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REVIEW

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REVIEW

Management of diabolical diabetes mellitus and periodontitis nexus: Are we doing enough?

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Abstract

Periodontitis is the commonest oral disease affecting population worldwide. This disease is notorious for the devastation of tooth supporting structures, ensuing in the loss of dentition. The etiology for this disease is bacterial biofilm, which accumulates on the teeth as dental plaque. In addition to the biofilm microorganisms, other factors such as environmental, systemic and genetic are also responsible in progression of periodontitis. Diabetes mellitus (DM) is metabolic disorder which has an impact on the global health. DM plays a crucial role in the pathogenesis of periodontitis. Periodontitis is declared as the "sixth" major complication of DM. Evidence based literature has depicted an enhanced incidence and severity of periodontitis in subjects with DM. A "two way" relationship has been purported between periodontitis and DM. Mutual management of both conditions is necessary. Periodontal therapy (PT) may assist to diminish the progression of DM and improve glycemic control. Various advanced technological facilities may be utilized for the purpose of patient education and disease management. The present paper clarifies the etio-pathogenesis of periodontitis, establishing it as a complication of DM and elaborating the various mechanisms involved in the pathogenesis. The role of PT in amelioration of DM and application of digital communication will be discussed. Overall, it is judicious to create an increased patient cognizance of the periodontitis-DM relationship. Conjunctive efforts must be undertaken by the medical and oral health care professionals for the management of periodontitis affected DM patients.

Key words: Cost-effectiveness; Advanced glycation end products; Complications; Glycated hemoglobin; Inflammation; Mobile health; Periodontitis; Periodontal therapy; Scaling and root planing; Type 2 diabetes mellitus

Core tip: Various studies have corroborated a two-way relationship between diabetes mellitus and periodontitis. Periodontal therapy (PT) can assist to ameliorate the

glycated hemoglobin levels. Metabolic control in diabetes may prevent further complications. Given the large scale epidemiology of both diabetes and periodontitis, it is prudent for the oral health care personnel to co-ordinate efforts with the diabetes care personnel, for the mutual management of these conditions. The implication of PT in metabolic control of diabetes and the various methods for the systematic management of diabetes-periodontitis nexus are explained in this review.

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INTRODUCTION

Periodontitis is a common oral disease afflicting humans worldwide, since centuries. Periodontitis is a chronic and painless condition; hence the subject seldom seeks any professional assistance. The lack of treatment results in the destruction of tooth supporting apparatus and further culminates into partial or complete loss of dentition[1,2]. Periodontitis is not only a localized condition but also influences systemic health of the individual. This association of periodontitis with systemic health led to the emergence of a novel branch in the field of periodontology, known as periodontal medicine. Periodontal medicine focuses on the aggregation of evidence based data, which establishes a substantial relationship between periodontitis and systemic health[3]. Throughout the years periodontitis has been associated with various conditions like diabetes mellitus (DM)[4], cardiovascular atherosclerotic disease[5], preterm low birth weight[6], rheumatoid arthritis[7], cancer[8], chronic kidney disease[9], inflammatory bowel disease[10], obesity[11], metabolic syndrome (MS)[12], dyslipidemia[13], respiratory diseases[14], Alzheimer's disease[15] and erectile dysfunction[16] and non alcoholic fatty liver disease (NAFLD)[17]. It is purported that periodontitis and NAFLD should be included as new components of MS. Both these components harbor a two-way relationship with MS[18,19]. Various mechanisms have been proposed for association of various systemic conditions with periodontitis[20-22]. The literature is amassed with various studies depicting a relation between periodontitis and DM[23].

DM is a chronic metabolic disorder, involving impaired glucose homeostasis. It is classified as type 1 DM (T1DM) and type 2 DM (T2DM). T1DM is manifested due to the failure of pancreatic β cells to produce sufficient insulin and it is an autoimmune condition. T2DM is due to the resistance offered by peripheral tissues to the action of insulin, regardless of enhanced insulin production by pancreatic β cells. The insulin secretion is augmented in the initial phase of T2DM. This increase in pancreatic β cells function undergoes further deterioration, as in obese individuals. This ensues in the failure of β cells to secrete insulin. This results in hypoinsulinemia with the manifestation of T2DM. Various risk factors are recognized for T2DM. These include genetic susceptibility, pre-existing obesity, smoking, increase in the systemic levels of free fatty acids and pro-inflammatory mediators[24,25]. Chronic hyperglycemia, a perennial feature of DM, affects practically all host organs and tissues. The five main cognizable complications of DM include retinopathy, neuropathy, nephropathy, altered wound healing and macrovascular disease. Periodontal disease is added to this list and it is now considered as the "sixth complication" of DM[26].

METHODS OF DATA COLLECTION

Studies examining the effect of DM on host tissues and periodontal tissues in particular, were identified using PubMed search with key search terms such as "advanced glycation end products", "complications", "cost-effectiveness", "epidemiology", "glycated hemoglobin", "inflammation", "meta-analysis", "mobile health", "oxidative stress", "periodontitis", "periodontal therapy", "telemedicine", "T2DM". Systematic reviews, meta-analysis were also screened. Studies published in English language were considered. The review has been prepared by screening PubMed database from 1992 to April 2015.

WHAT IS PERIODONTITIS?

Periodontitis is a chronic inflammatory disease of the gingiva. In the United States, the prevalence of periodontal disease is considerably high, affecting almost 47% to 58% of adults[27]. The etiology for periodontitis is bacterial plaque which accumulates on the teeth surfaces, in absence of optimal oral hygiene measures. The initial phase of the disease process is called "gingivitis", which clinically presents as swelling and bleeding of gingiva. However, gingivitis is reversible with the resumption of proper oral hygiene. If neglected gingivitis may extend into "periodontitis", which is an irreversible process. Periodontitis results in the gradual deterioration of the periodontium. The periodontium comprises of hard and soft tissue supporting the tooth structure. Clinically, a subject with periodontitis presents accretion of calcified deposits referred to as dental calculus, above (supragingival) and beneath (subgingival) the gingival margin. Edematous, bleeding gingiva, bad breath (halitosis), increase in spacing (diastema) between the teeth, suppuration from periodontal pockets are the other features of periodontitis. Periodontitis is characterized by deepening of the normal gingival sulcus into "periodontal pocket", destruction of supporting fibers and loss of bone. This results in clinical attachment loss, conventionally gauged by an instrument known as periodontal probe (Figure 1). In advanced periodontitis the subject may also reveal loose teeth (referred to as

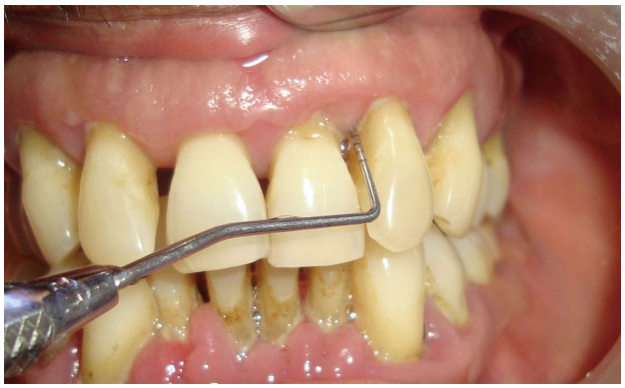

Figure 1 Deep pockets checked with a periodontal probe in a case of chronic generalized periodontitis.

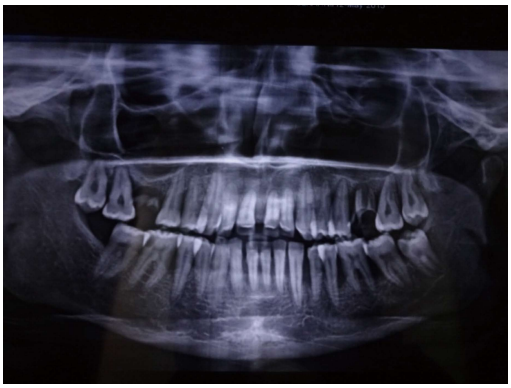

Figure 2 Radiograph showing bone loss in periodontitis patient.

mobile teeth). This condition is evidenced by severe bone loss as observed in the radiograph (Figure 2). The transition of gingivitis to periodontitis is a complex process, involving a qualitative change in microbial biofilm flora. There is an enormous diversity of microbial flora in the dental plaque[28,29]. Other factors like local, systemic background and genetic susceptibility also play a crucial role in the advancement of the disease[30,31]. Periodontitis is influenced by various modifiable and non modifiable risk factors, which need appraisal[32].

ETIO-PATHOGENESIS OF PERIODONTITIS AND SYSTEMIC LINK

Periodontitis is a microbial biofilm induced disease. Microbial flora of different strains and species are housed in the biofilm matrix. The transition of gingivitis to periodontitis is subjected to a number of factors including the shift of bacterial species from gram positive aerobic to gram negative anaerobic, host environmental factors and genetics[33,34]. Various microbiological molecular techniques have demonstrated the presence of gram negative periodontal pathogens in periodontal disease sites. These include *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium* species, *Treponema denticola*, *Tannerella forsythia*, *Prevotella intermedia*, *Campylobacter rectus*, *Dialister invisus/pneumosintes*[35]. With the advances in the field of medicine, the evolution of conceptual models addressing periodontitis has seen many changes. The early concept of the pathogenesis of periodontal disease purported a solo bacterial role in the initiation and progression of periodontitis. However, with ample research and studies, the crucial role of host immune-inflammatory response was highlighted. Eventually, the understanding in the pathogenesis of periodontitis amended with the consideration of microbiologic and immunologic characteristics of the disease. Presently, the most commonly accepted model for the pathogenesis of periodontitis is proposed by Page *et al*[36]. It is unanimously accepted by the experts in the domain of periodontal research that bacteria play a pivotal role in the initiation of the periodontal disease process. However, bacteria are not only adequate for the disease to occur. Host factors such as genetic susceptibility, tobacco and other risk factors play an important role in the severity and ultimate clinical outcome of the periodontal disease. The type of immune response demonstrated by the host periodontal cells on confronting the periodontal pathogen is of crucial significance. This factor determines the resistance or susceptibility of the host tissues to clinical outcome of periodontal disease. Several inflammatory mediators such as interleukin (IL)-1β, prostaglandin (PG) E_2, tumor necrosis factor (TNF)-α and matrix metalloproteinases (MMPs) orchestrate a significant role in the immuno pathogenesis of periodontal disease[37]. The expression of these pro-inflammatory mediators is regulated by the T helper cells. The periodontal bacteria stimulate the innate immune system to produce cytokines, which conduce to the periodontal disease progression[38]. The polymorphonuclear neutrophils (PMNs) are important sentinels and serve as the first line of defense in periodontal disease process. However, exaggerated response may transpose this protective action of PMNs into destroyers. Consequently, the periodontium is subjected to damage by an array of mechanisms. PMNs in periodontal disease may at times actually assist in the deterioration of the condition rather than curbing the disease process. Thus, the host immune-inflammatory responses would either be protective or destructive, resembling the proverbial "double edged sword"[39-41]. This concept commuted the character of periodontitis to a complex disease, the expression of which implied an obscure interaction between the microbial biofilm and host immune-inflammatory response. This interaction modulates the periodontal tissue homeostasis[42,43].

In a subject with generalized chronic severe periodontitis the total diseased surface area is large. This includes the ulcerated surface of the periodontal pocket epithelium. The total surface area of the periodontal lesions in a severe periodontitis patient is estimated to be 15-20 cm^2[44]. Some researchers quantified the periodontal inflamed surface area (PISA) in the range of 0.3 cm^2 in periodontal healthy subjects to 39 cm^2

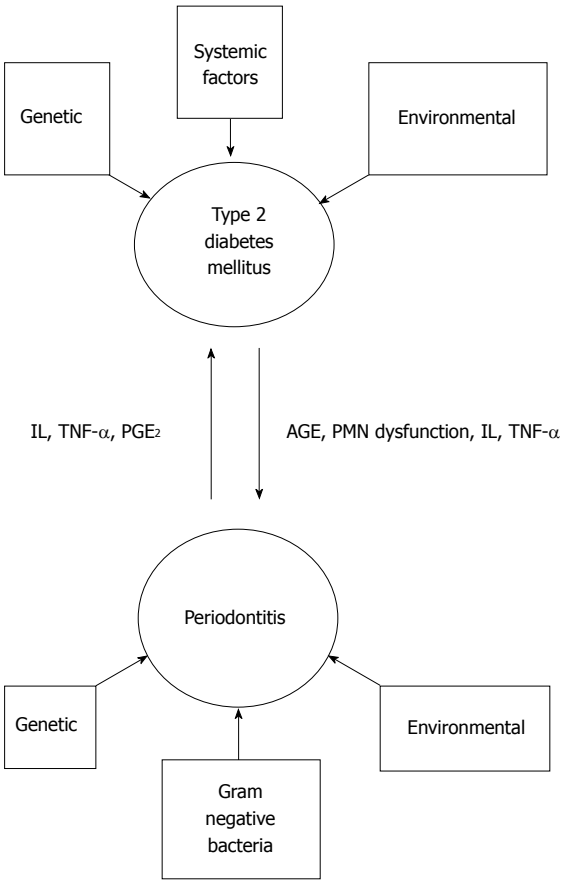

Figure 3 The bidirectional relationship between type 2 diabetes mellitus and periodontitis. IL: Interleukin; TNF-α: Tumor necrosis factor-α; PGE_2: Prostaglandin E2; AGE: Advanced glycation product; PMN: Polymorphonuclear neutrophil.

in subjects with severe generalized periodontitis. PISA reflects the diseased surface area of the pocket. According to the authors, PISA is an improved version of classification of periodontitis and effectively represents as a risk factor for other diseases[45]. The ulcerated pocket surface acts as a portal entry for the periodontal bacteria and various host mediated inflammatory mediators such as IL-1β, TNF-α, PGE_2 and MMPs. The host derived inflammatory mediators along with the bacterial toxic products including lipopolysaccharides are plunged into systemic circulation. Thus, the large surface area of pocket epithelium in periodontitis may pose an inflammatory burden to the body. This shifts the character of periodontitis from an indolent, localized disease to a potential systemic condition. Thus, severe periodontitis is capable of eliciting a low grade systemic inflammation[38,46]. A review of the published evidence substantiates modest affiliation between periodontitis and certain systemic diseases[47]. However, the relationship between periodontitis and DM is proven to be bidirectional, with both these conditions reciprocating each other (Figure 3). Subjects with DM are at a risk of developing periodontitis and on the other hand periodontitis perturbs the glycemic control in DM subjects[48]. The purpose of this review is to highlight the diabolical association of periodontitis and DM. The measures conducted to reduce the severity of both these chronic, yet debilitating conditions will also be discussed.

MANAGEMENT OF PERIODONTITIS

The etiology of periodontitis is distinctly associated with dental plaque and calculus deposits, accumulated on the teeth surfaces. Hence, it is prudent to remove these accretions. The initial phase of periodontal therapy (PT) is known as non surgical PT, which consists of scaling and root planing (SRP) of tooth/root surfaces. Periodontal debridement is the "gold standard" in PT[49]. SRP involves the mechanical removal of teeth deposits which is accomplished by hand instruments or powered ultrasonic instruments. Curettes and scalers are used for hand instrumentation. The powered ultrasonic scalers facilitate easy removal of calculus deposits. These powered instruments generate a high frequency (range 25000-42000 Hz) vibration of the scaler tip. Water irrigation assists to reduce the frictional heat of the ultrasonic scaler tip[50-52]. SRP may fail to eliminate the periodontal pathogens residing in the inaccessible areas like deeper portions of periodontal pockets, concavities on the tooth root and furcation regions of the molar teeth. Systemic antimicrobials serve as useful adjuvants for the treatment of periodontitis. These antimicrobials target the tissue invasive bacteria, not amenable to SRP. These antimicrobials are effective as an adjuvant therapy with SRP and not recommended to be administered as monotherapy[53,54]. With the consideration of risk to benefit ratio regarding systemic antimicrobials, the local delivery of antimicrobials proves beneficial. In this local drug delivery (LDD) system, the antimicrobial agents are delivered directly into the periodontal pocket site either in form of fibers, gel, microspheres or chip. The local delivery of antimicrobials counteracts adverse effects related the systemic antimicrobials and conveys a high concentration of the drug at the local periodontal site. These LDD systems act as valuable adjuvant to SRP[55]. There are also other adjuvant PT modalities along with SRP. These include photodynamic therapy[56] and lasers[57]. Lasers have also been used as a substitute or as an adjuvant with mechanical periodontal treatment. In PT laser irradiation has been used for calculus removal and detoxification of diseased root surface, removal of epithelial lining and granulation tissue. Lasers also exert a potential biostimulation effect on the cells in vicinity to the target tissue, thereby abbreviating the inflammation and enhancing the healing of periodontal tissues[58]. Host modulation therapy (HMT) may be utilized as an adjunct to SRP. HMT is directed to the manipulation of host inflammatory response. Periodontitis causes host tissue damage *via* the expression of inflammatory mediators such as IL-1, PGE_2, MMPs. HMT in periodontitis consists of sub antimicrobial dose of antibiotics like doxycycline, non steroidal anti-inflammatory agents like flurbiprofen and bone antiresorptive agents like bisphosphonates[59]. Host modulatory agents may be targeted against the expression of host inflammatory mediators and subverting

the inflammatory cell-signalling pathways[60]. Surgical therapy can be employed to gain complete access to the diseased periodontal sites and for implementation of regenerative periodontal procedures[61].

MECHANISMS OF DM INDUCED PERIODONTAL IMPAIRMENT

Epidemiological studies reveal that periodontitis is more prevalent in subjects with DM as compared with the non-diabetic population. DM may increase the risk of periodontitis by two to three folds[62].

DM induced periodontal tissue damage occurs *via* various mechanisms.

These may be categorized as follows: (1) Advanced glycation end products (AGEs) mediated tissue damage; and (2) Immune cell dysfunction.

Oxidative stress induced tissue damage: (1) Chronic hyperglycemia conduces to the formation of AGEs. This occurs as a result of nonenzymatic binding between the reducing sugar moieties with free amine residues of proteins. The AGEs exert their deleterious effects by binding to specific cellular receptor, known as receptor for AGE (RAGE). RAGE plays an important role in the development of DM related complications[63]. The AGE-RAGE coupling in DM-periodontitis induced murine models has demonstrated a substantial, sustained inflammatory response. This revealed a progressive bone loss in animal models with DM, compared to those without DM. It was hence deduced that the AGE-RAGE interaction intensifies the destructive process of periodontitis[64]. Immune cells such as monocytes, macrophages and PMNs carry a RAGE. AGE provokes these cells to produce excess of superoxide, when challenged by chemoattractants, resulting in tissue destruction[65,66]. AGEs are incriminated in exaggerating the periodontal inflammatory responses ensuing in the destruction of periodontal supporting bone[67]. The strong and sustained inflammatory response also enhances the process of apoptosis, thus yielding the periodontal tissues to the destructive process of periodontitis. This also diminishes the reparative capacity of the periodontal tissues[68]. AGEs combined with pro-inflammatory cytokines can motivate fibroblast apoptosis and impair periodontal wound healing[69]. Periodontal tissue collagen cross-linked with AGE shows decreased solubility and high resistance to proteolytic breakdown. This may compromise the physical and mechanical properties of periodontal tissues with greater susceptibility for periodontal disease[70]. AGEs also compromise the differentiation, growth and function of osteoblast cells[71]; (2) Several studies have analyzed the consequences of chronic hyperglycemia on periodontal tissues. These studies have indicated a dynamic role of exaggerated innate inflammatory response ensuing in microvascular damage, extracellular matrix destruction and ultimately debasement of periodontal tissues[72-75]. The PMNs are specialized immune cells which effectuate various protective and pathological immune responses[41]. The PMNs and monocytes are able to express an array of pro-inflammatory cytokines, which regulate the inflammatory process. However, this function is altered in DM. PMNs and monocytes from T2DM subjects expressed greater amount of cytokines as compared to non DM controls[76,77]. DM subjects display PMNs with higher vulnerability for oxidative DNA damage as compared to other peripheral blood cells[78]. Study on murine animal models has demonstrated that chronic hyperglycemia promotes the increase in the process of PMN margination and macromolecule extravasation in the gingival microvasculature. This may conduce to a pro-inflammatory environment, intensifying the severity of periodontal disease[79]. DM activates the innate immune mechanisms and limits the potential for repair. This aggravates the periodontal disease, thus the term "diabetic periodontitis"[80]; (3) DM is cognizant to be a state of oxidative stress with exuberant formation of reactive oxygen species (ROS). The increase of ROS in the mitochondrial environment poses a hazard for cellular function. These free radical species permeate through the mitochondrial membrane and gain access to the cellular organelles, resulting in cellular damage. An extensive review of literature by Chapple *et al*[81] highlight the far reaching and significant role of ROS in periodontal tissue destruction.

EFFECT OF DM ON PERIODONTIUM

Histological change in early periodontitis is characterized by the apical migration of the junctional epithelium. Studies conducted on DM rodents have demonstrated the apical recession of the junctional epithelium and inflamed connective tissue. The connective tissue fibers depicted altered arrangement when compared to the non DM controls[82]. The gingival epithelium revealed atrophic changes with diminished cellular organelles and increase in the intercellular spaces. DM caused thickening in the keratinized layer and altered differentiation of the epithelial cells[83]. Laboratory animal models with DM have shown diminished osteoblasts and periodontal fibroblast cells. A 5 fold increase in osteoblast apoptosis and 2.7 fold increase in periodontal fibroblast apoptosis was observed in these animals[84]. Gingival reactive hyperemia was diminished in periodontitis induced rats with DM. The researchers utilized laser flow Doppler flowmetry, to evaluate the attenuated gingival reactive hyperemia. This was attributed to the decrease in vascular endothelial dysfunction in the laboratory animals[85]. Gingival tissue in periodontitis human subjects with DM showed an increment in the expression of tissue inhibitors of metalloproteinase (TIMP)-3 and TIMP-4. This expression of TIMP corresponded to the severity of the periodontal disease activity. Increase in TIMP expression is considered as a reciprocate adjustment for the ongoing process of periodontal destruction. The authors have demonstrated a lateral up-regulation

of TIMP in DM subjects with periodontitis[86].

GLOBAL SCENARIO OF DM AND PERIODONTITIS

The global epidemiology of DM reveals a public health crisis afflicting nearly 382 million people. DM is responsible for the death of almost 5.3 million in 2013. The numbers of people affected with DM keep on escalating and it is proposed that in 2035 it will reach 592 million worldwide. DM is the leading cause of death in South Asian countries and it is menacing the economic status of many countries[87]. According to International Diabetes Federation, the South East-Asia region (India, Sri Lanka, Bangladesh, Bhutan, Mauritius, Maldives) inhabits a staggering number of more than 72 million diabetes subjects. Almost 95% of this population constitutes of T2DM[88]. China once the capital of DM has been overtaken by India, which is presently the diabetes capital of the world. The etiology of DM in India is multifactorial. This includes genetic and environmental factors, lifestyle of the population. However, it is peculiar to note that in spite of the alarming incidence of DM in India, there are fewer nationwide studies[89]. It is estimated that a large number of global population approximately 174.8 million remains to be undiagnosed[90]. The global health expenditure is projected to cost 490 billion United States dollars by the year 2030[91]. This enormous expenditure on DM is definitely corrosive to the world's greatest economies and poor nations.

Periodontal disease is a global disease afflicting mankind worldwide. Studies reveal that 5% to 20% of any given population is afflicted by severe periodontitis, whereas the mild and moderate forms of periodontitis affect most of the adult population[92,93]. The global prevalence of periodontal disease (including gingivitis and periodontitis) is 90%. A British study has reported 8% of the adult population exhibiting a periodontal site with pocket depth $\geqslant$ 6 mm[94]. According to statistical analysis committee on the survey of dental diseases 2005, it is estimated that 70% of Japanese population above the age of 15 years is affected by periodontal disease and 20% of the adult population above 40 years, demonstrate periodontal pocket depth $\geqslant$ 4 mm[95]. The picture in the Indian subcontinent is grave. Studies reveal that 50% of adult population above the age group of 35 years is affected by periodontal disease, ensuing in tooth loss[96]. Due to the variation in the global periodontal epidemiological methodology and difference in the case definitions of periodontitis, precise reports concerning periodontal disease prevalence is unavailable[97]. The community periodontal index for treatment needs introduced by World Health Organization (WHO) in 1987, is used for epidemiological studies of periodontal disease. This assists various nations to develop a profile of population periodontal status and also effective interventional programs to tackle periodontal disease related problems[98]. According to the 4th edition of the WHO manual for oral health surveys, the CPI scores are coded as follows: Score 0: Healthy periodontal status; Score 1: Gingival bleeding; Score 2: Gingival bleeding with presence of calculus; Score 3: Shallow periodontal pocket depth 4-5 mm; Score 4: Deep periodontal pockets $\geqslant$ 6 mm; Score 9: Excluded; Score X: Not recorded or visible.

The extent of loss of attachment (LA), recorded for a sextant is evaluated by utilizing the following codes: Score 0: LA 0-3 mm; Score 1: LA 4-5 mm; Score 2: LA 6-8 mm; Score 3: LA 9-11 mm; Score 4: LA $\geqslant$ 12 mm; Score X: Excluded; Score 9: LA not recorded or not visible.

It was observed that severe periodontal disease (with CPI score = 4) is prevalent globally in 10%-15% of adults. The most commonly observed, CPI score of 2 (gingival bleeding and presence of calculus), reflects poor oral hygiene.

The deficiencies of 4th edition CPI scoring system have been eliminated with the introduction of the 5th edition of the WHO manual for oral health surveys[93]. Several leading oral health surveys have used periodontal pocket and attachment loss as the criteria for identifying cases of periodontitis. Presently, epidemiological studies are more concentrated on the appraisal of attachment loss rather than pocket depth[99,100]. Workers have expressed mixed reports regarding the prevalence of periodontal disease. The prevalence of periodontal disease was reported to be on a decline in some parts of Europe. However, a surge in prevalence of periodontal disease was noted in Germany and Hungary[101,102]. Most of the epidemiological surveys include the population of developed nations. Epidemiological periodontal survey reports from countries like China and India are very limited. These countries harbor a vast population of DM and periodontitis subjects. Methodologies for the application of periodontal epidemiology have seen a steep change. Presently, the conglomeration of data is inadequate to draw tangible conclusions[92].

EVIDENCE BASED ASSOCIATION OF PERIODONTITIS AND DM

There is a high prevalence of periodontitis in DM subjects. Periodontitis is affirmed to be the sixth complication of DM. The mechanistic link between periodontitis and perturbed glycemic control is still unclear. It is believed that pro-inflammatory mediators such as IL-6 and TNF-α are expressed from the inflamed periodontal sites as a result of microbial stimulus or host response. These mediators enter the systemic circulation and interfere with the function of insulin receptors, thereby deranging the process of insulin signaling. The following cascade of events contributes to insulin resistance and impaired glucose homeostasis[103]. Thus, most of the studies carried out with periodontitis subjects and DM have indicated of poor metabolic control. Glucose binds

irreversibly to hemoglobin, leading to the formation of glycosylated hemoglobin (HbA1c). This non-enzymatic glucose moiety persists for the entire life span of the red blood cell. Hence, HbA1c levels reveal the glycemic control of the subject spanning for the previous 1 to 3 mo[104]. The recommended HbA1c goal for DM patients is levels < 7%[105].

A large sample size 5-year case-control cohort study was conducted on Japanese subjects, in two groups. The first group consisted of subjects without periodontal pocket depths ⩾ 4 mm at baseline. These subjects were exposed to an increased risk of developing periodontal pockets of ⩾ 4 mm after a 5-year period, with HbA1c levels ⩾ 6.5% at baseline. In the other group, subjects with HbA1c < 6.5% and periodontal pockets of 4-5 mm or ⩾ 6 mm at baseline were likely to display HbA1c levels ⩾ 6.5% after 5 years. This corroborated a direct relationship between periodontal health and glycemic status[106]. In a case control study by Wolff *et al*[107], it was concluded that periodontitis is associated with an escalation of HbA1c levels. Thus, periodontitis may skew the glycemic control in subjects without DM, subjecting them to an increased risk of T2DM. The presence of periodontitis in a German study sample without DM, was related to an elevation of HbA1c assay after 5 years of follow-up[108]. According to the National Health and Nutrition Examination Survey data, a statistically significant association was noted between HbA1c levels and periodontitis in United States. Subjects with higher HbA1c levels tend to demonstrate more severe periodontal disease[109]. A dose-response relationship was observed between PISA and HbA1c, suggesting a causal relationship between periodontitis and T2DM. In T2DM, an increase in PISA results in parallel elevation of the HbA1c levels. It was inferred that with an increase in 333 mm^2 of PISA, the HbA1c level advanced by 1%. Thus, an increase in the periodontal inflammatory burden causes a proportional impairment of glycemic control in T2DM patients[110]. PISA can be considered as a predictor of HbA1c along with CRP, in non T2DM subjects. Periodontitis may upset the glycemic control in healthy subjects[111].

MANAGEMENT OF DIABETES - PERIODONTITIS NEXUS

Therapeutic methods

Periodontitis compromises the quality of life[112]. Both, periodontitis and DM exert a bidirectional influence on each other. Poor glycemic control deteriorates the periodontal health and periodontitis can perturb the glycemic status in a subject with DM. It is noteworthy that the cumulative surface area of the diseased pocket epithelium, in a patient with generalized moderate periodontitis is approximately equal to the surface area of palm of adult hand. In severe periodontitis cases larger surface areas may be involved[113]. This is of concern for a health care professional involved in management of DM, whose primary objective is elimination of all potential foci of infection. It may be certainly anticipated that an infective surface of the magnitude mentioned above can be detrimental for effective glycemic control. Hence, it is prudent to incorporate PT as an important regimen in overall therapeutic management of a subject with DM[114]. Competent glycemic control improved periodontal conditions in periodontitis subjects, in absence of any periodontal intervention. This substantiated the "two-way relationship" between DM and periodontitis[115]. Various studies have assessed the effect of PT in T2DM patients with periodontitis. These studies included HbA1c as a common parameter to assess the improvement in metabolic control[116-167]. These studies have employed SRP alone or combined with systemic/topical antimicrobials. However, there is a variation in the results of these prospective studies. The range in reduction of HbA1c is 0.4% to 2%, with results persisting for 3 to 9 mo after PT. PT ensues in the diminution of serum pro-inflammatory factors such as TNF-α and CRP in T2DM individuals. This accounts for the reduction in systemic inflammatory burden and resultant complications associated with T2DM[168].

Table 1 depicts the various meta-analyses, showing the effect of PT in reduction of HbA1c levels[169-182]. Considering the heterogeneity of these studies and limitations in the designs, it would be too premature to draw any explicit conclusions and extrapolations[170,172]. To derive robust evidence for implications of PT in DM subjects, further studies should be carried out as per the suggestions furnished by Garcia[171]: (1) The trial should be single blind randomized, large sample size, consisting of subjects with DM and moderate/severe periodontitis; (2) The test group should receive the basic PT and the control group should be deferred from any PT; (3) Post PT, the follow-up period should be 6 mo; (4) Results to be evaluated should be based on the parameters assessing periodontal inflammation and metabolic control; and (5) Plasma should be checked for markers of systemic inflammation.

Anti-diabetes drugs are employed as single or combination regimen, for the effective metabolic control in DM patients. The dipeptidyl peptidase-4 inhibitors (known as gliptins) in combination with metformin reduce HbA1c level by 0.8%. When added to metformin and glimepiride, the HbA1c reduction is the same. In comparison to a placebo, gliptins mitigates HbA1c level by 0.6%-0.7%. For DM subjects failing to maintain adequate metabolic control on two anti-diabetic drugs, glucagon-like peptide-1 analogue (exenatide) can be added. Exenatide assists to reduce HbA1c level by about 1%. Pioglitazone, when added to an insulin regimen, favors the HbA1c reduction by about 0.54%[183]. The newer sodium-glucose co-transporter 2 inhibitors reduce HbA1c by 0.5%-1.0%[184]. It is strategically important to note that a decrement of HbA1c by 1% is associated with a decrease of microvascular complications by 37%, decrease in DM deaths by 21% and a decrease in the risk of myocardial infarction by

Table 1 Meta-analyses depicting the effect of periodontal therapy on glycated hemoglobin in type 2 diabetes mellitus patients

Ref.	Year	Results	Conclusion
Janket *et al*[169]	2005	7 studies, *n* = 456	With SRP ↓HbA1c by 0.66% PT and antibiotics ↓HbA1c by 0.71%
Darré *et al*[170]	2008	9 studies, *n* = 485	PT ↓HbA1c by 0.79%
Garcia[171]	2009	9 studies, *n* = 485	PT ↓HbA1c by 0.79%
Teeuw *et al*[172]	2010	9 studies, *n* = 371	PT ↓HbA1c by 0.4% in 3 mo
Vergnes[173]	2010	7 studies, 3 studies results pooled	SRP (with/without antibiotics) ↓HbA1c by 0.4% in 3-4 mo
Simpson *et al*[174]	2010	7 studies, 3 studies results pooled	SRP (with/without antibiotics) ↓HbA1c by 0.4% in 3-4 mo
Sgolastra *et al*[175]	2013	5 studies	SRP ↓HbA1c by 0.65%
Liew *et al*[176]	2013	6 studies, *n* = 422	SRP without antibiotics ↓HbA1c by 0.64% in 3 mo
Corbella *et al*[177]	2013	15 studies	PT ↓HbA1c by 0.38% in 3-4 mo and 0.31% in 6 mo
Engebretson and Kocher[178]	2013	9 studies	PT ↓HbA1c by 0.36%
Wang *et al*[179]	2014	10 studies, *n* = 1135	PT ↓HbA1c by 0.36% in 3 mo and 0.30% in 6 mo
Sun *et al*[180]	2014	8 studies, *n* = 515	PT ↓HbA1c by 1.03% in 3 mo, 1.17% in 6 mo, 1.21% in 3, 6, 9 mo
Engebretson[181]	2014	7 studies, *n* = 678	PT ↓HbA1c by 0.38% in 3-4 mo and 0.31% in 6 mo
Li *et al*[182]	2015	9 studies, *n* = 1082	PT ↓HbA1c by 0.27% in 3 mo

PT: Periodontal treatment; T2DM: Type 2 diabetes mellitus; HbA1c: Glycated hemoglobin; SRP: Scaling and root planing; ↓: Reduced.

14%. Thus, any reduction in HbA1c although miniscule may translate into a decrease in the risk of DM related complications[185].

The anti-diabetic agents are not without adverse effects. Sulfonylureas can cause hypoglycemia. Glucagon like peptide-1 receptor agonists and Metformin exert gastrointestinal side effects[186-188]. Thiazolidinediones cause weight gain, peripheral edema and increase the risk of cardiac failure. These agents also elevate the risk of bone fractures, particularly in females[189,190]. Sodium-glucose co-transporter 2 inhibitors induce albuminuria, reduce serum uric acid levels, possess diuretic effect and their use is accompanied by genital mycotic infections and urinary tract infections[191,192]. An important aspect of anti-diabetic drug therapy is the cost effectiveness. The drug therapy of DM levies a heavy cost, particularly for the developing and populous countries like India and China. Since the costs of newer medications continue to escalate, physicians should exercise their prudent decision regarding different possible options and resources[183,193,194]. Theoretically PT may substitute as one or more of the anti-diabetic drugs, employed in the treatment of T2DM. However, more studies should be implemented to substantiate this claim. The practical substitution may reduce the drug related adverse effects and also the cost, in DM patients with periodontitis. Non surgical PT, inclusive of antimicrobial therapy is highly cost effective for the management of periodontitis. This can be effectively used to treat large number of subjects[195].

Non therapeutic methods

Social support is an important aspect in the management of chronic diseases. Social support can augment the efforts of the health care professionals, ensuing in desirable results[196]. Presently, there is a growing body of evidence that peer support significantly assists in amelioration of chronic health conditions. Peer support works on the basis of non stratified reciprocal relationship developed as a result of sharing similar health ailments[197]. A meta-analysis by Qi *et al*[198] reveals improvement of HbA1c levels by 0.57% in T2DM patients with peer support approach. In a similar manner, a peer support method may be applied for the management of periodontitis-DM patients. According to an insurance claims data evaluating patients with dental and medical coverage, it was inferred that subjects undergoing PT were salvaged from the medical costs arising as a complication due to DM. This significant reduction measuring 20% to 40% appeared to persist for 3 years[199]. Oral diseases may be caused due to altered behavioral pattern. It is imperative to modify the patients' behavioral pattern, adoption of healthy oral care habits coupled with regular visits to the dentists[200,201]. As far as the Indian oral health scenario is concerned, the services available to the masses are provided by private and public sectors. Patients with DM are offered state-subsidized public dental care by the municipality. According to an Indian study the public health resources are not fully exploited to the benefit. This study also reported of inadequate oral hygiene in Indians with T2DM and stressed for an enhanced knowledge of periodontal ailments conjugated with oral hygiene methods for disease prevention[202]. According to a questionnaire study by Bowyer *et al*[203], it was reported that 69.1% of the participants were not advised by the health care professionals regarding the association between oral hygiene and DM. According to a Jordanian study only 47.7% of the patients with DM were aware of the reciprocal relationship between periodontitis and DM[204]. In a German study, 56% of the participants were unaware of the mutual association between periodontitis and DM. It was also noted that 66% of them were not cognizant of the fact that patients with DM are at a greater risk of periodontal disease as compared to the non diabetic counterparts[205]. Diabetic patients with periodontitis are often haunted by misconceptions. The most common being discontinuation of brushing and flossing, in order to prevent gums bleed. Patients with DM use alcohol containing

mouthwashes, which actually exacerbates the xerostomia. Thus, misconception and false information about oral hygiene may actually ensue in harmful behaviors. This may set a barricade to an efficient management of periodontal disease in diabetic patients[206,207]. Considering the bidirectional relationship between DM and periodontitis it is important to educate, create awareness and motivate patients with DM to maintain scrupulous oral hygiene. Various measures like tooth brushing, flossing and prescribed dental visits are efficacious in maintaining the periodontal health. It is overtly observed that patients with DM are least aware of their periodontal health, incognizant of the fact that poor periodontal health is a cause for perturbed glycemic control. An insignificant number of subjects with DM and periodontitis are aware that PT may assist in the improvement of glycemic status[208,209]. Patients with DM keep a routine follow-up with the health care professionals; hence the health care professionals possess a better opportunity to educate these patients about the oral manifestations and complications of DM. They can motivate these patients to dissuade from harmful habits like tobacco. A referral to the oral health professional is important to assess the periodontal status and initiate PT if deemed necessary[207]. The oral health professional can also play a crucial role in diagnosis of DM by discerning the typical gingival features in DM. The typical presentation of multiple periodontal abscesses, gingival bleeding and poor response to conventional PT should raise suspicion in the mind of the dentist. Undiagnosed uncontrolled hyperglycemia may be the underlying cause for exaggerated periodontal inflammation[210]. A Thai experimental study employed a combination of life-style change and periodontal care in DM patients. The study outcome revealed an improvement in glycemic control and periodontal status of the participants[211]. Dentist is traditionally considered specifically as an oral health care professional. Periodontal care in DM subjects is seldom considered by medical authorities. This attitude should undergo a dynamic change, wherein the oral care professional should be incorporated as a strategic member in the team for control of DM[212]. The team which disperses proper information about the relationship between DM and periodontal disease should consist of dentists, physicians, diabetes educators. Mass media such as newspaper and television play a key role in everyday life of the masses. The mass media can contribute to betterment in the health of public by the communication of valuable information through educational campaigns, programs and advertisements. The television network in particular has penetrated in all strata of the population constituting an important element. Thus television can sustain positive effects on the health knowledge, attitude and behaviour of the target population. Television programs or advertisements aired for the public health welfare may increase the awareness of the masses about a particular ailment and act as a valuable guide for treatment[213,214]. According to a study in Asian subjects, Tokuda *et al*[215] concluded that there exists considerable association between trust in mass media and health of public. This vertical trust of public on the mass media can be effectively exploited for the education of periodontitis-DM association. In today's age of wireless technology a sizeable world population is facilitated by mobile communication. The number of mobile phone subscribers exceeds 6.8 billion worldwide. In India there are 877 million mobile users. The mobile phones in India maintain a low tariff (1.6 United States dollars per month), prompting a large scale utility for communication purposes. This use is popular not only in the urban but also in the rural parts of India. Hence, mobile phones can be exploited as a powerful tool for health care and treatment compliance[216]. Health related information and follow-up protocols can be conveyed effectively *via* text messaging[217,218]. Text messaging is an effective mode of health education, particularly in rural population lacking computers and internet facility. Moreover, this facility can be utilized by strata of the population possessing basic education[219]. Use of mobile in health intervention is particularly encouraging in low and middle income countries. Mobile communication can be used for enhancement of treatment adherence, appointment scheduling, data collection and evolving a network for health care professionals for effectual collaboration[220,221]. Patients with medical conditions browse the internet to search for the needful information. The internet is utilized as an effective medium to share clinical information and converse with group of patients with the same ailment. Social networking is an important site to share the needful information. Facebook is one of the most prevalent networking sites with more than 400 million registered users across the globe. Such sites have proved to provide satisfactory support and amend the disease management, to ensue favorable outcomes[222,223]. Health care professionals can effectively utilize sophisticated communication devices to spread awareness amongst patients. One such exciting device is the smartphone. Smartphone is widely used by the masses for access of internet, email and data storage, including practicable software application. Management of DM *via* smartphones is an effective tool and holds a bright future[224,225]. In South Korea, Kim *et al*[226] have reported a smartphone application known as "Diabetes NotePad". This application was designed for the purpose of DM self management, recording of glycemic levels and DM education material. The application can be downloaded free of charge and it is showing increased acceptance and enhanced user satisfaction[226]. Gadgets like netbook and smartphone are highly effective for patient counseling, augment patient motivation and self care in management of DM[227,228]. Similarly on these lines an application can be developed, addressing the evaluation and recording of periodontal status at every visit. It can also enclose oral hygiene educational material. The smartphone application can remind the patient about the prescribed dental visit and improve communication with the oral health care professional. Application may also be designed to

render effective dissemination of DM-periodontal disease information. With the evolution of periodontal medicine and substantially cognizant periodontal-systemic association, the role of periodontist has evolved from a "gum specialist" to an important collaborator of the medical care team. By the prevention and treatment of periodontal disease periodontists can salvage potential complications arising due to chronic conditions like DM[229].

CONCLUSION

Oral diseases pose a major challenge to the global public health. It is perceptible that periodontal disease and tooth loss are associated to systemic metabolic disorders such as DM. The past decade has witnessed a plethora of literature unraveling the link between DM and periodontal disease. Various studies have amply elucidated the mechanistic links between the two conditions. It is now discernible that DM has pernicious effects on the periodontal tissues, supporting the tooth. The 2011 New York Academy of Sciences conference on diabetes and oral disease involved the participation of various leading authorities from the fields of medicine and dentistry. The league discussed on the various issues of DM-periodontal disease link and emphasized on the coherent efforts of the medical and oral health professional to achieve optimal outcome of the treatment in DM patients. It is also imperative to counsel the patient and bring home the DM-periodontal disease connection[230]. It is hence pertinent to perform epidemiological survey with standard methodologies. A major part of the survey should include population of developing and poor nations. The periodontal and diabetes health care professional community must embrace the technological innovations of information and communication. Mass media, mobiles, smartphones, internet, various social networking sites are all tools for the improved education about the periodontitis-DM and its compound management. Social support also plays a major role in the sustainability of these patients. It is crucial to fortify the public health plans by diagnosis and treatment of chronic oral diseases such as periodontitis. The common risk factors for both these conditions should be identified and necessary approach implemented. The medical professional should comprehend and affirm periodontitis as one of the occult complications of DM and interpolate the oral health professional as an important team member in the treatment of DM.

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REVIEW

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

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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.

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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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