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Histological profiling of the extracellular matrix of streptozotocin-induced diabetic nephropathy in experimental mice and rats, an analytical study

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Abstract

Diabetic nephropathy (DN) is characterized by dysfunction and a complication of the extracellular matrix (ECM) with an abnormal pattern of Glycosaminoglycan (GAG) synthesis. The present work also intends to monitor and analyse the ECM and GAG alterations responsible for the development of DN by employing streptozotocin (STZ)-induced diabetic models in albino mice. It also evaluates the effectiveness of pharmacological strategies in treating GAG changes. According to the PRISMA guidelines, the articles published between 1992 and 2024 in PubMed, Scopus, Science Direct, and Google Scholar were analyzed studies (n=18) that used experimental models of DN with histological analysis of ECM, which included GAGs only. Staining methods like Alcian blue and Periodic Acid -Schiff (PAS) were used to assess GAG content quantitatively. Some findings that were associated with diabetic conditions, including increased ECM deposition, thickening of the glomerular basement membrane, mesangial hypertrophy, and proteinuria, were elaborated. It was found that such structural alterations may cause GAG dysregulation and lead to renal fibrosis. The effects of propolis and human Mesenchymal stem cells (MSCs) on GAG balance, ECM deposition, and renal function of diabetic models were found. Aberrant GAG expression has also been found to affect the progression of DN directly.

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Introduction

Diabetic nephropathy (DN) is a frequent and severe Diabetes Mellitus (DM) complication; it is diagnosed in 30-40% of patients with diabetes. It is among the top five causes of End-Stage Renal Disease (ESRD) globally (1). A progressive decline in kidney function defines this condition, and the patient develops ESRD if the progression of the disease is not slowed down. The histological changes that occur during DN are an increase in the size of the glomerulus, mesangial hyperplasia, increased matrix production, increased glomerular basement membrane thickness, and tubular interstitial scaring (2). These changes gradually impair the kidney's capacity to filter blood, leading to protein urea, lowered glomerular filtration rate, and hypertension. DNA exposes the involvement of the extracellular matrix in the pathogenesis of DN since alterations in the Extra-Cellular Matrix (ECM) are accountable for the development of glomerulosclerosis and tubulointerstitial fibrosis of DN (3). The ECM is a composite of proteins, glycoproteins, and polysaccharides that form the structural framework of almost all tissues and organs and play an important role in signal trans. The matrix also contains Glycosaminoglycan (GAG), large straight-chain polysaccharides that associate with proteins to form proteoglycans and lend structural support and functional characteristics to the ECM. Under normal kidney function, the ECM regulates the glomerular basement membrane and the interstitial tissue so that the filtration function can be effectively facilitated and nutrients can be exchanged (4).

However, in diabetic nephropathy, chronic hyperglycemia initiates a series of biochemical alterations such as overproduction of Advanced Glycation end Products (AGEs), increase in oxidative stress, and activation of proinflammatory and profibrotic pathways (5). All these factors cumulatively lead to increased synthesis of ECM, deposition of abnormal ECM components, and, above all, alteration in the composition and distribution of GAG. Glycosaminoglycans (GAGs) are anionic polysaccharides that play important roles in many biological functions, such as control of cell behavior, osmotic pressure, and load-bearing capacity (6). These GAGs include heparin sulfate, chondroitin sulfate, dermatan sulfate, and hyaluronic acid, where they are linked to core proteins to form proteoglycans that bind growth factors, cytokines, and other constituents of ECM to regulate cell functions (7). In the kidney, GAGs maintain the structural and functional integrity of the glomerular filtration barrier, especially the charge selectivity properties that bar negative charge proteins such as albumin. In diabetic nephropathy, there is an alteration in the synthesis and degradation of GAGs, which affects the ECM and causes changes in fibrosis. Hyperglycaemia results in the formation of Advanced Glycated End products (AGEs), which modify the structure and function of GAGs (8). Moreover, hyperglycemia affects the balance between the synthesis and degradation of ECM components through the up-regulation of profibrotic cytokines, including TGF-β and CTGF (9). These cytokines promote the production of ECM components comprising GAGs, thus increasing the mesangial area. Rodents are particularly important for the understanding of molecular mechanisms of diabetic nephropathy and for the evaluation of potential therapeutic strategies. Diabetes mellitus is one of the most common chronic diseases; the most common method of obtaining animal models is the use of Streptozotocin (STZ), which destroys pancreatic beta cells and causes hyperglycemia and diabetic complications such as nephropathy (10).

The STZ-induced model of DN in rodents demonstrates several pathophysiologic features of human DN, including hyperglycemia-induced renal dysfunction, enhanced deposition of ECM, proteinuria, and glomerulosclerosis (11). Albino mice are preferred for these studies as their physiological state and response to hyperglycemia induced by STZ is well defined (12). Thus, the present study of DN in STZ-treated mice provided a model system to investigate the effect of diabetes on kidney morphology and function, as well as ECM and GAG synthesis. Therefore, histopathological analysis of the kidneys is essential for assessing the structural remodeling in DN, especially the modification of ECM. Renal histology is necessary for evaluating the structural alterations in DN, including the ECM. Numerous staining techniques are possible, allowing researchers to assess changes in the ECM components and GAGs, collagen, and other proteins in diabetic and non-diabetic conditions. Histological alterations typical for diabetes are increased ECM content in the glomerular and tubulointerstitial compartments in diabetic nephropathy (13). Alcian blue and Periodic Acid-Schiff (PAS) quantify the GAGs and ECM components that would inform the researchers of the extent of ECM hyperplasia and fibrosis (14).

These techniques may help extend current knowledge of diabetic nephropathy and the role of GAGs in renal lesion formation. Because both ECM and GAGs are implicated in the pathogenesis of DN, the current study seeks to establish the histologic change of GAGs in the kidneys of albino mice with STZ-induced DN. This work will further the understanding of specific changes in the individual molecular components of the ECM involved in DN progression and potential treatment strategies. This work will utilize histochemical staining methods to establish the deposition and levels of GAGs in renal sections of STZ-induced and control mice within glomerular and tubulointerstitial regions.

Materials and methods

The present systematic review also follows PRISMA guidelines so that this study can give a brief, non-ambiguous, and credible approach to the histopathological analysis of extracellular matrix (GAGs) in STZ-induced diabetic nephropathy in experimental mice and rats (15).

Search strategy

An intensive search for scientific literature was conducted concerning histopathological analysis of extracellular matrix in diabetic nephropathy using the STZ model. This study searched four databases: Pub Med, Scopus, Science Direct, and Google Scholar. Data collection was conducted between January 1992 and August 2024 to encompass the most up-to-date and relevant research in the area under consideration in this study. Terms like 'diabetic nephropathy,' 'extracellular matrix,' 'glycosaminoglycans,' 'STZ-induced models, ' 'streptozotocin-induced nephropathy,' and 'changes in ECM in diabetes' were used. Two or more keywords can be joined with the help of Boolean operators, including "AND," OR," and "NOT." Further, to check the completeness of the list of studies, the bibliographies of the identified articles were also hand-searched.

Inclusion and exclusion criteria

The inclusion criteria were carefully established to ensure the relevance, quality, and consistency of the selected studies. [1] Type of Studies: The present review only considered the peer-reviewed experimental schemes published in English. GAG alterations concerning ECM were specifically searched within animal models of diabetic nephropathy starting in 1992 till 2024. [2] Animal Model: Particular attention was paid to works that used STZ-induced

diabetic nephropathy models in albino mice to ensure the model's stability. Additional investigations exploring other kinds of rodents, such as Wistar and Sprague-Dawley rats, were considered in the case when they helped identify the profile of GAGs. [3] Outcome Measures: Original articles and case reports that offered the histological characterization of ECM components, especially GAGs, were included if performing histological staining methods such as Alcian blue or Periodic Acid Schiff (PAS).

The exclusion criteria were defined as follows; [1] Type of Disease: For some reason, prospective studies reporting on other types of kidney diseases or complications not directly associated with DN were not considered. [2] Incomplete Data: Ecological and clinical studies that reported inadequate data on ECM or GAGs or insufficient histological characteristics were not considered. [3] Study Design: The literature review, commentaries, conference papers, and research articles non-English research articles were not included.

Data extraction and synthesis

To reduce the risk of biases, data extraction was done separately by two authors. Identified information sources were aspects of the study design, animal model, intervention, histological staining methods, and significant findings concerning ECM/GAGs. The data collected were sorted, epitomizing characteristics of Excel sheets, and then cross-checked to eliminate all possibilities of inconsistency. Given this emphasis on assessing trends, similarities and differences, expected and diverse outcomes, and themes and gaps associated with the current state of knowledge, a narrative synthesis approach was deemed most suitable for the task (Table 1).

Results

The selection of the studies was done systematically in a step-by-step manner. At the start, the databases that were scrutinized yielded 1121 records. Initially, 972 pairs of duplicates were identified and excluded, and 149 studies advanced to the abstract level. Finally, 58 records were removed as they did not provide sufficient information and did not meet the required focus of the studies; thus, 91 records were selected for retrieval. However, because the full texts of 28 studies were inaccessible, the number was reduced to 63 studies that were evaluated for inclusion. After assessing the full text of the remaining 63 studies, 56 were excluded based on the pre-specified criteria, for example, lack of data on GAGs or employment of different diabetic models. In the end, 18 papers were considered for the review and analysis, as shown in Figure 1. The systematic approach facilitated the identification of only the best quality data relevant to the research objectives.

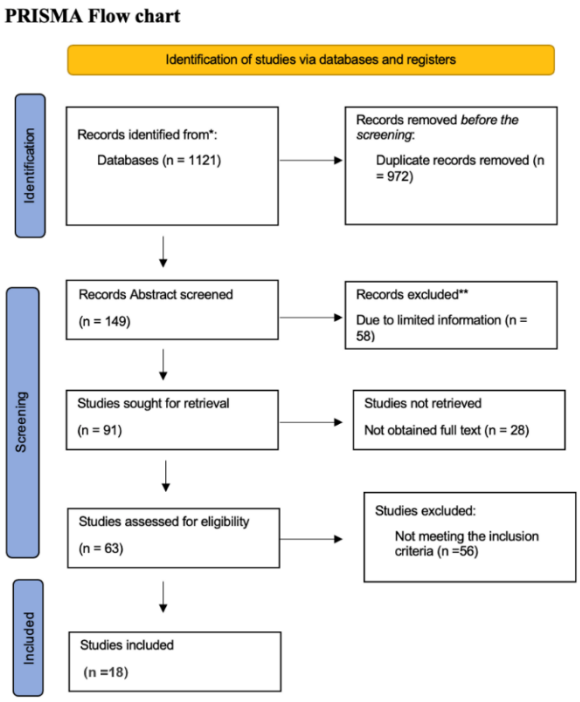

Figure 1: PRISMA flowchart of the systematic approach that demonstrates the facilitation and identification of studies via databases and registers

Structural changes in ECM composition

Structural changes in the extracellular matrix (ECM), particularly those involving GAGs, are critical in the pathogenesis of diabetic nephropathy (DN). The ECM is a network of proteins and polysaccharides that gives mechanical strength to tissues and preserves the organization of organs such as the kidneys. GAGs are the prominent component of the ECM and are pivotal in maintaining the structure of the glomerular filtration barrier necessary to philter blood in the kidneys. Nevertheless, under hyperglycaemic conditions that are inherent in diabetes, there is increased deposition and increased synthesis of the ECM. This process, known as ECM expansion, alters the normal architecture and function of the kidneys. Among the pathological changes in DN, the most obvious is the increase in the thickness of the glomerular basement membrane (GBM) and the increase in the size of the mesangial matrix (Figure 2) (16,33,34).

Table 1: The data and information of collected studies

Author(s)	Year	Aim	Method	Sample Size	Outcome Measures	Study Design	Statistical Analysis	Limitations	Ref.
Wahono et al.	2023	To evaluate a streptozotocin (STZ)-induced diabetic nephropathy model for assessing kidney histopathology, proteinuria, blood glucose, and body weight.	Inducing 75 mg/Kg BW of STZ to male Wistar rats, divided into control and diabetic groups. DN markers such as blood glucose, proteinuria, and histopathology were assessed.	18 rats (n=9 control group) (n=9 diabetic group) divided into 2 groups	Body weight, blood glucose levels, proteinuria, and histopathological changes.	Randomised controlled trial (RCT) using animal model.	ANOVA, followed by post-hoc tests to compare groups.	Limited to male Wistar rats; results may not generalise to other models/species.	(16)
Hafez et al.	2024	To determine the effect of propolis on the alleviation of diabetic nephropathy has been mediated through the study of the effects of propolis on STZ induced diabetic nephropathy in rats.	Twenty-eight days treatment with propolis was done on the diabetic rats produced through injection of STZ. Hence, biochemical, histopathological and ultrastructure changes were examined.	STZ induced diabetic rats Consistently, lipid profiles, antioxidant enzymes, renal cortical morphology as well as blood glucose level.	Lipid profiles, antioxidant biomarkers, renal cortical morphology, and blood glucose levels.	Experimental study with biochemical, histopathological, and ultrastructural assessments.	T-tests and ANOVA for biochemical and histopathological data analysis.	Short treatment period; It is a short-term study, and so the effect of propolis after its long-term use is still unknown.	(17)
He J, et al	2024	To explore the effects of human mesenchymal stromal cells (hUC-MSCs) on STZ-induced diabetic nephropathy in mice.	STZ-induced diabetic mice were treated with hUC-MSCs at 8- or 16-weeks post-induction, and kidney changes were assessed via histology and assays.	Diabetic mice, control groups	Histological assessment of glomerular and renal interstitial abnormalities, autophagy markers.	Interventional study using MSCs with diabetic mouse models.	Tukey's multiple comparison, and One-way ANOVA	Effectiveness of hUC-MSCs may vary based on the time of administration post-induction.	(18)
Alaofi al.	2020	To assess the effects of sinapic acid (SA) on STZ-induced diabetic nephropathy in rats via NRF2/HO-1 pathway.	Rats having STZ-induced diabetic were treated with SA at 20 or 40 mg/kg body weight, and kidney function and histology were evaluated.	24 rats, divided into 4 groups	Kidney function parameters, inflammation markers, oxidative stress levels, and fibrosis.	Experimental study evaluating dose-dependent effects of SA treatment on diabetic rats.	One-way ANOVA and post-hoc with Dennett's test.	Only two doses of SA were tested; further studies needed for optimised dosing.	(19)
Olaniyi KS, et al..	2021	To assess sodium acetate effect on nephrotoxicity in rats having STZ-nicotinamide-induced diabetic, focusing on xanthine oxidase activity.	Diabetic nephrotoxicity was induced in Wistar rats via STZ-nicotinamide, and the effect of sodium acetate treatment was evaluated on renal parameters.	6 groups of Wistar rats (n=6/group)	Renal parameters including xanthine oxidase activity and inflammatory mediator levels.	RCT evaluating sodium acetate effects on diabetic nephrotoxicity.	ANOVA and correlation analysis for renal parameter assessment.	Study focused on a single mechanism (xanthine oxidase); other pathways not explored.	(20)
Sasongko, H., et al.	2022	To analyse inflammation and metabolic profile in kidneys of nicotinamide and STZ induced diabetic rats.	Division of male Wistar rats into STZ induced diabetic and control groups without or with nicotinamide treatment, monitored for 6 weeks.	Wistar rats divided into diabetic and control groups	Metabolic profile, kidney inflammation, survival rates, and inflammation levels.	Comparative study monitoring metabolic and inflammation profile in diabetic rats.	Data were expressed as means ± SDs. One-way ANOVA and Duncan's post hoc test was conducted.	Nicotinamide did not significantly reduce inflammation despite improving survival rates.	(21)
Akinlade, O.M, et al.	2021	To compare the effects of high-dose Streptozotocin (STZ) low doses after high-fat diet induction on Diabetic Cardiac Autonomic Neuropathy (DCAN).	Two methodologies were employed in Wistar rats; for T1DM with STZ 50mg/kg and for T2DM using high fat diet for 8weeks with STZ 25mg/kg daily for 5 days. DCAN features were assessed using invasive biomarkers, histology patterns, and cardiac nerve densities.	84 Wistar rats	Induction rate of diabetes, weight loss, c-peptide level, insulin level, cholesterol, HOMA, catecholamine, choactase, nerve Grow factor, and cardiac nerve density Animal model experimentation using Wistar rats.	Experimental study on animal models (Wistar rats)	Data were analysed using comparison between experimental and control groups, considering factors like diabetes induction rate, biochemical markers, and histological features.	Potential variability in diabetes induction methods, small sample size limiting generalisation, need for further studies to confirm results in other animal models and humans.	(22)

Continue of Table 1

Author(s)	Year	Aim	Method	Sample Size	Outcome Measures	Study Design	Statistical Analysis	Limitations	Ref.
Gomes et al.	2014	To evaluate the clinical neproprotective efficacy of GAG-based drugs in rats with experimentally-induced diabetic nephropathy.	Controlled experimental study	Adult male Wistar rats were used in the study undergone a diabetic and control protocols (n =20).	Damage to podocytes, transcription of genes encoding proteoglycan core proteins and their enzymes, expression of TGF-β, infiltration of macrophages, Albuminuria, mesangial matrix deposition, tubulointerstitial expansion.	Experimental study on animal models (Wistar rats)	One-way ANOVA and Tukey's post-test were applied to analyse data and compare between experimental and control groups for biochemical markers, and histological features.	Limited to male Wistar rats; results may not generalise to other models/species.	(23)
Ceol et al.	2000	Rat model of diabetic glomerulosclerosis was used to investigate whether the chronic administration of mH GAG with the minimum anticoagulant effect counteracts the manifestation of DN. To determine whether GAG/mH can pull down the overexpression of TGF-b1 due to the disease.	In vivo experiment with cultured cell studies.	40 male Sprague-Dawley rats	TGF-beta1 mRNA overexpression, glomerular and tubular matrix accumulation, albuminuria.	Experimental study on Sprague-Dawley rats that used new data on TGF-b1, from previous reports.	One-way ANOVA were applied for the in vitro studies, for morphometric analysis of in situ hybridisation and for immunohistochemical data and Bonferroni's test was applied for multiple comparisons.	Limited to male Sprague-Dawley rats; results may not generalise to other models/species.	(24)
Gambaro et al.	1992	To investigate the role of exogenous GAGs in STZ induced diabetic nephropathy	In vivo experiment with diabetic rats.	45 male Sprague-Dawley rats	Kidney morphometric, and biochemical analysis, morphological and functional abnormalities such as Glomerular basement membrane thickening, Albuminuria, glomerular anionic charge reduction.	An experimental study on Sprague-Dawley rats model. Used administration in long-term of two low-molecular weight dermatan sulphate, and heparin and GAGs.	One-way ANOVA for albuminuria, creatinine clearance and glomerular filtration rate (GFR) and Two-way ANOVA for morphometric parameters.	Limited to male Sprague-Dawley rats; results may not generalise to other models/species.	(25)
Gambaro et al.	1994	To investigate the changes in GAG deposition over time and relate this to the degree of permeability alteration, which can be assessed using dextran clearance techniques. In order to understand the involvement of GAGs to revert DN and the impact of GAGs on renal ECM production.	Controlled experimental study	40 male Sprague-Dawley rats.	Kidney morphometric and biochemical analysis, morphological and functional abnormalities such as levels Albuminuria, glomerular basement membrane thickness and mesangial cell proliferation.	Sprague Dawley rats were studied for 12 months: two non-diabetic control groups, three STZ diabetic groups, two of received aGAG formulation, At five and twelve months, the biochemical, histopathological, and assessments	One-way ANOVA was performed for biochemical, histopathological, and assessments, two-way ANOVA for morphometric parameters, and the autoradiographic data. Bonferroni's test was applied for multiple comparisons	Limited to male Sprague-Dawley rats; results may not generalise to other models/species.	(26)
Mathison Natera et al.	2010	To evaluate the impact of PPS – Pentosan Polysulfate Sodium (PPS), which is the semi-synthetic glycosaminoglycan with the lowest effect on anticoagulant activity to study effects of kidney involvement in streptozotocin diabetes in rats.	Controlled experimental study.	Three groups of albino Sprague-Dawley rats.	Kidney morphometric analysis and morphological and functional abnormalities such as levels of urinary albumin excretion.	Animals were randomly allocated to three groups: control, STZ and STZ + PPS.	GraphPad Prism software was used to analyse mean ± SEM. The comparison between analysis of variance (ANOVA) was applied to the arithmetic means of the groups.	Limited to albino Sprague-Dawley rats; results may not generalise to other models/species.	(27)

Continue of Table 1

Author(s)	Year	Aim	Method	Sample Size	Outcome Measures	Study Design	Statistical Analysis	Limitations	Ref.
Jafri et al.	2024	The aim of this study is to investigate the effect of five GAGs: heparin, heparan, chondroitin, dermatan, hyaluronan in modulating cytokine IL-1β-induced mRNA expression IL-6 and IL-8 and their efficacy in decreasing inflammatory cytokines IL-6 and IL-8.	In vitro experimental study	Grouping to 5 well known GAGs group i.e. heparin, heparan sulfate, dermatan sulfate, chondroitin sulfate, and hyaluronan.	The inhibitory effect of GAGs on the IL-1β-stimulated mRNA expression of IL-6 and IL-8.	The present study focused on working with five typical exogenous GAGs among all the GAGs present.	GraphPad Prism version 9.4 (GraphPad, Boston, MA, USA) was used to perform the Student t-test with 95% CI	The findings provide the evidence base for further studies that would determine the efficacy of GAG's application in patients with conditions that require inflammation reduction	(28)
Eita et al.	2022	Evaluation of PPS in DN of rats with Losartan (LSR).	Controlled experimental	60 male Sprague–Dawley rats	Assessment of kidney function tests and biochemical analysis such as renal functions, albuminuria and renal histopathology were evaluated	Animals were divided into six groups: control group, untreated STZ induced diabetic groups, LSR-treated diabetic group and PPS-treated diabetic group and combination-treated diabetic group.	Data were expressed as means ± SDs. One way ANOVA was applied to assess the statistical significance of differences	Limited to male Sprague-Dawley rats; results may not generalise to other models/species	(29)
Lujain et al.	2022	This study aimed to investigate the impact of Rumex nervous (R. nervosus) methanol extract in preventing T1DM-induced nephropathy through STZ and whether its efficacy is associated with Nrf2 activation.	Controlled experimental study	Wistar rats were randomly selected for the study and adult male and female rats were included for the study and they were divided into 7 groups.	The general tests like kidney function tests which includes Blood Urea Nitrogen (BUN), Creatinine (Cr), albumin level and histopathological examination of the kidney were done.	The rats were divided into 7 groups, namely the control, control + R. nervosus, T1DM: diabetic rats + R. nervosus For the fourth, fifth and sixth groups T1DM +R. nervosus and for the latter T1DM +R. nervosus +brusatol	Data were presented as means ± SD. Kolmogorov-Smirnov test used to test the normality. The use of the one way ANOVA test was conducted in the analysis of the results. The post hoc test that was employed in this study was Tukey's and it determined the levels of significance.	Further studies may be conducted in Nrf2 knocked out animals as well as cultured mesangial cells. The studies showing that which aspects are dynamically involved in the regulation and activation of Nrf2 for future research should be considered.	(30)
Kiran et al.	2012	To analyse progression of diabetic neuropathy in rats that are induced by streptozotocin-induced diabetic over a period of time(several months)	Controlled experimental study	23 Male albino Wistar rats	Kidney morphometric and biochemical analysis, morphological and functional abnormalities such as kidney weight, microalbuminuria, urinary GAGs, urinary type IV collagen, glomerular area, glomerular volume.	Experimentally-induced diabetic rats were grouped based on fasting blood glucose levels. Various basic and kidney-related parameters such as kidney weight, urinary excretion of GAGs and total kidney GAGs, histopathology, glomerular area and volume were examined in control and diabetic rats.	By using paired, two tailed students' "t" test. Correlation analysis was made by linear regression analysis using Microsoft Excel.		(31)
Poluzzi et al.	2019	To detect new coreceptors and signaling outcomes of circulating biglycan that cause leukocyte recruitment in kidneys via TLR2/4 pathways	Controlled experimental study, In vivo and in vitro experimental study. A transgenic mouse model.	6 Transgenic mice	Leukocyte infiltration in kidneys, Mice and human peripheral blood macrophages, Autophagy in macrophages through Biglycan-TLR4-CD44-axis	Biglycan was de novo overproduced by hepatocytes. The synthetised and released biglycan was accumulated in the kidneys and detected by IHC.	Data were expressed as means ± SEM for in vivo data and ± SD for in vitro data and One-way ANOVA test with Dunnett's significance test.	Limited Transgenic mice; results may not generalise to other models/species.	(32)

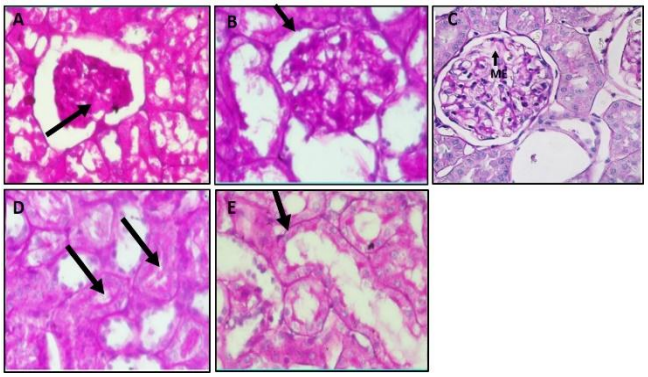

Figure 2: Histopathological Periodic Acid-Schiff (PAS) stained micrographs representing the mesangial area in glomeruli and the tubulointerstitial area from rats with Streptozotocin-induced diabetic nephropathy. Modified and adapted from (16,17,35). The PAS-stained sections (A, B, C, D) in Figure 2 show the glomeruli with mesangial cells that are within normal limits (A), slight GBM thickening (B), mild increase in mesangial expansion (ME) in glomeruli (C) (magnification ×400). The tubule interstitium has eosinophilic materials (D) thickened tubular basement membrane (E) (16,33).

Modifications were made in these studies on STZ-induced diabetic rat models (19). The overexpression of enzymes producing ECM components such as GAGs resulted in the deposition of matrix materials, which thickened the GBM and enlarged the mesangial matrix, two hallmarks of DN progression (19). The structural changes affect the ability of the kidney to filter and result in proteinuria and progressive kidney disease. GAG matrix's water content, the selective permeability of the molecular sieves' sieves extracellular matrix's water content, and the molecular sieves' selective permeability in the kidney (19). In diabetic nephropathy, high blood sugar levels cause the production of GAGs to increase and change the chemical makeup of GAGs, disorganizing the structure. Consequently, the structure of the kidney's filtration barrier is disrupted, and proteins, including albumin, are passed in the urine, a characteristic of DN (22). This process marks the beginning of structural ECM degradation that, in turn, leads to additional renal injury.

Subsequent research has investigated possible pharmacological therapies to reverse these changes in ECM. Propolis is a natural resinous substance with antioxidant and anti-inflammatory properties and its effects on STZ-induced diabetic rats (36). Their study showed that propolis treatment alleviated the reduction of ECM integrity to some extent. Propolis was influential in suppressing excessive GAG synthesis and adequately organizing the GBM and mesangial matrix. This suggests that modulation of the dysregulated GAG pathways might help manage the structural and functional decline characterizing DN. Since propolis may help to stabilize ECM composition, such therapies may help to avoid the detrimental impact of hyperglycemia on the matrix.

GAG-based treatments such as fucosylated chondroitin sulfate (FCS) and commonly prescribed GAG, enoxaparin (ENX), pentosan polysulfate sodium (PPS), a semi-synthetic glycosaminoglycan, have shown reno-protective by reducing mesangial expansion, modulating the expression of enzymes involved in GAG biosynthesis (Figure 3) (23,25), by preventing the tubular basement membrane thickening and the loss of cytoarchitecture (Figure 4) (23,27) and by reducing albuminuria, the mesangial matrix accumulation and collagen deposition in the glomerulus (Figure 5) (24,29,37).

The prevention of the thickening of glomeruli and reducing the expansion of the mesangial matrix are achieved by inhibition of mesangial cell proliferation and modulation of the expression of key mediators like TGF-β1, which are involved in kidney remodeling and fibrosis (Figure 6) (23). These findings suggest the potential therapeutic use of GAGs in mitigating the progression of DN.

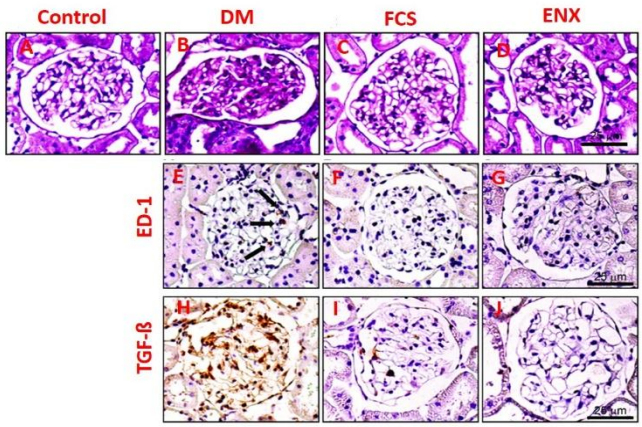

Figure 3: Histopathological PAS-stained and Immunohistochemical micrographs of the mesangial area in glomeruli from rats with Streptozotocin-induced diabetic nephropathy. Panels A-D represent PAS-stained glomerular micrographs, where a significant increase in the mesangial area is observed in the diabetic (DM) group (B) compared to the control group (A). No such increase is seen in the DM groups treated with FCS (C) or ENX (D). Panels E-G: Representative micrographs of glomerular sections stained with monoclonal mouse anti-rat antibody (ED-1), indicative of macrophage infiltration, by black arrows, in DM glomeruli (E) shows an enhanced micro-inflammatory response in the diabetic milieu when compared to control group, which is not shown, and FCS- (F), and enoxaparin- (G) treated rats. Panels H–J: Micrographs of glomerular sections stained for TGF-ß. Bar = 25 µm. Modified and adapted from (23).

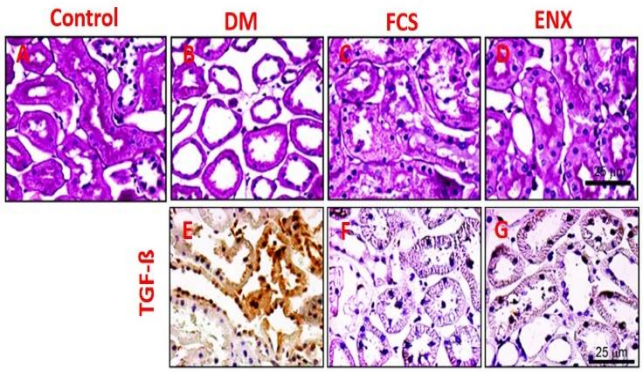

Figure 4: Histopathological PAS-stained and Immunohistochemical micrographs representing the tubulointerstitial area from rats with Streptozotocin-induced diabetic nephropathy. Panels A–D depict PAS-stained renal sections in Figure 4, representing the expansion of the interstitial area with tubular dilation in diabetic (DM) group B, compared with control animals A and GAG-treated groups, C and D. Panels E-G show the tubulointerstitial area that displayed increased localization of TGF-ß in the DM group compared to controls not shown and both GAG treated groups. Bar = 25 µm. Modified and adapted from (23). In Figure 5, panel (A) depicts PAS-stained renal sections from the control, DN, and (DN +SUL) groups, representing an increased glomerular surface area, mesangial expansion, thickening of GBM and Bowman's capsule, and increased deposition of matrix proteins in nuclei-free areas of the mesangium in glomeruli (arrows) compared with the control group. Panel (B) depicts Masson trichrome (MTC) stained renal sections from the control, DN, and (DN +SUL) groups, representing a reduced Collagen deposition in the glomerulus in the DN + SUL group compared with the high accumulation levels of Collagen in the DN group. Magnification: 400×. Modified and adapted from (37).

Abtoversynthesis of GAG aggravates kidney fibrosis and impairs the structure (38). This shows that there is a need to target ECM enlargement and GAGs to slow down the progression of DN. The proposed structural changes in the ECM and significantly increased synthesis of GAGs are the keys to developing diabetic nephropathy. Hyperglycaemia fosters GAG deposition that alters the organization of the kidney and increases the thickness of the GBM and the mesangial cells. It is possible that therapeutic targeting of ECM components could aid in decreasing the disease progression rate and maintaining renal function. For instance, the administration of glycosaminoglycan can normalize renal matrix composition by modifying collagen gene expression and increasing glomerular 35S-sulfate incorporation (26), which are important for maintaining renal structure and function.

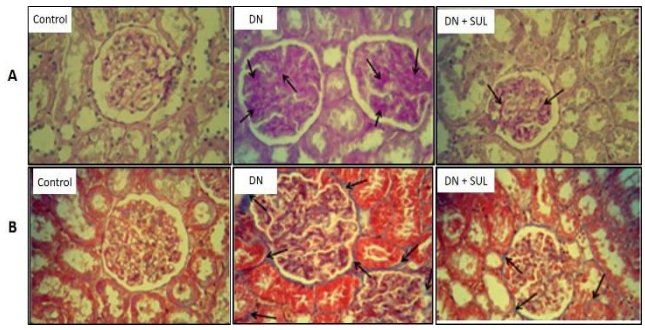

Figure 5: Histopathological PAS-stained (A) and Masson trichrome (MTC) stained (B) micrographs representing the tubulointerstitial area from rats with Streptozotocin-induced diabetic nephropathy. Similarly, the systemic impact of ECM overproduction, which has been quantified mainly regarding collagen accumulation, is a sign of fibrosis (23,38). The other major structural protein of the ECM is collagen, and its excessive deposition causes kidney fibrosis, which is a late-end-stage DN complication (23). The Sirius Red staining area in Figure 6 shows a trend towards the increased deposition of collagen fibers in the interstitial area in the DM animals (B) compared to the other groups, as shown in A, C, and D. Bar = 25 µm. Modified and adapted from (23).

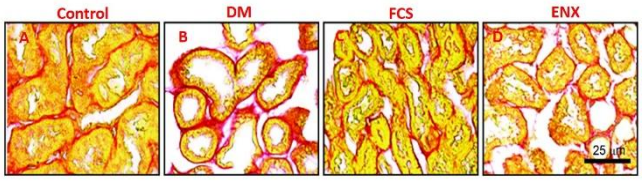

Figure 6: Histopathological Sirius Red-stained micrographs of the tubulointerstitial area from rats with Streptozotocin-Induced Diabetic nephropathy.

Correlation between GAG modifications and renal dysfunction

The alteration of GAGs in the ECM is associated with renal dysfunction in diabetic nephropathy. GAGs participate in the charge selectivity of the glomerular filtration barrier in the kidneys. This barrier helps to keep negatively charged proteins like albumin from spilling into the urine. However, in the context of diabetes, which is associated with hyperglycemia, the GAGs suffer structural and functional changes that weaken the structure of the filtration barrier. The effect of this degradation is a rise in protein permeability and proteinuria, a characteristic of early diabetic nephropathy.

Diabetic rats, when treated with, were well correlated with the GAG changes. The total amount of GAGs in the kidney depicted a significant reduction in diabetic rats compared to controls (31). Hyperglycaemia changed the

organization of GAGs within the glomerular filtration barrier and removed charge selectivity. Consequently, the proteins usually trapped within the blood are freely filtered through the blood filter and appear in the urine (31). This increase in proteinuria is one of the first and earliest markers of renal dysfunction in diabetic nephropathy (DN) and is caused by the degradation of GAGs. However, it has been proved that restoring GAGs can enhance renal dysfunction. Renal function markers such as proteinuria, serum creatinine, and blood urea nitrogen (BUN) were decreased after propolis treatment, in addition to the effects on GAG dysregulation (21). Because of the beneficial action of propolis on GAG, the filtration barrier was abated, and proteins were no longer leaking in the urine than before, indicating that the overall kidney function was improved. These outcomes highlight the role of GAGs in regulating renal function and suggest that approaches that enhance GAG homeostasis may help delay or arrest the development of DN.

MSCs also substantiate the relationship between GAG modifications and renal dysfunction. The impact of hUC-MSCs on diabetic mice demonstrated that replenishment of GAGs in the ECM ameliorated proteinuria and renal function (18). This study points to the application of regenerative therapies that work on GAGs to conserve kidney function in DN.GAG modification is central to kidney disease in diabetic nephropathy (18). Thus, the recovery of GAG integrity may explain the effects of propolis and MSCs in decreasing proteinuria and preserving kidney function. The inhibition of GAG degradation is crucial for treating renal dysfunction in DN.

Applicability of findings made on animal models for human pathology and tissues involving GAGs

The information available from animal models, mainly from STZ-induced diabetic nephropathy DN, serves as good background knowledge on the effects of glycosaminoglycans (GAGs) on human illness. GAGs also have structural support functions in any tissue. This is particularly significant in the context of kidney function since any alteration in the composition of ECM can disrupt the filtration barrier function. In the paradigm of DN, GAG accumulation contributes to ECM enlargement, mesangial cell hyperplasia, and an increase in the thickness of the GBM - alteration also detected in human patients with DN (1, 2). Using an animal model (16) revealed that alteration in the expression of GAG caused changes in renal protein excretion; this is an early sign of DN in human patients (16,17). These findings are significant because they suggest that the qualitative alterations found in GAG molecules play a role not only at the structural level of the kidney but also at a functional level. More definitively, GAG interventions, including natural compounds propolis or MSCs, which can rebalance the ECM, displayed potential for improvement in renal outcomes in rodent models (7,9). This opens the likelihood that similar therapies might also work in humans, for example, in delaying the advancement of DN and the development of ESRD.

Nonetheless, there are several limitations to translating these findings from animal models to human uses. Despite this, after comparing the structural and functional features of rodent models and human DN, differences in anatomy become an inevitable consideration. They have their way of metabolism and immunity towards diseases, which in many cases may vary with those of human beings, to impact how diseases progress and are treated. Therefore, although GAG-targeting therapy appears promising, more research is necessary to demonstrate the therapy's effectiveness and safety to patients (6).

Role of GAGs in promoting renal inflammation and fibrosis

The significant pathological changes in DN include inflammation and fibrosis, and glycosaminoglycans have been proven to affect these processes significantly. GAGs are rather involved in the modulation of cytokines and growth factors activities, which are responsible for inflammatory and fibrotic processes occurring in the kidney, heparan sulfate most significantly. Anti-inflammatory Biglycan is a modulator glycoprotein containing two glycosaminoglycan chains, either chondroitin or dermatan sulfate, that stabilizes HIF-2a, a hypoxia master regulator of the cellular response in the kidney (39). Biglycan-TLR4-CD44-axis triggers the polarization of M2 anti-inflammatory macrophage types, leading to the resolution of renal inflammation (32). A transgenic mouse model of steady-state overexpression of human biglycan in hepatocytes that causes a continuous release of biglycan into the circulation, featuring increased numbers of F4/80-positive macrophages in the kidney as detected by IHC (32).

Diabetic conditions are characterized by hyperglycemia, which affects GAGs and promotes increased inflammatory signaling and fibrosis. Both pathological processes contribute to the progression of renal damage, and knowledge of how GAGs contribute to these pathways is crucial for developing new therapeutic approaches to DN.

Inflammation cytokines are one of the significant areas in which GAGs affect kidney pathology in collaboration with GAGs. Degraded GAGs can lead to increased inflammation and cytokine dysregulation, as seen in conditions like chronic kidney disease (CKD) and acute kidney injury (AKI), suggesting that GAGs can modulate inflammatory responses (28,40). Usually, GAGs, like heparin and hyaluronic acid, are involved in cell signaling and modulation of cytokine expression, such as interleukin-6 (IL-6), IL-8 which would otherwise saturate the tissue with inflammation signals (28,29,40). This modulation is important in achieving normal kidney function. However, in diabetic nephropathy, the GAG dysregulation enhances these cytokines with chronic inflammation observed in the kidneys

of patients with DN (21). Diabetic STZ rats that induced the levels of IL-6 and TNF-α were significantly increased in these animals since GAGs modulate the production of these cytokines (21). Accordingly, in this hyperglycaemic model, GAG degradation or modification resulted in cytokine dysregulation and persistent inflammation within the kidney.

This persistent inflammation leads to severe injury to the renal tissues, especially the glomeruli and renal tubules, which are essential to kidney function. The accumulated effect of GAG dysregulation is that chronic inflammation raises cellular damage and cell death and ultimately affects the kidneys' capability to remove waste products from the bloodstream (21). Cytokine activity that caused inflammation within the kidney tissue contributed to glomerular and tubular lesioning. Changes in the structure of the kidney affect its efficiency and result in the characteristics of DN, including proteinuria (the presence of protein in the urine) and high serum creatinine levels (16).

Another critical outcome associated with GAG accumulation or its abnormal turnover is fibrosis in DN. Fibrosis is marked by the deposition of excessive ECM proteins such as collagen and progressively replaces normal renal tissue with fibrotic tissue. If fibrosis is allowed to continue, the kidneys become dysfunctional, resulting in end-stage renal disease. Changes in GAG levels in diabetic mice were strongly correlated to the augmentation of collagen content in the renal tissue, representing one of the significant hallmarks of renal fibrosis (16). The same study identified that diabetic mice produced excessive collagen due to chronic inflammation through GAG regulatory pathways disruption (38). This led to a progressive change in the normal renal architecture to more fibrotic and stiff ECM components such as collagen. This progressive fibrosis results in a gradual decline in renal function because the fibrotic tissue cannot filter and remove waste products needed to maintain the body's homeostasis (38).

GAG dysregulation not only leads to a continuation or aggravation of fibrosis due to the stimulation of ECM deposition but also aggravates chronic inflammation, thus forming a vicious circle. It also shows that chronic inflammation leads to fibrosis, which sustains inflammation, which all progresses to deteriorate renal function. Against this background, the function of GAGs is critical because they are considered the mediators that prevent excessive or insufficient activation of these processes in forming the ECM and regulating cytokines. In normal circumstances, GAGs maintain equilibrium, but when these are affected by diabetes, they contribute to DN (38). Potential therapeutic approaches that directly or indirectly affect the pathways associated with GAG dysregulation were identified to affect xanthine oxidase, an enzyme implicated in the dysregulation of GAGs, and significantly decreased inflammation and fibrosis in diabetic rats. Xanthine oxidase is involved in the synthesis of ROS, which are associated with renal inflammation and oxidative stress. Thus, it may be possible to prevent the harm done by GAG dysregulation by inhibiting xanthine oxidase. The authors found that diabetic rats treated with xanthine oxidase inhibitor had lower levels of proinflammatory cytokines, less collagen accumulation, and better renal function. This points towards the probability of preventing GAG-mediated pathways to protect against the negative impacts of inflammation and fibrosis within diabetic nephropathy (20). As observed in this study, GAGs are involved in regulating cytokine activity and collagen deposition, which can be halted through these molecules. The approach to targeting GAGs can be therapeutic in that it may help to ameliorate inflammation and fibrosis in DN and potentially slow the progression of the disease.

Discussion

This systematic review explores the role of ECM, the critical structural component of tissues and the modulator of organ function with significant roles in the kidneys. Several previous studies have proposed that the development of DN is associated with changes in the structure of the GBM matrix, particularly GAGs (21). Diabetes mellitus causes high blood glucose levels, which in turn brings about increased synthesis and deposition of ECM proteins, causing alterations in the glomerular ultrastructure, such as increased GBM thickness and mesangial matrix (41). These changes alter the dynamics of DN by reducing the effectiveness of the filtration membrane and, therefore, bringing about proteinuria and other associated renal dysfunctions.

Among various examples, studies employing the streptozotocin (STZ)-induced diabetic rat secondary models show that hyperglycemia enhances the enzyme-catalyzed formation of GAGs, or glycosaminoglycans, which make up the core of the ECM and are involved in the renal change (42). It was found that GAG synthesis leads to the dysregulation of ECM and is consequently implicated in DN development. In diabetic conditions, the GAGs arrangement blunders and leads to the poor filtration of the kidneys; abnormally huge slices of protein like albumin are filtered through the urine, which is a sign of early renal disease (43).

Some interventions targeted at reversing ECM alterations have been described. For example, propolis, an antioxidant and anti-inflammatory substance, has been prospective for the diminution of ECM in STZ-induced diabetic rats (29,44). Treatments using propolis show that GAG overproduction was reduced, and the GBM and mesangial matrix's structural organization was repaired, enhancing kidney function (45). Such therapies provided the foundation for the idea that managing ECM composition would truly act as an effective approach to slowing DN progression.

Subsequent studies have characterized collagen accumulation in ECM overproduction as a decisive factor of kidney fibrosis of DN, which usually takes a later stage of the disease (46). Therefore, some approaches can inhibit ECM enlargement with simultaneous GAG productive to

avoid fibrosis and preserve renal function (47). The observation made in this research helps justify the asserted hypothesis that GAG pathways should be resolved so that structure alteration linked to DN does not occur. The effects of hyperglycemia on syntheses of ECM, such that the glomerular filtration barrier is lost and proteinuria and renal dysfunctions result, underlines the importance of tactics directed at local ECM and GAG synthesis to maintain kidney integrity (48).

GAGs play a significant role in the mechanism of the charge selectivity of the glomerular filtration barrier and thus protect against the passage of negatively charged macromolecules such as albumin into the urine (49). All capillary endothelia, including those of the glomeruli, possess a luminal cell surface layer (ESL) composed of glycoproteins, glycolipids, proteoglycans (PGs), and GAGs. Previous studies have shown that an intact ESL is important for a normal filtration barrier (50,51).

In DN, glycaemic alterations change the structural and functional characteristics of GAGs, affecting the filtration membrane and damaging the ESL, causing proteinuria, the earliest sign of renal pathology. STZ-induced diabetic rat models also demonstrated that hyperglycemia in rats is responsible for altering the distribution of GAG and subsequent leakage of proteins and renal damage (52). This early-stage dysfunction is a strong and inverse predictor of DN's progression and makes it crucial to correct GAG abnormalities. Treatment with propolis has effectively alleviated proteinuria and positively changed serum creatinine and blood urea nitrogen, which is an index of renal function (53). Additional work on MSCs also demonstrated their reparative actions on GAGs and the decrease of proteinuria in diabetic mice, implying that regenerative approaches might preserve renal function in DN (54). Changes in GAG synthesis and degradation in early DN stages affect renal dysfunction, thus encouraging the use of treatments that correct the changes in the level of GAG to reverse the renal dysfunction (55).

Generalized nodular sclerosis, also known as subcutaneous hidradenitis, is representative of DN; accordingly, GAGs are implicated in inflammation and fibrosis in affected tissues (56). GAGs are also abnormally expressed under diabetic circumstances to stimulate cytokine production and sustain a state of uncontrolled inflammation in the kidneys. These GAGs typically regulate cytokine interlinkage, such as interleukin-6 (IL-6) tumor necrosis factor-alpha (TNF-α), and in the DN disease model, such cytokines become overstimulated (57). It has been reported that the increased concentration of IL-6 and TNF-α was associated with GAG in STZ-induced diabetic rats (58). GAG degradation is involved in glomerular and tubular inflammation, whereas fibrosis, defined by increased ECM components like collagen, is linked to GAG dysregulation (59). Dysregulation of GAG has been identified to relate to enhanced collagen deposits and fibrosis in diabetic models (60). With increases in fibrosis, functional, normal renal parenchymal tissue decreases and may be associated with the development of renal failure (61).

The approaches modulating GAG-dependent signaling have positively impacted inflammation and fibrosis in DN (62). For instance, using xanthine oxidase inhibitors associated with GAGs' improper distribution helped decrease inflammation and fibrosis in diabetic rats (63). These models indicated that xanthine oxidase inhibitors can alter cytokine levels, decrease collagen content, and improve renal function, which is standardized in these models, thereby showing a possibility of targeting the GAG pathway to check DN progress. The results indicate that the dysregulation of GAGs is implicated in inflammation and fibrosis in DN, further supporting the consideration of GAG-targeting therapies as potentially able to slow DN progression and preserve renal function.

However, (64) mentioned that the purpose of this work is to screen the alterations of the extracellular matrix (GAGs) staining patterns in the rodent diabetic nephropathy model induced by STZ. These include methods like using STZ (streptozotocin 60 mg/kg) to induce diabetes in the Wistar rats. Moringa oleifera extract was given at the dosage of 200 mg/kg through gavaging. The experimental rats comprised a total of 50 rats, which were divided into five groups of 10 rats each. Chronic toxicity assessment parameters include tissue morphology assessment monitoring, biochemical characterization (BGL, TAC, MDA), and gene expression test (pdx1, GLP-2, and VEGF) (64). The study was experimental analytical in which ANOVA post-hoc tests were conducted. The limitations include a single-species study, no consideration of chronic effects, and, overall, generalized use of biomarkers.

Another study investigated developmental changes in the pancreas from birth to puberty, with an emphasis on endocrine beta and alpha cells (65). Seventy-two adult male albino rats were used in this study, six of whom were grouped according to age (65). Histological examination and immunocytochemical expressions of the pancreatic tissue were assessed. Both serum insulin and glucagon levels were quantified by ELISA. The study had a fully experimental design with a random sampling technique, and the data collected were subjected to ANOVA with Duncan’s test using a 0.05 level of significance. What was observed is that pancreatic development and structure differentiation continued after birth. Some of the limitations of the study involved the use of only one species, the absence of functional assays, and a predetermined short duration of observation, thereby limiting the versatility of the outcomes to other species and or distant effects.

However, a study was conducted to assess the impacts of melatonin (MEL) on the vascular complications of diabetic rats with regard to the changes in AT1R, MasR, and ACE2 gene expression and aortic reactivity (66). Male albino rats

were used, and the groups included a non-diabetic group, STZ-induced diabetic, and MEL-treated diabetic groups. qRT-PCR was used to measure gene expression, and the organ bath method was employed for vascular reactivity assay. 86 rats, some of which were subjected to molecular study, physiological test, and histological examination, respectively (66). It was a controlled experimental design. MEL helped raise the endothelial function, change gene expression, and dilate the vessels. Limitations include a small sample size, a single-dose MEL regimen, and a short study duration.

Another research sought to determine the pathology changes caused by various methods of diabetes induction in rats (67). Six groups of adult male albino rats were selected for this study; they include a control group, an alloxan-induced diabetic group, a streptozotocin (STZ) induced diabetes group, a high fructose diet fed and alloxan-induced diabetes, high fructose diet fed and STZ-induced diabetes, and alloxan combined with STZ induced diabetes. Tissues in the pancreas, liver, and intestine of the animals were taken and subjected to histological analysis post-experience. There were significant histomorphological changes in blood glucose and pancreatic islets, hepatocyte necrosis, and intestinal villi (67). Variations include no attempt to perform long-term follow-up assessment and the absence of biochemical markers, and the study was conducted on only one animal model, which could be a limitation in translating it to human diabetes.

The findings of another research seek to explain the impact of zinc oxide (ZnO) and chromium oxide (Cr_2O_3) nanoparticles on glucose tolerance tests in diabetes mice (68). The diabetic condition was produced by alloxan, and the nanoparticle treatments were given for one month. It was observed that glucose and HbA1c lowered and insulin and C-peptide raised in the treated group; however, the maximum response was seen to be in the group having combination therapy. Statistical analysis confirmed significant improvements ($P<0.05$) (68). These findings prove that ZnO and Cr_2O_3 nanoparticles could improve glycemic control, which can be useful for diabetes treatment, but more research has to be conducted to determine the long-term side effects of these nanoparticles.

Another research seeks to assess the effects of Hylocereus polyrhizus (dragon fruit) skin on alloxan-induced diabetic Wistar mice (69). There were three groups, and each of them was given alloxan, peel extract in a dose of 100mg/kg and 300 mg/kg, glibenclamide at a dose of 600 mg/kg, and control. The experimental animals used in the study were thirty mice. Haemoglobin, cholesterol, and triglycerides of outhouse workers were taken on the first, seventh, and fourteenth days of work (69). The results demonstrated the effectiveness of the various treatments in decreasing the blood glucose level in the overall diabetic control groups, and the most fulsome results were noted from days 7 and 14. The results yield the proposition that soluble dragon fruit peel extract can be an effective natural remedy for controlling diabetes, and further studies are required.

Conclusion

Diabetic nephropathy is one of the leading diabetes mellitus complications and has serious consequences such as ESRD. This study has comprehensively discussed the structural and functional alterations of the ECM and GAGs involved in DN. The study postulates that due to hyperglycemia, ECM expands and causes structural changes like the glomerular basement membrane's thickening and the mesangial matrix's enlargement. Since GAGs are components of the ECM, these molecules are involved in the maintenance of the charge selectivity and structural organization of the filtration barrier. In diabetic conditions, the synthesis and organization of GAGs are dysregulated and interfere with the kidneys' filtration mechanism, thereby causing proteinuria and renal dysfunction. The outcomes derived from STZ-induced diabetic rat models suggest that the abnormalities of GAG are the key causative factor to the DN. Research has shown that high blood sugar levels lead to increased secretion of enzymes that build ECM and severely affect the kidneys. These structural changes influence the filter rate in the kidney and, therefore, result in proteinuria-a feature that is distinct from DN. Furthermore, persistent hyperglycaemic conditions cause inflammation and fibrosis due to changes in the activity of cytokines and collagen deposition, which GAGs regulate. Thus, the dysregulation of GAGs not only worsens kidney injury but also sustains inflammation and fibrosis, which contributes to a continual decline in renal function.

There is evidence that interventions that modulate GAG pathways can help alleviate the structural-functional deterioration in DN. The following therapeutic approaches suggest minimizing the rate of DN progression and kidney function decline. The natural antioxidant and anti-inflammatory compound Propolis has the potential to recover ECM and decrease proteinuria in diabetic rat models. Likewise, the mesenchymal stem cells (MSC) treatments have also revealed the potential for replacing GAGs and enhancing renal function in diabetic mice. Xanthine oxidase inhibitors have also demonstrated effectiveness in preventing the development of fibrosis and inflammation through GAG-mediated pathways. Finally, changes in the ECM and GAGs are essential to the development of DN. These alterations in the GAG synthesis pathway impair the charge selectivity of the filtration barrier and proinflammatory and fibrotic changes that accelerate renal function decline. However, studies are still being conducted to discover better treatments for such changes; the available treatments include propolis, MSCs, and xanthine oxidase inhibitors. Disruption of GAG synthesis and degradation may be a useful strategy to prevent DN progression and improve the quality of life of affected patients.

This systematic review also suggests that future research focuses on antifibrotic treatments for diabetic kidney disease and that routine monitoring of proteinuria and serum creatinine in diabetic patients could help identify renal disease early. It is argued that therapeutic approaches should address the issue of GAG synthesis and degradation to correct impaired nephritic filtration. More extensive searching is necessary regarding antioxidant and anti-inflammatory compounds, including propolis, MSC therapies, and xanthine oxidase inhibitors. Still, their effectiveness has yet to be confirmed through human experimental studies. The surrounding community, including diet, physical activity, and glycemia control, are also pro-active activities against the progression of DN. However, limitations are imposed by the STZ-induced diabetic rat models, which do not mimic human DN pathophysiologically. Leveraging rodent models has limitations. However, investigations in human-based models are essential to ascertain the efficacy of the treatment and its safety. This new focus on GAGs as the missing link between ECM remodeling and kinetics could mask other cogent pathways involved in DN progression, including oxidative stress AGEs and cytokines. Future research should use a broader research paradigm to investigate the above other pathways. The absence of human clinical data confines precise therapeutic recommendations; thus, further investigations should include human studies to confirm conclusions and elucidate well-defined treatment plans for DN.

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Conflict of interest

There is no conflict of interest.

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التنميط النسيجي للمصفوفة خارج الخلية لاعتلال الكلية السكري الناجم عن الستربتوزوتوسين في الفئران والجرذان التجريبية، دراسة تحليلية

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الخلاصة

يتميز اعتلال الكلية السكري بأنه خلل وظيفي في الكلى وتضخيم النسيج البيني خارج الخلية مع نمط غير طبيعي من تخليق الجليكوامينوجلايكان. يهدف العمل الحالي أيضا إلى مراقبة وتحليل تعديلات النسيج البيني خارج الخلية الجليكوامينوجلايكان المسؤولة عن تطوير اعتلال الكلية السكري من خلال استخدام نماذج السكري التي يسببها الستربتوزوتوسين في الفئران البيضاء. كما أنه يقيم فعالية الاستراتيجيات الدوائية في علاج تغيرات الجليكوامينوجلايكان. تم تحليل المقالات المنشورة بين عامي ١٩٩٢ و٢٠٢٤ في PubMed و Scopus و Science Direct وGoogle scholar. تم اختيار ثمانية عشر دراسة (ن = ١٨) التي استخدمت نماذج تجريبية من اعتلال الكلية السكري مع التحليل النسيجي للنسيج البيني خارج الخلية، بما في ذلك الجليكوامينوجلايكان فقط. وتم استخدام طرق التلوين مثل الألنين الأزرق وصبغة باس لتقييم المحتوى الكمي للجليكوامينوجلايكان بعض النتائج التي ارتبطت بحالات السكري التي زادت من ترسب النسيج البيني خارج الخلية، وسماكة الغشاء القاعدي للكُبَيْبَة الكلوية وتضخم الغِشاءُ المُتَوَسِّط الكُبَيْبَة الكلوية، وزيادة بروتينات البول. وجد أن مثل هذه التعديلات الهيكلية قد تسبب خلل في تنظيم الجليكوامينوجلايكان وتؤدي إلى التليف الكلوي. تم العثور على تأثيرات البروبوليس والخلايا اللحمية الوسيطة البشرية الميزنكيمية على توازن الجليكوامينوجلايكان وترسب النسيج البيني خارج الخلية والوظيفة الكلوية لنماذج السكري. كما وجد أن تعبير الجليكوامينوجلايكان المتغير يؤثر على تطور اعتلال الكلية السكري بشكل مباشر.