World Journal of Diabetes

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DOI: 10.4239/wjd.v7.i4.67

World J Diabetes 2016 February 25; 7(4): 67-73
ISSN 1948-9358 (online)

REVIEW

Glycosaminoglycan remodeling during diabetes and the role of dietary factors in their modulation

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Author contributions: All the authors have contributed by searching for relevant literature and writing of the manuscript.

Conflict-of-interest statement: The authors hereby declare that they have no conflict-of -interest to state with respect to this paper.

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Received: October 3, 2015
Peer-review started: October 9, 2015
First decision: November 10, 2015
Revised: November 23, 2015
Accepted: December 29, 2015
Article in press: January 4, 2016
Published online: February 25, 2016

Abstract

Glycosaminoglycans (GAGs) play a significant role in various aspects of cell physiology. These are complex polymeric molecules characterized by disaccharides comprising of uronic acid and amino sugar. Compounded to the heterogeneity, these are variously sulfated and epimerized depending on the class of GAG. Among the various classes of GAG, namely, chondroitin/dermatan sulfate, heparin/heparan sulfate, keratan sulfate and hyaluronic acid (HA), only HA is non-sulfated. GAGs are known to undergo remodeling in various tissues during various pathophysiological conditions, diabetes mellitus being one among them. These changes will likely affect their structure thereby impinging on their functionality. Till date, diabetes has been shown to affect GAGs in organs such as kidney, liver, aorta, skin, erythrocytes, *etc*. to name a few, with deleterious consequences. One of the mainstays in the treatment of diabetes is though dietary means. Various dietary factors are known to play a significant role in regulating glucose homeostasis. Furthermore, in recent years, there has been a keen interest to decipher the role of dietary factors on GAG metabolism. This review focuses on the remodeling of GAGs in various organs during diabetes and their modulation by dietary factors. While effect of diabetes on GAG metabolism has been worked out quite a bit, studies on the role of dietary factors in their modulation has been few and far between. We have tried our best to give the latest reports available on this subject.

Key words: Glycosaminoglycans; Diabetes; Proteoglycans; Remodeling; Dietary factors

Core tip: Glycosaminoglycans/Proteoglycans are important polymeric molecules which play important roles in cell physiology. Under pathological conditions such as diabetes, they are known to undergo remodeling affecting their structure-function relationship. This review article deals with its remodeling in various tissues and their modulation by dietary factors.

Gowd V, Gurukar A, Chilkunda ND. Glycosaminoglycan remodeling during diabetes and the role of dietary factors in their modulation. *World J Diabetes* 2016; 7(4): 67-73 Available from:

URL: http://www.wjgnet.com/1948-9358/full/v7/i4/67.htm DOI: http://dx.doi.org/10.4239/wjd.v7.i4.67

INTRODUCTION

Diabetes mellitus, henceforth referred as diabetes, is a disorder characterized by sustained hyperglycemia. According to World Health Organization studies, diabetes could be one of the leading causes of death in world population by 2030[1]. Approximately 80% of the deaths due to diabetes are reported to have occurred in low- and middle-income countries[2]. Diabetes could occur as a result of either decreased insulin secretion by pancreatic beta cells (Type 1 diabetes) or as a result of insulin resistance (Type 2 diabetes)[3]. In both these instances, glucose uptake by the cells and their disposal is affected. Insulin is required for storing glucose as glycogen in the liver and skeletal muscles. Lack of insulin secretion/insulin sensitivity, alter the glycogenolysis and gluconeogenesis results in the subsequent increase in blood glucose[4].

Sustained hyperglycemia in the long run results in the manifestation of micro- and macro-vascular complications. Nephropathy, retinopathy, and neuropathy are some of the serious secondary complications of diabetes which are known to affect kidney, eye and nerves, respectively[5]. In both micro- and macro-vascular complications, extracellular matrix components (ECM) are affected. ECM is composed of proteoglycans (PGs) and glycoproteins. PGs are complex polymeric molecules consisting of core proteins to which are attached the glycosaminoglycan (GAG) chains. They play an important role in various aspects of cell growth and behavior not only by acting as a supporting structure but also as a depot for growth factors and other signaling molecules. Changes in the structure-function relationship of GAGs/PGs impinge on their biological activities and influence the functioning of organ and the organ systems[6].

Controlling blood sugar levels will have a positive impact on the health of the organism. It can be managed by drugs, diet and exercise with positive outcomes. Diet, in particular, has been demonstrated to play a vital role in the management of diabetes. In recent years, with increasing emphasis being placed on functional foods, a lot of research efforts are being directed towards elucidating and deciphering novel bioactive molecules from dietary sources that could be used in tailoring functional foods. These foods are expected to increase the general wellness as well as attenuate the disease condition by modulating various processes.

GAGS- STRUCTURE AND BIOSYNTHESIS

GAGs are polymeric molecules that are present in all cells. There are 4 classes of GAGs known till date namely; hyaluronic acid (HA), chondroitin sulfate/dermatan sulfate (CS/DS), heparan sulfate/heparin (HS/Hep) and keratan sulfate (KS). CS/DS and HS/Hep are synthesized on a core protein through the linkage region tetrasaccharide of Xylose-Galactose-Galactose-Glucuronic acid. They contain repeating disaccharide units of uronic acid and amino sugar which are variously sulfated[7]. Disaccharides of CS/DS are glucuronic acid/iduronic acid and N-acetyl-D galactosamine and disaccharides of HS/Hep are glucuronic acid/Iduronic acid and N-acetyl-D glucosamine. The composite structure comprising of GAGs with core proteins are known as PGs. There are a few exceptions: HA which is composed of glucuronic acid and N-acetyl-D-glucosamine is not attached to the core proteins, and KS does not contain an uronic acid but contains galactose instead. KS chains are attached to core proteins *via* aspargine (N-linked) or serine/threonine (O-linked)[8]. All the classes of GAGs except for HA are variously sulfated.

Biosynthesis of all classes of GAGs with the exception of HA is synthesized in endoplasmic reticulum and Golgi. HA, is however synthesized by transmembrane hyaluronan synthases (HAS1, HAS2, and HAS3)[9]. Biosynthesis of GAGs is an energy-intensive process. Interestingly, one of the disaccharides, N-Acetyl-D-glucosamine is synthesized through hexosamine biosynthetic pathway that is also known as nutrient sensor pathway[10].

GAGs play vital roles in various aspects of cell physiology which brings about cell growth and development[11]. They can bring about biological activities by forming binding domains on growth factors and other proteins. GAGs undergo remodeling under various pathological conditions bringing about changes in their structure and function. In conditions of diabetes, changes in GAG structure and function have been observed in different tissues.

DIABETIC NEPHROPATHY AND GAGS

Nephropathy is one of the major secondary complications of diabetes which, in the long run, leads to end-stage renal failure. It is characterized by increased deposition of ECM components. ECM components maintain the integrity of the cell and their interactions with GAGs are essential for maintaining the extracellular morphology and cell adhesion[12]. The increase in the ECM components in kidney leads to the thickening of basement membrane and expansion of glomerular mesangial matrix, thereby affecting the filtration process. PGs/GAGs are the part of ECM components, and it is experimentally proved that PGs/GAGs are altered during diabetic nephropathy[13]. DN is marked by albuminuria and overt proteinuria at later stages. Earlier studies have implicated loss of heparan sulfate on the basement membrane as one of the reasons for leakage of proteins[13]. It was further supported by biopsies from patients with diabetes, in which structural modifications in HS GAGs was observed[14]. GAGs in the basement

membrane, especially HS are known to influence the permselectivity. This however, has been discounted by injecting heparinase, an enzyme which cleaves Hep/HS, intravenously which prevented albuminuria despite a decrease in HS chains[15]. Recent evidence further show that CS along with HA play equally important role in charge selectivity of the glomerular membrane[16]. Kidney GAGs comprises about 86% HS and 14% CS/DS among sulfated GAGs in adults whereas CS comprises 75% in embryonic kidney[17]. Studies on Streptozotocin-induced diabetic rats have shown that there is significant qualitative and quantitative changes in kidney GAGs. CS/DS from kidney was shown to be altered structurally which impinged on their functionality tested in terms of binding to laminin, fibronectin and type Ⅳ collagen[18]. Further, it has been observed that heparanase, an endosulfatase is involved in the pathogenesis of DN[19].

Multiple factors have been implicated in causation of diabetic nephropathy. Advanced glycation end products (AGEs) and oxidative stress has been considered as one of the major factors[20,21]. AGEs are the heterogeneous group of molecules which are formed *via* Maillard reactions from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids and nucleic acids[22]. Accumulation of AGEs in patients with diabetic nephropathy is due to enhanced formation and decreased the clearance of AGEs[23]. AGEs tend to alter properties of large matrix proteins like laminin, collagen, fibronectin and vitronectin, through AGE-AGE intermolecular covalent bonds or crosslinking with these proteins[23]. Formation of AGEs on laminin reduced polymer elongation as well as reduced binding of laminin to type Ⅳ collagen and HSPGs[24,25]. AGEs also play a significant role in thickening of GBM and mesangial expansions that are considered to be hallmarks of diabetic nephropathy because AGEs formation on ECM proteins dysregulates their degradation by matrix metalloproteinase[26,27]. AGEs are also implicated in the increased production of TGFβ, a cytokine which is responsible for increased synthesis of ECM components in the kidney[28-30]. However, the mechanism by which GAGs/PGs are modulated in the diabetic kidney has not been deciphered.

LIVER GAGS IN DIABETES

The liver is an organ of great metabolic importance. It is rich in GAGs and harbors CS/DS, HS, HA and KS[31,32]. Changes in liver GAGs have been observed during various physiological and pathological conditions such as diabetes[33], hypercholesterolemia[34], liver cirrhosis[35], and cholestasis[36], *etc*., to name a few. Diabetes is known to deregulate lipid metabolism and GAGs, in particular the HS class. It plays an important role in lipoprotein metabolism in liver by acting as a receptor or a co-receptor along with LDL-receptor, LRP and ApoE[37,38]. HSPGs such as syndecan-1 and perlecan, in particular, have been implicated in lipoprotein metabolism, and it is evidenced by impairment in the clearance of remnant lipoproteins in syndecan-1 knockout mice[39]. HS-GAGs are also known to be involved in hepatic clearance of apoB-48-containing lipoproteins[40]. During experimental diabetic conditions reduced N-sulfation has been observed in liver HS GAG as compared to control[33]. This was determined to be due to decreased glucosaminyl N-deacetylase activity and N-sulfotransferase activities in hepatocytes[41]. Decreased content of liver HS GAGs as a result of decreased HSPGs was associated with the decreased postprandial clearance of apoB-48-containing lipoproteins. It has been determined that decrease in HSPG perlecan was associated with the delayed clearance of apoB-48-containing lipoproteins[40]. However, Bishop *et al*[42] have shown that decrease in lipoprotein clearance during diabetes is not due to changes in HS as no differences were observed between normal and diabetic littermates in liver heparan sulfate content, sulfation and syndecan-1 protein levels. Some of the degradative enzymes of HS have been observed to affect the metabolism of lipoproteins. Noted amongst them is Sulf 2 which encodes heparan sulfate glucosamine- 6-O-endosulfatase 2 which is responsible for the degradation of HSPGs by removing 6-O sulfate groups. Involvement of HSPGs in hepatic clearance was further evidenced by the deletion of SULF2 in cultures hepatocytes. Knockdown of SULF2 showcased the increased HSPG-mediated catabolism of remnant lipoproteins in cultured cells[43].

Matrix PGs in the liver are affected by insulin and fatty acids. In a study conducted by Olsson *et al*[44], it was observed that insulin and non-esterified fatty acids modulate PG synthesis in hepatic cells so much so that the changes in PG composition affected their binding to remnant B-VLDL particles contributing to dyslipidemia of insulin resistance.

EFFECT OF DIABETES ON AORTIC GAGS

Cardio-vascular disease is one of the major complications of diabetes. Arterial walls are rich in PGs and are implicated in the pathogenesis of atherosclerosis by virtue of their ability to bind and trap LDL. In a study carried out in diabetic monkeys, it was observed that diabetes resulted in increased DS class of GAGs in arteries which was positively correlated with tissue cholesterol promoting atherosclerosis[45]. Three major CS/DSPGs present in the arterial wall are versican, decorin and biglycan[46]. In aortic endothelial cells, high glucose condition resulted in decreased perlecan level indicating remodeling of PGs[47]. Studies on BAEC suggested that reduced sulfate incorporation in the HSPGs[48].

Factors affecting the synthesis and degradation of PGs in the aorta as a result of diabetes have not been critically studied. TGFβ has been one of the factors implicated in changes in PG synthesis. It is known to be produced in hyperglycemic conditions and induces changes in PGs secreted by vascular smooth muscle

cells increasing their propensity to retain and bind lipoproteins in the vascular wall[49].

EFFECT OF DIABETES ON ERYTHROCYTE GAGS

Diabetes is known to affect erythrocytes by increasing their aggregation binding to endothelial cells and decreasing the deformability[50]. Diabetes is also associated with the increase in membrane lipids and changes in its fluidity. Reports on erythrocyte GAGs are scarce. HS expression was observed in human erythrocytes infected with the malarial parasite which helped in the rosette formation with uninfected erythrocytes[51]. Furthermore, HS was found to be a mediator for the binding of Plasmodium falciparum-infected erythrocytes to endothelial cells *via* the DBL1α domain of PfEMP[52]. Recent findings from our laboratory revealed the presence of CS/DS class of GAGs in erythrocytes of experimentally-induced diabetic rats. Erythrocytes from diabetic rats had increased levels of CS/DS when compared to age-matched non-diabetic control rats. They appeared to mediate the binding of erythrocytes to ECM[53]. Erythrocytes isolated from rats that were diabetic as well as hypercholesterolaemic showed higher binding to ECM components than that isolated from diabetic rats[54]. Further work on synthesis and regulation of GAGs in erythrocytes should be able to throw light on the function of these important molecules.

GAGS IN DIABETIC RETINOPATHY

Retinopathy is one of the secondary complications of diabetes. Diabetic retinopathy leads to vision loss with their associated abnormalities in vascular permeability[55]. Changes in the vascular permeability are associated with combination of abnormalities namely: Thickening of basement membrane, leakage of various compounds, capillary occlusion, and formation of new vessels along with fibrous tissue[56-58]. Fluorescent microscopic studies have found the presence of HS, CS/DS, HA throughout the retina but the presence of KS is found to be limited to the sclera[59]. Studies on the incorporation of [^{35}S]- and [^{14}C] glucosamine into GAGs that were isolated from retinal vessel basement membrane suggested that HS GAG is the major GAG present in basement membrane[60]. Various studies have been conducted to decipher the role of HS GAG in retinopathy. A study on the metabolism of GAGs in retina in streptozotocin-induced diabetic rats found decreased synthesis of HSPGs and was found to be associated with the decreased expression of perlecan[61]. It has also been demonstrated that quantitatively more GAGs is found in tears of patients with diabetic retinopathy than in non-diabetic people[62]. Furthermore, diabetic retinopathy was associated with the reduced production of HS GAG in the vitreous and increased expression of surface binding exogenous VEGF[63]. It is well known that HS GAGs are recognized as a co-receptor for fibroblast growth factor. FGF is a potent endothelial cell mitogen that has proposed to be involved in the development of proliferative diabetic retinopathy. Changes in the distribution of FGF during diabetes are associated with the development of retinopathy and retinal neovascularization. These studies reveal the possible role of FGF in the development of neovascularization and contribution of HSPGs in it[64]. In a study conducted on diabetic subjects, it was observed that there was a correlation between diabetic retinopathy, erythrocyte anionic charge and urinary GAG excretion[65].

DIABETES AND SKIN GAGS

Despite the fact that skin is rich in GAGs, not much work has been carried out to determine the effect of diabetes on its remodeling. The skin of STZ-induced diabetic rats showed decreased GAG content as a result of decreased GAG biosynthesis[66]. The decrease of GAG content in the skin of diabetic rats was earlier reported to be as a result of decreased circulating IGF-Ⅰ level, increased plasma content of LMW-BPs and increased proteolytic activity of the skin[66].

ROLE OF DIETARY FACTORS IN MODULATION OF GAGs

Diet plays major roles in the management of diabetes. The information with respect to the role of diet on GAG metabolism is scanty. In a study conducted by Taylor *et al*[67], it was observed that extracts from some of the plants present in Amazon rain forest stimulated GAG assembly in both wild type and mutant cell line defect in one of the key biosynthetic enzymes-xylosyltransferase. These findings suggest the importance of plant products in modulation of GAGs in animal cells. Various dietary factors have been implicated in attenuating diabetic nephropathy *per se*, but there are very few reports on their effect on GAG metabolism. Fiber-rich sources such as wheat bran and Guar gum altered decreased GAG synthesis in STZ-induced diabetic rats[68]. In another study, feeding of bitter gourd (*Momordica charantia* LINN) resulted in amelioration of decreased synthesis of GAGs in the kidney of diabetic rats[69]. In a similar vein, dietary feeding of *Tinospora cordifolia* resulted in attenuation of decreased CS/DS in STZ-induced diabetic rat kidney[70]. Not only in diabetes, even in normal conditions are some of the dietary factors known to affect GAGs. Noted among them, Genistein has been determined to decrease synthesis of GAGs[71]. Dietary manganese has been found to affect aortic GAGs in rats by altering composition and sulfation pattern of heparan sulfate GAG[72]. Similarly, wild blue berry consumption altered the GAG composition in the aorta[73]. In a study conducted, *Annona squamosa* showed beneficial effect on wound healing by increasing the synthesis of GAGs and collagen in STZ-induced diabetic rats[74].

GAG consumption can also occur by consuming foods of animal origin[75]. However, not much work has been carried out with respect to its metabolic effects in the body. The mixture of GAGs, called sulodexide has been demonstrated to contain proteinuria and ameliorate markers of diabetic nephropathy in clinical studies[76]. It has also been observed that oral administration of high molecular weight hyaluronan controls immune system *via* Toll-like receptor 4 in the intestinal epithelium[77].

FUTURE PERSPECTIVES

Despite the fact that rapid strides have been made with respect to deciphering the importance of GAGs in health and disease of the organism, more needs to be done especially with relation to their regulation under various conditions both normal and pathological. Also, evaluating various dietary molecules which could influence GAG metabolism will go a long way in therapeutic applications and development of functional foods.

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P- Reviewer: Gómez-Sáez J
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