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Review

Fluoroquinolone-Induced Tendinopathy: Etiology and Preventive Measures

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Tendinopathy is a serious health problem and its etiology is not fully elucidated. Among intrinsic and extrinsic predisposing factors of tendinopathy, the impact of therapeutic agents, especially fluoroquinolone (FQ) group antibiotics, is recently being recognized. FQs are potent bactericidal agents widely used in various infectious diseases, including community acquired pneumonia and bronchitis, chronic osteomyelitis, traveler's diarrhea, typhoid fever, shigellosis, chronic bacterial prostatitis, uncomplicated cervical and urethral gonorrhea and prophylaxis of anthrax. FQs have an acceptable tolerability range. However, many lines of evidence for developing tendinitis and tendon rupture during FQ use have resulted in the addition of a warning in patient information leaflets. FQ-induced tendinopathy presents a challenge for the clinician because healing response is poor due to low metabolic rate in mature tendon tissue and tendinopathy is more likely to develop in patients who are already at high risk, such as elderly, solid organ transplant recipients and concomitant corticosteroid users. FQs become photo-activated under exposure to ultraviolet light, and this process results in formation and accumulation of intracellular reactive oxygen species (ROS). The subsequent FQ-related oxidative stress disturbs mitochondrial functions, leading to apoptosis. ROS overproduction also has direct cytotoxic effects on extracellular matrix components. Understanding the mechanisms of the FQ-associated tendinopathy may enable designing safer therapeutic strategies, hence optimization of clinical response. In this review, we evaluate multi-factorial etiology of the FQ-induced tendinopathy and discuss proposed preventive measures such as antioxidant use and protection from natural sunlight and artificial ultraviolet exposure.

Keywords: apoptosis; fluoroquinolone; oxidative stress; pharmacology; tendinopathy
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Tendon is a collagenous dense fibrous tissue, anchoring muscles to bones and operating in a uniaxial manner. Both of its cellular and extracellular components work in coordination to provide optimal flexibility and tensile strength (Table 1) (Kjær 2004; Sharma and Maffuli 2005; Alberts et al. 2008a). Many of these components are shown to be potential targets for tendinopathic agents.

The term "tendinopathy" is recommended as a more appropriate generic description for tendon related disorders, whereas the terms "tendinitis" and "tendinosis" can be used only after confirmation of tendon inflammation and degeneration, respectively (Wang et al. 2006). Age over 60, solid organ transplantation and concurrent corticosteroid use are well established risk factors for fluoroquinolone (FQ) related tendinopathy (Stahlmann and Lode 2010; Petri 2011), but gender, muscle constitution and musculotendineous flexibility, biomechanical faults, high serum lipids, ischemia, reperfusion injury, hyperthermia, mechanical strain and environmental factors are also known as predisposing (Paavola et al. 2002; Young and Maffuli 2007).

Tendinopathy is a contemporary challenge in clinical practice, healing response is poor and the etiology is still unclear (Battery and Maffuli 2011). Within the last decade, awareness about drug-induced tendinopathy increased considerably. In 2008, a black box warning regarding the risks of tendinopathy and tendon rupture was added to product labels of all FQ antibiotics in US patient information leaflets (Tanne 2008). Today, drug induced tendinopathy is accepted as a class effect of FQs.

When we fully understand pathophysiology of FQ-induced tendinopathy, we will be able to design optimal therapeutic strategies.

Structure Safety Relationship

Development of FQs by addition of a fluorine molecule at R6 position of the quinolone core was considered to

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Table 1. Tendon tissue components and their functions*.

MAJOR COMPONENTS	FUNCTION
Cells	
Tenoblasts and tenocytes	Synthesis and maintenance of collagenous and non- collagenous constituents of ECM
Chondrocytes	Biomechanical support function, attachment to bones
Synovial cells	Biomechanical support function
Capillary endothelial cells	Passage of various substances
Smooth muscle cells	Blood supply
Extracellular Matrix (ECM)	
Water	Spacing and lubrication
Glycosaminoglycans (GAGs)	Resistance against compression on the matrix; facilitation of rapid diffusion of water soluble molecules (nutrients, metabolites etc) between blood and cells; most covalently linked to a protein core in proteoglycans
Proteoglycans	
Decorin, fibromodulin, lumican, keratocan, perlecan, syndecan, aggrecan, biglycan, proteoglycan 4	Lubrication and providing a viscous environment, for optimal dissipation of load stress by collagen fibers; tendon integrity
Collagen	Strengthening and organization of the matrix; high tensile strength by parallel arrangement
Type I, II, III, V,VI, XI	
Elastin	Tissue elasticity
Fibronectin	Adhesion of cells to ECM and guidance during embryogenesis, using integrins as their receptors.
Laminin	Primary component of basal laminae, which forms a two-dimensional sheet network with collagen IV, perlecan and nidogen.

* Kjær 2004; Sharma and Maffuli 2005; Alberts et al. 2008a.

be a promising advance in antimicrobial therapy (Peterson 2001). Structural formulas of quinolone core and some selected FQs are given in Fig. 1. FQs are usually well tolerated although some were associated with rare but potentially fatal side effects, such as phototoxicity, hypoglycemia, cardiotoxicity or hepatotoxicity (Petri 2011).

Most of the class side effects of FQs have been linked to substitutions at 1, 7 and 8 positions of the quinolone core (Peterson 2001; Mandell and Tillotson 2002). The severity of Achilles tendon lesion was correlated with R-7 position of the quinolone core. Fleroxacin, pefloxacin, levofloxacin and ofloxacin, all sharing a methyl piperadinyl substituent at R-7, were shown to be more toxic on tendons, as compared to enoxacin, norfloxacin and ciprofloxacin, each of which lacks this substituent (Kato et al. 1995; Kashida and Kato 1997).

Clinical retrospective surveys have not provided supportive clues for an objective evaluation of molecular structure-safety relationship. This inconsistent outcome may be attributed to many factors including treatment (dosage, duration/medication discontinuation, concommitant drug use), patient (age, gender, comorbid diseases), physician (diagnostic attitude), different protocol designs and market disparities (Wilton et al. 1996; Stahlmann 2002; Leone et al. 2003; Khaliq and Zhanel 2003; van der Linden et al. 2003).

Similarly, animal studies have yielded controversial results, which may be due to dosing schedules, animal or tissue species, differential tissue distribution kinetics of agents and experimental design as we discussed more in detail in our recent paper (Olcay et al. 2011).

Pharmacokinetics Safety Relationship

FQs have favorable pharmacokinetics with a bioavailability rate over 50%. Following oral administration, high tissue concentrations are reached due to high apparent volume of distribution and low protein binding. FQ concentrations are found to be higher in kidney, lung, and prostate tissues, urine, stool, bile, macrophages, and neutrophils than serum (Lode et al. 1998; Petri 2011).

High penetration ability to the site of infection is a desirable pharmacokinetic property in antibacterial therapy. Penetration of the FQs into brain, cerebrospinal fluid, saliva, and vitreous humor is dependent on their lipophilic properties (Liu et al. 1998; Li et al. 2002). However, FQ-induced tendinopathy is a dose dependent adverse effect. For this reason, lipid solubility may influence exposure rate related toxicity. Lower intrinsic toxic potential of a FQ may be counteracted by its lipophilic ability to reach the target organ (Delon et al. 1997).

FQs display differential tissue distribution profiles. After repeated dosing in dogs, detected concentrations in heart, lung, liver, kidney, spleen and muscle are 2.7 to 9.4 and 1.5 to 5 times higher than plasma levels for pefloxacin and enoxacin, respectively (Montay et al. 1984). FQs may have variable tissue distribution profiles, even if their

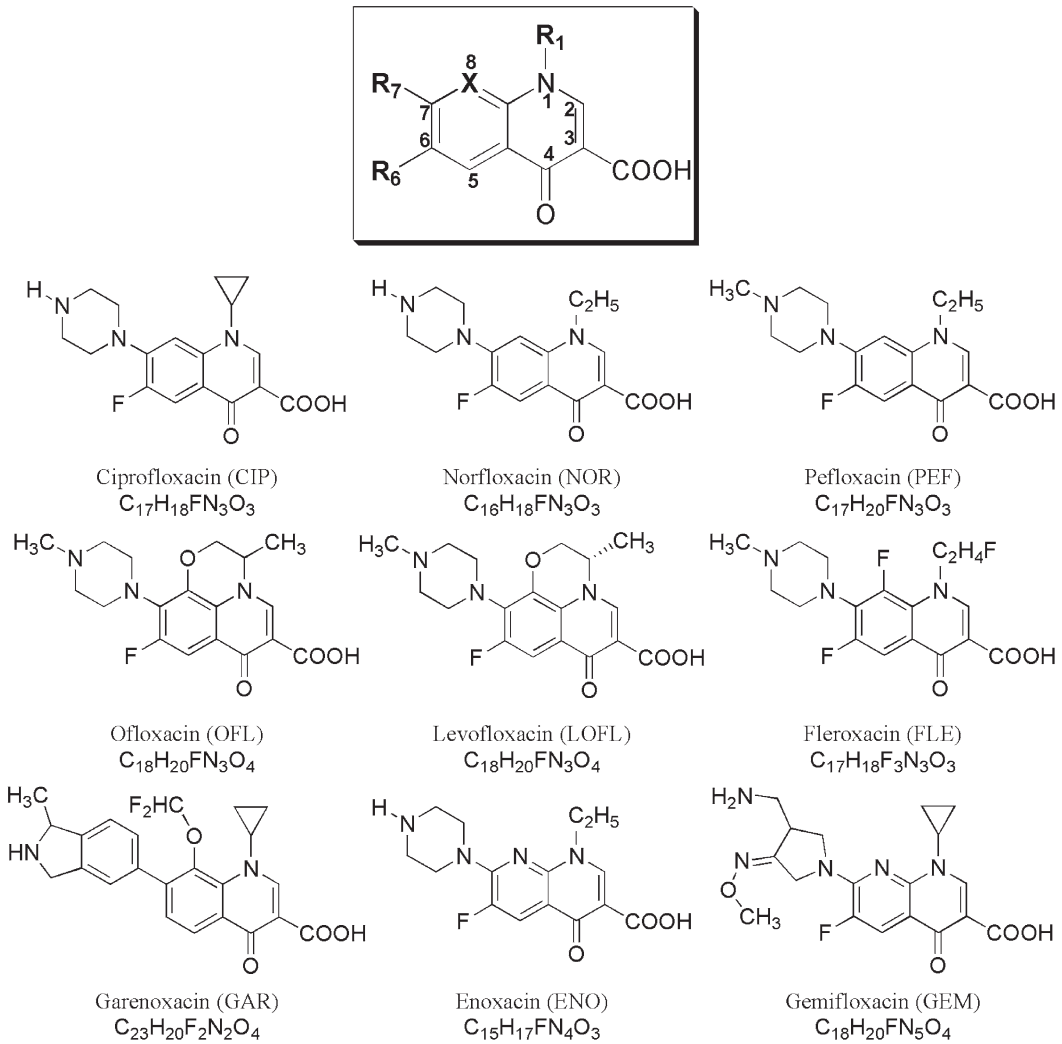

Fig. 1. Structural formulas of selected FQs.
The quinolone core is shown at top.

unbound (free) concentrations in the venous plasma and the tissue interstitial fluids are consistent. For example, unbound concentrations of ciprofloxacin, ofloxacin and pazufloxacin in the interstitial fluids and the venous plasma were close, but ciprofloxacin and ofloxacin were mainly distributed in muscle cells, rather than the interstitial space, whereas pazufloxacin was distributed equally in these two compartments, as demonstrated in a muscle microdialysis study in rats (Araki et al. 2002). Muscles, constituting up to 50% of body weight (Thibodeau and Patton 2007), serve as a large volume organ for drug distribution and tendons receive their blood supply partly from myotendinous junction, where perimysial vessels continue towards and within the tendon (Sharma and Maffuli 2005). For this reason, if a drug is highly distributed in muscle tissues, then tenocytes may also be exposed to high drug concentrations.

Tissue binding is another important pharmacokinetic determinant of drug distribution and actualized via binding to cellular substructures. Higher distribution of grepafloxacin to lung tissue has been associated with its binding to phosphatidylserine (Suzuki et al. 2002).

Ultrastructural Degenerative Changes Indicative of Apoptosis

FQ-induced tendon lesions were investigated in many histopathological surveys (Table 2). Levofloxacin and pefloxacin induced severe lesions in juvenile rats' tendons. These lesions were characterized by edema with mononuclear cell infiltration, and irregularly arranged and detached collagen deposition in the matrix of the synovial membrane and tendon sheath (Kato et al. 1995; Kashida and Kato 1997). Myxomatous degeneration can be observed in ciprofloxacin and pefloxacin treated rats (Olcay et al. 2011). Following exposure to pefloxacin, ofloxacin (Kato et al. 1995) or enrofloxacin (Lim et al. 2008), nuclei of tenocytes became pyknotic and fragmented. Such degenerative ultrastructural changes observed in the Achilles tendon samples from rats treated with gemifloxacin, ofloxacin or ciprofloxa-

Table 2. FQ associated ultrastructural and biochemical changes in tendon cells.

TEST AGENT	ULTRASTRUCTURAL CHANGES	REFERENCE
Ciprofloxacin Enrofloxacin Fleroxacin Garenoxacin Gemifloxacin Ofloxacin Pefloxacin	Swelling and dilatation of cell mitochondria and endoplasmic reticulum Multiple vacuoles and large vesicles Densified nuclei and clumped chromatin Decrease of fibril diameter Increase of distance between collagenous fibrils Cell detachment from extracellular matrix Hyalinization of collagen bundles	Kato et al. 1995; Shakibaei et al. 2000; Shakibaei and Stahlmann 2001, 2003; Bae et al. 2006; Lim et al. 2008; Olcay et al. 2011
Ciprofloxacin Levofloxacin	Decrease of beta(1)-integrin receptors	Shakibaei et al. 2001; Sendzik et al. 2005, 2010
Ciprofloxacin Levofloxacin	Reduction of cytoskeletal and signaling proteins	Sendzik et al. 2005
Ciprofloxacin Pefloxacin	Inhibition of collagen synthesis Decrease of elastin and fibronectin Inhibition of proteoglycan synthesis	Bernard-Beaubois et al. 1998; Simonin et al. 2000; Williams et al. 2000; Shakibaei et al. 2001; Sendzik et al. 2005, 2010
Ciprofloxacin Levofloxacin Norfloxacin	Increase of matrix metalloproteinases MMP-1, MMP-2, and MMP-13	Corps et al. 2005; Sendzik et al. 2010; Tsai et al. 2011
Ciprofloxacin Levofloxacin	Increase of caspase-3	Sendzik et al. 2005, 2010
Ciprofloxacin	Down-regulation of cyclin B and cyclin dependent kinase (CDK-1) mRNA and protein expression; down-regulation of check point kinase 1 (CHK-1) expression; up-regulation of polo like kinase 1 (PLK-1) protein expression	Tsai et al. 2008
Ciprofloxacin	Inhibition of focal adhesion kinase phosphorylation	Tsai et al. 2009

cin were accompanied by detachment of tenocytes from the extracellular matrix (ECM) (Bae et al. 2006). Multiple vacuoles and vesicles were formed due to swelling and dilatation of mitochondria and endoplasmic reticulum in Achilles tendon cells of rats treated with ofloxacin (Shakibaei et al. 2000), fleroxacin (Shakibaei and Stahlmann 2001), or ciprofloxacin and garenoxacin (Shakibaei and Stahlmann 2003). Signaling proteins and beta-1 integrin receptors were markedly reduced in human-derived tendon cells exposed to ciprofloxacin and levofloxacin in tissue culture (Shakibaei et al. 2001; Sendzik et al. 2005, 2010). Ciprofloxacin caused a decrease in collagen type I, elastin, fibronectin and proteoglycan synthesis (Williams et al. 2000; Shakibaei et al. 2001). Decrease of proteoglycan synthesis was also reported for pefloxacin (Bernard-Beaubois et al. 1998; Simonin et al. 2000). FQ-induced deterioration in proteoglycan synthesis was characterized by a biphasic pattern, an early inhibition followed by a repair like phase (Simonin et al. 2000). Treatment with FQs increased expression of matrix metalloproteases (MMPs), such as MMP-1 (Corps et al. 2005; Sendzik et al. 2010), MMP-2 (Tsai et al. 2011), and MMP-13 (Sendzik et al. 2010), as well as the apoptosis marker, caspase-3 (Sendzik et al. 2005, 2010). In contrast, the expression levels of tissue inhibitors of MMPs, TIMP-1 and TIMP-2, remained unchanged (Tsai et al. 2011).

Reported toxic effects of FQs on tendon cells, like chromatin condensation, nuclear fragmentation, cell membrane blebs, swelling, and dilatation of cell organelles (mitochondria and endoplasmic reticulum) cell shrinkage followed by phagocytosis, reduction of cytoskeletal and signalling proteins are indicative of ongoing apoptosis. The above observations suggest that regular turnover of ECM is disturbed due to apoptotic changes in tendon cells.

Furthermore, FQs retard tendon healing by decreasing tenocyte proliferation, migration and motility. FQs inhibit cell proliferation (Kempka et al. 1996). Ciprofloxacin causes cell-cycle arrest at G2/M phase by down-regulating protein and mRNA levels of cyclin B and cyclin dependent kinase-1 (CDK-1), and suppressing expression of check point kinase 1(CHK-1) protein (Tsai et al. 2008). Ciprofloxacin also decreases tenocyte migration by inhibiting focal adhesion kinase phosphorylation (Tsai et al. 2009).

Role of Oxidative Stress and Mitochondria

Photosensitizing effect of FQs is well known (Petri 2011). FQs may become photo-activated under exposure to

natural or artificial ultraviolet, leading to formation and accumulation of intracellular reactive oxygen species (ROS) (Onoue et al. 2009). The formation of ROS, especially singlet oxygen, was found to be responsible for FQ-induced DNA damage, which was guanine specific and FQ concentration-dependent (Hiraku and Kawanishi 2000). Thus, doses of sunlight that are regarded as harmless may cause phototoxic reactions with FQs (Pierfitte et al. 2000; Onoue et al. 2009). For this reason, utilization of ROS generation assays was recommended to identify less phototoxic FQ molecules during drug screening and development (Seto et al. 2011).

It has been reported that FQs increase intracellular ROS accumulation, which is partly responsible for FQ-induced lethality (Wang et al. 2010). FQs also increase ROS levels in serum (Mutinati et al. 2008), polymorphonuclear leukocytes (Koshio and Ono 2009), and macrophages (Bekay et al. 2002). ROS production was dependent on FQ-concentration and increased significantly at therapeutic and supra-therapeutic concentrations (Pouzaud et al. 2004a). High ROS generation by FQs was suggested to reduce glutathione content rapidly, hence disable modulation of oxidative stress by intracellular antioxidant enzymes (Pouzaud et al. 2004a). Peroxiredoxin 5, an antioxidant enzyme, was upregulated in tendinopathy (Wang et al. 2001). Increase of the carbonyl derivatives of Type I collagen following pefloxacin treatment is another supportive clue, indicating oxidative damage (Simonin et al. 2000). Overall, oxidative stress seems to play an important role in the development of FQ-induced tendon toxicity.

Highly altered mitochondrial activity following FQ use was reported by many investigators. Mitochondria were shown to be a biological target of pefloxacin and norfloxacin in cultured rabbit Achilles tendon cells (Bernard-Beaubois et al. 1998). Mitochondrial swelling (Shakibaei and Stahlmann 2001), mitochondrial membrane damage (Lowes et al. 2009), and loss of mitochondrial DNA content (Kaminski et al. 2010) were reported with various FQs. An antioxidant targeted to mitochondria (MitoQ) was able to protect mitochondria membrane permeability better than a non-mitochondria targeted antioxidant, idebenone in ciprofloxacin and moxifloxacin associated oxidative stress and mitochondrial damage in cultured normal human Achilles' tendon cells (Lowes et al. 2009).

The electron transport chain embedded in the inner membrane of mitochondrion operates through three membrane bound enzyme complexes. Ubiquinone (CoQ) is a freely moving electron transporter in the inner mitochondrial membrane. Ubiquinone picks up electrons from NADH dehydrogenase complex (Complex I) and donates them to cytochrome b-c_1 complex (Complex II) (Alberts et al. 2008b). ROS generation in Complex I is enhanced in the presence of an inhibitor which binds to the CoQ binding site (Murphy 2009). Plastoquinone in chloroplasts is almost structurally identical to ubiquinone and cytochrome b_6-f complex in chloroplasts resembles Complex II, as well (Alberts et al. 2008b). In a recent ecotoxicological study, it was shown that FQs cause severe growth inhibition and morphological deformities in spinach plant (Aristilde et al. 2010). Quinolone containing compounds inhibit photosystem II and cytochrome b_6-f complex in spinach chloroplasts. FQ antibiotics seem to act as quinone site inhibitors in photosynthetic pathways (Aristilde et al. 2010).

Mitochondrial ROS production is a redox signal, mod-

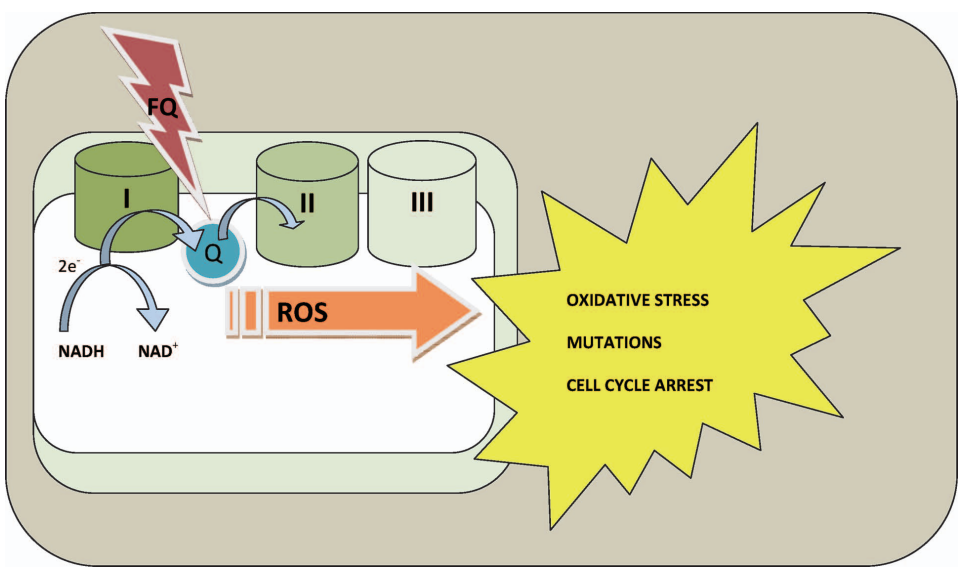

Fig. 2. Summary of FQ-induced ROS production and consequent cellular effects.
I, NADH dehydrogenase complex; II, cytochrome b-c1 complex; III, cytochrome oxidase complex; Q, ubiquinone; FQ, fluoroquinolone; ROS, reactive oxygen species.
(Monboisse et al. 1984; Bernard-Beaubois et al. 1998; Shakibaei et al. 2000; Reed 2000; Yuan et al. 2003; Pouzaud et al. 2004a; Sendzik et al. 2005; Alberts et al. 2008b; Lowes et al. 2009; Murphy 2009; Aristilde et al. 2010; Kaminski et al. 2010).

ulating a wide range of cellular functions. However, high ROS production can result in oxidative damage to mitochondrial DNA, membranes, and proteins (Murphy 2009). Mitochondria participate in apoptosis by releasing cytochrome c which starts the signaling pathway leading to activation of caspase 9. Caspase 9 is the apical caspase of mitochondrial pathway for apoptosis and directly activates the effector protease, caspase-3 (Reed 2000). Oxidative stress related apoptosis in human tendon fibroblasts was shown to be mediated via release of cytochrome c from mitochondria to the cytosol and activation of caspase-3 (Yuan et al. 2003). ROS additionally have direct cytotoxicity on ECM components. ROS can oxidize susceptible amino acids in collagen, changing protein conformation (Monboisse et al. 1984), and can also activate MMPs, which in turn may synergistically increase toxicity. FQ induced ROS overproduction and its consequences are schematized and summarized in Fig. 2.

ROS production may be increased in ischemia. However, oxygen consumption in tenocytes is low due to low metabolic rate (Vailas et al. 1978). Mature tendon cells have well established energy production capacity even under anaerobic conditions so that risk of ischemia is reduced (Sharma and Maffulli 2005). On the other hand, low metabolic rate in adult tenocytes is an obstacle for healing (Sharma and Maffulli 2005). Accordingly, young adult tenocytes were shown to be more susceptible to FQ toxicity than immature ones (Pouzaud et al. 2006).

Concomitant use of antioxidants, such as *N*-acetylcysteine (Simonin et al. 2000), anethole dithiolethione (Pouzaud et al. 2004b), and MitoQ (Lowes et al. 2009), was reported to attenuate toxic effects of FQs on tendon cells. Cotreatment with platelet rich plasma was proposed as a novel strategy to restore the reduced tenocyte viability and promote healing following FQ exposure (Zargar et al. 2011). Another option is to avoid from ultraviolet irradiation during FQ treatment. As reported in an epidemiological study, phototoxic reactions to FQs significantly decrease, if the patients protect themselves from exposure to solar and artificial radiation (Pierfitte et al. 2000).

Closing Remarks

Review of experimental studies highlight several facts about toxic effects of FQs on tendon cells. FQ related ROS production and oxidative stress are shown to be important contributing factors, which may result in degenerative changes in cellular and extracellular components of tendon tissue. FQ-induced tendinopathy seems to be associated with a mitochondria-associated mechanism. ROS overproduction results in mitochondrial DNA damage, which triggers apoptosis by releasing caspase activating proteins into cytosol.

Low metabolic rate and depletion of ROS scavenger systems in the mature or aged tendons retard healing. FQs impair healing process further by inhibiting tenocyte proliferation and migration to the site of injury.

Insufficient vascularization, low tendon perfusion and low metabolic rate may render the elderly more prone to FQ toxicity. Additionally, decreased renal clearance may increase serum drug concentrations and subsequent toxicity.

Concomitant uses of antioxidant agents and growth factors, as well as protection from sunlight, are shown to be useful measures against development of FQ associated toxicity. Therefore, before starting FQ therapy, patient specific risk factors should be carefully evaluated to employ tendon protective strategies for optimal therapeutic benefit.

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Conflict of Interest

Both authors do not have potential conflict of interest regarding this review article.

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