International Orthopaedics (SICOT) (2015) 39:1465–1473
DOI 10.1007/s00264-015-2775-x

REVIEW ARTICLE

Alterations of tendons in diabetes mellitus: what are the current findings?

Liu Shi[1] · **Yun-feng Rui**[1] · **Gang Li**[2,3] · **Chen Wang**[1]

Received: 19 January 2015 / Accepted: 23 March 2015 / Published online: 6 May 2015

Abstract As a connective tissue, tendon connects the muscle and bone, and plays the key role in the locomotor system. Some previous studies have shown the pathological alternations in diabetic tendons, which might result in the structural and functional changes, and even accelerate the process of diabetic foot. In this review, we examined the current findings of the diabetic tendons in the form of various aspects, and summarized the clinical presentation, imaging, biomechanical, histopathological, cellular and molecular abnormalities in the diabetic tendons. The progress of diabetic tendon damage is complicated and the main hypotheses include the excessive accumulation of AGEs, the altered inflammatory response, neovascularization and insensitive neuropathy. However, the cellular and molecular mechanisms of these alterations are still ambiguous. Tendon stem/progenitor cells (TSPCs) have been discovered to play important roles in both tendon physiology and tendon pathology. Recently, we identified TSPCs from patellar tendons in our well-established diabetic rat model and found impaired tenogenic differentiation potential of these cells. We proposed a new hypothesis that the impaired cell functions of diabetic TSPCs might be the underlying cellular and molecular mechanism of the diabetic tendon alternations. These findings should be helpful to establish a better therapeutic strategy for diabetic tendon repair and regeneration.

Keywords Diabetes mellitus · Tendon stem/progenitor cells · Tendon repair and regeneration

✉ Yun-feng Rui
ruiyunfeng@126.com

[1] Department of Orthopaedics, Zhongda Hospital, School of Medicine, Southeast University, 87 Ding Jia Qiao, Nanjing, Jiangsu 210009, China

[2] Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, China

[3] Program of Stem Cell and Regeneration, School of Biomedical Science, and Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, China

Background

As a metabolic disease, diabetes mellitus (DM) is associated with many diseases and complications, such as retinopathy [1], nephropathy [2], osteoporosis [3] and impaired wound healing [4]. Currently, the influences of DM on the musculoskeletal system have been noted. The negative impacts of DM on the tendons may contribute to tendinitis [5], tendon ruptures [6], adhesive capsulitis [7] and even the diabetic foot [8].

Epidemiological studies revealed higher prevalence of Dupuytren's disease, carpal tunnel syndrome and shoulder adhesive capsulitis in both type I and type II diabetic patients with poor glycaemic control [9, 10]. Patients with insulin-dependent diabetes were significantly associated with chronic rotator cuff tendinitis and limited range of motion (ROM) in the shoulders [5].

Recently, some studies reported the tendon alternations in patients with diabetes following imaging examinations, such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) [11]. In this review, we summarized the current evidence on the alternations of tendons from both clinical patients and animal models of DM. The clinical manifestation, imaging examination, biomechanical properties, histopathological features and cellular and molecular changes in tendons of patients with diabetes were summarized. The aim of this review was to explore the links between the DM

and the underlying cellular and molecular mechanisms of diabetic tendon alternations.

Clinical manifestation of tendon pathologies in diabetic patients

Patients with DM with poor glycaemic control often suffer from chronic pain, limited range of motion (ROM) of the joints and have a higher risk of tendon tears [10]. The prevalence of connective tissue diseases, such as Dupuytren's disease, trigger finger, carpal tunnel syndrome, rotator cuff tears and shoulder adhesive capsulitis (frozen shoulder), were increased in both patients with type 1 and type 2 diabetes [9, 12, 13]. These diabetic patients with stiff shoulder have poor prognosis of nonoperative treatment [14].

Symptomatic rotator cuff tears and acute Achilles tendon ruptures are common in patients with DM [6, 15]. After surgical repair, these patients showed a limited ROM and a higher incidence of re-tears [16, 17]. For the ruptured Achilles tendons, patients with DM have higher rate of postoperative infection and poorer tendon healing [6, 18]. Clinical research revealed that patients with diabetes with poor glycaemic control easily develop severe lower limb infection and even diabetic foot, and are at a higher risk of lower extremity amputation [8]. There is increasing evidence that reduced ankle joint ROM, static stiffness of the Achilles tendon and the diabetic neuropathy may be responsible for the development of diabetic foot [19–21].

However, not all the patients with DM are symptomatic, some of them are asymptomatic, even with an increased thickness or structural abnormalities in supraspinatus and biceps tendons and Achilles tendons found with imaging exams [11]. It is suggested that the insensitive neuropathy may reduce or even block the transmission of pain signal, thus leading to asymptomatic conditions in some patients with DM [21].

Imaging findings

Many imaging techniques, such as ultrasonography, MRI and CT, have been used in investigating the changes of tendons and ligaments in patients with diabetes. Currently, there is no longitudinal study to examine the thickness and the structural abnormalities in the tendons of patients with diabetes.

In a clinical study, Giacomozzi et al. [21] discovered a tendency for increased thickness of the Achilles tendon in patients with DM compared to healthy subjects, although there was no statistical difference. However, in diabetic patients with neuropathy, the thickness of the tendons was increased significantly. In another study, Akturk et al. [22] found that the average thickness of the Achilles tendon was increased in patients with type 2 DM by ultrasound, but the significance was only among the female groups. Batista et al. [8] discovered disorganization of the Achilles tendon fibers as well as calcification in some asymptomatic individuals with diabetes by ultrasound, but they were not able to demonstrate any statistical relationship between the structural abnormality with age, length of time of diagnosis, or diabetes management, and no data about the location of disorganization and calcifications in the Achilles tendon were provided. In addition, the anterior-posterior thickness of the Achilles tendon was greater in the control subjects than in the diabetic patients, but still lacked a statistical analysis. The latest study showed the degenerative features and calcifications localized at the enthesis of the Achilles tendons were significantly increased in the asymptomatic patients with diabetes [12]. Papanas et al. [23] found a significantly greater volume of the Achilles tendon in patients with DM than controls in both male and female groups, while the thickness of the Achilles tendon showed no difference.

Recently, a study by Abate et al. [24] revealed the thickness of the supraspinatus tendon and the biceps tendon in asymptomatic elderly patients with diabetes, which were greater than that in controls by sonographic evaluation. Besides, they also found more sonographic appearances of degenerative features in the rotator cuff and biceps in DM subjects. Another study also discovered that the quadriceps tendons had more buckling in diabetic patients with MRI examination [25].

All these studies presented abnormal changes of the thickness and structure of collagen fibers in diabetic tendons, although the association between diabetes mellitus and tendon alterations could not be sustained due to methodological drawbacks [11]. However, all the studies reported the increasing trend of thickening tendons in diabetic patients. Overuse and increasing BMI in DM subjects are considered as the major pathogenic factors for the increased tendon thickness and reduced ROM of joints [12].

Biomechanical changes

A few reports focused on the biomechanical properties of tendons in DM patients. In the DM animal models, most of the studies indicated DM having negative impacts on the mechanical properties of the tendons [26–32]. Most of the tendons were isolated from the diabetic animal models induced by streptozotocin (STZ) or other methods. The main findings are summarized in Table 1.

In the STZ induced diabetic rat model, a decreased Young's modulus which was calculated as stress divided by strain was found in both the diabetic Achilles and patellar tendons, as well as the accumulation of advanced glycation end products (AGEs) in tendon extracellular matrix (ECM) [26, 27]. In the study by De Oliveira et al. [27], besides the decreased elastic

Table 1 Characteristics of studies in biomechanical properties of diabetic tendons

Source	Species model	Groups	Duration of DM	Tendon analysed	Biomechanical properties of diabetic tendons
Kesava Reddy 2003 [28]	New Zealand rabbits tendons glycated in vitro	Non-glycated and glycated (n=10, each)	60 days	Achilles tendon	Significantly increased maximum load, Young's modulus of elasticity, energy to yield and toughness of glycated tendons
Bedi et al., 2010 [30]	Lewis rats Type 1 diabetes rotator cuff repair	CG and DG (n=16, each)	One and two weeks post operation	Supraspinatus tendon	Significantly reduced mean load-to-failure and stiffness of the tendon-bone complex at both one and two weeks postoperatively
Fox et al., 2011 [26]	Lewis rat Type 1 diabetes	CG (n=18); DG (n=20)	12 and 19 days post induction	Patellar tendon	Significantly reduced Young's modulus at both time points
De Oliveira et al., 2011 [27]	Wistar rats Type 1 diabetes	CG and DG (n=11, each)	Ten weeks post-induction	Achilles tendon	Significantly reduced elastic modulus Increased energy/tendon area, specific strain and maximum specific strain
De Oliveira et al., 2012 [29]	Wistar rats Type 1 diabetes	SCG, SDG; TCG, TDG (n=11, each)	Nine weeks post-induction	Achilles tendon	Significantly reduced elastic modulus of the SDG Increased specific deformation, the deformation at maximum force, and energy / tendon area of the SDG
Ahmed et al., 2012 [31]	GK and Wistar rats Type 2 diabetes	Wistar intact and ruptured (n=10, each); GK intact and ruptured (n=11, each)	One year of DM; Two weeks post operation	Achilles tendon	Lower stiffness (P=0.02) and peak load (P=0.14) in the injured diabetic tendons
Lehner et al., 2012 [32]	Lewis rats high glucose fed and Type 1 diabetes	CG (n=12); high glucose feeded (n=5); Type 1 diabetes (n=12);	Five days post induction	Achilles tendon	Significant reduction of the maximum tensile load
Sakoma et al., 2014 [34]	OLETF rats Type 2 diabetes	CG (LETO rat, n=2); DG (OLETF rat, n=4)	Five weeks	Achilles tendon	No difference in the Young's elastic modulus and toughness The ultimate stress of the Achilles tendon decreased as the amount of pentosidine deposition increased
David et al., 2014 [33]	Male C57BL/6 J mice	High fat and low fat diet (n=7 at 12 weeks and n=5–6 at 24 weeks)	High fat or low fat diet for 12 and 24 weeks; At 0, 7,14 and 28 days post-injury	Flexor digitorum longus (FDL) tendon	No difference of the uninjured FDL tendon after 12 weeks; decreased maximum force after 24 weeks; the impaired biomechanical properties of high fat feed at day 28 post injury

CG control group, *DG* subjects with diabetes, *SCG* sedentary control group, *SDG* sedentary subjects with diabetes, *TCG* trained control group, *TDG* trained subjects with diabetes, *OLETF* Otsuka Long-Evans Tokushima fatty

modulus, specific strain patterns were also seen in the subjects with diabetes. Lehner et al. [32] also discovered the significantly decreased maximum tensile load of Achilles tendon in the STZ treated animals. All these data indicated a tendency of impairing biomechanical properties in the diabetic tendons. De Oliveira et al. [29] compared the sedentary and aerobic physically trained diabetic rats with the matched controls, the elastic modulus of the sedentary diabetic group was decreased when compared to the trained diabetic subjects, meanwhile the deformation at maximum force and energy/tendon area was significantly decreased.

In the acute rotator cuff repair diabetic rat model, the supraspinatus tendon-bone complex of animals with diabetes demonstrated a significantly reduced mean load-to-failure and the stiffness of constructs [30]. Ahmed et al. [31] discovered that the injured tendons of the diabetic group exhibited 35 % lower stiffness compared to the control tendons. In the intact diabetic tendons, the stiffness was 19 % lower than that of the non-diabetic controls. In the mice with type 2 diabetes, the mice fed with high fat diet showed decreased maximum force of uninjured flexor digitorum longus (FDL) tendons compared with lean diets at 24 weeks. What's more, impaired

biomechanical properties of FDL tendon in high fat diet mice at day 28 post injury were also observed, and the subsequent histological examination of the injury site showed a smaller area and lower cell content which showed a defective repair in the mice with type 2 diabetes [33].

More evidence suggested that the micro-structure of the tendons was altered in the diabetic patients. The latest study by Yoshimasa et al. [34] revealed the accumulation of the pentosidine (a well-characterized AGEs) in the diabetic tendons. They also found the ultimate stress of the Achilles tendon decreased as the amount of pentosidine deposition increased in the diabetic rats simultaneously, and suggested that accumulation of AGEs might deteriorate the biomechanical properties of the tendons in patients with diabetes.

In the diabetic subjects, a markedly increased accumulation of AGEs in the tendon was noted, forming covalent cross-links within the collagen fibers and interacting with the receptor for advanced glycation end products (RAGE) on the cell surface, which may lead to deterioration of the biomechanical properties of the diabetic tendons [26, 35].

On the contrary, the glycated Achilles tendons of rabbits in vitro exhibited significantly increased mechanical properties [28]. It has also been shown that the hyperglycemia could reduce proteoglycan levels in the tendon cells in high glucose condition exposure to AGEs. Decreased proteoglycan levels could increase intracellular water and cellular edema, and these alterations may lead to the increased stiffness in diabetic tendons [36].

All these studies indicated a tendency of impairing biomechanical properties in the diabetic tendons. These reduced biomechanical properties may lead to the easy tendon rupture and ROM of the affected joints limited in patients with DM.

Histopathological changes

Gross observation and histological features

The diabetic tendons appeared fragile, atrophic and demonstrated a yellowish discoloration compared to the more robust, healthy tissue observed in the healthy control subjects [26, 30]. In the STZ induced diabetic rat model, the thickness of the Achilles tendon increased [37]. In the injured diabetic tendons, cross-sectional area of the healing site decreased compared to the control group [30].

Pathological changes were seen in the diabetic tendons. In contrast to the tight, parallel, bundled appearance in the healthy Achilles tendons, some collagen fibres in the diabetic tendons were separated and lost their parallel orientation, unequal and irregular with a decrease in fibre diameter and density of collagen. In addition, there were some chondrocyte-like cells within the Achilles tendon in the subjects with diabetes and the micro-tears were observed [38]. We have also successfully built an STZ-induced DM rat model, and similar alternations were also observed in diabetic patellar tendons with H&E staining (Fig. 1d and e). Besides the disordered collagen fibers in diabetic tendons, we also found the tendon cells in diabetic tendons surrounding the micro tear sites were rounding changed (Fig. 1e). In a clinical study with ultrasound examination, the calcifications localized at the enthesis of the Achilles tendons were found in asymptomatic patients with diabetes [8]. What's more, the significant increase of fibrocartilage metaplasia and granulation tissue hyperplasia were reported in patients with diabetes with stenosing flexor tenosynovitis compared to those subjects without diabetes [39]. Local hypoxia, which is induced by rupture of collagen fibers, and disturbance of microcirculation, may contribute to calcifications [24]. Some studies suggested that calcifications might be attributed to the erroneous differentiation of tendon-derived stem cells (TDSCs) towards to osteogenesis [40]. In our study, we found that the expression of osteopontin (OPN) was significantly increased in diabetic tendons when compared to the healthy tendons with immunohistochemical staining (IHC) (Fig. 1c and f).

In the STZ-induced DM rats, the increased type I collagen was observed with a disorganized manner. This may attribute to the increased cellularity in diabetic tendons, and the cells with excessive accumulation of collagen fibers and other extracellular matrix components may lead to tissue fibrosis resulting in the thickening of diabetic tendons [37, 41]. In the tendon-healing model, less organized collagen fibers were found at the tendon-bone interface in the subjects with diabetes [30]. The tendons in the rats with diabetes had lower regenerating activity, with a smaller transverse area, poorly organized collagen fibers, and decreased vascularity [37]. Most of the collagen fibers were of yellowish red colour and arranged irregularly, the collagen III-like fibers were less at the rupture site of the diabetic animals while the highest density of collagen III-like fibers were found in the controls [31]. The decreased transverse area as well as collagen III production might hamper the tendon repair.

Vasculopathy and neuropathy

It was reported that an adequate circulation and neuronal supply are beneficial for collagen synthesis at the injured site of the tendons [42]. However, reduced neovascularization in the degenerated tendons was found in type 2 diabetes patients [43], which is consistent with the findings in the injured diabetic rat tendons [41]. The reduced numbers of macrophages in the diabetic tendons impaired angiogenesis and tendon healing since macrophages mainly take part in the inflammatory process are also important in initiating angiogenesis [41]. Down-regulated expression of peroxisome proliferator activated receptor gamma (PPAR-γ) has been reported, which can reduce the vessel and nerve ingrowth involved in the

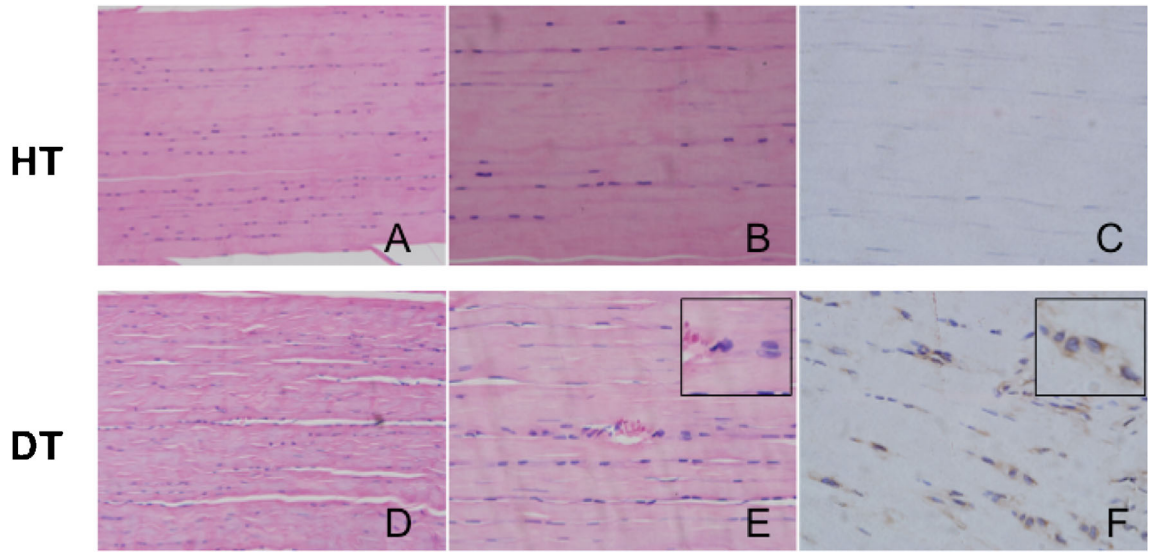

Fig. 1 Normal structure of patellar tendon from healthy SD rats (H & E staining, *A*×200; *B* ×400). Altered structure of patellar tendon from STZ induced diabetic rats (H&E staining, *D* ×200; *E* ×400). Negative expression of OPN in healthy tendon (IHC staining, *C*×400). Positive expression of OPN in diabetic tendon (IHC staining, *F*×400). (unpublished data)

pathogenesis of diabetic tendinopathy [38]. The insensitive neuropathy in the diabetic subjects could lead to excessive use of tendons, and might be a possible reason for those patients who were clinically asymptomatic and only had thickening and disorganized changes in tendons.

One study reported the vascular hyperplasia in human patellar tendinosis, and the increased prevalence of mast cells may be associated with these changes [37, 44]. In the STZ induced rat model, the average number of blood vessels per field was statistically higher in the diabetic group, and the blood vessels were often present in the tendons of the diabetic group. The cross-sectional area of the blood vessels was significantly larger and the VEGF expression was significantly higher in the diabetic rats [37]. The higher expression of VEGF in diabetic tendons may be related to the chronic degeneration of tendons, hypoxia and increased mechanical load, and the accumulation of AGEs may also be involved [45–47].

Inflammatory responses

In the diabetic patients with stenosing flexor tenosynovitis, the presence of a small number of inflammatory cells was found in the hyperplastic granulation tissue [39]. In the diabetic rats, a higher accumulation of nitrite/nitrate (NOx) was also found indicating chronic inflammatory status in the diabetic tendons [37]. However, in the injured diabetic tendons, the inflammatory factors were reduced compared to the normal controls, which resulted in a reduced numbers of PMNs and macrophages, and aborted tendon healing [41]. A transitory inflammatory response is necessary for the normal progression of tissue healing by releasing cytokines that regulate chemotaxis and fibroblast proliferation and extracellular matrix synthesis and remodeling [48]. Reduced inflammatory response in the injured diabetic tendons might account for the impaired normal tendon healing capacity in DM condition. Chronic inflammatory status was found in the DM condition, and this might be one of the proper reasons for the tendons' alternations in DM [37, 39]. Many studies also demonstrated that inflammatory enzymes, cytokines and reactive oxygen species (ROS) contribute to cell death and many diseases [49]. In the diabetic tendon, the chronic inflammatory condition is also harmful to tendon repair. Although there was still no report that decreasing the chronic inflammatory status could help to regain the normal inflammatory response in tendon, all these findings suggested that regaining the normal inflammatory response might be a way for DM tendinopathy treatment.

One study reported that the inflammation could promote mineralization of human bone marrow stem cells [50]. Although accumulation of calcium was found in both human and animal models, however, up to now, no studies reported the connection between inflammatory response and TDSCs differentiation.

AGEs

The excess of AGEs deposited in ECM is an important pathological change of DM, and it correlated with the histological and biomechanical changes of the diabetic tendons [26, 30]. The key characteristic of reactive AGEs is the formation of covalent cross-links among the collagen, which could be

generated via the enzymatically driven and the non-enzymatic glycation or oxidation-induced pathways [10]. Once formed, the cross-links within the collagen fibrils could dysfunction the ECM of diabetic tendons and deteriorate the biomechanical properties [10]. Recently, one study reported the catalyst Fe^{2+} could accelerate the formation of AGEs in type I collagen, and lead to the glycosylation of collagen and other matrix proteins in diabetic tendons [51]. AGEs interact with RAGE on the cell surface and activate several critical molecular pathways including pro-oxidant events and up-regulation of inflammatory mediators; the intracellular accumulation of AGEs could lead to negative effects, such as inhibiting cell growth, destruction of nitric oxide and promoting apoptosis [52–54]. AGEs is also involved in the scar formation and cause of tendon cell death [36]. The tendon cells treated with high glucose concentrations showed the decreased proteoglycans and increased transforming growth factor β1 (TGF-β1) levels in an AGE-independent manner, and high TGF-β levels is reported to associate with scar formation in tendon and tenocyte death [55].

With histological analysis, tendons in subjects with DM showed degenerative features, and the inflammatory responses were accelerated with the accumulations of AGEs in the ECM, which deteriorated tendon biomechanical properties as well as the functions of tendon cells. However, the differences in the findings in vasculopathy may be attributed to the different duration of DM.

Cytological and molecular changes

Tendon cells

Tenocytes are the basic functional unit of tendon and secrete ECM maintaining tendon function [56]. In the diabetic tendons, the density of mast cells were four-fold higher than the controls, and mast cells play an important role in soft tissue remodeling through releasing fibroblastic factors and tryptase [37, 44]. The effects of hyperglycemia on the proliferation of different cell types, such as human periodontal ligament fibroblasts, notochordal cells, tenocytes and peritoneal fibroblasts, are divers [57–60]. It was reported that the proliferation of tenocytes were not affected by glucose concentrations up to 25 mM in vitro [61]. Recent studies reported that the proliferations of rat notochordal cells were significantly decreased in high glucose concentration while the autophagy and apoptosis were increased via high glucose-induced oxidative stress [59, 60]. And the senescence of young annulus fibrosus cells was also accelerated in such conditions [62]. The expression of sox9 and scleraxis (Scx) of primary human tenocytes were up-regulated and the collagen synthesis was increased when they were treated with low extracellular glucose [63]. There were also reports that the cell proliferation of tendon cells in diabetic rats was reduced [41], with reduced collagen III expression, and decreased collagen I (Col 1a1) expression in the injured diabetic tendons [31].

Table 2 Alternations in diabetic tendons

Clinical	Symptomatic: chronic pain, limited range of motion of the joint, tendon tears, etc. Asymptomatic: increased thickness, higher prevalence of tear
Imaging	Increased thickness, greater volume, disorganization of tendon fibers, calcifications, degenerative features
Biomechanics	Decreased Young's modulus and stiffness in both intact and injured diabetic tendons. Increased Young's modulus and stiffness in the glycated tendons in vitro
Histopathology	
Gross and histological findings	Fragile, atrophic and yellowish appearance, increased thickness, reduced transverse area of healing site. Unequal and irregular crimping, loosening, and increased waviness, with a decrease in fibre diameter and density of collagen. Micro-tears and obvious ruptures. Increased collagen I at 24 days post induction. Irregularly arranged and ruptured collagen I at the rupture site as well as less presented collagen III-like fibers
Vasculopathy and neuropathy	Reduced neovascularization in type 2 diabetic patients. Reduced neovascularization in the injured diabetic rat tendons. Increased neovascularization in STZ induced rat model. Insensitive neuropathy
Inflammatory response	Chronic inflammatory status in the diabetic tendons. Reduced inflammatory response in injured diabetic tendons
AGEs	Excess of AGEs deposition in extracellular matrix. Covalent cross-links, interact with AGE-binding receptors on the cell surface, up-regulate inflammatory mediators, etc.
Cytological and molecular changes	
Tendon cells	Higher density of mast cells, reduced proliferation in the paratenon at day 7 post-trauma. The proliferation could not be affected by glucose concentrations up to 25 mM in vitro
TDSCs	The populations of insulin expressing tendon cells express scleraxis and nestin
MMPs	Increased MMP-13 and decreased MMP-3 mRNA levels in the tendon healing callus. Up-regulated the mRNA expression of MMP-9 and MMP-13 in tendon cells treated with high glucose concentration

Tendon stem/progenitor cells (TSPCs)

Besides the tenocytes in the normal tendon tissues, there is a small population of TSPCs present in tendons. TSPCs have stem cell characteristics, including clonogenicity, self-renewing capacity and the multi-differentiation potential in vitro and in vivo [64]. TSPCs could promote tendon repair and regeneration, and might play important roles in maintaining tendon homeostasis [43, 65]. Mechanical loading could promote BMP-2 expression in TDSCs, which could induce osteo-chongdrogenic and adipogenic differentiation of TDSCs in vitro. Our recent work found that the properties TDSCs isolated from patellar tendons in the collagenase-induced (CI) tendinopathy rat model were altered with higher osteo-chondrogenic differentiation potential, lower tenogenic differentiation potential and lower proliferative capacity, when compared to healthy TDSCs [40]. These findings suggested that erroneous differentiation of TDSCs might play a role in the pathogenesis of tendinopathy.

There are a few studies which investigated the properties of TSPCs in diabetic tendons. Recently, we isolated TDSCs from the STZ-induced diabetic rat patellar tendons, and found that the mRNA expression of Scx and Col1a1 were significantly lower in the diabetic TDSCs than that of the healthy TDSCs. High glucose could suppress the mRNA expression of Scx, tenomodulin (Tnmd) and Col1a1 of healthy TDSCs in vitro. One study reported that there were insulin expressing cells in diabetic tendon and these cells express tendon progenitor markers such as Scx and nestin [32]. The brain and thymus have been reported as the extra-pancreatic insulin producing tissues upon glucose stimulation [66]. Our unpublished data has also found that the mRNA expression of insulin in diabetic TDSCs was significantly lower than that in the healthy TDSCs. Taken together, TSPCs might participate in the process of the pathological alternations in diabetic tendons and might be a therapeutic target for diabetic tendinopathy [67].

Metalloproteinases (MMPs)

MMPs play important roles in ECM network remodeling [68]. Previous studies revealed the altered MMPs levels during tendon healing [69, 70]. In a diabetic rat model, both diabetic and healthy tendons exhibit strong expression of MMP-13 and MMP-3 in tenocytes. Meanwhile, in the tendon healing model, MMP-13 expression was upregulated and MMP-3 expression decreased [31]. Both MMP-3 and MMP-13 participate in collagen degradation; MMP-3 could activate other MMPs and is also involved in ECM remodeling [61]. Up-regulated mRNA expression of MMP-9 and MMP-13 in tendon cells treated with high glucose concentration was reported, as well as the enzymatic activity of MMP-9; these results indicated that high glucose concentration might induce collagen degradation and lead to a negative impact on the tendon structure [61].

Conclusions

Many studies in both patients with diabetes and animal models suggested a strong association of diabetes mellitus and alternations in tendon quality (Table 2). Excessive accumulation of AGEs, the altered inflammatory responses, neovascularization and insensitive neuropathy may account for the altered tendon biomechanical properties, cytological and molecular changes in the diabetic tendons. Formations of cross-links among collagens, increased tenocyte apoptosis, dysregulation of TDSCs differentiation, and altered expression of MMPs may be the underlying mechanisms of pathological alternations in diabetic tendons. Our latest findings speculated that the erroneous differentiation of TDSCs may be attributed to the pathological changes in diabetic tendons.

Acknowledgments This work was supported by the National Natural Science Foundation of China (No. 81201422 and No. 81172177), China Postdoctoral Science Foundation (No. 2012 M520983), National Student Innovation Training Program of China (No. 1210286090), Jiangsu Province Science Foundation for Youths (No. BK2012334), Innovative Foundation of Southeast University (No. 3290002401) and Shenzhen Science and Technology Bureau Grant (JCYJ20130401171935811). These works were also supported in part by the National Basic Science and Development Programme (973 Programme, 2012CB518105) and SMART program seed funding, Institute of Innovative Medicine, The Chinese University of Hong Kong.

References

1. Stitt AW, Curtis TM (2005) Advanced glycation and retinal pathology during diabetes. Pharmacol Rep 57(Suppl):156–168
2. Smit AJ, Gerrits EG (2010) Skin autofluorescence as a measure of advanced glycation end product deposition: a novel risk marker in chronic kidney disease. Curr Opin Nephrol Hypertens 19:527–533
3. Stolzing A, Sellers D, Llewelyn O, Scutt A (2010) Diabetes induced changes in rat mesenchymal stem cells. Cells Tissues Organs 191:453–465. doi:10.1159/000281826
4. Ackermann PW (2013) Hart DA influence of comorbidities: neuropathy, vasculopathy, and diabetes on healing response quality. Adv Wound Care 2(8):410–421
5. Miranda H, Viikari-Juntura E, Heistaro S, Heliovaara M, Riihimaki H (2005) A population study on differences in the determinants of a specific shoulder disorder versus nonspecific shoulder pain without clinical findings. Am J Epidemiol 161: 847–855. doi:10.1093/aje/kwi112
6. Maffulli N, Longo UG, Maffulli GD, Khanna A, Denaro V (2011) Achilles tendon ruptures in diabetic patients. Arch Orthop Trauma Surg 131:33–38. doi:10.1007/s00402-010-1097-0
7. Sukenik S, Weitzman S, Buskila D, Eyal A, Gross J, Horowitz J (1987) Limited joint mobility and other rheumatological manifestations in diabetic patients. Diabete Metab 13:187–192

8. Batista F, Nery C, Pinzur M, Monteiro AC, de Souza EF, Felippe FH, Alcantara MC, Campos RS (2008) Achilles tendinopathy in diabetes mellitus. Foot Ankle Int 29:498–501. doi:10.3113/fai.2008.0498
9. Aydeniz A, Gursoy S, Guney E (2008) Which musculoskeletal complications are most frequently seen in type 2 diabetes mellitus? J Int Med Res 36:505–511
10. Abate M, Schiavone C, Pelotti P, Salini V (2010) Limited joint mobility in diabetes and ageing: recent advances in pathogenesis and therapy. Int J Immunopathol Pharmacol 23(4):997–1003
11. de Oliveira RR, Lemos A, de Castro Silveira PV, da Silva RJ, de Moraes SR (2011) Alterations of tendons in patients with diabetes mellitus: a systematic review. Diabet Med 28:886–895. doi:10.1111/j.1464-5491.2010.03197.x
12. Abate M, Salini V, Antinolfi P, Schiavone C (2010) Ultrasound morphology of the Achilles in asymptomatic patients with and without diabetes. Foot Ankle Int 35:44–49
13. Ramchurn N, Mashamba C, Leitch E, Arutchelvam V, Narayanan K, Weaver J, Hamilton J, Heycock C, Saravanan V, Kelly C (2009) Upper limb musculoskeletal abnormalities and poor metabolic control in diabetes. Eur J Intern Med 20:718–721
14. Ando A, Sugaya H, Hagiwara Y, Takahashi N, Watanabe T, Kanazawa K, Itoi E (2013) Identification of prognostic factors for the nonoperative treatment of stiff shoulder. Int Orthop 37:859–864. doi:10.1007/s00264-013-1859-8
15. Cole A, Gill TK, Shanahan EM, Phillips P, Taylor AW, Hill CL (2009) Is diabetes associated with shoulder pain or stiffness? Results from a population based study. J Rheumatol 36:371–377
16. Namdari S, Green A (2010) Range of motion limitation after rotator cuff repair. J Should Elb Surg 19:290–296. doi:10.1016/j.jse.2009.07.009
17. Clement ND, Hallett A, MacDonald D, Howie C, McBirnie J (2010) Does diabetes affect outcome after arthroscopic repair of the rotator cuff? J Bone Joint Surg (Br) 92:1112–1117. doi:10.1302/0301-620x.92b8.23571
18. Bruggeman NB, Turner NS, Dahm DL, Voll AE, Hoskin TL, Jacofsky DJ, Haidukewych GJ (2004) Wound complications after open Achilles tendon repair: an analysis of risk factors. Clin Orthop Relat Res 427:63–66
19. Pascual Huerta J, Garcia JM, Matamoros EC, Matamoros JC, Martinez TD (2008) Relationship of body mass index, ankle dorsiflexion, and foot pronation on plantar fascia thickness in healthy, asymptomatic subjects. J Am Podiatr Med Assoc 98:379–385
20. Cronin NJ, Peltonen J, Ishikawa M, Komi PV, Avela J, Sinkjaer T, Voigt M (2010) Achilles tendon length changes during walking in long-term diabetes patients. Clin Biomech 25:476–482
21. Giacomozzi C, D'Ambrogi E, Uccioli L, Macellari V (2005) Does the thickening of Achilles tendon and plantar fascia contribute to the alteration of diabetic foot loading? Clin Biomech 20:532–539. doi:10.1016/j.clinbiomech.2005.01.011, Bristol, Avon
22. Akturk M, Ozdemir A, Maral I, Yetkin I, Arslan M (2007) Evaluation of Achilles tendon thickening in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes: Off J Ger Soc Endocrinol Ger Diabetes Asso 115:92–96. doi:10.1055/s-2007-955097
23. Papanas N, Courcoutsakis N, Papatheodorou K, Daskalogiannakis G, Maltezos E, Prassopoulos P (2009) Achilles tendon volume in type 2 diabetic patients with or without peripheral neuropathy: MRI study. Exp Clin Endocrinol Diabetes: Off J Ger Soc Endocrinol Ger Diabetes Assoc 117:645–648. doi:10.1055/s-0029-1224121
24. Abate M, Schiavone C, Pelotti P, Salini V (2010) Limited joint mobility in diabetes and ageing: recent advances in pathogenesis and therapy. Int J Immunopathol Pharmacol 23(4):997–1003
25. Altinel L, Kose KC, Degirmenci B, Petik B, Acarturk G, Colbay M (2007) The midterm effects of diabetes mellitus on quadriceps and patellar tendons in patients with knee arthrosis: a comparative radiological study. J Diabetes Complicat 21:392–396. doi:10.1016/j.jdiacomp.2006.07.003
26. Fox AJ, Bedi A, Deng XH, Ying L, Harris PE, Warren RF, Rodeo SA (2011) Diabetes mellitus alters the mechanical properties of the native tendon in an experimental rat model. Orthop Res: Off Pub Orthop Res Soc 29:880–885. doi:10.1002/jor.21327
27. de Oliveira RR, de Lira KD, Silveira PV, Coutinho MP, Medeiros MN, Teixeira MF, de Moraes SR (2011) Mechanical properties of Achilles tendon in rats induced to experimental diabetes. Ann Biomed Eng 39:1528–1534
28. Reddy GK (2003) Glucose-mediated in vitro glycation modulates biomechanical integrity of the soft tissues but not hard tissues. J Orthop Res 21:738–743. doi:10.1016/s0736-0266(03)00006-8
29. de Oliveira RR, Bezerra MA, de Lira KD, Novaes KA, Teixeira MF, Chaves Cde C, Moraes SR (2012) Aerobic physical training restores biomechanical properties of Achilles tendon in rats chemically induced to diabetes mellitus. J Diabetes Complicat 26:163–168. doi:10.1016/j.jdiacomp.2012.03.017
30. Bedi A, Fox AJ, Harris PE, Deng XH, Ying L, Warren RF, Rodeo SA (2010) Diabetes mellitus impairs tendon-bone healing after rotator cuff repair. J Should Elb Surg Am Should Elb Surg 19:978–988. doi:10.1016/j.jse.2009.11.045
31. Ahmed AS, Schizas N, Li J, Ahmed M, Ostenson CG, Salo P, Hewitt C, Hart DA, Ackermann PW (2012) Type 2 diabetes impairs tendon repair after injury in a rat model. J Appl Physiol 113:1784–1791. doi:10.1152/japplphysiol.00767.2012, Bethesda, Md: 1985
32. Lehner C, Gehwolf R, Wagner A, Resch H, Hirzinger C, Augat P, Stephan D, Aigner L, Rivera FJ, Bauer HC, Tempfer H (2012) Tendons from non-diabetic humans and rats harbor a population of insulin-producing, pancreatic beta cell-like cells. Horm Metab Res 44:506–510. doi:10.1055/s-0032-1312672
33. David MA, Jones KH, Inzana JA, Zuscik MJ, Awad HA, Mooney RA (2014) Tendon repair is compromised in a high fat diet-induced mouse model of obesity and type 2 diabetes. PLoS One 9:e91234
34. Yoshimasa Sakoma TF, Ozaki T (2014) Pentosidine deposition affects biomechanical properties of Achilles tendon in diabetic rats. Orthop Muscul Syst 3:150. doi:10.4172/2161-0533.1000150
35. Vazzana N, Santilli F, Cuccurullo C, Davi G (2009) Soluble forms of RAGE in internal medicine. Intern Emerg Med 4:389–401. doi:10.1007/s11739-009-0300-1
36. Burner T, Gohr C, Mitton-Fitzgerald E, Rosenthal AK (2012) Hyperglycemia reduces proteoglycan levels in tendons. Connect Tissue Res 53:535–541
37. de Oliveira RR, Martins CS, Rocha YR, Braga AB, Mattos RM, Hecht F, Brito GA, Nasciutti LE (2013) Experimental diabetes induces structural, inflammatory and vascular changes of Achilles tendons. PLoS One 8:e74942. doi:10.1371/journal.pone.0074942
38. Ji J, Wang Z, Shi D, Gao X, Jiang Q (2010) Pathologic changes of Achilles tendon in leptin-deficient mice. Rheumatol Int 30:489–493. doi:10.1007/s00296-009-1001-9
39. Kameyama M, Chen KR, Mukai K, Shimada A, Atsumi Y, Yanagimoto S (2013) Histopathological characteristics of stenosing flexor tenosynovitis in diabetic patients and possible associations with diabetes-related variables. J Hand Surg [Am] 38:1331–1339
40. Rui YF, Lui PP, Wong YM, Tan Q, Chan KM (2013) Altered fate of tendon-derived stem cells isolated from a failed tendon-healing animal model of tendinopathy. Stem Cells Dev 22:1076–1085. doi:10.1089/scd.2012.0555
41. Chbinou N, Frenette J (2004) Insulin-dependent diabetes impairs the inflammatory response and delays angiogenesis following Achilles tendon injury. Am J Physiol Regul Integr Comp Physiol 286:R952–957. doi:10.11522/ajpregu.00536.2003

42. Bring DK, Kreicbergs A, Renstrom PA, Ackermann PW (2007) Physical activity modulates nerve plasticity and stimulates repair after Achilles tendon rupture. J Orthop Res 25:164–172
43. Abate M, Schiavone C, Salini S (2012) Neoangiogenesis is reduced in chronic tendinopathies of type 2 diabetic patients. Int J Immunopathol Pharmacol 25:757–761
44. Scott A, Lian O, Bahr R, Hart DA, Duronio V, Khan KM (2008) Increased mast cell numbers in human patellar tendinosis: correlation with symptom duration and vascular hyperplasia. Br J Sports Med 42:753–757
45. Nakama LH, King KB, Abrahamsson S, Rempel DM (2006) VEGF, VEGFR-1, and CTGF cell densities in tendon are increased with cyclical loading: an in vivo tendinopathy model. J Orthop Res 24:393–400
46. Stein V, Laprell H, Tinnemeyer S, Petersen W (2000) Quantitative assessment of intravascular volume of the human Achilles tendon. Acta Orthop Scand 71:60–63
47. Goldin A, Beckman JA, Schmidt AM, Creager MA (2006) Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 114:597–605
48. Ignotz RA, Massague J (1986) Transforming growth factor-beta stimulates the expression of fibronectin and collagen and their incorporation into the extracellular matrix. J Biol Chem 261:4337–4345
49. Bertolini A, Ottani A, Sandrini M (2002) Selective COX-2 inhibitors and dual acting anti-inflammatory drugs: critical remarks. Curr Med Chem 9:1033–1043
50. Ferreira E, Porter RM, Wehling N, O'Sullivan RP, Liu F, Boskey A, Estok DM, Harris MB, Vrahas MS, Evans CH, Wells JW (2013) Inflammatory cytokines induce a unique mineralizing phenotype in mesenchymal stem cells derived from human bone marrow. J Biol Chem 288:29494–29505. doi:10.1074/jbc.M113.471268
51. Xiao H, Cai G, Liu M (2007) Fe2+−catalyzed non-enzymatic glycosylation alters collagen conformation during AGE-collagen formation in vitro. Arch Biochem Biophys 468:183–192
52. Franke S, Sommer M, Ruster C, Bondeva T, Marticke J, Hofmann G, Hein G, Wolf G (2009) Advanced glycation end products induce cell cycle arrest and proinflammatory changes in osteoarthritic fibroblast-like synovial cells. Arthritis Res Ther 11:7
53. Huijberts MS, Schaper NC, Schalkwijk CG (2008) Advanced glycation end products and diabetic foot disease. Diabetes Metab Res Rev 24:861
54. Sakoma YFT, Ozaki T (2014) Pentosidine deposition affects biomechanical properties of Achilles tendon in diabetic rats. Orthop Muscul Syst 3:150
55. Sharir A, Zelzer E (2011) Tendon homeostasis: the right pull. Curr Biol 21:025
56. Leadbetter WB (1992) Cell-matrix response in tendon injury. Clin Sports Med 11:533–578
57. Liu JQ, Liu HC, Wang Y, Feng Y, Gao H (2011) The biological effect of high glucose on human periodontal ligament fibroblast. Shanghai Kou Qiang Yi Xue 20:225–229
58. Higuchi C, Sanaka T, Sato T, Omata M, Watanabe M, Mine S, Inuzuka N, Nihei H (1997) The effect of glucose on the proliferation of peritoneal fibroblasts. Adv Perit Dial 13:253–256
59. Park EY, Park JB (2013) High glucose-induced oxidative stress promotes autophagy through mitochondrial damage in rat notochordal cells. Int Orthop 37:2507–2514. doi:10.1007/s00264-013-2037-8
60. Park EY, Park JB (2013) Dose- and time-dependent effect of high glucose concentration on viability of notochordal cells and expression of matrix degrading and fibrotic enzymes. Int Orthop 37:1179–1186. doi:10.1007/s00264-013-1836-2
61. Tsai WC, Liang FC, Cheng JW, Lin LP, Chang SC, Chen HH, Pang JH (2013) High glucose concentration up-regulates the expression of matrix metalloproteinase-9 and −13 in tendon cells. BMC Musculoskelet Disord 14:255. doi:10.1186/1471-2474-14-255
62. Park JS, Park JB, Park IJ, Park EY (2014) Accelerated premature stress-induced senescence of young annulus fibrosus cells of rats by high glucose-induced oxidative stress. Int Orthop 38:1311–1320. doi:10.1007/s00264-014-2296-z
63. Poulsen RC, Knowles HJ, Carr AJ, Hulley PA (2014) Cell differentiation versus cell death: extracellular glucose is a key determinant of cell fate following oxidative stress exposure. Cell Death Dis 20:52
64. Rui YF, Lui PP, Li G, Fu SC, Lee YW, Chan KM (2010) Isolation and characterization of multipotent rat tendon-derived stem cells. Tissue Eng Part A 16:1549–1558. doi:10.1089/ten.TEA.2009.0529
65. Ni M, Lui PP, Rui YF, Lee YW, Lee YW, Tan Q, Wong YM, Kong SK, Lau PM, Li G, Chan KM (2012) Tendon-derived stem cells (TDSCs) promote tendon repair in a rat patellar tendon window defect model. J Orthop Res 30:613–619. doi:10.1002/jor.21559
66. Kojima H, Fujimiya M, Terashima T, Kimura H, Chan L (2006) Extrapancreatic proinsulin/insulin-expressing cells in diabetes mellitus: is history repeating itself? Endocr J 53:715–722
67. Rothan HA, Suhaeb AM, Kamarul T (2013) Recombinant human adiponectin as a potential protein for treating diabetic tendinopathy promotes tenocyte progenitor cells proliferation and tenogenic differentiation in vitro. Int J Med Sci 10:1899–1906. doi:10.7150/ijms.6774
68. Vu TH, Werb Z (2000) Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev 14:2123–2133
69. Sharma P, Maffulli N (2005) Tendon injury and tendinopathy: healing and repair. J Bone Joint Surg Am 87:187–202
70. Ireland D, Harrall R, Curry V, Holloway G, Hackney R, Hazleman B, Riley G (2001) Multiple changes in gene expression in chronic human Achilles tendinopathy. Matrix Biol 20:159–169