androgens in female sexual dysfunction. *Mayo Clin Proc*. 2004 Apr;79(4 Suppl):S19-24
27. Riley AJ. Life-long absence of sexual drive in a woman associated with 5-dihydrotestosterone deficiency. *J Sex Marital Ther*. 1999 Jan-Mar;25(1):73-8

28. Penotti M, Sironi L, Cannata L, Vignano P, Casini A, Gabrielli L, Vignali M. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. *Fertil Steril*. 2001 Aug;76(2):235-40
29. Castelo-Branco C, Vicente JJ, Figueras F, Sanjuan A, Martinez de Osaba MJ, Casals E, Pons F, Balasch J, Vanrell JA. Comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in postmenopausal women. *Maturitas*. 2000 Feb 15;34(2):161-8
30. Studd JWW, Colins WP, Chakravarti S. Estradiol and testosterone implants in the treatment of psychosexual problems in postmenopausal women. *Br J Obstet Gynaecol* 1977;84:314-5
31. Burger HG, Hailes J, Menelaus M. The management of persistent symptoms with estradiol-testosterone implants: clinical, lipid and hormonal results. *Maturitas* 1984;6:351-8
32. Burger HG, Hailes J, Nelson J, Menelaus M. Effect of combined implants of estradiol and testosterone on libido in postmenopausal women. *Br Med J* 1987;294:936-937
33. Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. *Am J Obstet Gynecol*. 1985 Jan 15;151(2):153-60
34. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom Med*. 1985 Jul-Aug;47(4):339-51
35. Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual functioning in oophorectomized women. *Psychosom Med* 1987 Jul-Aug;49(4):397-409
36. Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. *Br J Obstet Gynaecol* 1983 Apr;90(4):361-6

Testosterone and physical appearance/body composition in women

Sarcopenia in women: the association with lower testosterone levels

37. Douchi T, Yoshimitsu N, Nagata Y. Relationships among serum testosterone levels, body fat and muscle mass distribution in women with polycystic ovary syndrome. *Endocr J*. 2001 Dec;48(6):685-9

Sarcopenia in women: the improvement with testosterone treatment

38. Elbers JM, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroid hormones on regional fat depots as assessed by magnetic resonance imaging in transsexuals. *Am J Physiol*. 1999 Feb;276(2 Pt 1):E317-25

Lean body mass in women: the association with lower testosterone levels

39. Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M. Testosterone concentrations in women aged 25-50 years: associations with lifestyle, body composition, and ovarian status. *Am J Epidemiol*. 2001 Feb 1;153(3):256-64
40. Douchi T, Yamamoto S, Oki T, Maruta K, Kuwahata R, Nagata Y. Serum androgen levels and muscle mass in women with polycystic ovary syndrome. *Obstet Gynecol*. 1999 Sep;94(3):337-40

Lean body mass in women: the improvement with testosterone treatment

41. Dobs AS, Nguyen T, Pace C, Roberts CP. Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab*. 2002 Apr;87(4):1509-16
42. Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause*. 2000 Nov-Dec;7(6):395-401
43. Floter A, Nathorst-Boos J, Carlstrom K, Ohlsson C, Ringertz H, Schoultz B. Effects of combined estrogen/testosterone therapy on bone and body composition in oophorectomized women. *Gynecol Endocrinol*. 2005 Mar;20(3):155-60

Testosterone and age-related diseases in women

Atherosclerosis in women: the association with lower testosterone levels

44. Golden SH, Maguire A, Ding J, Crouse JR, Cauley JA, Zacur H, Szklo M. Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. *Am J Epidemiol.* 2002 Mar 1;155(5):437-45
45. Bernini GP, Sgro' M, Moretti A, Argenio GF, Barlascini CO, Cristofani R, Salvetti A. Endogenous androgens and carotid intimal-medial thickness in women. *J Clin Endocrinol Metab.* 1999 Jun;84(6):2008-12

Atherosclerosis in women: the improvement with testosterone treatment

46. Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR. Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab.* 2001 Jan;86(1):158-61

Coronary artery disease in women: the association with lower testosterone levels

47. Kaczmarek A, Reczuch K, Majda J, Banasiak W, Ponikowski P. The association of lower testosterone level with coronary artery disease in postmenopausal women. *Int J Cardiol.* 2003 Jan;87(1):53-7
48. Golden SH, Maguire A, Ding J, Crouse JR, Cauley JA, Zacur H, Szklo M. Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. *Am J Epidemiol.* 2002 Mar 1;155(5):437-45

Coronary artery disease in female subjects: the improvement with testosterone treatment

49. Chou TM, Sudhir K, Hutchison SJ, Ko E, Amidon TM, Collins P, Chatterjee K. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation.* 1996 Nov 15;94(10):2614-9
50. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. *J Clin Endocrinol.* 1946;6:549-557.

Osteoporosis and osteopenia in women: the association with lower testosterone levels

51. Deng X, Wang W, Wu X, Huang G, Peng J, Liao E, Wu H. Correlation between bone mineral density and sexual hormones in healthy Chinese women. *J Environ Pathol Toxicol Oncol.* 2000;19(1-2):167-9
52. Nilas L, Christiansen C. Bone mass and its relationship to age and the menopause. *J Clin Endocrinol Metab.* 1987;65:697-9
53. Slemenda C, Longcope C, Peacock M, Hui S, Johnston CC. Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri- and postmenopausal women. *J Clin Invest.* 1996;97:14-21
54. Simberg N, Titinen A, Silfrast A, Viinikka L, Ylikorkala O. High bone density in hyperandrogenic women: effect of gonadotropin-releasing hormone agonist alone or in conjunction with estrogen-progestin replacement. *J Clin Endocrinol Metab* 1995;81:646-51

Osteoporosis and osteopenia in women: the improvement with testosterone treatment

55. Miller BE, De Souza MJ, Slade K, Luciano AA. Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause*. 2000 Sep-Oct;7(5):318-26
56. Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *J Reprod Med*. 1999 Dec;44(12):1012-20
57. Castelo-Branco C, Vicente JJ, Figueras F, Sanjuan A, Martinez de Osaba MJ, Casals E, Pons F, Balasch J, Vanrell JA. Comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in postmenopausal women. *Maturitas*. 2000 Feb 15;34(2):161-8
58. Raisz EG, Wiita B, Artis A, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab*. 1995;81:37-43
59. Watts NB, Notelovitz M, Timmons MC. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol*. 1995;85:529-37
60. Savvas M, Studd JWW, Fogelman I, Dooley M, Montgomery J, Murby B. Skeletal effects of oral estrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women. *Br Med J*. 1988;297:331-3
61. Savvas M, Sludd JWW, Norman S, Leather AT, Garnett, TJ. Increase in bone mass after one year of percutaneous oestradiol and testosterone implants in post menopausal women who have previously received long-term oral oestrogens. *Br J Obstet Gynaecol*. 1992;99:757-60
62. Davis SR, McCloud PI, Strauss BJG, Burger HG. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas*. 1995;21:227-36
63. Kasra M, Grynblas MD. The effects of androgens on the mechanical properties of primate bone. *Bone*. 1995;17:265-70

Height loss and hip fractures in women: the association with lower testosterone levels

64. Jassal SK, Barrett-Connor E, Edelstein S. Low bioavailable testosterone levels predict future height loss in postmenopausal women. *J Bone Min Res*. 1995;10(4):650-3
65. Davidson BJ, Ross RK, Paganini-Hill A, Hammond GD, Siiteri PK, Judd HL. Total and free estrogens and androgens in postmenopausal women with hip fractures. *J Clin Endocrinol Metab*. 1982 Jan;54(1):115-20

Rheumatism in women: the association with lower testosterone levels

66. Sambrook PN, Eisman JA, Champion GD, Pocock NA. Sex hormone status and osteoporosis in postmenopausal women with rheumatoid arthritis. *Arthritis Rheum*. 1988;31(8):973-8

Rheumatism in women: the improvement with testosterone treatment

67. Booji A, Biewenga-Booji CM, Huber-Bruning O, Cornelis C, Jacobs JW, Bijlsma JW. Androgens as adjuvant treatment in postmenopausal female patients with rheumatoid arthritis. *Ann Rheum Dis*. 1996 Nov;55(11):811-5

Obesity in women: the improvement with testosterone treatment

68. van Kesteren PJ, Asscheman H, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42
69. Elbers JM, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroid hormones on regional fat depots as assessed by magnetic resonance imaging in transsexuals. *Am J Physiol*. 1999 Feb;276(2 Pt 1):E317-25

Cancer in women: the association with lower testosterone levels

70. Inutsuka S, Kodama Y, Natsuda Y, Kumashiro R, Maekawa T. Serum testosterone level of patients with gastric carcinoma before and after gastrectomy. *Cancer*. 1986 Dec 15;58(12):2675-9

Cancer: the improvement with testosterone treatment?

71. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause*. 2004 Sep-Oct;11(5):531-535
72. Natrajan PK, Soumakis K, Gambrell RD Jr. Estrogen replacement therapy in women with previous breast cancer. *Am J Obstet Gynecol*. 1999 Aug;181(2):288-95
73. Deng X, Wang W, Wu X, Huang G, Peng J, Liao E, Wu H. Correlation between bone mineral density and sexual hormones in healthy Chinese women. *J Environ Pathol Toxicol Oncol*. 2000;19(1-2):167-9

Longevity in women: the association with lower testosterone levels

74. Suzuki M. Centenarians in Japan. Nakayamshoten Tokyo (Japan). 1995: 64-78

Testosterone diagnosis in women

Clinical testosterone evaluation in women

75. Rivera-Woll LM, Papalia M, Davis SR, Burger HG. Androgen insufficiency in women: diagnostic and therapeutic implications. *Hum Reprod Update*. 2004 Sep-Oct;10(5):421-32 (*"key symptoms of the female androgen insufficiency syndrome include reduced libido, diminished well being and lowered mood"*)
76. Miller KK. Androgen deficiency in women. *J Clin Endocrinol Metab*. 2001 Jun;86(6):2395-401
77. Braunstein GD. Androgen insufficiency in women: summary of critical issues. *Fertil Steril*. 2002 Apr;77 Suppl 4:S94-9
78. Sullivan DA, Sullivan BD, Evans JE, Schirra F, Yamagami H, Liu M, Richards SM, Suzuki T, Schaumberg DA, Sullivan RM, Dana MR. Androgen deficiency, Meibomian gland dysfunction, and evaporative dry eye. *Ann N Y Acad Sci*. 2002 Jun;966:211-22
79. Sullivan DA, Belanger A, Cermak JM, Berube R, Papas AS, Sullivan RM, Yamagami H, Dana MR, Labrie F. Are women with Sjogren's syndrome androgen-deficient? *J Rheumatol*. 2003 Nov;30(11):2413-9

Serum androgen tests in women

80. Fears TR, Ziegler RG, Donaldson JL, Falk RT, Hoover RN, Stanczyk FZ, Vaught JB, Gail MH. Reproducibility studies and interlaboratory concordance for androgen assays in female plasma. *Cancer Epidemiol Biomarkers Prev*. 2000 Apr;9(4):403-12
81. Gryngarten M, Bedecarras P, Ayuso S, Bergada C, Campo S, Escobar ME. Clinical assessment and serum hormonal profile in prepubertal hypertrichosis. *Horm Res*. 2000;54(1):20-5

Serum total testosterone in women

82. Stanczyk FZ, Cho MM, Endres DB, Morrison JL, Patel S, Paulson RJ. Limitations of direct estradiol and testosterone immunoassay kits. *Steroids*. 2003 Dec;68(14):1173-8
83. Judd HL, Yen SS. Serum androstenedione and testosterone levels during the menstrual cycle. *J Clin Endocrinol Metab* 1973 Mar;36(3):475-81
84. Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, Lacroix I, Somma-Delpero C, Boudou P. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem*. 2003 Aug;49(8):1381-95
85. Ly LP, Handelsman DJ. Empirical estimation of free testosterone from testosterone and sex hormone-binding globulin immunoassays. *Eur J Endocrinol*. 2005 Mar;152(3):471-8

86. Herold DA, Fitzgerald RL. Immunoassays for testosterone in women: better than a guess? Clin Chem. 2003 Aug;49(8):1250-1
87. Nahoul K, Castanier M, Gervasi G, Scholler R. Assay of plasma progesterone and testosterone. Comparison of enzyme immunoassays and radio-immunoassays. Ann Biol Clin (Paris). 1989;47(3):127-34

Serum free testosterone in women

88. Miller KK, Rosner W, Lee H, Hier J, Sesmilo G, Schoenfeld D, Neubauer G, Klibanski A. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. J Clin Endocrinol Metab. 2004 Feb;89(2):525-33.

Serum dihydrotestosterone and androstenediol glucuronide in women

89. Toscano V, Horton R. Circulating dihydrotestosterone may not reflect peripheral formation. J Clin Invest. 1987 Jun;79(6):1653-8
90. Greep N, Hoopes M, Horton R. Androstenediol glucuronide plasma clearance and production rates in normal and hirsute women. J Clin Endocrinol Metab. 1986 Jan;62(1):22-7
91. Rittmaster RS, Thompson DL, Listwak S, Loriaux DL. Androstenediol glucuronide isomers in normal men and women and in men infused with labeled dihydrotestosterone. J Clin Endocrinol Metab. 1988 Jan;66(1):212-6
92. Falsetti L, Rosina B, De Fusco D. Serum levels of 3alpha-androstenediol glucuronide in hirsute and non hirsute women. Eur J Endocrinol. 1998 Apr;138(4):421-4
93. Pasupuleti V, Lobo R, Horton R. Conversion of dihydrotestosterone to androstenediol glucuronide by female sexual skin. Steroids. 1988 Mar-Apr;51(3-4):269-82
94. Andre M, Valsamis J. Reference values for androstenediol glucuronide. Clin Chem. 1994 Jan;40(1):162.
95. Kirschner MA, Samojlik E, Szmaj E. Clinical usefulness of plasma androstenediol glucuronide measurements in women with idiopathic hirsutism. J Clin Endocrinol Metab. 1987 Oct;65(4):597-601

Serum androsterone in women

96. Zwicker H, Rittmaster RS. Androsterone sulfate: physiology and clinical significance in hirsute women. J Clin Endocrinol Metab. 1993 Jan;76(1):112-6
97. Thompson DL, Horton N, Rittmaster RS. Androsterone glucuronide is a marker of adrenal hyperandrogenism in hirsute women. Clin Endocrinol (Oxf). 1990 Mar;32(3):283-92

24-hour urine testosterone tests in women

Urinary testosterone in women

98. Doberne Y, New MI. Urinary androstenediol and testosterone in adults. J Clin Endocrinol Metab. 1976 Jan;42(1):152-4
99. Karila T, Kosunen V, Leinonen A, Tahtela R, Seppala T. High doses of alcohol increase urinary testosterone-to-epitestosterone ratio in females. J Chromatogr B Biomed Appl. 1996 Dec 6;687(1):109-16
100. Borts DJ, Bowers LD. Direct measurement of urinary testosterone and epitestosterone conjugates using high-performance liquid chromatography/tandem mass spectrometry. J Mass Spectrom. 2000 Jan;35(1):50-61
101. Makino H, Kobegawa A. Radioimmunoassay of urinary testosterone. Hormon To Rinsho. 1974 Jul;22(7):893-6
102. Bezverkhaya TP. Method of determining urinary testosterone levels. Lab Delo. 1981;(5):285-8
103. Osada H, Osawa K, Makino T, Kandogawa A. Proceedings: Determination of urinary testosterone by radioimmunoassay. Nippon Naibunpi Gakkai Zasshi. 1974 Feb 20;50(2):190
104. Tresguerres JA, Tamm J. Urinary and plasma testosterone glucosiduronate measurement by a simple RIA method. J Steroid Biochem. 1979 Jul;11(1A):143-6
105. Sayo H, Hosokawa M. Spin immunoassay of urinary testosterone. Yakugaku Zasshi. 1980 Jan;100(1):56-60

106. Rudd BT, Rosenfield RL, Bongiovanni AM, Eberlein WR. The measurement of urinary testosterone glucuronide by competitive protein binding and validation by a double isotope derivative assay. *Steroids*. 1969 Feb;13(2):227-45
107. Futterweit W, Eng Y, Griboff SI. Gas chromatographic determination of urinary testosterone and epitestosterone glucuronide. *Mt Sinai J Med*. 1971 May-Jun;38(3):281-3
108. Venturelli E, Cavalleri A, Secreto G. Methods for urinary testosterone analysis. *J Chromatogr B Biomed Appl*. 1995; 671 (1-2): 363-80
109. Vermeulen A. A study of the urinary excretion of testosterone. *Verh K Vlaam Acad Geneesk Belg*. 1966;28(5):461-519
110. Andino N, James VH, Parker V, Rippon AE. Excretion of non-conjugated androstenedione and testosterone in human urine. *Steroids*. 1976 Dec;28(6):837-46
111. Wilkins RB, Carlson L. Qualitative studies of neutral 17-ketosteroids in normal subjects. *J Clin Endocrinol Met*. 1952; 12: 647-3
112. Vestergaard P, Raabo E, Vedso S. Determination of urinary testosterone in men, women and children. *Clin Chim Acta*. 1966 Oct;14(4):540-52
113. Krawczynska H, Zachmann M, Prader A. Urinary testosterone glucuronide and sulphate in newborns and young infants. *Acta Endocrinol (Copenh)*. 1976 Aug;82(4):842-50
114. Raynaud E, Audran M, Pages JC, Brun JF, Fedou C, Chanal JL, Orsetti A. Study of urinary excretion of testosterone and epitestosterone glucuronides in children and adolescents *Pathol Biol (Paris)*. 1993 Feb;41(2):159-63
115. Bandelow B, Sengos G, Wedekind D, Huether G, Pilz J, Broocks A, Hajak G, Ruther E. Urinary excretion of cortisol, norepinephrine, testosterone, and melatonin in panic disorder. *Pharmacopsychiatry*. 1997 Jul;30(4):113-7
116. Gode JD, Singh RH, Settiwar RM, Gode KD, Udupa KN. Increased urinary excretion of testosterone following a course of yoga in normal young volunteers. *Indian J Med Sci*. 1974 Apr-May;28(4-5):212-5
117. Yamamoto A, Ito M. Sebaceous gland activity and urinary androgen levels in children. *J Dermatol Sci*. 1992 Sep;4(2):98-104

Urinary 17-ketosteroids in women

118. Lloyd CW, Lobotsky J, Segre EJ, Kobayashi T, Taymor ML, Batt RE. Plasma testosterone and urinary 17-ketosteroids in women with hirsutism and polycystic ovaries. *J Clin Endocrinol Metab*. 1966 Mar;26(3):314-24
119. Johnsen SG. Fractionation of urinary 17-ketosteroids. II. Normal values for men and women at different ages. *Acta Endocrinol (Copenh)*. 1956 Feb;21(2):146-56
120. Balassi GP. Examination of the true significance and semiological limitations of determination of urinary neutral steroid catabolites with 17-keto-steroid function in women: urinary elimination of 17-ketosteroids in physiological conditions in women from infancy to menopause. *Minerva Ginecol*. 1954 Jan 15;6(1):34-43
121. Ferraris G. Influence of physiological conditions on urinary excretion of 17-ketosteroids by women. *Minerva Ginecol*. 1952 Jan;4(1):18-24

Urinary androsterone

122. Gilad S, Chayen R, Tordjman K, Kisch E, Stern N. Assessment of 5 alpha-reductase activity in hirsute women: comparison of serum androstanediol glucuronide with urinary androsterone and aetiocholanolone excretion. *Clin Endocrinol (Oxf)*. 1994 Apr;40(4):459-64

Corrective testosterone treatment in women

Testosterone medications for women

123. Buckler HM, Robertson WR, Wu FC. Which androgen replacement therapy for women? *J Clin Endocrinol Metab.* 1998 Nov;83(11):3920-4

Transdermal testosterone for women

124. Singh AB, Lee ML, Sinha-Hikim I, Kushnir M, Meikle W, Rockwood A, Afework S, Bhasin S. Pharmacokinetics of a testosterone gel in healthy postmenopausal women. *J Clin Endocrinol Metab.* 2006 Jan;91(1):136-44
125. Warnock JK, Swanson SG, Borel RW, Zipfel LM, Brennan JJ; ESTRATEST Clinical Study Group. Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal women. *Menopause.* 2005 Jul-Aug;12(4):374-84
126. Mazer NA, Shifren JL. Transdermal testosterone for women: a new physiological approach for androgen therapy. *Obstet Gynecol Surv.* 2003 Jul;58(7):489-500
127. Slater CC, Souter I, Zhang C, Guan C, Stanczyk FZ, Mishell DR. Pharmacokinetics of testosterone after percutaneous gel or buccal administration. *Fertil Steril.* 2001 Jul;76(1):32-7
128. Javanbakht M, Singh AB, Mazer NA, Beall G, Sinha-Hikim I, Shen R, Bhasin S. Pharmacokinetics of a novel testosterone matrix transdermal system in healthy, premenopausal women and women infected with the human immunodeficiency virus. *J Clin Endocrinol Metab.* 2000 Jul;85(7):2395-401

Sublingual/buccal testosterone for women

129. Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R. Time course of effects of testosterone administration on sexual arousal in women. *Arch Gen Psychiatry.* 2000 Feb;57(2):149-53
130. Wren BG, Day RO, McLachlan AJ, Williams KM. Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women. *Climacteric.* 2003 Jun;6(2):104-11

Intramuscular injections of testosterone or nandrolone for women

131. Sherwin BB, Gelfand MM, Schucher R, Gabor J. Postmenopausal estrogen and androgen replacement and lipoprotein lipid concentrations. *Am J Obstet Gynecol.* 1987 Feb;156(2):414-9
132. Neff MS, Goldberg J, Slifkin RF, Eiser AR, Calamia V, Kaplan M, Baez A, Gupta S, Mattoo N. A comparison of androgens for anemia in patients on hemodialysis. *N Engl J Med.* 1981 Apr 9;304(15):871-5

Testosterone treatment in women: dose and frequency

133. Hirshland H, Hill J. Effect of the frequency of injection on the clinical responses of postmenopausal women to testosterone enanthate with estradiol valerate. *Am J Obstet Gynecol.* 1963 May 15;86:177-82

Testosterone treatment in women: safety

134. Barrett-Connor E, Timmons MC, Young R, Wiita B, Estratest Working Group. Interim safety analysis of a two-year study comparing oral estrogen-androgen and conjugated estrogens in surgically menopausal women. *J Women's Health* 1996;5:593-602
135. Sherwin BB, Gelfand MM, Schucher R, Gabor J. Postmenopausal estrogen and androgen replacement and lipoprotein lipid concentrations. *Am J Obstet Gynecol.* 1987 Feb;156(2):414-9 (*"testosterone did not induce an increased atherogenic lipid profile"*)
136. Davison S, Thippawong J, Blanchard J, Liu K, Morishige R, Gonda I, Okikawa J, Adams J, Evans A, Otulana B, Davis S. Pharmacokinetics and acute safety of inhaled testosterone in postmenopausal women. *J Clin Pharmacol.* 2005 Feb;45(2):177-84

Testosterone treatment in women: side effects

137. Maguire HC Jr. Facial hair growth over site of testosterone injection in women. *Lancet*. 1964 Apr 18;42:864
138. Gitlin N, Korner P, Yang HM. Liver function in postmenopausal women on estrogen-androgen hormone replacement therapy: a meta-analysis of eight clinical trials. *Menopause*. 1999 Fall;6(3):216-24

Testosterone treatment in women: interferences

139. Kuhn W, Staks T, Jutting G. Pharmacokinetics of levonorgestrel and ethinylestradiol in 14 women during three months of treatment with a tri-step combination oral contraceptive: serum protein binding of levonorgestrel and influence of treatment on free and total testosterone levels in the serum. *Contraception*. 1994 Dec;50(6):563-79
140. Mathur RS, Landgreve SC, Moody LO, Semmens JP, Williamson HO. The effect of estrogen treatment on plasma concentrations of steroid hormones, gonadotropins, prolactin and sex hormone-binding globulin in post-menopausal women. *Maturitas*. 1985;7:129-33
141. Krug R, Psych D, Pietrowsky R, Fehm HL, Born J. Selective influence of menstrual cycle on perception of stimuli with reproductive significance. *Psychosom Med*. 1994;56:410-7
142. Castlo-Branco C, Martinez de Osaba MJ, Fortuny A, Iglesias X, Gonzalez-Merlo J. Circulating hormone levels in menopausal women receiving different hormone replacement therapy regimens. A comparison. *J Reprod Med*. 1995;40:556-60
143. Goh HH, Wong PC, Ratnam SS. Effects of sex steroids on the positive estrogen feedback mechanism in intact women and castrate men. *J Clin Endocrinol Metab*. 1985 Dec;61(6):1158-64
144. Vermesh M, Silva PD, Rosen GF, Vijod AG, Lobo RA. Effect of androgen on adrenal steroidogenesis in normal women. *J Clin Endocrinol Metab*. 1988 Jan;66(1):128-30

Testosterone treatment in women: follow-up

145. Bird CE, Finnis W, Boroomand K, Murphy J, Clark AF. Kinetics of testosterone metabolism in normal postmenopausal women and women with breast cancer. *Steroids*. 1978 Oct;32(3):323-35
146. Bassindale T, Cowan DA, Dale S, Hutt AJ, Leeds AR, Wheeler MJ, Kicman AT. Effects of oral administration of androstenedione on plasma androgens in young women using hormonal contraception. *J Clin Endocrinol Metab*. 2004 Dec;89(12):6030-8
147. White T, Jain JK, Stanczyk FZ. Effect of oral versus transdermal steroidal contraceptives on androgenic markers. *Am J Obstet Gynecol*. 2005 Jun;192(6):2055-9