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
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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 Medicine Antievejenimiento 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


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;
2. Screening should be done for participation in professional sports;
3. 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 Hypogoadism, 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 to 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 Respiration.

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 consensuses 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 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 patient’s 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. 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.” Perhaps the best known example is

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

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.” The FDA has, however, traditionally viewed manufacturer dissemination of such materials as promotion that constitutes advertising and thus violates the FD&C Act. 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. 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.

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

Senescence is associated with alterations in the circadian cycle of serum GH:
a reduced amplitude and aphase advance

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

Failure of repair systems: GH accelerates repair

Immune deficiency: GH stimulates the immune system


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


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


**Progressive telomere shortening:** GHRH may stimulate telomerase


**GH and psychic well-being**

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


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


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


Depression: the improvement with GH treatment


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


Anxiety: the improvement with GH treatment


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


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

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

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

Loss of sexual potency: the improvement with GH treatment

GH and physical appearance/body composition

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

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

Lean body mass: the improvement with GH treatment

Physical appearance, body morphology improvement with GH treatment

GH and age-related diseases

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

Hypercholesterolemia: the improvement with GH treatment
117. Olsovska 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
Atherosclerosis: the association with lower GH and/or IGF-1 levels


Atherosclerosis: the improvement with GH treatment


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

Arterial hypertension: the improvement with GH treatment

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

Coronary heart disease: the improvement with GH treatment

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


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


Obesity: the improvement with GH treatment


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

**Diabetes: the improvement with GH treatment**


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


**Rheumatism: the improvement with GH treatment**


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


**Osteoporosis: the improvement with GH treatment**


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


Cancer: improvement with GH treatment?


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


Longevity: the improvement with GH treatment


GH diagnosis


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

GH clinical evaluation


Serum GH tests

Serum IGF-1


Low serum IGF-1 for diagnosis of GH deficiency


Serum IGF-1 and IGFBP-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

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


Insulin stimulation test


How many lab tests


24-hour urine GH tests

Urinary Growth Hormone


254. Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkebæk NE. The ratio between serum levels of insulin-like growth factor (IGF-I) and the IGFB 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


Corrective GH Therapy


GH Medications

GH subcutaneous injections


**Intranasal GH**


**GH treatment: dosage**


310. Weksler ME. Hormone replacement therapy for men: has the time come? Geriatrics. 1995;50:52-4


**GH treatment: interferences or associations**

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


**GH treatment: safety, side effects, complications**


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


**GH secretagogues**


nightly injections of growth hormone-releasing hormone GHRH 1-29 in healthy elderly men. Metabolism. 1997;46:89-96


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. Wurzburger 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


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


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


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

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

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.

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.


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


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.

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)

39
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

Treatment of GH-deficient children: higher incidence of diabetes
2. Cutfield WS, Wilton P, Benmmarker 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)

Acromegaly is associated with an increased incidence of diabetes

Arguments pro GH use:

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

GH is an anti-hypoglycemic hormone: it neutralizes hypoglycaemia
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)
IGF-1 therapy has insulin-like effects: it reduces glycemia and serum insulin in controls and type 2 diabetic patients


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


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 hemoglobin HbA1C


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 gonadotrophins 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.”)


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


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

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

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
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)


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 ”)

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


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

GH improves the heart function

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

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

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

Hypopituitarism increases the cerebrovascular mortality

GH deficient patients have a higher incidence of cerebrovascular events

GH TREATMENT

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

GH treatment may improve coronary heart disease

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

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)

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

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


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


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 acromegalic & 100 x greater in male acromegalic 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 ”)


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)

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.


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


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


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)


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)


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


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


**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.**


**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**

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, individual 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
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, Behlouli 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

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.
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

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

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


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


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


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


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


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

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 mammmary carcinoma in female rats

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

A lower serum GH level is found in gastric cancer patients

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

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

Conclusion on the cancer studies and GH

- GH therapy raises both the levels of both IGF-I and IGFBP-3. IGFBP-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)

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,

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-I 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 (mise) may not be necessarily true for species with a long life such as humans)

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)

**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


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


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

**survival of HIV patient from pneumonia**


**survival from typhus**


**NEUTRAL information on GH and longevity**

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


**Arguments pro GH use**

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

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


**Higher mortality in GH deficient women**


**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)


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


GH TREATMENT: Corrective GH hormone treatment increases survival

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


GH treatment of normal elderly mice, extended the mean and maximal life span. - 8-9


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


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**

**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
4. Becker DV, Bigos ST, Gaitan E, Morris JCr,d, 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”)

**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!)
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)
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
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

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

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.)

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

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

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


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 unjustifiably skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range should therefore be lower than in whites


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, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos 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 peroxidise antibodies are detected”


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


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


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

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

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)

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

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.

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

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

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

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

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

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.

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.


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.


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


Serum thyroid hormone levels may not reflect the cellular thyroid status

64. Escobar del Rey F, Ruiz de Ona C, Bernal J, Oregón 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


Conditions or factors that DEPRESS the serum TSH

**Aging**

**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

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

**Pregnancy (first trimester)**

**Depression and anxiety disorders**

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


94. Bacci V, Schussler GC, Kaplan TB. The relationschip between serum triidothyronine 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 thyroxin changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab. 1986 Apr;62(4);717-22


Medications: thyroid therapy, estroprogestative birth control pills, progestogens, anti-inflammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antirhythmics (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


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


Toxic foods: MSG, alcohol


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


FACTORS that ELEVATE the serum TSH

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

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

Auto-immune thyroiditis and hypothyroidism: primary, iodine-deficient, thyroid hormone resistance
137. Volpe R. Subacute (de Quervain's) thyroiditis. J Clin Endocrinol Metab. 1979 Mar;8(1):81-95

TSH-secreting tumors (rare)
FACTORS that ELEVATE or DEPRESS serum TSH

Physiological serum TSH fluctuations

Variations in the biological activity of TSH
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


105. Laurberg P. Persistent problems with the specificity of immunometric TSH assays. Thyroid. 1993 Winter;3(4):279-83


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


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


After intake of thyroid hormones, 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 patients who exhibit reversion of an initially high TSH level back into the reference range, are found to subsequently develop mild thyroid failure


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.


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


Other tests: urinary T3 as a complementary test

**Testosterone in men**

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


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)


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


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


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


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


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


**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**

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


**Testosterone**


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


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


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

**Testosterone**


**Dihydrotestosterone**

Testosterone and psychic well-being in men

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

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


**Depression in men: the association with lower testosterone levels**


53. Werner AA. The male climacteric JAMA. 1946; 132 (4):188-94


Depression in men: the improvement with testosterone treatment
64. Lamar CP. Clinical endocrinology of the male: with special reference to the male climacteric. J Fla Med Assoc. 1940; 26:398–404

Anxiety in men: the association with lower testosterone levels
69. Werner AA. The male climateric JAMA. 1946;132(4):188-94

Anxiety in men: the improvement with testosterone treatment

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


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


**Sleep disorder in men: the improvement with testosterone treatment**


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


89. Younes AK. Low plasma testosterone in varicocele patients with impotence and male infertility. Arch Androl. 2000 Nov-Dec;45(3):187-95


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


**Fertility:**

**Loss of fertility in men: the improvement with androgen treatment**
75


Testosterone and physical appearance/body composition

Sarcopenia in men: the association with low testosterone levels

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

Sarcopenia in men: the improvement with testosterone treatment

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

Lean body mass in men: the improvement with testosterone treatment


Testosterone and age-related diseases in men

Hypercholesterolemia in men: the association with lower testosterone levels


Hypercholesterolemia in men: the improvement with testosterone treatment


Atherosclerosis in men: the association with lower testosterone levels

Atherosclerosis in men: the improvement with testosterone treatment

Arterial hypertension in men: the association with lower testosterone levels

Arterial hypertension in men: the improvement with testosterone treatment

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

Stroke in men: the association with lower testosterone levels

Stroke in men: the improvement with testosterone treatment
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
Obesity in men: the improvement with testosterone treatment

Diabetes in men: the association with lower testosterone levels

Rheumatism in men: the association with lower testosterone levels
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

Rheumatism in men: the improvement with testosterone treatment
Osteoporosis in men: the association with

**Lower estrogens and androgen levels**


Osteoporosis in men: the improvement with testosterone treatment


Hip fractures in men: the association with lower testosterone levels

Cancer in men: the association with lower testosterone levels

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


**Longevity in men: the association with testosterone levels**


**Testosterone diagnosis**


**Clinical testosterone evaluation in men**


232. Werner AA. The male climacteric. JAMA. 1946;132(4):188-94


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


Serum FSH in men


Serum testosterone in men


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

Serum dihydrotestosterone and androstanediol glucuronide in men


Serum PSA in men


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


24-hour urine androgen tests in men

Urinary testosterone androgen tests in men


271. Callow, Nancy H. The isolation of two transformation products of testosterone from urine. Biochem J. 1939;33:559-64
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


Urinary 7-ketosteroids in men


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


Corrective testosterone/androgen therapy for men

Various testosterone/androgen medications for men


Transdermal testosterone for men

337. Findlay JC, Place VA, Snyder PJ. Transdermal delivery of testosterone. J Clin Endocrinol Metab. 1987;64:266-8

Oral testosterone for men

(The absorption is not sufficiently reliable for routine use. The large doses required to achieve therapeutic levels, make oral administration of free testosterone impractical)

Oral mesterolone for men


**Oral testosterone undecanoate for men**


**Sublingual testosterone for men**


**Intramuscular injections of testosterone enanthate or cyprionate for men**


Intramuscular injections of nandrolone decanoate for men


Intramuscular injections of testosterone undecanoate for men


Testosterone pellets for men


Transdermal dihydrotestosterone for men


**Importance of reducing excessive levels of estradiol in men**


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**


**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**


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


**Testosterone/androgen treatment in men: interferences – associations**


**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

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


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)


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

**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

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.")

7. Baron E et al. Arch Path. 1941,32:787-93

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.”)


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

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 signif icant 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

Androgen deprivation causes impotence

Androgen deprivation therapy may cause urinary incontinence
Androgen deprivation therapy generates a greater rate of bone loss in men with prostate cancer

Testosterone deprivation therapy increases arterial stiffness in men with prostate cancer

Dihydrotestosterone deprivation therapy increases the risk of aggressive prostate cancer

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

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

Low serum testosterone is associated with an increased prostate cancer risk
Low serum testosterone levels have been found in prostate cancer patients

Close to statistical significance lower testosterone levels in prostate cancer patients

Low testosterone levels are found in prostate cancer patients and in their (not yet affected) relatives with familial predisposition to prostate cancer
A high serum SHBG (and thus less bioavailable testosterone) is found in men with family history of prostate cancer


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


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)


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


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


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


High grade prostate cancers are associated with low testosterone levels


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


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


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)


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


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


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


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


Men with chronic prostatitis have often low testosterone

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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

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

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

Studies where testosterone treatment reduces prostate dysfunction complaints (dysuria, nocturia)
74. Flamm J, Kiesswetter H, Engisch 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
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
Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)


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

ANIMAL STUDIES:

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

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

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.

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

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

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

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


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


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


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


A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells


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

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


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. 2001 Nov;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 2002Feb;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


Studies with no correlation between serum testosterone and serum PSA

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


**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**


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


**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 tumors were even inhibited by the treatment; the responses were extremely variable


121. Trunnell JD, Duffy BJ Jr. The influence of certain steroids on the behavior of human prostate cancer. Trans. NY Acad Sci. 1950;II:12:238-41


123. Pearson OH. Discussion of Dr. Huggins’ paper: “Control of cancers of man by endocrinological methods.” Cancer Res. 1957;17:473-9


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


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)


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

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


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

Studies where DHT treatment had no effect on the prostate volume


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, nore was serum SHBG analysed: dehydrated persons have usually high SHBG, and thus higher total testosterone, which is bound to it, but generally low active, bioavalable and free testosterone levels)


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


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


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

D-stege 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)


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

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


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


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


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)


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


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


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


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

A study where estrogen treatment stimulate prostate stromal hyperplasia

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
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

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

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

Testosterone and psychic well-being in women

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

Quality of life in women: the improvement with testosterone treatment

Vasomotor symptoms in women: the improvement with testosterone treatment

Depression in women: the association with lower testosterone levels

Depression in women: the improvement with testosterone treatment

Negative symptoms in women: the association with lower serum testosterone levels
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 vs. 2.2+/-.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

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

Love in women: the association with higher testosterone in women

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

Sexuality decline in women: the improvement with testosterone treatment

Testosterone and physical appearance/body composition in women

Sarcopenia in women: the association with lower testosterone levels

Sarcopenia in women: the improvement with testosterone treatment

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

Lean body mass in women: the improvement with testosterone treatment

Testosterone and age-related diseases in women
Atherosclerosis in women: the association with lower testosterone levels

Atherosclerosis in women: the improvement with testosterone treatment

Coronary artery disease in women: the association with lower testosterone levels

Coronary artery disease in female subjects: the improvement with testosterone treatment

Osteoporosis and osteopenia in women: the association with lower testosterone levels
Osteoporosis and osteopenia in women: the improvement with testosterone treatment

Height loss and hip fractures in women: the association with lower testosterone levels

Rheumatism in women: the association with lower testosterone levels

Rheumatism in women: the improvement with testosterone treatment

Obesity in women: the improvement with testosterone treatment
Cancer in women: the association with lower testosterone levels

Cancer: the improvement with testosterone treatment?

Longevity in women: the association with lower testosterone levels

Testosterone diagnosis in women

Clinical testosterone evaluation in women

Serum androgen tests in women

Serum total testosterone in women

**Serum free testosterone in women**

**Serum dihydrotestosterone and androstanediol glucuronide in women**

**Serum androsterone in women**

**24-hour urine testosterone tests in women**

**Urinary testosterone in women**


**Urinary 17-ketosteroids in women**


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


**Urinary androsterone**

Corrective testosterone treatment in women

Testosterone medications for women


Transdermal testosterone for women


Sublingual/buccal testosterone for women


Intramuscular injections of testosterone or nandrolone for women


Testosterone treatment in women: dose and frequency


Testosterone treatment in women: safety

Testosterone treatment in women: side effects


Testosterone treatment in women: interferences

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

Testosterone treatment in women: follow-up