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# CIPROFLOXACIN INDUCED CHONDROTOXICITY AND TENDINOPATHY

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## ABSRACT

Ciprofloxacin is one of the fluoroquinolones with a wide clinical acceptability. Rescently there are increasing reports on Ciprofloxacin induce Chondrotoxicity and Tendinopathy in Animal experiment and clinical experience which is of great clinical concern. A comprehensive survey and review of literaure on reported ciprofloxacin induced Chondrotoxicity and Tendinopathy in Humans and Animals was performed. It was observd that ciprofloxacin is a potential inducer of Chrondrotoxicity and Tendinopathy which could be potentiated by coadministration with corticosteroids.This conditions were reported to be characterised by cartilage lesion, matrix swelling, inhibition of chondrocytes proliferation, secretion of soluble proteoglycan, modification of the metabolism and integrity of extracellular proteins, decrease in epiphyseal growth plate, humerus and femur.The mechanism behind this phenomenon is said to be multifactoral. Ciprofloxacin induced Chrondrotoxicity and Tendinopathy in growing animals is attributed to oxidative stress (lipid peroxidation, Deoxyribonucleic Acid (DNA) oxidative stress). Ciprofloxacin induced cartilage damage may also be attributed to formation of Ciprofloxacin chelates and complexes which possesses the potential to induce a deficiency of functionally available divalent ions resulting in cytoskeletal changes. Animal studies showed that oxidative damage or metabolism of tissues was also found suggesting the involvement of a reactive oxygen species. Administration of magnesium, zinc chloride and vitamin E (α tocopherol) were found to prevent or reverse ciprofloxacin induced Chrondrotoxicity and Tendinopathy. Through excess formation of collagen, increase osteoblastic activity, increase bone growth, inhibition of free oxidation radicals' formation thereby preventing DNA oxidation and oxidative stress. Zinc also directly stimulates DNA synthesis either by enzyme stimulation or altering, the binding of f1 and f3 histones to DNA so as to affect RNA synthesis. Patient medical history should be considered before Ciprofloxacin recommendation. Coadministration with corticosteroid should be done with caution. Further evaluation of antioxidants effect in Ciprofloxacin induce Chonrotoxicity, Tendinopathy in humans could be of clinical importance as observed in Animal studies.

**Keywords:** Ciprofloxacin, Chrondrotoxicity, Tendinopathy, Tendon Rupture

## 1. INTRODUCTION

The first Quinolone, nalidixic acid was first isolated as a byproduct of the synthesis of chloroquine in early 1960s (Hall *et al*., 2011) Later in the 1980s fluorinated derivatives e.g., ciprofloxacin were synthesized (Stahlmann, 2002). Ciprofloxacin is a second generation fluoroquinolone with a broad spectrum of antibacterial activity. It has a good bioavailability after oral administration, good to excellent tissue penetration and relative safe (Ball and Tillotson, 1995; Papich, 1998). It is very active against wide variety of pathogenic bacteria including some gram-positive and most grain-negative organism (Hooper and Wolfson, 1985). It is used in a variety of human clinical infections (Sub and Lorber, 1995).

Ciprofloxacin exerts its action by blocking bacterial DNA synthesis through inhibition of bacterial topoisomerase ii (DNA gyrase) and topoisomerase iv. Inhibition of DNA gyrase prevents the relaxation of positively super coiled DNA that is required for normal transcription and replication (Lica and Zhao, 1997; Alovero *et al*., 2000; Hooper, 2000). Inhibition of topoisomerase iv interferes with separation of replicated chromosomal DNA into respective daughter cells during cell division (Mitscher and Mao, 2003).

Ciprofloxacin is generally well tolerated and remains one of the safest of all antibiotics with remarkably few reactions (Hooper and Wolfson, 1985; Ball, 1986). These reactions include gastrointestinal tract, central nervous system and hematological system (Petri, 2001; Lode *et al*., 1998).

Despite its safe profile there are reported cases of Ciprofloxacin induced chrondrotoxicity, Tendinopathy and tendon rupture in animals and humans (Khaliq and Zhanel 2003; Channa *et al*., 2008). It was reported that Ciprofloxacin decreased thickness of the articular cartilage of the femoral condyle, inhibit proliferation of cultivated chondrocytes and secretion of soluble proteoglycans in a concentration and time dependant manner (Li *et al*., 2004). Ciprofloxacin induced damage of the articular and epiphysical growth plate cartilage of knee joint, tendinopathy and tendon rupture (Halawa, 2010; Kim, 2010).

The pathogenesis of Ciprofloxacin induced chrondrotoxicity, tendinopathy and tendon rupture is a multifactoral event (Halawa, 2010). Previous studies attributed cartilage damage in growing animals to oxidative stress, lipid peroxidation and DNA oxidative damage of the chondrocytes and collagen (Simonin *et al*., 1999; Li *et al*., 2004).

Other authors' referred to Ciprofloxacin induced tendinopathy to their inhibitory effects on DNA, collagen and proteoglycan synthesis (Maslanka *et al*., 2004). As of July 2008, the United State Food and Drug Administration mandated that Ciprofloxacin product should have a black-box warning indicating an increased risk in adverse events including tendon rupture (Kim, 2010). This study reviews reported Ciprofloxacin induced Chrondrotoxicity, Tendinopathy and tendon rupture in humans and animals due to rising trend.

## 1.1. Animal Studies

Experiments with animals have reported cases of Ciprofloxacin induced chrondrotoxicity, tendinopathy and tendon rupture (Li *et al*.,1990; Stahlmann, 2003; Tsai *et al*., 2008). It was observed that Ciprofloxacin at a dose level of 20 mg $kg^{-1}$ day administered to rats for 15 days induced articular damage, cavity Formation wide clefts and decrease in both articular and epiphyseal growth plate (Halawa, 2010). This report is in resonance with the report of Channa *et al*. (2008) who administered 20 mg $kg^{-1}$ of Ciprofloxacin to wistar albino pulps. He observed decrease in the width of epiphyseal growth plate cartilage, humerus and femur as compared to the control.

In another study where Ciprofloxacin was administered to newly born rat-litters intraperitonealy. Ciprofloxacin induced growth plate retardation by inhibiting mitosis in the proliferative zone. Ciprofloxacin also affected the mean length of humora and femora leading to reduction in Limb length of rat pulps (Channa *et al*., 2008). The above reports could be consistent with the study of Stahlmann *et al*. (2000) who reported that 200 mg $kg^{-1}$ of Ciprofloxacin administered to immature Beagles induced cleft formation and erosion of joint cartilage. Male wistar rats exposed to 50mg $kg^{-1}$ of Ciprofloxacin for 21 days inhibit fracture healing with decreased cartilage cellullarity and fibrous proliferation and matrix degeneration (Huddleston *et al*., 2000).

Furthermore, 30 and 90 mg $kg^{-1}$ oral doses of Ciprofloxacin was found to induce a characteristic arthropathy (blister and erosions) in Juvenile beagle with persisted lesions after five (5) months treatment free period (Keutz *et al*., 2004). Ciprofloxacin in a 2 weeks study induced cartilage blisters when 100 and 200 mg $kg^{-1}$ were administered to Juvenile dogs. In another study, cartilage alterations in Knee joints were seen after 30-100 mg $kg^{-1}$ of Ciprofloxacin was administered for 3 weeks (Schuter, 1987). Several cartilage lesions marked by matrix swelling and loss of chondrocytes were observed when 400, 800 and 1200 mg $kg^{-1}$ of Ciprofloxacin was administered to 4 week-old rats for 7 days consecutively. The thickness of the femoral condyle was significantly decreased compare to the control. Proliferation of chondrocytes and secretion of soluble proteoglycans were also inhibited (Li *et al*., 2004; Pfister *et al*., 2007).

Other authors found that single high oral doses and multiple low doses of Ciprofloxacin were chondrotoxic in Juvenile rats. Ciprofloxacin induced scars and erosions of the joint surface as well as chondrocytes clusters with non Cellular areas of the articular matrix (Foster *et al*., 1997; Stahlmann, 2003). The study of Li *et al*. (2004) is in support of the above report. He reported that Ciprofloxacin inhibited chondrocytes proliferation in a dose dependant and time dependant manner. 10-80 mg $L^{-1}$ of Ciprofloxacin decreased secretion of soluble proteoglycans after incubation with chondrocytes for 5 days.

Subcutaneous injection of 600 mg $kg^{-1}$ of Ciprofloxacin administered to 34-day old wistar rats induced cartilage lesion in 11 of 12 (92%) rats (Stahlmann *et al*., 1999; Pfister *et al*., 2007). Ultra structural changes were observed in Achilles tenocytes of Ciprofloxacin treated Spraque Dawley rats (Stahlmann, 2002; Bae *et al*., 2006). These reports are at variance with the study of Kashida and Kato (1997), who observed that 200mg and 900 m $kg^{-1}$ of Ciprofloxacin administered to rats did not induce Achilles tendon toxicity.

Some researchers observed that Ciprofloxacin induced cartilage damage in experimental animals when administered during certain developmental stages via

changes of cytoskeleton morphology (Water *et al*., 1998; Egerbacher *et al*., 2000). Ciprofloxacin at a dose level of 50 mg $kg^{-1}$ administered to rats for 3 weeks revealed significant deterioration of Biochemical parameters, hyaline degeneration and fibre disarrangement in the tendon of rats (Olcay *et al*., 2011).

Findings showed that Ciprofloxacin exerts a negative impact on migration and proliferation as well as the collagen metabolism of tenocytes (Mehra *et al*., 2004; Tsai *et al*., 2011). Pauzaud *et al*. (2004) reported that Ciprofloxacin showed moderate Cytotoxicity after 28 hours and more severe significant toxicity after 72 hours on tendon cells. This agrees with the study which observed that Ciprofloxacin inhibits tendon cell proliferation and cause cell cycle arrest in rats (Tsai *et al*., 2008). It was reported that cell proliferation in horse and dog chondrocytes decreased in Ciprofloxacin cultivated groups (Egerbacher *et al*., 2001).

Incubation of Achilles tendon, Achilles paratenon and shoulder capsule fibroblast with Ciprofloxacin hydrochloride (5-50 pg $mL^{-1}$) significantly decreased cell proliferation, collagen synthesis and proteoglycan synthesis in fibroblast cell line (Williams *et al*., 2000). Degenerative changes in tenocytes due to swelling and dilatation of cell organelles, densified nuclei and clumped chromatin cell detachment from extracellular matrix, decrease in fibril diameter and increase distance between collagenous fibrils were induced by Ciprofloxacin in immature wistar rats (Shakibaei *et al*., 2000).

## 1.2. Human Studies

There is increasing trend of Ciprofloxacin induced tendinopathy and tendon rapture in human (McEwan and Davey, 1988; Movin *et al*., 1997; Short *et al*., 2006). There is a reported case of Ciprofloxacin associated Achilles tendon diseases. Microscopic evaluation revealed irregular collagen fibre arrangement, hypercellularity and increase interfibrillar glycosaminoglycan (West and Gow, 1998; Pantalone *et al*., 2011). Ciprofloxacin induced Achilles tendon rupture characterized by degenerative changes in left Achilles tendon, cystic changes with focal necrosis (Hugo-Persson, 1996; Jagose *et al*., 1996; Petersen and Lapress, 1998).

Khazad and Schwenk (2005) reported a case of non traumatic rupture of Achilles tendon in a patient who received oral Ciprofloxacin 500 mg twice orally for urinary tract infection. This agrees with the report of other authors (Lee and Collins, 1992; Poon and Sundaram, 1997; Caspirian *et al*., 2000).

In a case study, 32 patents (76%) had tendinitis and 10 patents (24%) had tendon rupture. 13 (31%) were attributed to Ciprofloxacin (Linden *et al*., 2001). This is at variance with a study where no cases of Achilles tendon rupture were found in 2, 122 Ciprofloxacin treated patients (Shinohara *et al*., 1997). In France Pierfitte *et al*. (2000) reviewed 421 cases of Fluoroquinolones associated tendinopathy. They reported that only 5% of Fluoroquinolones associated tendinopathy was attributed to Ciprofloxacin.

In a critical literature review of fluoroquinolones associated tendinopathy in humans. It was observed that Ciprofloxacin is one of the agents associated with tendinopathy (Khaliq and Zhanel, 2003; Mirovsky *et al*., 1995; Brava *et al*., 1996; Carrasco *et al*., 1997). In a case study, 98 cases of fluoroquinolones induced tendon injury were reported. It was observed that the second most commonly implicated fluoroquinolone associated with tendon injury was Ciprofloxacin (25.5% of all cases) with total daily doses ranging from 500-200 mg for a mean duration of 24±29.3 days (Khaliq and Zhanel, 2003).

In an observed cohort study of fluoroquinolones and other antibiotics induced tendon disorder. It was reported that Ciprofloxacin is also associated with tendon disorder but with effects lesser than that of Ofloxacin (Wilton *et al*., 1996). In 1795 case report forms for children receiving Ciprofloxacin which were collected up to the end of 1994 by Bayer cooperation Germany (Chysky *et al*., 1991; Hampel *et al*., 1997) shows that Ciprofloxacin is safe for children, adolescents and do not have negative effects on the linear growth children. This is at variance with what was observed in animal studies (Kato, 2008).

The confirmation of the safety of Ciprofloxacin especially in relation to the skeletal system in large scale clinical studies has led to it being approved for use in pediatric patients with cystic fibrosis (Kato, 2008). This report could be at variance with the report of Adefurin *et al*. (2011). Who stated that a total of 16184 pediatric patients who were exposed to Ciprofloxacin and 1065 reported cases of musculoskeletal adverse effects were observed.

Furthermore, monolayers of human tenocytes were incubated with Ciprofloxacin. Ciprofloxacin significantly decreased type 1 collagen, beta (1)-integrin receptors, cytoskeletal and signaling proteins. It increased matrix metalloproteinases as well as the apoptosis marker activated caspase 3 effects are intensified at higher concentrations and longer incubation periods (Corps *et al*., 2005; Sendzik *et al*., 2005; 2010).

## 1.3. Pathogenesis

The pathogenesis of fluoroquinolones (Ciprofloxacin) induced chrondrotoxicity, tendinopathy and tendon rupture has not been fully established (Khaliq and Zhanel

2003). Although a number of suggestions have been made, previous studies attributed articular cartilage damage in growing animals to oxidative stress lipid peroxidation and DNA oxidative damage of chondrocytes and collagen. Those factors collectively resulted in modification of the metabolism and integrity of extracellular proteins (Simonin *et al*., 1999; Maslanka *et al*., 2004; Li *et al*., 2010).

Ciprofloxacin induced chrondrotoxicity was also explain on the basis that Ciprofloxacin chelates magnesium ions or divalent ions resulting in change function of chondrocytes surface integrin receptors (Stahlmann *et al*., 1995; Shakibaei *et al*., 2000; Lozo *et al*., 2004). This report is supported by the ability of magnesium to reverse or inhibit Ciprofloxacin induced chrondrotoxicity (Stahlmann *et al*., 1999; Stahlmann, 2002). This shows that patients with latent magnesium deficiency could be at an increase risk of Ciprofloxacin induce tendon disorder. Pfister *et al*. (2007), also supported this view when he demonstrated that Ciprofloxacin induced cartilage lesions was reversed in animals treated with vitamin E (α tocopherol) and magnesium or both. This also agrees with other studies (Stahlmann *et al*., 1999).

It was also reported that Zinc chloride minimized epiphyseal cartilage damaged induced by Ciprofloxacin in wistar albino rats. This agrees with other observations (Channa *et al*., 2008). Hickory *et al*. (1979) reported that zinc helps in excess formation of collagen, increase osteoblastic activity and increase rate of longitudinal growth and bone remodeling in experimental rats. Zinc also directly stimulates DNA synthesis either by enzyme stimulation or altering the binding of $f_1$ and $f_3$ histones to DNA so as to affect RNA synthesis (Prasad, 1991).

Animal studies showed that oxidative damage or metabolism of tissues was also found suggesting the involvement of a reactive oxygen species (Thuong-Guyot *et al*., 1994; Hayem *et al*., 1996; Khaliq and Zhanel, 2003).

Corticosteroid may precipitate Ciprofloxacin induce rupture of Achilles tendon. The exact mechanism by which corticosteroids cause tendon damage is not clear. It is said that steroids have the ability to alter the collagen structure of tendons by contributing to dysplasia of collagen fibrils, thus reducing the tensile strength of the tendon (Kelly *et al*., 2004). Corticosteroids can also interfere with collagen fibre cross-linking which can lead to disruption in the normal healing process of the tendon (Orava *et al*., 1996; Kotnis *et al*., 1999; Kelly *et al*., 2004).

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