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Review

Drug-induced tendinopathy: From physiology to clinical applications

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ABSTRACT

Drug-induced tendon toxicity is rare but often underestimated. To date, four main drug classes have been incriminated in tendinopathies. Quinolones and long-term glucocorticoids are the most widely known, but statins and aromatase inhibitors can also induce tendon damage. The specific pathophysiological mechanisms responsible for drug-induced tendinopathies remain unknown. Proven risk factors have been identified, such as age older than 60 years, pre-existing tendinopathy, and potentiation of toxic effects when several drug classes are used in combination. Mean time to symptom onset varies from a few days with quinolones to several months with statins and several years for long-term glucocorticoid therapy. The most common sites of involvement are the lower limb tendons, most notably the body of the Achilles tendon. The first part of this review discusses tendon anatomy and the pathophysiology and radiological manifestations of tendinopathies. The second part provides details on the main characteristics of each of the drugs classes associated with tendon toxicity.

1. Introduction

Drug-induced tendinopathy is an underestimated problem. To date, four drug classes have been incriminated in most of the reported cases. The best known are quinolones and long-term glucocorticoid therapy, but statins and aromatase inhibitors have now been added to the list of culprits. A review of drug-induced tendinopathy is timely, given the inadequate awareness of this potentially early and severe adverse effect of drugs that are widely prescribed in everyday practice.

2. Tendon anatomy and physiology

2.1. Histology

Upon gross examination, the normal tendon is seen as a fibrillar and generally rounded structure that is white and elastic with a slight sheen from the muscle–tendon junction to the enthèses (Fig. 1a). The fibroblasts in tendons are called tenoblasts, and tenocytes are tenoblasts that have a lower level of metabolic activity. Tenoblasts and tenocytes account for 90% of tendon cells and produce collagen type I and elastin fibers, as well as many extracellular matrix components (cytokines, enzymes, glycosaminoglycans). Tendons are chiefly composed of collagen fibers, which make up 70% to 80% of the dry weight of the tendon (Fig. 1b). The remaining 10% of cells are chondrocytes at the entheses and a few synovial cells in the synovial tendon sheath if present [1,2]. The extracellular matrix between the collagen fibers and tenocytes is composed of glycosaminoglycans, glycoproteins, and proteoglycans, whose high hydrophilicity contributes to the elasticity of the tendon [2].

The collagen fibers are aggregated into fibrils (primary fibrils), which are assembled into fascicles (secondary fibrils) and finally into tertiary fibrils, to constitute the tendon itself (Fig. 1b). Most of the collagen fibers are aligned longitudinally, although a few may be arranged transversally, usually at the ends of the tendons (Fig. 1c) [1,2].

The epitenon that envelops the tertiary fibrils contains the full contingent of tendon blood vessels, lymphatics, and nerves. The endotenon is formed of epitenon extensions within the tendon itself. Superficially, the paratenon composed of collagen fibers types I and III surrounds the epitenon. When a synovial sheath is present, it is in close contact with the

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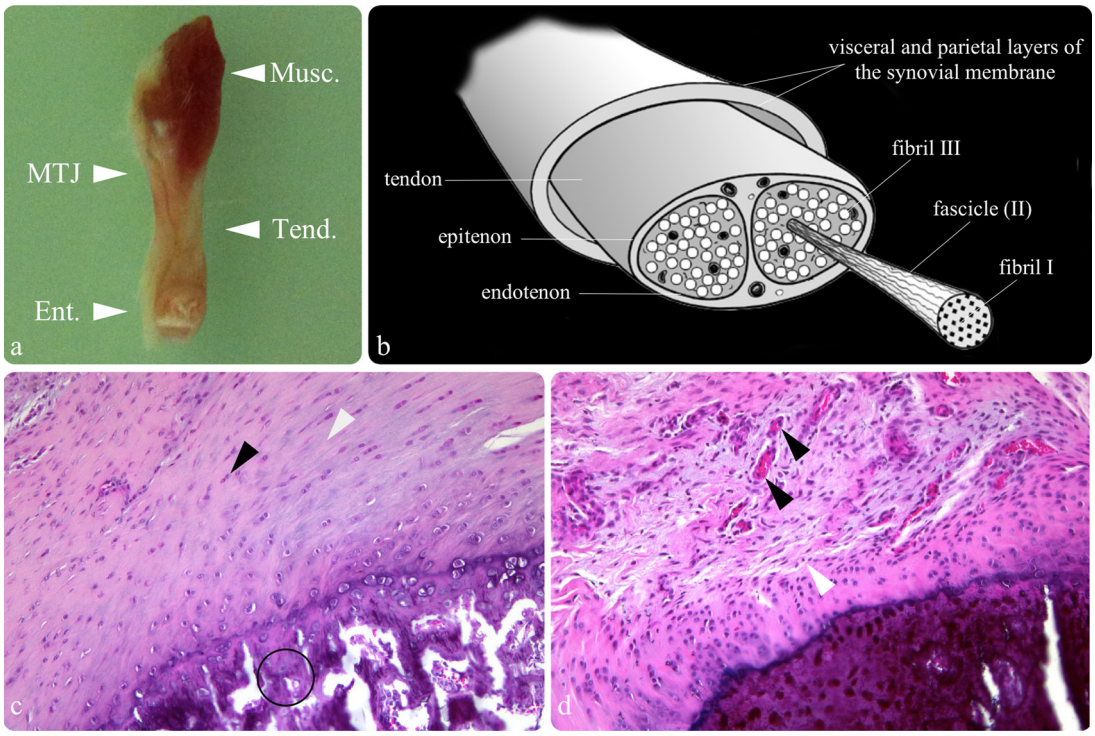

Fig. 1. Anatomy and histology of the tendon. a: gross appearance of the rat Achilles tendon. Musc., muscle; Tend., tendon; MTJ, muscle–tendon junction; Ent., calcaneal enthesis; b: diagram of the tendon with its various components (inspired by RA Berger, AP Weiss. Hand Surgery, 1st edition. Lippincott Williams & Wilkins, 2004); b: gross appearance of the rat Achilles tendon; c: normal rat calcaneal entheses at ×50 magnification, stained with hematoxylin–eosin (white arrowhead, collagen fibers; black arrowhead, tenocytes, black circle, red hematopoietic marrow of the calcaneus); d: abnormal rat calcaneal entheses at ×50 magnification, stained with hematoxylin–eosin (white arrowhead, disorganized collagen fibers; black arrowheads, neovessels within the tendon).

paratenon. The synovial sheath has a parietal and a visceral layer, between which a thin film of synovial fluid circulates [3].

2.2. Vascularization

The normal blood supply to the tendon is highly vulnerable, and many tendon areas receive few or no vessels. The vessels are located about the tendon and arise chiefly from three sources: the muscle–tendon junction, the bone–tendon junction (entheses), and the paratenon or synovial membrane. The vessels originating from the muscle–tendon junction extend along only one-third of the length of the tendon, and the vessels at the bone–tendon junction supply only the entheses [4]. Many hypovascularized zones have been identified in the Achilles tendon 2 to 6 cm proximally to the calcaneal attachment and may be characterized by decreased mechanical strength and therefore by a higher risk of rupture [5,6]. Areas where the tendon is twisted, bent, or compressed also contribute to the vulnerability of the vascular supply to the tendon.

2.3. Innervation

The nerve supply to the tendon comes from the skin, muscles, and peritendinous structures. The nerves travel alongside the blood vessels. The Golgi tendon organs are sensory receptors formed by the ends of myelinated fibers that slip between the collagen fibrils. Golgi organs are most abundant at the tendon attachments and ensure proprioception, detecting changes in tendon pressure and stretching. Unmyelinated nerve fibers ensure nociception [7].

3. Pathophysiology of tendinopathies

3.1. Histology

Tendinitis and tendonitis are inappropriate terms for designating tendon diseases, as no inflammatory cells are present within the tendon. The term “tendinopathy” therefore seems preferable. Upon gross examination of the damaged tendon segment, the normally white tendon is seen to be thickened, uneven, and brownish. Histological studies show no macrophages, neutrophils, or other inflammatory cell types; the main findings are collagen fiber disorganization, tenocyte apoptosis, the development of multiple neovessels (Fig. 1d), and an increased amount of interfibrillar glycosaminoglycans [8,9]. These tissue changes progress to chronic mucoid and/or lipoid degeneration of the tendon with a variable amount of fibrocartilaginous metaplasia and calcium hydroxyapatite deposits (most notably in rotator cuff tendinopathies) [10]. Thus, tendinopathy is an imbalance between tendon tissue production and degeneration.

In preclinical studies of the natural history of tendinopathies, local administration of proinflammatory cytokines and prostaglandins induces chemical tendinopathy. Repeated mechanical loading induces and augments the production of PGE2, interleukins (IL-6, IL-1B), cyclooxygenase-2 (COX-2), and metalloproteinases 1 and 3 [11,12]. These enzymes break down the extracellular matrix and mediate the development of tendinopathy. They are associated with the production of vascular growth factors, which induce neovessel formation within the tendon [11]. Neovessels present within normally avascular tendon areas exert pathogenic effects via the transportation at the early phase of various substances, particularly hydrogen peroxide (H_2O_2) and superoxide ions ($O_2^{\bullet-}$). However, another factor transported by