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Review Article

Diabetes and Collagen: Interrelations

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Abstract

This review summarizes information on interrelations between diabetes development and collagen metabolism and structure. The growing global problem of diabetes requires the search for new strategies of its complications correction. Among them collagen structure violations and/or its impaired metabolism most often lead to profound disability. Even after several decades of intense studies, pathophysiological mechanisms underlying collagen changes in diabetes mellitus are still not well clear. The main complication is that not only diabetes cause changes in collagen metabolism and structure. Collagens via some mechanisms also may regulate glucose homeostasis, both directly and indirectly. The author also presented the results of own studies on bone and skin type I collagen amino acid composition changes with diabetes. Deepening our understanding of collagen metabolism and diabetes interrelations allows us to optimize approaches to overcome the collagen-mediated consequences of this disease. Recently, it has been clearly demonstrated that use of only antidiabetic agents cannot fully correct such violations. Preparations on the base of flavonoids, collagens and amino acids could be considered as perspective directions in this area of drug development.

Collagen-Mediated Consequences of Diabetes

Diabetes consequences associated with collagen structure and/or metabolism violations are extremely diverse. In general, the accumulation of overglycosylated collagens and the diminution of sulfated proteoglycan concentrations cause such morphological changes as basement membrane thickening along with skin thickening and induration (1). In addition, diabetes is correlated with increased skeleton fragility and the risk of fracture (2). In this case, increased bone mineral density with diabetes is accompanied by impaired bone architectural structure and mineral properties (3). Further, the accumulation of advanced glycation end products (AGEs) changes collagen fibrils structure with the simultaneous impairment of collagen metabolism resulting in the suppression of bone turnover, the violations of skeleton repair, and adaptation mechanisms. AGEs crosslinking with diabetes inhibits biomechanical plasticity, namely, a characteristic form of nanoscale collagen fibril damage containing serial fibril kinking and collagen denaturation (4). Discrete plasticity could be an important physiological mechanism, which becomes pathologically disabled by the formation of AGE crosslinks in diabetes. At the same time, diabetes also can exert its influence on collagen indirectly by unbalancing bone formation, bone resorption, the inflammatory cytokine, muscular and incretin system, bone marrow adiposity, and calcium metabolism, which, in turn, are involved in the processes of collagen synthesis and catabolism (5). The pathophysiological mechanisms underlying collagen changes in diabetes mellitus (DM) include hyperglycaemia and the accumulation of advanced glycation endproducts in addition to oxidative stress (6).

Similarly, serious collagen-mediated consequences of diabetes are a diabetic foot and the processes of wound healing general impairment (7,8). Furthermore, diabetic foot ulcers are considered as an important clinical problem since diabetic complications (including collagens structure and metabolism) may delay healing and increase the risk of amputation. A non-healing ulcer could be associated with overglycosylated collagens with changed crosslinks and an excess of collagenases (1,8). In such conditions, it is also impossible to exclude the presence of reactive perforating collagenosis which transepidermally eliminates the altered collagen through the epidermis (9).

Diabetic nephropathy is generally considered as a major microvascular complication of diabetes (10). The altered expression of collagenases and its functioning in diabetic nephropathy cause extracellular collagen fibril deposition and glomerular hypertrophy leading to proteinuria and renal insufficiency (11). Altered expression of collagenases is also accompanied by the accumulation of not only collagen, but other extracellular matrix proteins such as laminin and fibronectin in the mesangium and renal tubulo-interstitium of the glomerulus and basement membranes.

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Such an increased expression of collagen and other proteins leads to tubulointerstitial fibrosis. Similarly, collagen accumulation plays a critical role in the development of diabetic nephropathy and the major collagen types involved in these processes are I and IV (12). In vitro investigations on murine proximal tubule cells demonstrated that the increased levels of glucose are a sufficient stimulus for cellular hypertrophy and the increased biosynthesis of collagen type IV, which is the predominant constituent of tubular basement membrane (13). Moreover, high glucose levels increase steady-state collagen IV mRNA via the transcriptional activation of the cis-acting elements of the gene which are controlled by putative glucose-responsive trans-acting proteins (13). The alpha 1 (IV) procollagen specific mRNA concentration elevates in DM, particularly in the kidney, and type IV collagen protein is accumulated in the thickened basement membranes (14). Likewise, type IV collagen overproduction is inhibited by aldose reductase inhibitors. Transforming growth factor-beta (TGF-β) also may be involved in type IV collagen oversecretion, as diabetes increased TGF-β expression, inducing fibrosis via Smad-independent pathways, mitogen-activated protein kinases, and Akt activation (15). Among type IV collagen overproductions, its posttranslational alterations, especially glycation are also present. This leads to its interactions with advanced glycation end-products and violations in crosslinks formation. Such processes decrease collagen extractability and susceptibility to collagenases and cause basement membrane thickening. Disaccharide unit-specific alpha-glucosidase activity is inhibited by glucose (Kp = 7.5 mM). Type IV collagenase activity secreted by endothelial cells cultured at high glucose concentrations appears to be diminished as well. Therefore, type IV collagen catabolism may be decreased in DM (14). Additionally, diabetic nephropathy is associated with collagenofibrotic (collagen Type III) glomerulopathy (16). The extensive investigation of its molecular mechanisms demonstrates that some of the new signaling pathways or molecules (e.g., Notch, Wnt, mTOR, TLRs, and small GTPase) are involved in the modulation of collagen regulation and expression in diabetic nephropathy. This process is mediated by Notch through Notch1/Jagged1 signaling, Wnt by Wnt/β- catenin pathway, and mTOR via PI3-K/Akt/mTOR signaling pathways (10). All these pathways are probably critical in the modulation of extracellular matrix protein expression and tubulo-interstitial fibrosis. In addition, TLRs, mainly the TLR2 and TLR4, by TLR2- dependent and TGF-β-dependent conduits, may modulate collagen and other proteins expression and thus generate a fibrogenic response. Small GTPase like Rho, Ras, and Rab family may also influence the accumulation of extracellular matrix proteins and renal fibrosis in hyperglycemic states by targeting relevant genes (10). In another study, Tung et al demonstrated in the glomeruli of streptozotocin-induced diabetic mice the upregulated cannabinoid type 1 receptor CB1R, interleukin-1β, interleukin-6, tumor necrosis factor-α, c-Jun, and type 4 collagen , with the simultaneous decreased expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) (17). They noted that the interaction between miR-29a, CB1R, and PPAR-γ could be important for protecting diabetic renal glomeruli from fibrotic injuries. In these experiments, miR-29a, as a negative regulator of CB1R, blocked the expressions of profibrogenic mediators and attenuated renal hypertrophy. The overexpression of miR-29a restored PPAR-γ signaling in the renal glomeruli of diabetic animals.

Skeletal muscle extracellular matrix remodelling is considered as the recently discovered feature which is associated with obesity and metabolic dysfunction (18). A total of thirty-seven human and animal studies reports overall increases in gene and protein expression of different types of collagen related to the skeletal muscle extracellular matrix in obesity. Patients with DM often suffer from many musculoskeletal disorders such as tendon rupture and tendinopathy (19). Further, diabetes is accompanied by thickened or increased volume of the tendons, abnormalities in the arrangement of collagen fibrils, and the presence of tendon calcification. Some researchers suppose that the disorientation of collagen fibril arrangement and the increased tendon calcification of diabetic individuals may be due to collagen hyperglycation and non-enzymatic crosslinking with AGEs (1, 8). However, the exact pathogenesis of these alternations remains unclear. Previous evidence suggests that several parameters could be responsible for this process, including tendon-derived stem cell erroneous differentiation, decreased proliferation, and increased osteogenic and chondrogenic differentiation abilities, accompanied by significantly higher expression of BMP2, ALP, OPN, OCN, SOX9, and Col II, and finally, the decreased expression of Col I and tenomodulin (20).

Such a well-known consequence of diabetes as cardiac dysfunction is also caused by hyperglycaemia leading to the development of cardiomyopathy which is independent of cardiovascular disease or hypertension (21). Diabetic cardiomyopathy (as the main cause of morbidity and mortality in diabetic patients) is accompanied by myocardial fibrosis which is a pathological entity of extracellular matrix remodeling that induces myocardial stiffness and exaggerates cardiac dysfunction (22). Furthermore, the contractile dysfunction appears to be the result of disrupted F-actin in conjunction with the increased type I collagen, with decreased myofilament Ca^{2+} sensitivity which is contributed to the slowed relaxation (21). Smad1 is identified as a transcriptional regulator of type I collagen and alpha-smooth muscle actin (12). Diabetic cardiomyopathy also changes the functioning of collagenases which participate in the breakdown of collagen and myocardial remodelling. Moreover, the impaired angiogenesis, as a consequence of collagenases

violated activities, mediates the development of diabetic peripheral arterial disease (11). Experimental data support an integral role of collagenases in cerebral circulation and stroke volume in diabetes (11). In addition, it is found that dimethylarginine dimethylaminohydrolase 2 (DDAH2) is involved in processes which lead to higher expression levels of collagen I, matrix metalloproteinase 2 (MMP2), and the tissue inhibitor of metalloproteinase 2 (TIMP2), leading to myocardial fibrosis manifestation with diabetes. DDAH2 is an enzyme which metabolizes the competitive endogenous inhibitors of nitric oxide synthase, including asymmetric NG, NG dimethyl-L-arginine (ADMA), and NG -monomethyl-L-arginine. MMP2 and MMP9 are implicated in the migration of human cardiomyocyte progenitor cells as well (22). TIMP2 is found to be responsible for enhancing the migration of epidermal keratinocytes and dermal fibroblasts. Additionally, the overexpression of DDAH2 could correct collagen metabolism violations with diabetes by activating the DDAH/ADMA/NOS/NO pathway (22).

Likewise, collagen metabolism disturbances mediate serious diabetic consequence such as retinopathy. Type IV collagenases (e.g., MMP-2 and MMP-9) play an important role in the processes of endothelial cell invasion occurring during neovascularization (diabetic retinopathy) since angiogenesis needs extracellular matrix protein degradation. These enzymes can degrade pigment epithelium-derived factor, namely, the principal antiangiogenic protein of the eye (23).

Periodontitis is a common problem in patients with diabetes (24). Collagen structure and metabolism disturbances, in this case, are obviously the same as the other mineralized tissues (1-5, 8).

Collagen Structure and Turnover Changes During Diabetes Development

Despite a large amount of data related to extracellular matrix protein (especially collagens) glycation with diabetes, little is known on how such a modification by glucose affects collagen structure mechanics and damage, cell-collagen fibrils interactions, and collagen turnover during this pathology development (25). There are sufficient grounds demonstrating that collagen glycation could be a potentially critical player in tissue fibrosis related to diabetes (25). The crosslinking of the collagen in the organism is detected by two mechanisms including enzymatic and nonenzymatic crosslinking. Nonenzymatic crosslinks are formed as a result of the reactions which create advanced glycation end products such as pentosidine and glucosepane (26). Detailed studies regarding the molecular mechanisms of collagen structure and metabolism disturbances with diabetes indicate that AGEs have a leading role in these processes (1).

These compounds form a family of protein, peptide, amino acid, nucleic acid, and lipid adducts received as a result of interaction with the carbonyl-containing products of glucose metabolism (27). AGE formation in diabetes contributes to collagen-mediated complications, as well as retinopathy, nephropathy, and neuropathy, among which, carboxymethyl-lysine and glucosepane are the most prevalent AGE and protein crosslinks of the extracellular matrix in diabetes (27). In addition, hyperglycemia and oxidative stress caused by diabetes could inhibit the formation of enzymatic crosslinks and stimulate AGE synthesis (28). Another AGE such as pentosidine alters the formation and propagation of microdamage by making the bone more brittle (29).

In DM, AGE affects the crosslinking between the lysine or arginine residues of collagen molecules and between the triple-helical domains of adjacent molecules in the fibre resulting in major changes in physical properties (e.g., fibre stiffness, thermal denaturation temperature, and enzyme resistance). In this regard, AGEs could simultaneously cause side-chain modifications, which alter the charge profiles of collagen molecules, their interactions within the fibre, and the functioning of specific sites responsible for cell-collagen interactions (30). Meanwhile, the modification of arginine residues within the sites RGD and GFOGER is recognised by two specific integrins (i.e., alpha1 beta2 and alpha2 beta1) serving for the collagen, that reduces cell interactions during turnover, and platelet interactions such as alpha 1 beta 2 (30). These changes could affect repairing processes and cause vascular damage or poor wound healing in DM (30). Both the intermolecular and side-chain types of AGE-mediated collagen modifications are deleterious to collagen's optimal properties as a supporting framework structure and a controlling factor in cell-matrix interactions (30).

However, the effect of diabetes on the quality and quantity of collagen is not limited to the formation of AGEs. According to our results, statistically significant changes were registered in bone type I collagen amino acid composition in rats with diabetes type 1 and the skin– for 16 and 15 amino acids, respectively (31). Bone type I collagen of diabetic rats differs from the norm by lower contents of hydroxylysine (-75.0%), hydroxyproline (-87.5%), proline (-31.3%), glycine (-51.2%), and alanine (-25.5%), which are all regarded as amino acid residues with a strong effect on collagen helix structure (its structure presumably contains Gly-X-Pro or Gly- X-Hyp triplets), rigidity, and crosslinking (32). Simultaneously, the content of arginine (+65.4%), aspartic acid (+200.0%), threonine (+67.5%), serine (+ 57.1%), glutamic acid (+100.0%), methionine (+117.7%), isoleucine (+70.8%), leucine (+124.0%), and phenylalanine (+209.0%) is increased in diabetic rats. Other studies demonstrated the disturbances of collagen ultra-structure in streptozotocin-induced diabetes (33,34), which is in line with our results. Skin type I collagen of diabetic rats also differs from the norm by lower contents of hydroxyproline (-74.4%), proline

(-16.5%), glycine (-49.0%), alanine (-12.0%), and valine (+19.7%) residues and simultaneously the higher contents of lysine (+78.2%), histidine (+60.4%), arginine (+51.0%), aspartic acid (+99.0%), threonine (+75.0%), serine (+34.6 %), glutamic acid (+86.7 %), methionine (+117.6 %), leucine (+68.0%), tyrosine (+218,0%), and phenylalanine (+162.3%) residues. Thus, in this tissue, diabetes causes similar quantitative changes in the collagen molecule as it is in the bone.

Based on our report, the profound diabetes-mediated changes in collagen amino acid composition might induce disturbances in its physicochemical properties as well. Hydroxylysine residues, along with lysine and histidine (32) participate in collagen crosslinking and changes in the ratio of hydroxylysine: lysine: histidine residues could seriously influence the number and the type of (i.e., enzymatic and nonenzymatic) crosslinks in collagen fibrils. Therefore, this might induce changes in the mechanical strength and the elasticity/rigidity of the extracellular matrix. Our results respecting the changes in hydroxylysine, lysine, and histidine residues are in accordance with data of other studies on changes in collagen crosslinks in animals with hyperglycemia (35). Further, alterations in the number of arginines, aspartic acid, threonine, serine, and glutamic acid residues could greatly modify the collagen molecule surface charges (32,36) whereas the quantitative modifications of isoleucine, tyrosine, and phenylalanine residues could influence the level of collagen helix rigidity (32). In addition, changes in arginine, glycine, and aspartic acid residues might affect the number of domains Arg-Gly-Asp which are responsible for the processes of cell adhesion on collagen structures (31,38,39,40). Arginine and glycine residues in collagen molecule are also part of special loci responsible for interactions with chaperones and for procollagen processing to mature collagen (41). These modifications could lead to the alterations of the helix structure, surface charge, rigidity, the levels of nonenzymatic glycosylation, the number and types of crosslinks, and specific loci responsible for cell adhesion, interaction with chaperons, and procollagen processing to collagen. Such collagen molecule alterations could hence affect the properties and correct functioning of a number of tissues. It is suggested that such shifts could be caused by the deficiency of insulin which is involved in collagen synthesis regulation at different stages of this process (42-45). In addition to the direct influence of insulin deficiency on collagen synthesis, pathologic changes in amino acid metabolism of the entire organism (46) could also influence collagen metabolism. Further, the ability of the majority of amino acids to regulate protein biosynthesis at the level of translation by the stimulation of 70kD-ribosomal protein S_6-kinase is established *in vitro* (47). On the other hand, taking into account the existence of collagen gene polymorphisms (48,49), such changes could also be due to the disturbances in the rates of different gene transcription from the same collagen type I superfamily, as it was previously demonstrated for osteogenesis imperfecta (50). Furthermore, it could be hypothesized that diabetes-mediated changes could be partially related to oxygen reactive forms produced via cytochrome P450 2E1 (51). These reactive oxygen species were reported to mediate the paracrine stimulation of type I collagen synthesis on different stages of this process (52).

Reverse Effects of Collagen-containing Structures on Diabetes Development

Thus, the above-mentioned data support the previous assumption by Kanazawa (2) indicating that bone can be considered as an endocrine organ. Based on *in vitro* and animal studies, it was shown that osteocalcin, which is specifically expressed in osteoblasts and secreted into the circulation, may regulate glucose homeostasis. Although several clinical studies reported the relationship between osteocalcin and glucose metabolism (2,3). Therefore, it is assumed that the bone matrix collagens play a similar role. Osteocalcin can also affect collagen directly (53) thus changes in glucose metabolism can be produced by osteocalcin directly and through the modification of collagen structures and 1α,25-dihydroxycholecalciferol metabolism (53,54). The feedback between collagen metabolism and structure on the one hand, and the pathological processes in diabetes, on the other hand, can be more extensive than it seems at first glance. Collagen matrix supports Langerhans islets and thus the number of collagen fibrils sites for cells adhesion could influence pancreas structure and function (31). Moreover, the collagen matrix (especially collagens types I and IV and their receptors) plays a critical role in pancreatic islet survival and function (55). Considering their multiple functions, collagen molecules not only provide structural integrity of the organs but also mediate cellular signaling. In the pancreas, collagens I and IV are abundant and support cell structures by simultaneously stimulating the cell surface receptors to influence pancreatic cell processes (55). Additionally, it is shown that the loss of cellular paracrine communication and extracellular matrix remodeling fibrosis in young animals and humans may lead to a dysfunctional insulino-acinar-ductal-incretin gut hormone axis, resulting in pancreatic insufficiency and glucagon-like peptide deficiency, which are known to exist in prediabetes and overt type 2 diabetes in humans (56).

Optimization of Collagen-Mediated Diabetes Consequences Correction

Deepening our understanding of collagen metabolism and diabetes interrelations provides the possibility for optimizing approaches to correct the collagen-mediated consequences of this disease. Therefore, the greatest attention of researchers is now given to the investigation of antidiabetic drug abilities to regulate collagen

metabolism, among which metformin demonstrates the most pronounced effect (57). In experiments with *in vitro* 3T3 fibroblast cell incubation in high glucose conditions, metformin exposure leads to the increased production of collagen I-III while the decreased activation of NF-kB (p65). Based on the results of another research, AMPK activation by metformin could suppress abnormal collagen synthesis (58). Similarly, metformin regulates the metabolic and nonmetabolic pathways of collagen modification in skeletal muscle and subcutaneous adipose tissues, including pyruvate metabolism and DNA repair in muscle and PPAR and SREBP signaling, mitochondrial fatty acid oxidation, and collagen trimerization in adipose (59). This agent also could promote wound healing and cutaneous integrity in the skin (60).

However, the use of metformin did not allow the complete correction of the collagen-mediated effects of diabetes in all cases. This encourages researchers to conduct an extensive search for drugs that can regulate collagen metabolism in diabetes without causing additional adverse effects. The encouraging results were obtained in the study on a number of herbal preparations. The protective effect of *Withania somnifera (Solanaceae)* ethanolic extract on collagen glycation and crosslinking is comparable to metformin (61). *Momordica charantia* fruit extract also demonstrates some effects on fibrosis development (62). Such effects may be due to the ability of flavonoids contained in these preparations to regulate the metabolism of collagen (63). For example, resveratrol (e.g., metformin) also can down-regulate the gene expressions of Col3α, Col6α, elastin, and lysyl oxidase and thus reduce collagen deposition in adipose tissue (64), but it represents negligible effects on wounds healing (60). Flavonoids increase the migration and proliferation of fibroblasts and collagen synthesis. Likewise, they possess antioxidant and anti-inflammatory activities, reduce the reactive oxygen species, and modulate the inflammatory pathways and their activity can vary depending on the source, chemical structure, and glycosylation pattern. The topical application of flavonoids also reduces epithelialization and the wound closure time of diabetic foot ulcers in diabetic patients (63).

Collagen-based wound dressings, among others, are considered as perspective and effective treatment tool for diabetes-related foot ulcers (65). CellerateRx (e.g., activated, fragmented, and nonintact type I collagen), in a gel and powder form, may contribute to a more rapid healing process due to the inherent properties of type I collagen (66). Recently, nanofibrous drug-loaded collagen/poly-D-L-lactide-glycolide scaffold membranes were developed which provided the sustained release of glucophage for the wounds associated with diabetes (67).

The investigations of the interrelations between the processes of diabetes development and the metabolism of connective tissue proteins (31) and amino acids (68) pave the way for further evaluation of the effective regulators of collagen biosynthesis in hyperglycemia among these low-molecular compounds. The targeted amino acid supplementation with arginine, glutamine, and beta-hydroxy-beta-methylbutyrate may improve the healing of diabetic foot wounds via increased collagen production as well (69). Amino acid-containing preparation like Diabetex, (patency# EP 0877617 A1) significantly improves the wound healing and collagen formation while it induces re-epithelialization and neovascularization of diabetic foot wounds, exhibiting a safe profile on liver and kidney function tests and a significant reduction in fasting blood sugar (70). Thus, medicines on the base of free amino acids could be considered as a novel approach for treating diabetic resistant wounds by a possibly more economic and safe strategy.

Conclusion

Overall, diabetes consequences associated with collagen structure abnormalities and/or its impaired metabolism are extremely different. In addition, the pathophysiological mechanisms underlying collagen changes in DM include hyperglycaemia, the accumulation of advanced glycation endproducts, and oxidative stress (Figure 1). In turn, collagens via some mechanisms may regulate glucose homeostasis, directly and indirectly. Accordingly, developing in-depth insight into the collagen metabolism and diabetes interrelations provides the chance to optimize different approaches for modifying the collagen-mediated consequences of this disease.

Conflict of Interest Disclosures

None.

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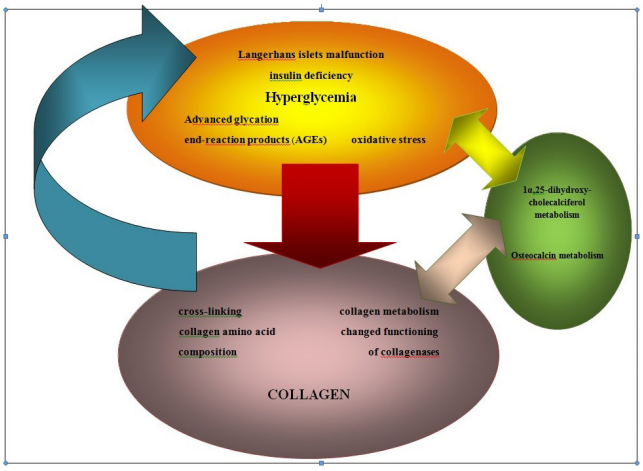

Figure 1. The Scheme of Diabetes Development and Collagen Structure and Metabolism Interrelations.

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