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RESEARCH ARTICLE
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RELATIONSHIP BETWEEN GLYCOCALYX COMPONENTS AND MICROALBUMINURIA IN PATIENTS WITH DIABETES MELLITUS

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Abstract

Diabetes mellitus is a disease of deregulated blood glucose homeostasis. Microalbuminuria has been described as an early sign of kidney damage. The aim of the study was to determine the association of glycocalyx metabolites with microalbuminuria in type 1 diabetic patients. To determine the association of glycocalyx metabolites with microalbuminuria in diabetic patients. This cross-sectional study was recruited from the 90 patient's department of Children's Hospital on the recommendation of a consultant endocrinologist. Patients were designated as having microalbuminuria if they had a 24-h urine measurement >30 mg or an albumin-to-creatinine ratio >30 mg/g albumin-to-creatinine. Total cholesterol, HDL cholesterol, and triglycerides were measured by standard enzymatic methods. Blood and urine samples were obtained from diabetic patients. A probability value of $P<0.05$ was determined to be statistically significant. The analysis of patient ages indicated a mean age of 12.62±1.73 years. Out of the total of 90 patients, 55 (61.11%) were identified as male, while 35 (38.89%) were identified as female. The Mean albumin to creatinine ration in patients was 356.17±139.24 respectively. The Mean cholesterol level in patients was 182.43±50.89. The mean

triglyceride level in patients was 154.17±118.49. Mean HbA1c level in patients was 11.52±1.36. Mean hyaluronic acid level in patients was 283.83±29.51. Hyaluronic acid displayed weak positive correlations with creatinine (r=0.348) and HbA1c levels (r=0.209), and a moderate correlation with the albumin-to-creatinine ratio (r=0.424). A positive significant correlation was observed between hyaluronic acid and ACR. This study suggests that there is a correlation between hyaluronan and ACR in children with T1DM, indicating the importance of monitoring these measures in the management of T1DM.

Keywords: Diabetes; Microalbuminuria; Glycocalyx metabolites.

Introduction

Diabetes is a prevalent chronic disease characterized by high blood glucose levels due to defects in insulin secretion, insulin action, or both, leading to various complications including chronic kidney disease (CKD), cardiovascular disease, neuropathy, and retinopathy (Popoviciu *et al*., 2023). One of the earliest indicators of CKD in diabetic patients is microalbuminuria, defined as the excretion of albumin in the urine at a rate of 30-300 mg/day. The presence of microalbuminuria is a critical marker for the onset and progression of diabetic nephropathy and is associated with an increased risk of cardiovascular events (Nadhiya *et al*., 2024). According to the Centers for Disease Control and Prevention (CDC), over 34 million Americans have diabetes (Herman *et al*., 2023). Of these, 90-95% have type 2 diabetes mellitus (T2DM). The prevalence of diabetes is disproportionately high in specific populations, including African Americans, Hispanics/Latinos, Native Americans, and Asian Americans (Fayfman and Haw, 2017). People with T2DM are at a higher risk of developing microalbuminuria than those with type 1 diabetes mellitus (T1DM). The incidence of microalbuminuria in people with type 2 diabetes ranges from 20-40% (Kazemzadeh *et al*., 2024).

Microalbuminuria is associated with an increased risk of developing overt diabetic nephropathy in patients with both T1DM and T2DM. However, the relationship between the two is less evident in T2DM due to the greater heterogeneity of the disease and additional risk factors in these typically elderly patients (Sana *et al*., 2020). Although microalbuminuria may regress spontaneously in certain instances, it remains a strong indicator of a high risk of developing diabetic nephropathy in both T1DM and T2DM. The pathophysiology of microalbuminuria in diabetes is multifactorial. Several mechanisms contribute to its development, including endothelial dysfunction, glomerular hyperfiltration, and inflammation (Selby and Taal, 2020). High blood sugar levels damage the walls of blood vessels in people with diabetes, leading to endothelial dysfunction. This dysfunction releases pro-inflammatory cytokines, exacerbating vessel damage (Poredos *et al*., 2021). Damaged vessels lose their ability to filter out albumin, leading to its leakage into the urine. Glomerular hyperfiltration, another mechanism, increases the glomerular filtration rate due to high blood sugar levels, damaging the glomeruli and impairing their ability to filter out albumin (Premaratne *et al*., 2015). Inflammation also contributes to microalbuminuria by activating the immune system and producing pro-inflammatory cytokines, which damage the blood vessels and glomeruli (Cortinovis *et al*., 2022).

Endothelial glycocalyx damage is characteristic of T1DM, and microalbuminuria exacerbates this damage (Yu *et al*., 2023). The glycocalyx, a complex sugar coating covering the surface of most cells, plays a crucial role in regulating vascular permeability and maintaining the structural integrity of the endothelial barrier. Studies suggest that glycocalyx alterations in diabetes contribute to complications (Hu *et al*., 2021). Chronic diseases such as diabetes, atherosclerosis, hypertension, and sepsis can alter the glycocalyx's composition and cause structural integrity loss (Franceković and Gliemann, 2023). Hyaluronan levels are found to be elevated in the urine of diabetic patients with microalbuminuria, indicating its potential role in the development of this condition. Conversely, chondroitin sulfate, heparan sulfate, and syndecan-1 levels are reduced, suggesting a degradation or shedding of the glycocalyx in diabetic nephropathy (Qi *et al*., 2024). These changes could compromise the integrity of the glomerular filtration barrier, leading to increased albumin leakage (Balbotkina and Kutina,

2023). Recent research has highlighted the role of the endothelial glycocalyx, a carbohydrate-rich layer lining the vascular endothelium, in maintaining vascular integrity and permeability (Aldecoa *et al*., 2020). The glycocalyx is composed of various glycosaminoglycans such as hyaluronan, chondroitin sulfate, heparan sulfate, and core proteins like syndecan-1. These components are crucial in regulating endothelial function, including the filtration barrier of the glomeruli in the kidneys (Dogné and Flamion, 2020). Alterations in the structure and function of the glycocalyx have been implicated in the pathophysiology of diabetes and its vascular complications. This research aims to explore the association between glycocalyx components and microalbuminuria in diabetic patients.

Methodology

This cross-sectional study was conducted over six months at the Children's Hospital's out-patient department. A total of 90 subjects were recruited through non-probable convenient sampling, based on a consultant endocrinologist's recommendation. The inclusion criteria were patients aged 10-17 with at least five years of T1DM, while patients with anemia, transfusions, other metabolic disorders, renal failure, endocrine dysfunction, or treatment were excluded. Blood and urine samples were collected from T1DM patients to assess glycocalyx metabolites and microalbuminuria. Patients were classified as having microalbuminuria if a 24-hour urine measurement showed >30 mg or an albumin-to-creatinine ratio (ACR) >30 mg/g. Standard enzymatic methods were used to measure total cholesterol, HDL cholesterol, and triglycerides. Blood samples were processed to separate plasma, which was stored at -80°C for analysis for hyaluronan concentration using enzyme-linked immunosorbent assay (ELISA). Urinary ACR was calculated by dividing albumin concentration in milligrams by creatinine concentration in grams from spot urine samples. Lipid profiles were obtained through lipid panel tests, and HbA1c levels were measured using high-performance liquid chromatography (HPLC) or immunoassay kits. Data were analyzed using SPSS version 24, with descriptive data reported as means ± SD and a significance threshold of $P<0.05$.

Results

The age distribution of the 90 patients revealed a mean age of 12.62±1.73 years, indicating that the average age was approximately 12.62 years with a standard deviation of 1.73 years. The patients' ages ranged from 10 to 17 years. These findings are summarized in Table 4.1. The ACR was assessed in the patients, providing valuable information about kidney function and potential abnormalities. The Mean albumin to creatinine ration in patients was 356.17±139.24 respectively. The cholesterol levels of the patients were analyzed to gain insights into their cardiovascular health and lipid profiles. The Mean cholesterol level in patients was 182.43±50.89. The triglyceride levels of the patients were assessed as part of the study's investigation into lipid profiles and metabolic health. The mean triglyceride level in patients was 154.17±118.49. The HbA1c (glycated hemoglobin) levels of the patients were analyzed to assess their long-term glucose control and diabetes management. Mean HbA1c level in patients was 11.52±1.36. The analysis of hyaluronic acid level in the patients was conducted to obtain insights into potential indicators of tissue health and inflammation. Mean hyaluronic acid level in patients was 283.83±29.51.

Table-1: Characteristics of Study Participants

n	**90**
Age (years)	12.62±1.73
Albumin to creatinine ratio	356.17±139.24
Cholesterol Level	182.43±50.89
Triglycerides Level	154.17±118.49
HbA1C Level	11.52±1.36
Hyaluronic acid level	283.83±29.51

In Table 2, correlation matrix in this section demonstrates the relationship between hyaluronic acid and other critical parameters such as creatinine, cholesterol, triglycerides, and HbA1c. The analysis showed weak positive correlations of hyaluronic acid with creatinine (r=0.348, *p-value*=0.001) and HbA1c levels (r=0.209, *p-value*=0.048), and a moderate correlation with the albumin-to-creatinine ratio (r=0.424, *p-value*<0.001). The correlation matrix provides valuable insights into the relationships between these key variables, aiding in a deeper understanding of the patient population (Table 3).

Table 2: Correlation of all parameters with Hyluronic acid, Creatinine and HbA1c

		Hyaluronic Acid	Creatinine	HbA1C
Hyaluronic Acid	Pearson Correlation	1	.348**	.209*
	p-value		.001	.048
Creatinine	Pearson Correlation	.348**	1	.012
	p-value	.001		.910
HbA1C	Pearson Correlation	.209*	.012	1
	p-value	.048	.910	
ACR	Pearson Correlation	.424**	.022	.044
	p-value	.000	.836	.679
Cholesterol	Pearson Correlation	-.026	.047	.326**
	p-value	.809	.663	.002
Triglycerides	Pearson Correlation	.115	-.069	.161
	p-value	.281	.516	.130

r: Correlation Coefficient, ***p-value***<0.05 (Statistically significant)

Table 3: Correlation of all parameters with ACR, Cholesterol and Triglycerides

		ACR	Cholesterol	Triglycerides
Hyaluronic Acid	Pearson Correlation	.424**	-.026	.115
	p-value	.000	.809	.281
Creatinine	Pearson Correlation	.022	.047	-.069
	p-value	.836	.663	.516
HbA1C	Pearson Correlation	.044	.326**	.161
	p-value	.679	.002	.130
A.C.R	Pearson Correlation	1	-.239*	.006
	p-value		.023	.957
Cholesterol	Pearson Correlation	-.239*	1	.145
	p-value	.023		.171
Triglycerides	Pearson Correlation	.006	.145	1
	p-value	.957	.171	

r: Correlation Coefficient, *p-value*<0.05 (Statistically significant)

Below scatter plot matrix shoes correlation of Hyaluronic acid with HbA1c, Triglycerides, Cholesterol and creatinine level (Figure 1,2 and 3).

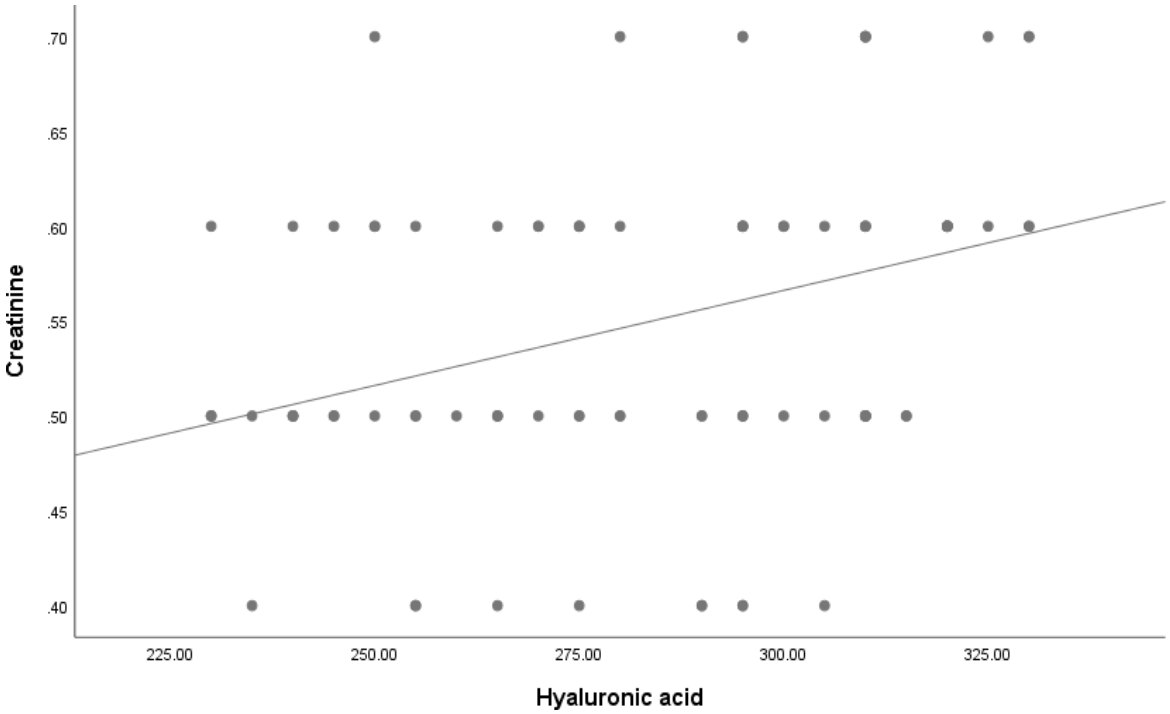

Figure 4.1: Scatterplot matrix for correlation between Hyaluronic acid and creatinine level.

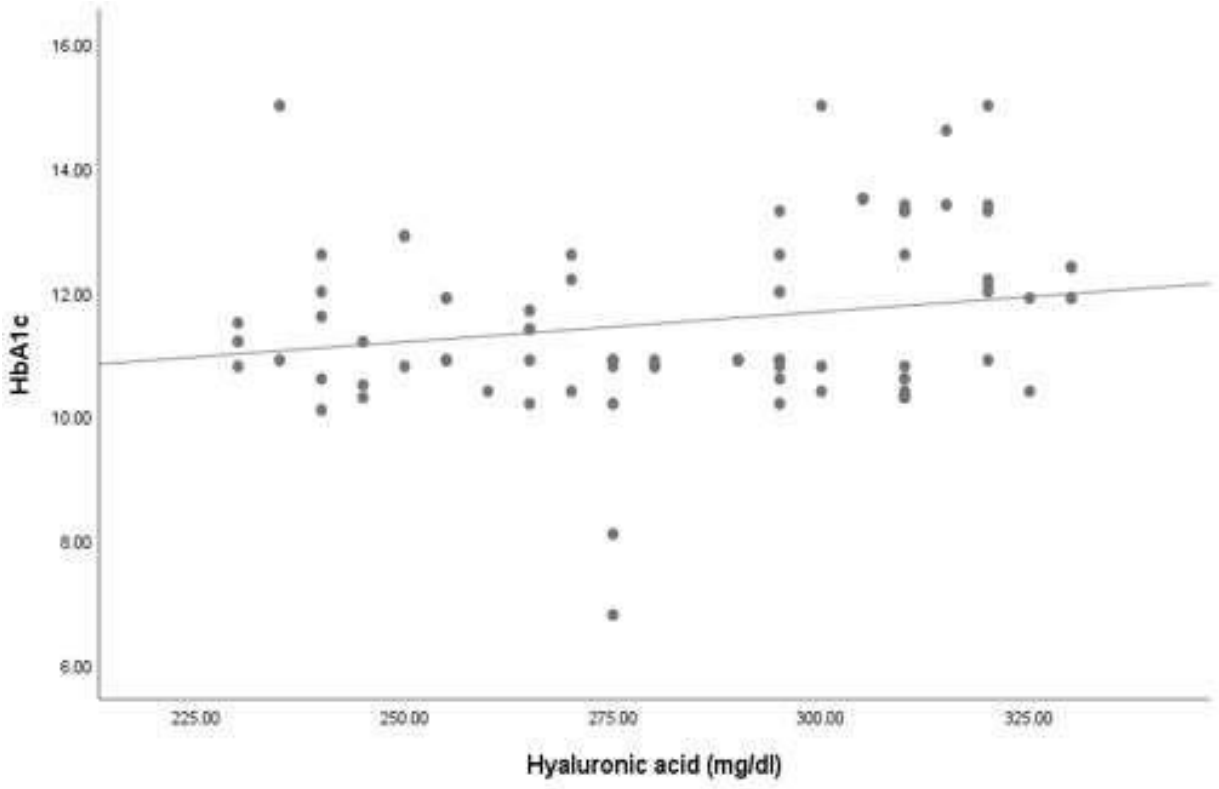

Figure 2: Scatterplot matrix for correlation between Hyaluronic acid and HbA1c level.

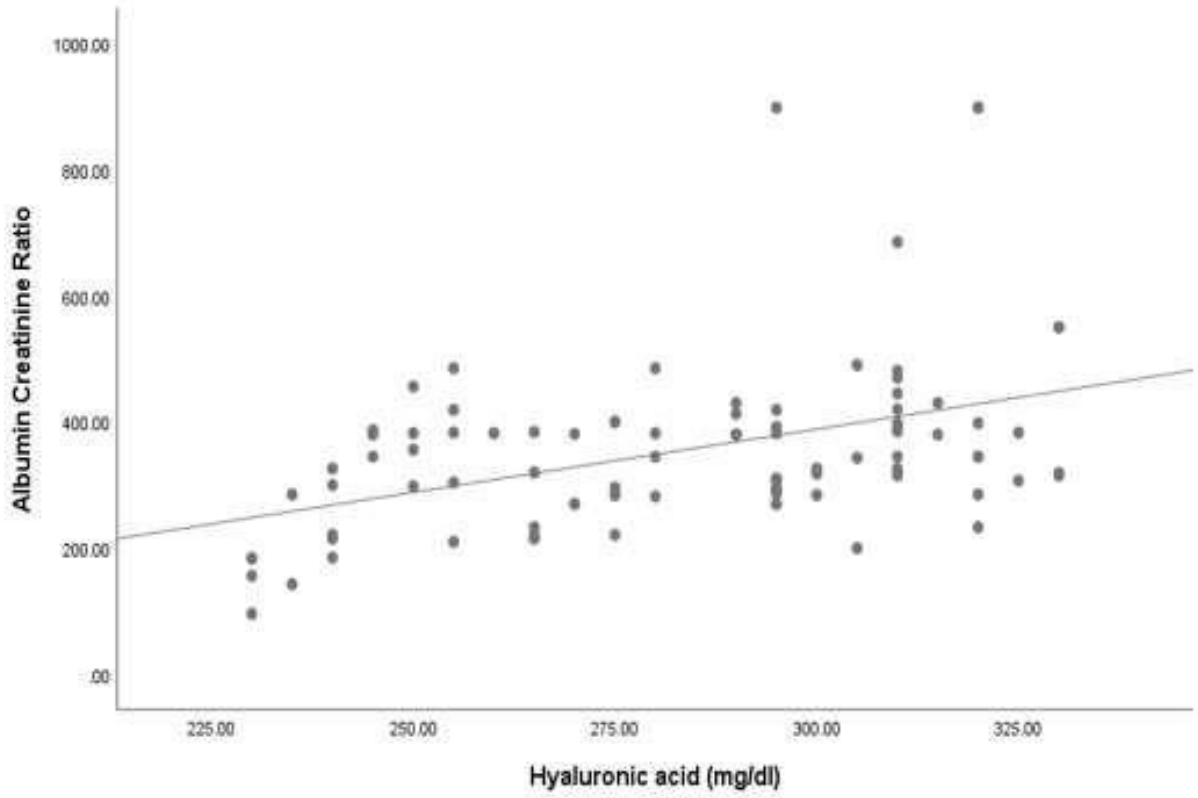

Figure 3: Scatterplot matrix for correlation between Hyaluronic acid and ACR level.

Discussion

Diabetes is a growing global health issue, affecting approximately 425 million people worldwide (Dong *et al*., 2019). One significant complication of diabetes is diabetic nephropathy, a leading cause of end-stage renal disease that imposes a considerable burden on individuals, families, and healthcare systems (Nasri and Rafieian-Kopaei, 2015). The endothelial glycocalyx, a complex layer of sugars and proteins covering the inner walls of blood vessels, plays a critical role in maintaining vascular integrity, regulating blood flow, and preventing fluid and protein leakage into surrounding tissues. Diabetes-related damage to the glycocalyx is believed to contribute to complications such as atherosclerosis, heart disease, and kidney disease (Alphonsus and Rodseth, 2014).

Microalbuminuria, characterized by the leakage of small amounts of albumin into the urine, serves as an early indicator of kidney damage and diabetic nephropathy (DKD) (Scilletta *et al*., 2023). The presence of microalbuminuria in diabetic patients signifies damage to the endothelial glycocalyx, a protective layer that lines the vascular endothelium and has vital physiological functions (Salmon and Satchell, 2012). The glycocalyx, composed of glycoproteins, proteoglycans, and glycans, acts as a barrier between the bloodstream and tissues, and its damage has been implicated in the development of DKD (Wu *et al*., 2024).

Glycocalyx metabolites such as heparan sulfate, hyaluronan, and sialic acid are crucial in regulating vascular permeability, inflammation, and oxidative stress. Studies have shown that glycocalyx damage is present in diabetic individuals with microalbuminuria, suggesting it may play a causative role in the development of DKD (Masola *et al*., 2021). For instance, increased urinary excretion of glycocalyx metabolites like syndecan-1 and heparan sulfate in T2DM patients with microalbuminuria has been observed, indicating glycocalyx degradation (Yu *et al*., 2023).

Our study revealed a mean hyaluronan level of 282.83±29.08 in patients, with no significant correlation between hyaluronan levels and other variables. This finding aligns with a study by Hull *et al*, (2015), which found elevated hyaluronan levels in T1DM children associated with poor glycemic control (Hull *et al*., 2015). Additionally, Sharma *et al*. (2022) reported higher serum hyaluronan levels in T1DM children with diabetic nephropathy, correlating with increased urinary albumin excretion

(Sharma *et al*., 2022). The study also showed mean creatinine and triglyceride levels of 0.52±0.07 and 142.25±100.54, respectively. Similar studies by Ledeganck *et al*. (2021) and Marcovecchio *et al*. (2020) found positive correlations between creatinine levels and early kidney dysfunction in T1DM children (Ledeganck *et al*., 2021; Marcovecchio *et al*., 2020). Elevated cholesterol levels were observed, with a mean of 175.96±43.66, consistent with findings by Ahn *et al*. (2021) and Rathsman *et al*. (2021), who reported higher cholesterol levels in T1DM children with poor glycemic control and macroalbuminuria (Ahn *et al*., 2021; Rathsman *et al*., 2021).

The study's findings underscore the importance of glycocalyx components in understanding the pathophysiology of diabetic complications. The correlation of glycocalyx damage with microalbuminuria suggests a potential mechanism involving increased vascular permeability, inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system (RAAS) (Butler, 2018; Korakas *et al*., 2020; Rabelink and De Zeeuw, 2015). Further research is essential to elucidate these mechanisms and develop targeted therapies for diabetic nephropathy and related complications.

Conclusion

This study highlights a significant correlation between glycocalyx metabolites and microalbuminuria in diabetic patients, suggesting that glycocalyx alterations contribute to renal dysfunction. Elevated levels of hyaluronan, creatinine, cholesterol, triglycerides, and HbA1c in T1DM children indicate potential organ damage and increased cardiovascular risk. Monitoring and targeting these biomarkers are crucial to mitigating long-term complications in these patients. The weak positive correlations of hyaluronic acid with creatinine and HbA1c imply links to kidney function and glucose control, underscoring the importance of understanding hyaluronic acid dynamics as a biomarker for various health conditions. Further research should explore causal relationships and mechanisms underlying these correlations to gain insights into diabetic kidney disease pathogenesis and identify potential therapeutic targets.

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