Journal of Orthopaedic Translation 31 (2021) 80–90

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Inflammatory mechanisms linking obesity and tendinopathy

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ARTICLE INFO

Keywords:
Adipose tissue
Inflammation
Obesity
Tendinopathy
Tendon overuse

ABSTRACT

Chronic tendinopathy is a debilitating tendon disorder with disappointing treatment outcomes. This review focuses on the potential roles of chronic low-grade inflammation in promoting tendinopathy in obesity. A systematic literature search was performed to identify all clinical studies supporting the actions of obesity-associated inflammatory mediators in the development of tendinopathy. The mechanisms of obesity-induced chronic inflammation in adipose tissue are firstly reviewed. Common inflammatory mediators potentially linking obesity and the development of tendinopathy, and their association with mechanical overuse, are discussed, along with pre-clinical evidences and a systematic literature search on clinical studies. The potential contribution of local adipose tissues in the promotion of inflammation, pain and tendon degeneration is then discussed. The future research directions are proposed.

Translational potential statement: Better understanding of the roles of obesity-associated inflammatory mediators on tendons will clarify the pathophysiological drivers of tendinopathy in patients with obesity and identify possible treatment targets. Further studies on the mechanisms of obesity-induced chronic inflammation on tendon are a promising direction for the treatment of tendinopathy.

1. Introduction

Chronic tendinopathy is a debilitating tendon overuse disorder characterized by activity-related tendon pain with various degrees of incapacity, tenderness and localized swelling [1]. Hypoechogenic regions and increase in tendon thickness with loss of the imaging signals typical of well-aligned collagen fibres are often observed in ultrasonography (US). Tendon enlargement and heterogeneity, with high focal T1 and T2 signal, are typical findings at the tendon insertion or mid-substance in magnetic resonance images (MRI). There are clear distinctions between acute tendon injury and chronic tendinopathy. Acute tendon injury has no persistent pain prior to tendon rupture whereas the tendinopathic tendon is symptomatic and shows histopathological changes. Tissue metaplasia in the tendon proper may exist in tendinopathy which is not present after acute tendon injury before healing occurs. While tendinopathy causes tendon degeneration and may predispose the tendon to rupture, it may not be presented with tendon rupture in the clinical setting. Chronic tendinopathy is common. It accounts for 30–50 % of all sports-related injuries [2], and almost half of all occupational illnesses in the United States [3], costing billions of dollars in healthcare each year. The prevalence of chronic tendinopathy increases with age and severely limits the physical activity of the aging population. The outcomes of both conservative treatments and surgeries are not satisfactory. The etio-pathogenesis of tendinopathy is multi-factorial and remains unclear, though mechanical overload is an important risk factor. Various risk factors such as environmental factors, metabolic diseases, genetics, demographics and drug used modify the risk of development and prognosis of overuse-induced tendinopathy. Tendon overuse initiates an inflammatory cascade and erroneous tendon-derived stem cell (TDSC) differentiation, causing tissue metaplasia and failed healing [4,5]. Recent studies have suggested a close link between obesity and the onset and progression of chronic tendinopathy [6]. While the link between obesity and chronic tendinopathy was historically attributed to the wear and tear of tendon as a result of increased body weight, growing evidence suggests that systemic chronic low-grade inflammation associated with obesity plays a more important role than body weight in the development of tendinopathy. This is due to compelling evidence suggesting that inflammation is causal in the development of many disorders associated with obesity such as diabetes mellitus (DM), cardiovascular disease and cancer.

This review aims to discuss the potential roles of chronic low-grade inflammation in promoting chronic tendinopathy in patients with

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https://doi.org/10.1016/j.jot.2021.10.003
Received 30 July 2021; Received in revised form 9 September 2021; Accepted 10 October 2021
Available online 9 December 2021

obesity. A systematic literature search was performed in Pubmed database to identify all clinical studies supporting the actions of obesity-induced inflammation on tendinopathy on 23 Apr 2021. All original clinical studies involving clinical tendinopathy tissues or cells and studying the association/effects of adiposity-induced inflammatory mediators with/on tendinopathy in all languages are included. Reviews, commentary, animal and cell culture studies not involving clinical samples are excluded but will be included for discussion in text where appropriate. Papers on clinical problems other than tendinopathy such as tendon adhesion and acute tendon injuries are excluded. Duplicates are removed. Four, fifteen and nine relevant clinical studies studying the effects of adipokines, free fatty acid (FFA) metabolites and alarmins, repectively, which are frequently dysregulated in obesity, in the pathogenesis/treatment of tendinopathy were identified and included in this review. The mechanisms of obesity-induced chronic inflammation in adipose tissue are briefly summarized. Common inflammatory mediators potentially linking obesity and the development of tendinopathy, and their association with mechanical overuse, are discussed**.** The potential contribution of local adipose tissues in the promotion of inflammation, pain and tendon degeneration is then discussed. The future research directions are proposed. Better understanding of the influence and the underlying mechanisms of obesity-induced chronic inflammation in the development of tendinopathy will identify promising mechanistic targets and strategies for disrupting the obesity-tendinopathy link.

2. Obesity-induced chronic inflammation in adipose tissue

2.1. Overproduction of inflammatory adipokines

Adipose tissue is one of the largest endocrine organs in the body. Rather than an inert tissue for energy storage, adipose tissue plays a more complex role and regulates many physiological functions such as immunity and inflammation. It secretes a plethora of cytokines, chemokines and hormone-like factors that have pro-inflammatory or anti-inflammatory activities. Collectively, these factors are called adipokines. Some examples of pro-inflammatory adipokines are TNF-α, IL-1β, IL-6, leptin, resistin, fatty acid-binding protein 4 (FABP4), visfatin and chemerin as well as anti-inflammatory adipokines such as adiponectin, omentin-1 and fibroblast growth factor 21 (FGF21). Some adipokines such as leptin and adiponectin are more specific to adipose tissue while others like TNF-α, IL-1β and IL-6 are non-specific to adipose tissue. There are more pro-inflammatory compared to anti-inflammatory adipokines that have been discovered. Leptin, the first adipokine discovered, stimulates monocyte proliferation and differentiation into macrophages, modulates the activation of natural killer cells and induces the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12 [7]. Adiponectin exerts opposite immuno-modulatory actions to leptin. It inhibits the phagocytic activity and TNF-α production by macrophages, suppresses the differentiation of monocyte precursors, inhibits the synthesis of endothelial adhesion molecules, and reduces the formation of foam cells [8]. Adiponectin also inhibits CRP and TNF-α production in adipose tissue [9]. In addition, adiponectin stimulates the release of anti-inflammatory interleukins such as IL-10 and IL-1 receptor agonist [7]. IL-10 stimulates tissue inhibitor of matrix metalloproteinase (TIMP) expression that inhibits matrix metalloproteinase (MMP) activities in macrophages [10]. The adipokines are mainly produced by immune cells, adipocytes and fibroblasts, endothelial cells in adipose tissue. The serum levels of inflammatory adipokines elevate in individuals with obesity [11] and the levels reduce with reduction of fat mass [12]. The dysregulated production or secretion of these adipokines because of adipose tissue dysfunction contributes to the pathogenesis of obesity-linked complications. The readers are referred to a recent comprehensive review on the roles of adipokines in obesity and metabolic dysfunction for more information [13].

2.2. Infiltration of immune cells

Adipose tissue contains multiple immune cells that control tissue integrity and metabolic homoeostasis. Indeed, immune cells, especially macrophages, are the major inflammatory cells that release most inflammatory molecules in adipose tissue of animals and humans with obesity [14]. Under healthy condition, immune cells maintain an anti-inflammatory type 2 environment and polarize adipose tissue macrophages to an M2 state. However, in obesity, immune cells exhibiting a type 1 pro-inflammatory phenotype infiltrate into adipose tissue in response to pro-inflammatory signals.

$CD8^+$ T cells are among the first immune cell population that is recruited to the adipose tissue at the early stages of obesity, prior to the accumulation of adipose tissue macrophages, and they continue to increase thereafter [15]. The $CD8^+$ T cells polarize into a pro-inflammatory phenotype expressing high level of IFN-γ. In mice, the depletion of $CD8^+$ T cells attenuated while the adoptive transfer of $CD8^+$ T cells exacerbated adipose tissue macrophage accumulation and inflammation in obesity, supporting an important role of $CD8^+$ T cells in inducing inflammation [15].

There was also an early transient infiltration of neutrophils prior to macrophage infiltration in a high-fat diet mouse model, suggesting the role of neutrophils in the initiation of the inflammatory cascade [16]. Neutrophils might contribute to inflammation of adipose tissue by secreting elastase, myeloperoxidase, IL-1β and interacting with macrophages [14].

By contrast, the numbers of both anti-inflammatory $CD4^+$ helper T cells (TH) and Treg decreased in the adipose tissue of individuals with obesity [17]. The ratio of $CD4^+$ helper 1 T cells to helper 2 T cells (TH1/TH2) increased in high fat diet-induced obesity.

Macrophages are the effectors of the complex type 1 immune response triggered by various immune cell types. Monocytes are recruited to the adipose tissue from bone marrow in response to various inflammatory signals at the late stage of obesity. The infiltrated monocytes differentiate into the pro-inflammatory M1 phenotype, which are a major source of pro-inflammatory cytokines such as TNF-α and IL-6 [18]. The adipose tissue resident macrophages also polarize from the anti-inflammatory M2 to the pro-inflammatory M1 phenotype. The increase in macrophage number and M1 to M2 macrophage ratio are hallmarks of adipose tissue inflammation that accompanies obesity [18–20]. The infiltrating macrophages surround the necrotic adipocytes, forming crown-like structures. Interestingly, weight loss is associated with a reduction in the filtration of macrophages into adipose tissue and an improvement in inflammatory profiles [20].

2.3. Initiating factors of obesity-induced inflammation

There have been many studies on the initiating factors of obesity-induced inflammation in rodent models of dietary and genetic obesity, but the precise triggers remain unclear. Obesity increases intestinal permeability, which increases the circulating levels of lipopolysaccharides (LPS) from intestinal Gram-positive bacteria [21]. The bacterial LPS initiates an inflammatory cascade via activation of pattern recognition receptors (PRRs) such as Toll-like receptor 4 (TLR4) in adipocytes. Besides, different lipid species that are elevated due to diet or lipolysis may contribute to inflammation. The increase in saturated fatty acids (SFA) promotes inflammation via indirect binding to TLR4 through the adaptor protein feutin A, resulting in NF-kB and JNK1 activation in macrophages, adipocytes and cells in other tissues or organs [22]. There is also evidence that the hyperplasia of adipose tissue and the hypertrophy of adipocytes cause hypoxia due to the relative under perfusion of the enlarged adipose tissue or increased oxygen consumption. The increase in cellular hypoxia in turn induces inflammation by activating HIF-1α, which controls the expression of chemokines such as MCP-1 and LTB4 in adipocytes,

expression of adiponectin and leptin in adipocytes as well as M1-like polarization of macrophages [23]. Reactive oxygen species (ROS) production also increases in parallel with adipocyte hypertrophy and adipose tissue hyperplasia, promoting tissue inflammation. Furthermore, the endoplasmic reticulum (ER) stress and its downstream signalling cascades governing the unfolded protein response (UPR) are activated in obesity and they are closely tied to both the inflammatory JNK-1 and NF-kB pathways [24]. Both ROS production and ER stress contribute to the dysregulation of adipokine production. In addition, the release of alarmins, also called damage-associated molecular patterns (DAMP) [25–30], as a result of hypertrophy or necrosis of adipocytes, is closely associated with the infiltration of macrophages and the development of inflammation. Furthermore, the switch from aerobic to anaerobic glycolysis also increases the production and release of lactate from adipocytes [31]. Lactate has been shown to stimulate inflammation in macrophages [32]. Fig. 1 summarizes the initiators and mediators of obesity-induced systemic chronic low-grade inflammation.

3. Common inflammatory mediators linking obesity and tendinopathy

3.1. Histopathological changes of tendinopathy

Tendinopathy is histologically characterized by a failed healing response of hypercellularity, hypervascularity and rounding of tenocytes with loss of parallel cell arrangement [33–35]. The collagen type III/type I ratio and sulfated glycosaminoglycan production increase in tendinopathy. The degeneration of extracellular matrix with bone, fat and chondroid metaplasia are observed. The collagen fibers are smaller and disorganized, resulting in reduced mechanical strength of tendon, predisposing the tendon to rupture. The ingrowth of vascular and neural structures causes pain in tendinopathy.

3.2. Overexpression of inflammatory markers

Tendinopathy is previously considered as a degenerative disease with an absence of infiltration of inflammatory cells [36–38]. However, recent studies have reported signs of inflammation, including the presence of inflammatory cells or an increase in inflammatory markers in the pathological clinical samples [33,34,39–41]. The discrepancy is likely due to the sub-optimal method used for the detection of inflammatory cells in the earlier studies. The availability of clinical specimens only from patients who are symptomatic and at chronic disease stage as well as the appropriateness of the controls used for comparison may have caused the presence of inflammation at the early phase of tendinopathy being missed.

Using matched subscapularis tendon from patients with full-thickness rotator cuff tears as an early human tendinopathy model, the upregulation of inflammatory cytokines and the infiltration of inflammatory cells were observed, contrary to the belief that tendinopathy is not an inflammatory process [42,43]. Macrophages, lymphocytes and mast cells were observed in torn supraspinatus tendons and matched subscapularis tendons [43–45]. Similarly, chronic painful supraspinatus tendons also showed higher mRNA expression of CD206 (M2 macrophage marker) and CD45 (pan-leucocyte marker) compared to that in pain-free controls after shoulder surgery [46]. In another study, the numbers of mast cell increased and was associated with the duration of pain symptom in human samples of patellar tendinopathy [47]. Moreover, macrophages, T lymphocytes, mast cells, and natural killer cells were observed in the majority of biopsy specimens from non-ruptured chronic tendinopathic Achilles tendons and macrophages were significantly more numerous in tendinopathic tendons compared with the numbers in healthy tendons [48]. Furthermore, there were increased numbers of $CD14^+$ and $CD68^+$ cells in both mid-portion tendinopathic Achilles tendons and ruptured tendons compared with healthy hamstring tendons [49]. In another study, lymphocytes, mostly macrophages, were also present in both tendinopathic and chronic ruptured Achilles tendons [50]. Besides the infiltration of immune cells, the upregulation of inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10, IL-17, IL-21 receptor, IL-33, COX-1, COX-2, TGF-β, TNF-α, bFGF and more were reported in human samples of tendinopathy in the previous studies [51]. There was increased expression of macrophages and inflammatory cytokines in tendons of patients with chronic lateral epicondylitis [52]. Single cell and spatial transcriptomics analysis has shown that the stromal cell clusters in clinical tendinopathy samples expressed genes that promoted immune cell recruitment and activation as well as enhanced cytokine responses in diseased tendons [53].

3.3. Common inflammatory adipokines in obesity and tendinopathy

The balance of pro- and anti-inflammatory adipokines is perturbed, favoring a chronic pro-inflammatory status in individuals with obesity. Some obesity-associated adipokines such as IL-1β, TNF-α and IL-6 were expressed in clinical samples of tendinopathy. There was significant

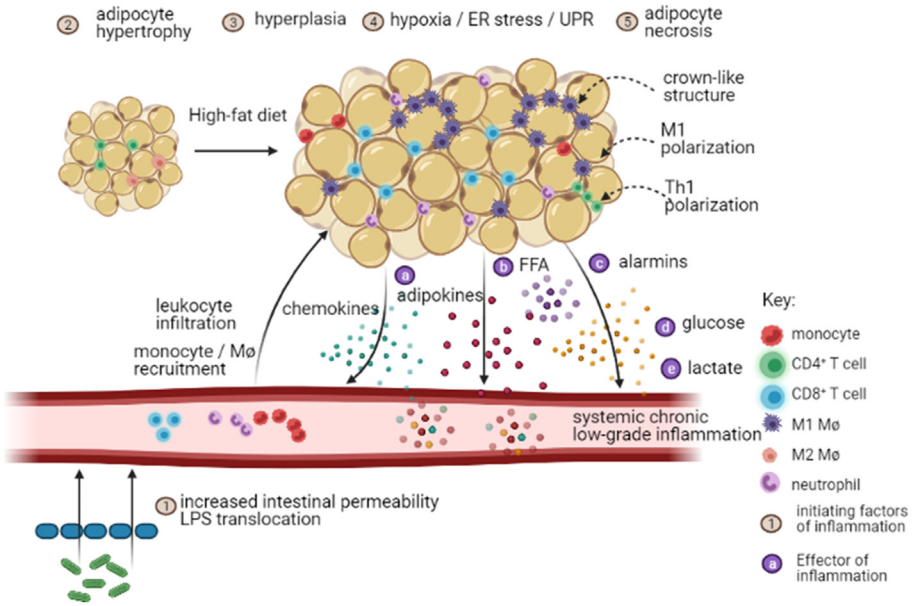

Fig. 1. Schematic diagrams summarizing the initiators and mediators of obesity-induced systemic chronic low-grade inflammation. Under healthy condition, the immune cells maintain an anti-inflammatory type 2 environment and polarize the resident adipose tissue macrophages to an M2 state. In obesity, the increase of bacterial LPS, adipocyte hypertrophy, hyperplasia, hypoxia, ER stress, UPR and adipocyte necrosis induces the release of adipokines, FFA, alarmins, glucose and lactate. Immune cells exhibiting a type 1 inflammatory phenotype are recruited to the adipose tissue in response to various inflammatory signals and chemokines. Macrophages, the key effectors of the complex type 1 immune response triggered by various immune cell types, are polarized to a pro-inflammatory M1 phenotype. The release of the adipokines, FFA, alarmins, glucose and lactate to the circulation creates a systemic chronic low-grade inflammatory milieu which causes various obesity-associated comorbidities.

increase in the expression of IL-1β in the synovium of patients with full-thickness supraspinatus tendon tears [54]. Besides, the mRNA and protein expression of IL-18, IL-15, IL-6, TNF-α and MIF were upregulated in the supraspinatus and subscapularis tendons harvested from patients with rotator cuff tears [42]. In addition, there was stronger expression of TNF-α and its receptors in rounded/widened tenocytes in human Achilles tendinopathy samples [55]. Furthermore, there was an increase in the mRNA expression of COX-2 and IL-6 in both painful and ruptured human Achilles tendons compared with that in the normal tendons [56]. The increased expression of these inflammatory signals that were also highly expressed in obesity may promote the onset and progression of tendinopathy. They may trigger cell proliferation, angiogenesis, overexpression of MMPs and pain mediators, resulting in extracellular matrix degeneration, tissue metaplasia and tendon pain [57]. However, these adipokines are not specific to adipose tissue and the clinical studies only reported the association between the adipokines and tendinopathy. The role of obesity in overproducing these inflammatory mediators in tendinopathy were not examined.

A systemic search with keywords "tendon" and "adipokine" was done. Fourteen articles are identified and 4 articles were included after detailed examination (Online Resource 1A). The findings of these 4 clinical studies, together with *in vitro* and *in vivo* studies, about the link between the more specific adipokines and tendinopathy were discussed according to the adipokines.

3.3.1. Leptin

Obesity causes hyperleptinemia and leptin resistance [58]. Interestingly, the knock-down of leptin was reported to induce chondrocyte-like phenotype, degeneration of tenocytes, vascular proliferation, and ruptures at the tendon-to-bone junction in mouse Achilles tendons [59]. On the contrary, another study has reported that leptin expression was associated with ectopic ossification in healing Achilles tendon in rats [60]. Another more recent study has confirmed this finding and reported that leptin treatment enhanced osteogenic differentiation of TDSCs and promoted heterotopic ossification in rat Achilles tendon after tenotomy [61]. The interaction of an injury with leptin level might explain the contradictory findings. Indeed, a cohort study has shown that higher serum level of leptin showed a tendency to predict a lower rate of recovery from upper extremity soft tissue disorders including rotator cuff tendinitis, humeral epicondylitis, tenosynovitis and other non-specific disorders at 8-weeks (OR = 0.73, 95 % CI 0.51, 1.02) [62].

3.3.2. Nesfatin-1

The association of nesfatin-1 with obesity is controversial with studies showing positive [63] and negative relationships [64,65]. In this context, the mRNA expression of nesfatin-1 in human tendinopathy samples was significantly higher than that in tendon samples from healthy controls [66]. Besides, nesfatin-1 reduced the migration and tenogenic differentiation but increased the osteogenic differentiation of rat TDSCs [66]. The peri-tendinous injection of nesfatin-1 also enhanced heterotrophic ossification in an Achilles tenotomy rat model [66].

3.3.3. Adiponectin

Adiponectin was reported to promote the proliferation and tendon-related marker expression in human diabetic-ridden TDSCs [67]. The expression of adiponectin is downregulated in humans with obesity [68], supporting the poor outcomes of tendon healing and higher risk of tendinopathy as a result of repeated microtraumas in patients with obesity. However, serum adiponectin level could not predict the recovery from upper extremity soft tissue disorders at 8-week follow-up (OR: 1.02, 95 % CI 0.69, 1.50) [62]. Self-reported dichotomized outcome of fully or substantially recovered versus unchanged or exacerbated symptoms were used which might affect the reliability of the outcome. Moreover, Klatte-Schulz et al. [50] have reported no significant difference in the mRNA expression of adiponectin in the Achilles tendinopathy samples compared to that in the acute ruptured tendons, but the sample size of the study was small. A larger sample size is required to confirm the findings.

3.3.4. Other adipokines

There was higher mRNA expression of FABP4 in chronic ruptured Achilles tendons compared to that in acute ruptured tendons in patients [50]. The expression of FABP4 increased and localized predominantly in the area of fat accumulation in torn rotator cuff muscle compared to intact deltoid muscle [69]. FABP4 was a plasma biomarker of obesity [70], supporting the potential roles of adipokines in the development of tendinopathy in patients with obesity. The expression of FABP4 and HIF-1α increased in the rat rotator cuff tear model established by detachment of supraspinatus tendon [69]. Local injection of FABP4 inhibitor into the supraspinatus muscle 4 times at 3-day intervals starting from week 2 after surgery significantly decreased FABP4 expression but has no effect on HIF-1α, reduced fatty infiltration and improved the tensile strength of the rotator cuff muscle [69]. Higher serum level of resistin at baseline predicted a higher recovery rate in patients with upper extremity soft tissue disorders at 8-week follow-up (OR: 1.56, 95 % CI 0.90, 2.71) and the higher level of serum visfatin showed a similar trend (OR: 0.92; 95 %CI 0.36, 2.35) [62].

3.4. Association of FFA metabolites in obesity with tendinopathy

A systemic search with keywords "tendon" and "fatty acid" was done. Three-hundred and forty articles were identified and 15 clinical articles were included after detailed examination (Online Resource 1B). FFA overload in obesity has been demonstrated to damage non-adipose tissues and contributes to DM, chronic kidney disease, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and cancer, by boosting the production of ROS, lipid peroxidation, mitochondrial damage and production of inflammatory cytokines [71,72]. SFA were also shown to exert lipotoxic effects on cartilage and subchondral bone similar to osteoarthritis in rats [73]. Despite the lack of evidence supporting the direct effects of FFA overload on tendon, there is evidence supporting the association of FFA levels with tendon health and pathology. In this context, the serum levels of two linoleic acid derived oxylipins were significantly higher in Achilles tendinopathy samples compared to those in the controls in a cross-sectional study, suggesting that FFA overload might contribute to pain in Achilles tendinopathy [74]. Besides, patients with full thickness degenerative rotator cuff tears had a significantly lower Omega-3 Index than controls without rotator cuff tendinopathy in a cross-sectional study [75]. In addition, the supplementation with long-chain ω3 polyunsaturated FFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) for 8 weeks reduced shoulder pain [76]. On the contrary, supplementation with ω3 FFA and vitamins (A, B6, C, E, selenium and zinc) for 8 weeks has no effects on pain level and maximal grip force compared to the placebo group after 6 months in patients with epicondylitis [77]. Obesity was associated with high pro-inflammatory PGE2 level in blood [78]. Although the early studies from Alfredson's group reported no change in the peri-tendinous level of PGE2 in patents with Jumpers' knee, tennis elbow and Achilles tendinopathy [79–81], other studies have reported marked production of PGE2 [82] and increased expression of COX-2 [56,83,84]. Bergqvist et al. [83] have shown higher expression of prostacyclin receptor and enzymes catalyzing the biosynthesis of prostaglandins, including COX-1, COX-2, prostacyclin synthase (PGIS) and microsomal prostaglandin E synthase-1 (mPGES-1) in the supraspinatus and Achilles tendon biopsies of symptomatic patients with tendinopathy or rupture compared to that in the healthy tendon samples. In another case, there was also significantly higher protein expression of COX-2 in the patellar tendinopathy samples compared to that in the healthy controls [84]. High concentration of PGE2 reduced cell proliferation, increased protein and mRNA expression

of MMP1 and MMP3 of tendon fibroblasts as well promoted non-tenocyte differentiation of TDSCs via BMP-2, which might cause matrix degeneration and metaplasia in tendinopathy [85–87]. We have shown overexpression of BMPs in clinical samples of patellar tendinopathy [88,89]. Many FFA metabolites are involved in the resolution of inflammation in tendons. The inflammation pro-resolving power of tendinopathic tendons was compromised, which may be associated with the dysregulation of FFA metabolites. In this regard, IL-1β markedly induced prostaglandin biosynthesis in tendinopathic tendon cells compared to healthy tendon cells, and up regulated several specialized pro-resolving mediators (SPM) including 15-epi-LXA4 and MaR1 [90]. 15-epi-LXA4 or MaR1 down-regulated PGE2 and PGD2 production in IL-1β stimulated healthy tendon cells but has a modest effect in tendinopathic cells [90]. Symptomatic human Achilles tendinopathy cells showed significantly higher levels of 15-epi-LXB4, PGE2 and PGF2α, compared to acute Achilles rupture tendons, suggesting the SPM, while increased, may not be sufficient to counteract the ongoing inflammatory process in tendinopathic cells [91]. Besides, clinical samples from patients with symptomatic Achilles tendinopathy showed lower expression of ALOX15 mRNA (an enzyme for SPM synthesis) compared to healthy human hamstring tendons [49]. On the other hand, patients who were pain-free after treatment had higher expression of ALOX15 mRNA (an enzyme for SPM synthesis) in supraspinatus tendons compared to tendons from patients who continued to experience pain after surgical treatment, suggesting that FFA metabolism was affected, causing tendon pain [92].

3.5. Association of alarmins in obesity with tendinopathy

A systemic search with keywords "tendon" and ("alarmin" or "IL-33" or "DAMP" or "HMGB1", "heat shock" or "hsp" or "S100" or "IL-1β") was done. Nine relevant clinical articles were identified (Online Resource 1C). The release of alarmins by stressed or necrotic cells, has been highlighted recently in the pathogenesis of tendinopathy. Alarmins are key effectors of innate immune system for host defence and tissue repair after cell damages. The hypertrophy or necrosis of adipocytes in obesity activates alarmins such as high-mobility group box-1 (HMGB1), S100 family proteins, heat shock proteins (HSP) and cytokines such as IL-1β and IL-33 [25–30], many of which were also overexpressed in tendinopathy [43,50,93–101]. For instances, torn supraspinatus tendon and matched intact subscapularis tendon demonstrated significantly increased expression of HMGB1 compared with the control tissues, with early tendinopathy tissue showing the greatest expression [93]. Besides, elevated levels of TREM-1, HMGB-1 and RAGE were observed in biceps tendons of patients with rotator cuff injury with or without glenohumeral arthritis [94]. The mRNA expression of HMGB-1 and fat accumulation in rotator cuff muscles were higher in smokers compared to that from non-smokers with rotator cuff tears [95]. Regarding the possible mechanisms of HMGB1 on tendinopathy, HMGB1 was reported to increase the mobility, proliferation, as well as the expression of IL-1β, IL-6, IL-33, CCL2, CXCL12, TNF-α, MMP3. MMP13, collagen type 3, tenascin C and decorin in tenocytes via TLR4/NF-kB/MAPK activation [93,102]. The short-term administration of HMGB1 was reported to induce hyper-cellularity of rat Achilles tissues, accompanied with enhanced immune cell infiltration [102].

Besides HMGB1, there was significant upregulation of HSP27 and HSP70 in the torn human supraspinatus tendons compared to the matched intact subscapularis tendons, highlighting the involvement of alarmins in early tendon disease [97]. The overexpression of HSP may be a protective responses of tendon cells to repetitive injuries as the expression of HSP72 was downregulated in the rat tendon injury model and the overexpression of HSP72 reduced tendon inflammation, inflammatory cell infiltration and fibrosis [103]. The overexpression of HSP70 was also associated with tendon repair after photobiomodulation therapy in another study [104].

In addition, the expression of alarmin IL-33 was significantly higher in the chronic Achilles tendon rupture group compared to that in the acute Achilles tendon rupture group and intact tendon group [50]. Similarly, IL-33 and its receptor, ST-2, were significantly elevated in early tendinopathy samples (subscapularis tendon) compared to that in healthy subscapularis tendons or matched torn supraspinatus tendon biopsies [43,98]. Both *in vivo* and *in vitro* studies have shown that IL-33/ST2 triggered the release of inflammatory cytokines (IL-6, IL-8 and MCP-1) and switched collagen production towards the biomechanically inferior collagen type III [98]. The increased expression of IL-33 in tendons therefore might contribute to matrix degeneration and impaired healing response, increasing the susceptibility of tendon to rupture as seen in tendinopathy. Both TNF-α and TNF-α + IL-1β increased the expression of IL-33 in human tenocytes [98], suggesting that adipose tissue might also induce the release of IL-33 in tenocytes and hence predispose the development of tendinopathy via overproduction of TNF-α and IL-1β.

Besides, there was significant higher expression of alarmins including SRRM2, VCAM1, IL-33, and NES but not CD248, PDPN in diseased (tendinopathic peroneus longus, the Achilles tendon and the extensor digitorum tendon associated with a painful fixed flexion deformity of the proximal inter-phalangeal joint) versus healthy endothelium [99]. A sub-set of tenocytes isolated from the diseased tendon expressed higher levels of CXCL1, CXCL6, CXCL8 and alarmin genes CD248, VCAM1, and PDPN compared with the healthy cells [99].

In the subacromial bursa of patients with pain, the expression of TAC1, MCP1, PANX1, P2X7, TNF-α, IL-6, MMP1, and S100A4, -A10, -A11 was higher than that of the rotator cuff tendon of asymoptomatic patients [100]. Furthermore, immunohistochemistry and quantitative RT-PCR showed that the expression of S100A8 & A9 was significantly upregulated in the tendinopathic tissue compared with that in the control. Furthermore, treating primary human tenocytes with exogenous S100A8 & A9 significantly increased the release of IL-6, IL-8, CCL2, CCL20 and CXCL10 proteins [96]. Mosca et al. [101] have reported different findings. They have shown that painful diseased human supraspinatus tendon samples expressed higher HIF-1α and S100A9 compared to post-treatment pain-free tendon samples and healthy supraspinatus tendon samples. However, the expression of IL-33 reduced in the diseased compared to the healthy tendons [101]. Moreover, the expression of HMGB1 increased in the post-treatment pain-free tendon samples compared to that in the healthy and diseased tendons [101]. On the contrary, the expression of alarmins including HMGB1, IL-33, HIF-1α and S100A9 increased in a mouse rotator cuff tendinopathy model induced by subacromial impingement [105].

3.6. Association of advanced glycation end products and hyperglycemia with tendinopathy

Obesity is an important risk factor for the development of metabolic syndrome and DM. The epidemiology and potential mechanisms of DM in causing and exacerbating tendinopathy have been discussed in another systemic review [106]. This review therefore only highlights the roles of hyperglycemia as a result of obesity-induced insulin resistance in promoting tendon inflammation.

In this context, hyperglycemia was reported to increase ROS production and mRNA expression of NADPH oxidase 1 and 4, IL-6, MMP-2, MMP-9, MM-13, TIMP-1 and TIMP-2 in tendon cells [107,108]. Besides, a high glucose concentration was also reported to upregulate the mRNA expression of COX-2 in healthy TDSCs and tendinopathic TDSCs [109]. The expression of ALOX15 was significantly reduced in IL-1β stimulated healthy TDSCs at a high glucose level, suggesting that the inflammation pro-resolving response of TDSCs was weakened in a high glucose environment [109]. In addition to the direct effects of glucose on tendon cells, the excess blood glucose nonenzymatically glycates and oxidizes collagens in tendons to form advanced glycation end products (AGEs). The increase in collagen cross-links in tendon reduces fiber sliding and viscoelasticity; and hence increases its brittleness. The binding of AGEs to their receptors triggers pro-oxidant and pro-inflammatory events via

NF-kB signaling. A previous study has shown that AGEs induced NF-kB activation, cell cycle arrest, and pro-inflammatory cytokine release (IL-6 and TNF-α) as well as reduced the viability of human osteoarthritic fibroblast-like synovial cells [110]. Streptozotocin-induced hyperglycemia was reported to increase the expression of IL-1β and AGEs in the insertion and mid-substance of supraspinatus tendon as well as TNF-α expression in the superior capsule of rotator cuff in rats, further supporting the role of hyperglycemia in inducing tendon inflammation [111]. AGEs can also form on lipids such as high-density lipoprotein (HDL) and low-density lipoprotein (LDL). The production of AGEs is hence accelerated in patients with obesity as a result of the increased availability of lipids and glucose, increasing the risk of development of tendinopathy.

3.7. Common inflammatory mediators of obesity and tendinopathy are mechano-sensitive

Tendon overuse is an important risk factor for the development of tendinopathy. Microdialysis showed a net release of PGE2 and thromboxane B2 (TXB2) from the peritendinous space of Achilles tendon during exercise in healthy individuals [112], suggesting that inflammatory activity was accelerated in tendon under dynamic loading. The peritendinous concentration of lactate was higher in patients with chronic painful Achilles tendinopathy compared to that in the controls with normal Achilles tendon [113]. While the level of lactate did not increase in Alfredson et al. [113]'s study during 4 h exercise, the net release of lactate from the peritendionous space of Achilles tendon increased during intermittent isometric exercise in healthy individuals in Langberg et al. [112]'s study.

There is mounting evidence showing that many common inflammatory mediators of obesity and tendinopathy including adipokines, FFA metabolites and alarmins are mechano-sensitive. For instances, regarding FFA metabolites, the expression of COX-1, COX-2, PGE2 and LTB4 in tenocytes, TDSCs, or tendon explants was induced by mechanical loading [114–118]. 5-lipoxygenase activating protein (FLAP) and COX-2 are the inflammatory markers of the leukotrienes and prostaglandins pathways of FFA metabolism, respectively. The mRNA expression of FLAP and COX-2 increased in a rat supraspinatus tendon overuse injury model [119]. However, mechanical loading of human tendon fibroblasts increased the expression of LTB4 and PGE2 but has no effect on the expression of 5-lipoxygenase (5-LOX).

In an overuse degenerative rat supraspinatus tendon model, the mRNA expression of IL-15, IL-18, MIF, T-cell CD3 gamma chain, T-cell receptor variable β chain, IL-6, TNF-α receptor and receptor activator of NF-kB ligand was upregulated while the expression of T cell receptor α chain, IL-2 and T-cell receptor was downregulated after daily treadmill running for four weeks [42].

Regarding alarmins, mechanical loading also increased the expression of HSP72 in human tenocytes [120]. In one study, the mRNA expression of obesity-associated alarmins, HSP27 and HSP70, was upregulated in rat supraspinatus tendons subjected to daily treadmill running for four weeks [42]. Besides, the mRNA expression of HSP27 and HSP70 increased in the supraspinatus tendon of a rat model of tendon overuse [121]. The expression of HSP72 also increased in flexor digitorum muscles and tendons of a rat model of tendon overuse [122]. Furthermore, mechanical strain also induced alarmin IL-33 secretion in murine fibroblasts in the absence of cellular necrosis [123]. In another case, cyclic stretching enhanced the maturation of IL-1β via promoting H_2O_2-induced NLRP3 inflammasome activation in tenocytes *in vitro* [124], suggesting that mechanical overuse and obesity might act synergistically to produce IL-1β and damage tendon. Besides HSP and IL-33, tendon overuse by treadmill running also increased the expression of S100 in rat supraspinatus tendons [125]. HMGB1 is another mechanical-sensitive alarmin. In this regard, mechanical overloading induced HMGB1 release and increased the production of PGE2 and MMP3 in rat tendon cells *in vitro* [126]. Moreover, mechanical overloading *in vivo* induced the release of HMGB1 into tendon extracellular matrix and induced tendon inflammation in a mouse treadmill running model [126,127]. In addition, the administration of glycyrrhizin or metformin, both are HMGB1 inhibitors, inhibited the development of Achilles tendinopathy induced by long-term intensive treadmill running in mice [102,126,127].

3.8. Contribution of local adipose tissue in the development of tendinopathy

Besides the visceral and subcutaneous fat depots, fatty deposition in pathological muscles and tendons as well as fat pads adjacent to tendons such as the entheses, the Hoffa's fat pad located posterior to the patellar tendon and the Kager fat pad located anterior to the Achilles tendon can be local sources of adipose tissue-associated inflammatory mediators [128]. In this regard, the infiltration of fat and blood vessels, together with increased expression of inflammatory cytokines and MMPs, VEGF, hypoxia-inducible factor (HIF) were commonly reported in tendinopathy [129]. People with obesity can have fat accumulation in tendon, which disrupts its integrity [130]. There was an increase in peritendinous fat, an accumulation of oxidized lipoprotein lipase (oxLDL) and an increase in mRNA expression of MMP2 in tendons of mice fed with a high-fed diet [131]. Moreover, oxLDL increased the proliferation, enhanced mRNA expression of MMP2 as well as reduced the mRNA expression of Col1a1 and Col3a1 in human tenocytes *in vitro* [131]. These findings supported the importance of local fat metabolites in tendon functions and pathology. Besides, muscle dysfunction due to fat deposition may also indirectly affect tendon function and hence the development of tendinopathy and surgical outcomes. Indeed, a systematic review has shown that rotator cuffs with moderate or significant fatty infiltration in rotator cuff muscles preoperatively had a significantly higher re-tear rate than those with no or minimal fatty infiltration [132]. In addition, fatty infiltration of the rotator cuff muscle was also reported to be the most influential factor on clinical outcome 20 years after the repair of isolated supraspinatus tendon tears [133]. A recent study has shown that fibro-adipogenic progenitors mediated rotator cuff muscle degeneration is related to the poor quality of rotator cuff repair [134].

The fat pad adjacent to tendon is not a static structure. It is a well-vascularized, highly innervated tissue. An animal study has shown histopathological changes in the fat pad with increased cellularity and vascularity in a rat model of patellar tendinopathy [135]. Case-control studies have shown that Hoffa's fat pad impingement was associated with proximal patellar tendinopathy [136] and quadriceps fat pad edema was associated with increased quadriceps tendon alterations and quadriceps tendon thickness in patients [137]. The Kager fat pad underwent significant deformation during plantar flexion in a cadaveric ankle study, suggesting that it acts as a shock absorber to the Achilles tendon and pathological changes to the fat pad may be clinically important in the development of Achilles tendinopathy [138].

The fat pad shares a blood supply with tendon and cytokines produced in the fat pad only need to travel a short distance in order to affect the tendon. Fat tissues adjacent to common sites of tendinopathy hence are also a key local source of adipose tissue-associated inflammatory mediators. In this regard, individuals with chronic Achilles tendinopathy have elevated mRNA expression of cytokines in Kager's fat pad compared with healthy individuals, suggesting the potential roles of Kager' fat pad in tendon inflammation and development of tendinopathy [139]. Besides, fat pad size also differed between individuals with and without tendinopathy [140]. Larger fat pads produce more cytokines, which may contribute to tendinopathy and pain. Repetitive stress of the fat pads close to tendon may induce subtle chronic low-grade inflammation and predispose the development of tendinopathy. A recent study has also reported the presence of nerve endings in fat at the enthesis [141], implying that it may have mechanosensory role and damage of the fat tissue may contribute to pain in tendinopathy. Similarly, adipose tissues inside pathological tendon and adjacent muscle can be a local source of

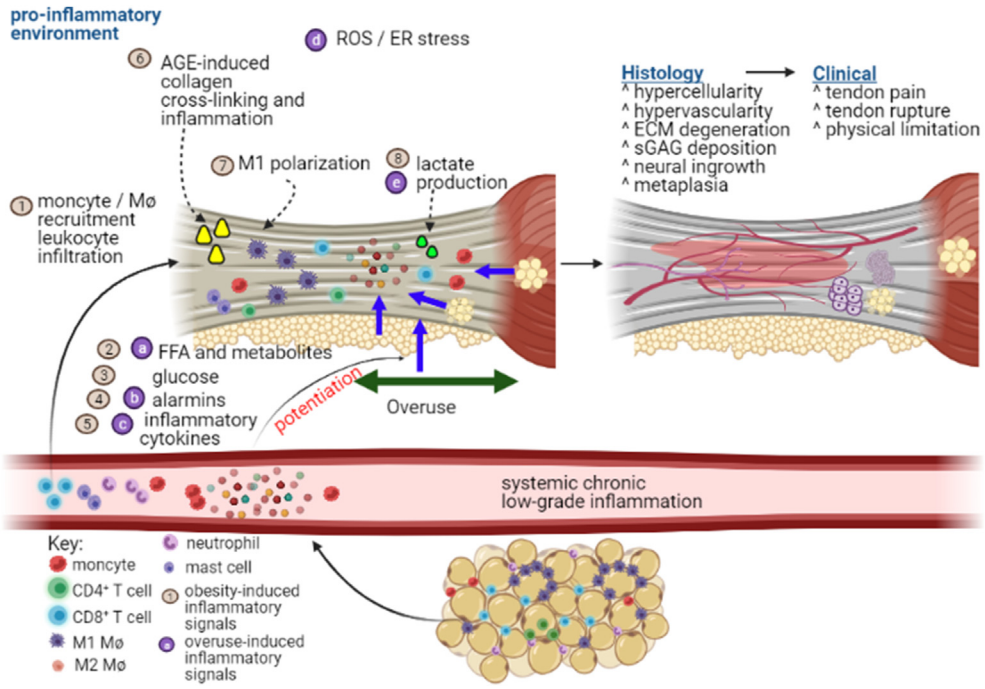

Fig. 2. Schematic diagram summarizing the common inflammatory mediators potentially linking obesity and the development of tendinopathy. Many common inflammatory mediators of obesity and tendinopathy are also mechano-sensitive, supporting that obesity may reduce the capacity of tendon to resolve inflammation and tolerate load, and amplify the deleterious effect of tendon overuse. The immune cells are chemo-attracted to tendon, triggering further inflammatory responses and tendon damages. People with obesity can have fat accumulation in muscles and tendons. The accumulation of fat in tendons disrupts its integrity. Muscle dysfunction due to fat deposition may also indirectly affect tendon function. Besides the visceral and subcutaneous fat depots, fatty deposition in pathological muscles and tendons as well as fat pads adjacent to tendons can be local sources of adipose tissue-associated inflammatory mediators. The metabolic effects associated with systemic obesity therefore can extend to the local fat tissues, which can promote inflammation, pain, and tendon degeneration, contributing to the development and progression of tendinopathy.

adipose-tissue associated inflammatory mediators in people with obesity.

Taken together, metabolic effects associated with systemic obesity can extend to the local fat tissues in adjacent muscles, entheses, nearby fat pads and even in tendon itself, which can promote inflammation, pain, and tendon degeneration within the local tendon environment, thus contributing to the development and progression of tendinopathy.

Fig. 2 summarizes the common inflammatory mediators potentially linking obesity and the development of tendinopathy.

4. Conclusion and future research directions

Obesity, a known mechanical risk factor for tendinopathy, is now recognised to induce systemic inflammation which may drive the onset and progression of tendinopathy. Obesity overproduces inflammatory adipokines, skewing the immune system to a pro-inflammatory state. The increase of bacterial LPS, adipocyte hypertrophy, hyperplasia, hypoxia, ER stress, UPR and adipocyte necrosis induce the release of adipokines, FFA metabolites, alarmins, glucose and lactate, which induce systemic chronic low-grade inflammation. We summarized the evidence linking the actions of adipokines, FFA metabolites, alarmins, glucose and AGEs in obesity with tendinopathy. The release of these inflammatory signals may chemoattract immune cells to tendon, triggering further inflammatory responses and tendon damages. Many common inflammatory mediators of obesity and tendinopathy are also mechano-sensitive such as FFA metabolites, alarmins and inflammatory cytokines. As common sites of tendinopathy have adjacent fat tissues or fat infiltration, the metabolic effects associated with obesity can also extend to the local fat tissues. Further studies should examine the relative contributions of systemic and local fat depots in the development and progression of tendinopathy.

Despite the recent advances in understanding the role of obesity in the pathogenesis of tendinopathy, much remains unknown about their causal relationship, underlying mechanisms and treatment. Most of the studies examining the relationship between adipose tissue-associated inflammatory mediators and tendinopathy in human are only association studies. On the other hand, there are some *in vitro* and *in vivo* data examining the direct effects of adipose tissue-associated inflammatory mediators on tendon cells and animal model of tendinopathy. Further studies are needed to show their causal relationship. While the infiltration of immune cells into tendon has been reported, the mechanisms of their recruitment into tendon and their role in tendinopathy have not been defined. Although there is evidence demonstrating adipokines, FFA metabolites, alarmins and hyperglycemia as the link between obesity and tendinopathy, studies are needed to fully understand their mechanism of action and their interactive effects with mechanical loading to underscore their therapeutic value. Lifestyle intervention such as exercise and diet modification has been shown to improve inflammation and obesity [142]. It is not clear if it will also improve tendinopathy. Future studies are required.

Besides, studies on new intervention targeting adipose tissue-induced inflammation for the promotion of healing in tendinopathy are needed. References can be made to the interventions under trial for other obesity-induced co-morbidities. Indeed, there were some early *in vitro* and *in vivo* studies on the effects of metformin and glycyrrhizin for the treatment of tendon overuse with encouraging results [102,126,127]. However, recent studies have shown that statins use was associated with higher risk of trigger finger and shoulder tendinopathy, possibly through MMP release [143,144], suggesting that the medication used for the management of obesity may also do harm more than good on tendons. However, a systematic review reported the opposite and suggested that statins could decrease the risk of developing rotator cuff disease and the incidence of revision after rotator cuff repair [145]. Another study also reported the beneficial effects of simvastatin in the suppression of inflammation and promotion of tendon healing in inflamed tenocytes and collagenase-induced tendinopathy animal model [146]. Further high-quality studies are needed to clarify these contradictory findings.

NF-kB plays a converging role in mediating the effects of various inflammatory stimuli in obesity – activation of Toll-like receptors, ROS production and pro-inflammatory cytokine release. Targeted deletion of I-kappa-B kinase, targeted mutation of Ikbkb or pharmacological inhibition of NF-kB with high dose of salicylates reduced inflammation and improved insulin sensitivity in animal models and in human with obesity [147]. The inhibition of NF-kb therefore can be a potential direction of research for tendinopathy management. There are studies showing the beneficial effects of aspirin, a salicylates, on tendon but the studies were not specifically on tendinopathy [148,149]. Further studies are needed to show if salicylates or other NF-kB inhibitors can reduce tendon inflammation and promote healing of tendinopathy. The serum levels of

inflammatory markers have been applied for the prognosis and diagnosis of obesity-associated complications [150,151]. There are already some early data on the usefulness of adipose-associated pro-inflammatory and anti-inflammatory factors as clinical biomarkers for tendinopathy (Online Resource 1). As the levels of adipose tissue-associated pro-inflammatory and anti-inflammatory factors in tendons can be influenced by systemic, adjacent tissues and tendon sources, their credibility as clinical biomarkers for tendinopathy may depend on the demographics and medical history of patients. Further studies are required to understand their values as clinical biomarkers of tendinopathy in different patient subgroups, which will have implications for the early diagnosis prior to clinical report of tendon pain and rupture as well as optimal management of patients after surgical or non-surgical treatment.

Chronic tendinopathy is a multi-factorial disorder. Various risk factors modify the risk of development and prognosis of overuse-induced tendinopathy. A higher risk does not imply that obesity is a necessary and sufficient factor for the development of tendinopathy. While it is generally believed that people with obesity are sedentary, there are people who are genetically obese and hence they may not live sedentary lifestyle for their high body weight. However, because of their high body weight, the tendon is mechanically overloaded, in addition to the obesity-induced chronic low-grade inflammation that can increase the risk of tendon damage. The tendon loading intensity also affects tendon health. Moderate intensity exercise is good for tendon while high-intensity exercise is detrimental to tendon. Depending on the loading intensity, the "fat but fit" people may or may not have tendinopathy. The exercise that they engaged can have positive or negative effects on their tendon health. Moderate-intensity exercise reduces the risk while high-intensity exercise increases the risk of tendinopathy. Although the consumption of a high fat diet often coincides with a sedentary lifestyle, there is not always the case: a notable excepton being athletes who compensate for high levels of caloric expenditure with a high fat diet. Taken together, the interaction between obesity-induced tendon overload, obesity-induced systemic chronic low-grade inflammation and tendon overuse is complicated and requires further research to understand their relationships.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Pauline Po Yee LUI conceived, performed the literature search, interpreted the data, drafted and finalized the manuscript. Patrick Shu Hang YUNG interpreted the data and revised the manuscript. All authors read and approved the final work.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

We thank Ms Angelina Yui Ling CHU for editing the manuscript and preparing the figures. The figures were created with Biorender.com.

Online Resource. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2021.10.003.

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