Original Article

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Study of Microvascular Complications in Type 2 Diabetes Mellitus with Special Reference to Advanced Glycation End-Products (AGEs) and Pentosidine Levels

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Abstract:

Objective: This cross-sectional study aimed to assess and compare the association between the serum levels of Advanced Glycation End-Products (AGEs), Pentosidine, and microvascular complications (retinopathy, nephropathy, and neuropathy) in patients with type 2 diabetes mellitus to explore the potential of AGEs and Pentosidine as predictive biomarkers for the early detection of microvascular complications in T2DM.

Material and Methods: The study involved 149 patients, divided into five groups based on the presence of microvascular complications: non-diabetic volunteers, type II diabetics without microvascular complications and with retinopathy, nephropathy, and peripheral neuropathy. AGEs and Pentosidine levels were measured and compared across these groups.

Results: The results showed statistically significantly higher AGE levels in diabetics (354.5 ng/ml) compared to non-diabetics (193.8 ng/ml) (p-value<0.001), indicating a clear association between AGEs and diabetic status. Additionally, diabetic patients with retinopathy had markedly higher AGE levels (443.6 ng/ml) compared to those without retinopathy (325.7 ng/ml) (p-value<0.001). Pentosidine levels were also elevated in diabetics (793.8 ng/ml) compared to non-diabetics (95.4 ng/ml) (p-value=0.043), with the most significant elevation observed in diabetics with peripheral neuropathy (p-value<0.001). The study found a positive correlation between AGE and the duration of diabetes and also between AGE levels and HbA1c, indicating that inadequate glycaemic control and long-term hyperglycaemia may contribute to AGE accumulation.

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Conclusion: The findings emphasize the critical role of AGEs and Pentosidine in the progression of diabetic microvascular complications and conclude that these biomarkers could serve as valuable tools for identifying and monitoring the progression of T2DM complications.

Keywords: Advanced Glycation End products (AGEs), Diabetes Mellitus, Microvascular complications, HbA1c, Pentosidine

Introduction

Diabetes mellitus is a chronic, progressive metabolic disorder that primarily manifests as prolonged hyperglycaemia due to insufficient insulin production or action. The disease is a leading global cause of morbidity and mortality, contributing to numerous complications. Among these, microvascular complications—such as diabetic retinopathy, nephropathy, and neuropathy—are critical factors affecting the quality of life and survival of individuals with diabetes. These complications result from long-standing hyperglycaemia, though hyperglycaemia alone is not the sole contributor to diabetic pathogenesis. Instead, a combination of metabolic abnormalities, including oxidative stress, inflammation, and vascular dysfunction, underpins the development and progression of both macrovascular and microvascular complications. To reinforce this, substantial studies have provided evidence that low-grade systemic inflammation is crucial in the initiation and progression of microvascular complications like diabetic peripheral neuropathy, retinopathy, and nephropathy[1-3]. Therefore, understanding the precise mechanisms contributing to diabetic complications is essential for effective management and the identification of therapeutic targets[4-6].

The pathogenesis of diabetic microvascular complications is complex and multifactorial, involving a combination of hyperglycaemia-induced pathways. Key among these is the polyol pathway, the formation of AGEs, the activation of protein kinase C (PKC)-diacylglycerol (DAG) pathway, and the hexosamine pathway. These pathways converge on promoting endothelial dysfunction, inflammation, and fibrosis, leading to vascular damage in various organs. Although these pathways play a role in both macrovascular and microvascular complications, AGEs have garnered significant attention due to their widespread involvement in the complications associated with diabetes[7,8].

AGEs are a diverse group of molecules formed through the non-enzymatic glycation of proteins, lipids, and nucleic acids, a reaction that occurs when reducing sugars like glucose react with free amino groups on proteins. This process, called the Maillard reaction, is accelerated in the hyperglycaemic state characteristic of diabetes. As glucose levels remain elevated over time, AGEs accumulate and form irreversible cross-links, which lead to structural and functional changes in tissues. AGEs were involved in inducing chronic immune imbalance in diabetic patients, representinga risk factor of type 2 diabetes and several diabetes complications, including neuropathy and atherosclerosis (macro-vasculopathy and micro-vasculopathy)[9]. AGEs contribute to oxidative stress, promote inflammation, and alter extracellular matrix components, thereby exacerbating endothelial damage, vascular permeability, and tissue fibrosis. The accumulation of AGEs has been linked to the development of diabetic complications such as retinopathy, nephropathy, and neuropathy[10].

Pentosidine is a well-characterized AGE formed by the non-enzymatic glycation of proteins and the oxidative modification of sugars. Unlike some other AGEs, pentosidine formation requires the involvement of both glycation and oxidative stress, which further underscores its significance in diabetes pathology. Elevated levels of pentosidine in diabetic patients have been correlated with the severity

of microvascular complications, suggesting its potential as a diagnostic marker for diabetic complications[11,12]. Studies have shown that patients with diabetic retinopathy and nephropathy, for example, have higher pentosidine levels compared to those without these complications, further supporting its role in the pathogenesis of these disorders[13,14].

Given the growing body of evidence suggesting the importance of AGEs and pentosidine in diabetic complications, this study aimed to investigate whether these biomarkers are elevated in patients with type 2 diabetes mellitus (T2DM) and whether their levels correlate with the presence of microvascular complications. The identification of AGEs and pentosidine as biomarkers for early detection of complications could revolutionize diabetes management by enabling earlier interventions and more personalized treatment strategies. Furthermore, by establishing a clear link between these biomarkers and the development of microvascular complications, this study may help pave the way for the development of novel therapies aimed at targeting AGE formation or reducing their detrimental effects on tissues[15].

Material and Methods

Ethical consideration

This prospective comparative cross-sectional study was conducted at the departments of General Medicine, Ophthalmology, and Nephrology at a tertiary care centre for 18 months. All procedures were conducted in accordance with the ethical standard guidelines laid down in the Declaration of Helsinki 1964 and as revised later.

Dataset description

The study included 149 participants from the inpatient and outpatient departments of the General Medicine, Ophthalmology, and Nephrology at JSSH. Subjects were aged 40-75 years and classified into five groups: Non-diabetic volunteers (group 1), type II diabetics without microvascular complications (group 2), diabetics with retinopathy (group 3), diabetics with nephropathy (group 4), and diabetics with peripheral neuropathy (group 5). Individuals with macrovascular complications or outside the age range were excluded. The sample size was determined through purposive sampling, with an initial estimate of 139, later adjusted to 149 to account for potential non-responses.

Running the test

AGEs and pentosidine concentrations were measured using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the manufacturers' protocols. Biological samples (e.g., serum, plasma, or tissue homogenates) were prepared by centrifugation and appropriate dilution. The ELISA plates were pre-coated with antibodies specific to AGEs or pentosidine. Standards and samples were added in duplicate or triplicate to ensure accuracy and reproducibility. After incubation and washing steps to remove unbound substances, a biotin-conjugated secondary antibody and streptavidin-HRP conjugate were applied. Colorimetric detection was performed using a tetramethylbenzidine (TMB) substrate, and absorbance was measured at 450 nm using a microplate reader. The concentration of AGEs or pentosidine was determined by interpolating absorbance values against a standard curve generated from known concentrations.

Data analysis

The data collected were analysed using Statistical Package for the Social Science (SPSS) version 28, with descriptive statistics such as percentage, mean, frequency, and standard deviation. Inferential statistics, including one-way ANOVA, correlation, and chi-square tests, were applied to compare means. Subgroup analysis focused on diabetic retinopathy, nephropathy, peripheral neuropathy, and the variation in AGE and pentosidine levels across these groups. All statistical tests helped to assess relationships and differences within the study data.

Results

As shown in Table 1, this study analysed 149 diabetic patients. The mean age of the study population was 58.24 years, with most participants(45%) aged 51–60 years. Males comprised 54.4% and females 45.6%; 56.11% had diabetes for 0–5 years, and more than 10 years in 14.39% of the study population. Diabetic patients with peripheral neuropathy (Group 5) represented the largest study subset (27.5%). Among 34 patients with diabetic retinopathy, 38.2% had moderate NPDR, followed by mild NPDR (29.4%) and severe NPDR in 11.6% cases. HbA1c levels were 7.0–10.0 in 48.2%, with 38.1% exceeding 10. These distributions highlight demographic and clinical patterns in diabetes-related complications and glycemic control.

As shown in Table 2, the study found significantly higher mean levels of AGEs and Pentosidine in diabetics (354.5 ng/ml and 793.8 ng/ml, respectively) compared to non-diabetics (193.8 ng/ml and 95.4 ng/ml), with "p-value" of 0.0002 and 0.043, confirming a strong association between these biomarkers and diabetes.

As shown in Table 3, the mean AGE levels varied significantly across diabetes groups, with the lowest in Group 1 non-diabetic volunteers (193.8 ng/ml) and the highest in Group 3 diabetics with retinopathy (443.6 ng/ml), indicating differences in AGE accumulation linked to specific diabetes-related complications.

As shown in Table 4, the study found significantly higher mean AGE levels in diabetic retinopathy patients (443.60 ng/ml) compared to those without it (325.68 ng/ml), with a p-value<0.001, indicating a strong association. However, mean Pentosidine levels showed no significant difference between the groups (677.61 ng/ml vs. 831.44 ng/ml, p-value>0.05). These findings suggest that AGEs may be more strongly linked to diabetic retinopathy than Pentosidine.

Table 1 Baseline characteristics of the overall population

Distribution of patients according to their Age group (N-149)		
Age (years)	Frequency	Percent
40–50	25	16.8
51–60	67	45.0
61–70	51	34.2
Above 70	6	4.0
Mean±S.D.	58.24±7.87	
Distribution of patients according to their sex (N-149)		
Sex	Frequency	Percent
Female	68	45.6
Male	81	54.4
Total	149	100.0
Distribution of patients according to duration of diabetes		
Duration of diabetes	Frequency	Percent
0–5 years	78	56.11
6–10 years	41	29.50
Above 10 years	20	14.39
Total	139	100
Distribution of patients according to various study groups (N-149)		
Study group	Frequency	Percent
1	10	6.7
2	28	18.8
3	34	22.8
4	36	24.2
5	41	27.5
Total	149	100.0

S.D.=standard deviation

Table 2 Mean AGEs and pentosidine level comparison between non-diabetics and diabetics

Group		N	Mean ng/ml	S.D.	Standart error Mean	p-value
AGEs	Non-Diabetics	10	193.8	55.1	17.4	0.0002
	Diabetics	139	354.5	131.0	11.1	
Pentosidine levels	Non-Diabetics	10	95.4	41.2	13.0	0.043
	Diabetics	139	793.8	1081.4	91.7	

AGEs=advanced Glycation end-products, S.D.=standard deviation

Table 3 Descriptive statistics of diabetes groups and AGEs, pentosidine level

Diabetes group	Numbers	Mean ng/ml	S.D.	95% Confidence interval	
				Lower bound	Upper bound
AGEs					
1 Non-diabetic volunteers	10	193.8	55.06	154.39	233.17
2 Diabetic without complications	28	414.5	149.4	356.55	472.41
3 Diabetics with retinopathy	34	443.6	131.6	397.68	489.52
4 Diabetics with nephropathy	36	273	80	245.93	300.07
5 Diabetics with peripheral neuropathy	41	311.3	84.25	284.68	337.87
Pentosidine Levels					
1 Non-diabetic volunteers	10	95.42	41.24	65.91	124.92
2 Diabetic without complications	28	807.6	1096	382.5	1232.75
3 Diabetics with retinopathy	34	677.6	994.2	330.73	1024.48
4 Diabetics with nephropathy	36	361.7	425.6	217.68	505.71
5 Diabetics with peripheral neuropathy	41	1,260	1,359	831.21	1,689.09

AGEs=advanced Glycation end-products, S.D.=standard deviation

Table 4 Mean AGEs and pentosidine level comparison in diabetic retinopathy

Diabetic retinopathy		N	Mean ng/ml	S.D.	Standart error Mean	p-value
AGEs	No	105	325.68	117.66	11.14	<0.001
	Yes	34	443.60	131.61	22.57	
Pentosidine levels	No	105	831.44	1110.10	100.77	0.473
	Yes	34	677.61	994.15	170.50	

AGEs=advanced Glycation end-products, S.D.=standard deviation

Table 5 Mean AGEs and pentosidine level comparison in diabetic peripheral neuropathy

Diabetic peripheral neuropathy		N	Mean ng/ml	S.D.	Standart error Mean	p-value
AGEs	No	98	372.73	142.72	14.41	0.011
	Yes	41	311.3	84.25	13.16	
Pentosidine levels	No	98	598.70	878.53	88.83	0.0008
	Yes	41	1,260	1,359	212.34	

AGEs=advanced Glycation end-products, S.D.=standard deviation

As shown in Table 5, mean AGE levels were lower in the diabetic peripheral neuropathy group (311.3 ng/ml) compared to the other diabetic groups (372.73 ng/ml, "p- value" 0.011), while mean pentosidine levels were significantly higher in the neuropathy group (1,260 ng/ml) versus others (598.70 ng/ml, "p-value" 0.0008). This suggests the differing roles of these biomarkers across diabetic complications.

As shown in Table 6, mean AGE levels were significantly lower in the diabetic nephropathy group (273

Table 6 Mean AGEs and pentosidine level comparison in diabetic nephropathy

Diabetic peripheral neuropathy		N	Mean ng/dl	Standard deviation	Standart error Mean	p- value
AGEs	No	103	383.01	133.64	13.16	0.0001
	Yes	36	273	80	13.13	
Pentosidine levels	No	103	944.84	1,196.28	117.87	0.004
	Yes	36	361.7	425.6	70.93	

AGEs=advanced Glycation end-products

ng/ml) compared to the others (383.01 ng/ml, "p-value" 0.0001), and mean pentosidine levels were also reduced in nephropathy (361.7 ng/ml) versus the other groups (944.84 ng/ml, "p-value" 0.004), reflecting distinct biomarker patterns.

As shown in Figure 1, the data exhibit an upward trend from left to right (r=0.272, "p- value" 0.001), indicating a positive correlation between AGE levels and the duration of diabetes; as the duration increases, AGE values also rise. The significant moderate correlation between diabetes duration and AGE levels highlights the need for long-term glycemic control and monitoring to reduce the adverse effects of AGEs and prevent diabetes-related complications.

As shown in Figure 2, the data show a nearly straight line (r =-0.036, "p-value" 0.676), indicating a very weak negative correlation between the duration of diabetes and pentosidine levels, and the "p-value" suggests that this relationship is not statistically significant. The absence of a significant correlation suggests that the duration of diabetes does not have a strong impact on pentosidine levels in this sample. Pentosidine levels in this study suggest that other factors may play a more substantial role in determining pentosidine levels.

As shown in Supplementary figure 1, the data show an upward trend from left to right (r=0.111, "p-value" 0.195), indicating a positive correlation between HbA1c levels and AGE levels. As HbA1c levels increase, AGE values also tend to rise. This observed positive correlation is consistent with findings from the literature, which suggests that elevated HbA1c levels, indicative of poor long-term glycaemic control, are associated with higher AGE levels.

Discussion

The present study focused on microvascular complications in patients with type II diabetes mellitus, with a particular emphasis on AGEs and pentosidine levels. Since there are no studies exactly like ours to compare with, we have incorporated well-known knowledge in the field and gathered data from related areas of study. By doing so, we aimed to provide a comprehensive understanding of the implications of our work.

The distribution of patients according to age groups revealed significant insights. The largest proportion of patients fell within the 51-60 years age group, comprising 45.0% of the total sample. This finding was consistent with Kerkeni et al.'s study, in which similar age distributions (52±9 in control subjects and 57±12 in the diabetic group) were observed[16]. This suggests that the middle-aged population is at a heightened risk, possibly due to the cumulative effects of prolonged hyperglycemia and the resulting accumulation of AGEs over time. It also underlines the critical role of aging in the development and progression of diabetes-related microvascular complications[17].

The present study's findings revealed that 54.4% of the patients were male, while 45.6% were female. This male predominance was consistent with several

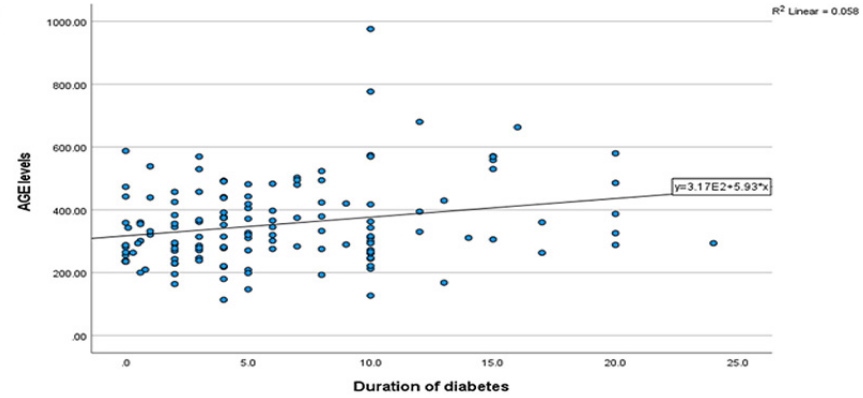

Figure 1 Scatter diagram for correlation of Advanced glycation end products (AGEs) levels with duration of diabetes

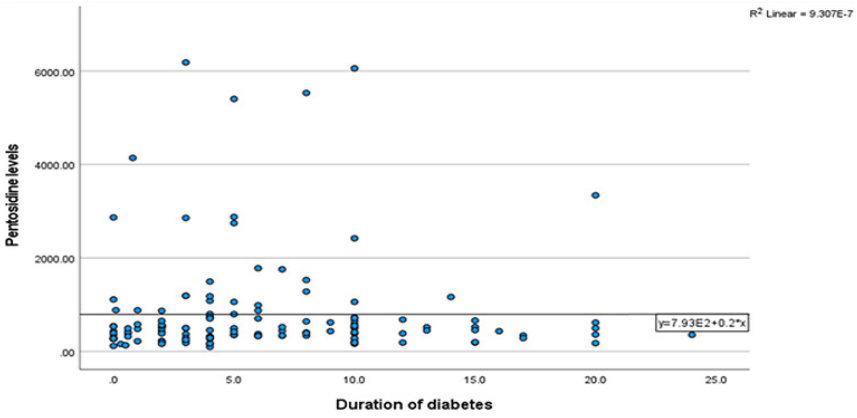

Figure 2 SScatter diagram for correlation of pentosidine levels with duration of diabetes

previous studies that have explored the prevalence of microvascular complications in diabetic populations[18]. Research has suggested that men may develop diabetes at a lower body mass index (BMI) and may experience a more rapid progression to complications, potentially due to differences in fat distribution and hormonal influences [19]. These findings contribute to the understanding of how sex differences influence the epidemiology of diabetes-related microvascular complications, emphasizing the need for targeted interventions that consider these variations.

The comparison of AGEs and Pentosidine levels between the diabetic and non-diabetic groups reveals significant differences, highlighting the impact of diabetes on these biomarkers. Non-diabetic individuals had a mean AGE level of 193.8ng/ml (S.D.=55.1) with a standard error of 17.4, whereas diabetic patients had a substantially higher mean AGE level of 354.5 ng/ml (S.D. 131.0) and a standard error of 11.1, with "p-value" of 0.0002, indicating a highly significant difference. Similarly, Pentosidine levels were markedly elevated in diabetic patients, with a mean

of 793.8 ng/ml (S.D.=1081.4) and a standard error of 91.7, compared to 95.4 (S.D.=41.2) and a standard error of 13.0 in non-diabetics, with a "p-value" of 0.043. These findings underscore the significant increase in both AGEs and Pentosidine associated with diabetes, reflecting higher oxidative stress and advanced glycation processes. The significant p-values for both biomarkers underscore their potential as important indicators of diabetes-related pathology and stress the need for further investigation into their roles in disease progression and management [20,21].

We compared AGEs and Pentosidine levels in diabetic retinopathy, and it reveals significant insights into their respective roles in the condition. The mean level of AGEs was notably higher in individuals with diabetic retinopathy (443.60 ng/ml) compared to those without the condition (325.68 ng/ml), with a highly significant p-value<0.001. This suggests a strong association between elevated AGEs and the presence of diabetic retinopathy, showing the potential role of AGEs in the pathogenesis or progression of the disease. In contrast, Pentosidine levels did not show a significant difference between the two groups, with a "p-value" of 0.473, indicating that Pentosidine may not be as closely related to diabetic retinopathy in this comparison. This discrepancy highlights the importance of AGEs as a potential biomarker for diabetic retinopathy and suggests that further research is needed to explore the role of Pentosidine in diabetic complications. A study by Kerkeni et al. indicated that increased levels of AGEs, including pentosidine, were associated with the severity of diabetic retinopathy[16]. However, the lack of a significant difference in our study might reflect variability in individual patient factors or differences in measurement techniques. Overall, while AGEs were significantly higher in patients with diabetic retinopathy, pentosidine levels did not show a significant association.

In this study, we compared the mean AGEs and Pentosidine levels between diabetic groups, which revealed significant differences in the biochemical markers associated with peripheral neuropathy. For AGEs, the group of type 2 diabetics with peripheral neuropathy (Group 5) has a mean level of 311.3 ng/ml, which is lower compared to the mean of 372.73 ng/ml in the broader category of diabetics without neuropathy. Although this difference was statistically significant with a "p-value" of 0.011, it suggests that AGEs are relatively lower in those with peripheral neuropathy. In contrast, Pentosidine levels showed a more pronounced disparity. The group with peripheral neuropathy had a mean level of 1,260 ng/ml, markedly higher than the mean of 598.70 ng/ml observed in the broader diabetic group without neuropathy, with a highly significant "p-value" of 0.0008. This stark difference highlights that while AGEs may not be as elevated in individuals with peripheral neuropathy, Pentosidine levels are substantially increased, pointing to its potential role as a more sensitive biomarker for assessing the severity of diabetic complications like peripheral neuropathy. The significant increase in Pentosidine levels among those with neuropathy found its relevance in monitoring and potentially predicting the progression of diabetic complications.

In this study, we compared AGEs and Pentosidine levels between diabetic groups, which revealed significant differences that reflect the impact of different diabetic complications, such as nephropathy. For AGEs, the group of type 2 diabetics with nephropathy (Group 4) showed a mean level of 273 ng/ml, which was substantially lower than the mean of 383.01 ng/ml observed in the broader category of diabetics without nephropathy, with a p-value of 0.0001, indicating a significant difference. This suggests that individuals with nephropathy have comparatively lower AGEs, which may reflect variations in the metabolic or pathological processes associated with nephropathy versus other diabetic complications. Similarly, Pentosidine levels present a contrasting pattern. The group with nephropathy had a mean level of 361.7 ng/ml, which was markedly

lower than the mean of 944.84 ng/ml in the broader diabetic group without neuropathy, with a "p-value" of 0.004, indicating statistical significance. This highlights that while AGEs may be lower in those with nephropathy, Pentosidine levels are significantly reduced, suggesting that Pentosidine may be less prominent in nephropathy compared to other complications. These findings underscore the need to consider specific complications when evaluating biomarkers like AGEs and Pentosidine, as their levels can vary significantly depending on the type of diabetic complication present.

As shown in Figure 1, additionally, a positive correlation between the duration of diabetes and AGE levels was found, emphasizing the need for long-term glycaemic control to prevent complications. However, no significant correlation was observed between diabetes duration and Pentosidine, as shown in Figure 2[22,23]. This suggests that factors other than duration, like treatment strategies or individual metabolic differences, may influence Pentosidine levels.

As seen in supplementary figure 1, The study also observed a weak positive correlation between HbA1c and AGE levels, confirming that poor glycaemic control tends to increase AGE accumulation. However, this weak positive correlation between HbA1c levels and AGE levels was not statistically significant. The weak correlation suggests that while there is a slight tendency for higher HbA1c levels to be associated with increased AGE levels, the relationship is not strong enough to reach statistical significance in this study. The lack of significant correlation in this study may be influenced by factors such as sample size, individual variability, or the specific characteristics of the study.

Interestingly, the relationship between HbA1c and Pentosidine was unexpected, with a weak negative correlation, suggesting that other factors may be at play[24]. These results highlight the complexity of diabetes-related biomarkers, in which the impact of glycaemic control, diabetes duration, and specific complications like nephropathy can vary[25]. While some correlations, like between HbA1c and AGE levels, align with the established literature, others, such as the unexpected negative correlation between HbA1c and Pentosidine, point to the need for further research[26].

Overall, this study underlines the importance of monitoring specific biomarkers in diabetic patients, as levels of AGEs and Pentosidine may vary depending on complications and glycaemic control. It also suggests the necessity for a comprehensive approach to diabetes management, considering both long-term control and individual variations that influence biomarker levels and disease progression.

Conclusion

This study revealed significantly elevated levels of AGEs and pentosidine in individuals with diabetes compared to non-diabetics. AGE levels were notably higher in patients with diabetic retinopathy, while pentosidine levels were elevated in those with diabetic peripheral neuropathy, suggesting its potential as a biomarker. Additionally, the duration of diabetes showed a positive correlation with AGE levels. These findings highlight the important role of AGEs and pentosidine in the progression of microvascular complications in type 2 diabetes, offering insights into their potential as biomarkers for these conditions.

Limitations of the study

The sample size of 149 diabetic patients, although substantial, may not be large enough to generalize the findings to the broader diabetic population. The cross-sectional design of the study captures data at a single point in time, limiting the ability to infer causality or observe changes over time, which could be addressed by longitudinal studies to track the progression of AGE and Pentosidine levels and their impact on complications. Confounding factors such as variations in diet, exercise,

medication adherence, and other comorbidities were not fully accounted for, which could influence the levels of AGEs and Pentosidine and the development of complications.

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Conflicts of interest

There is no potential conflict of interest to declare.

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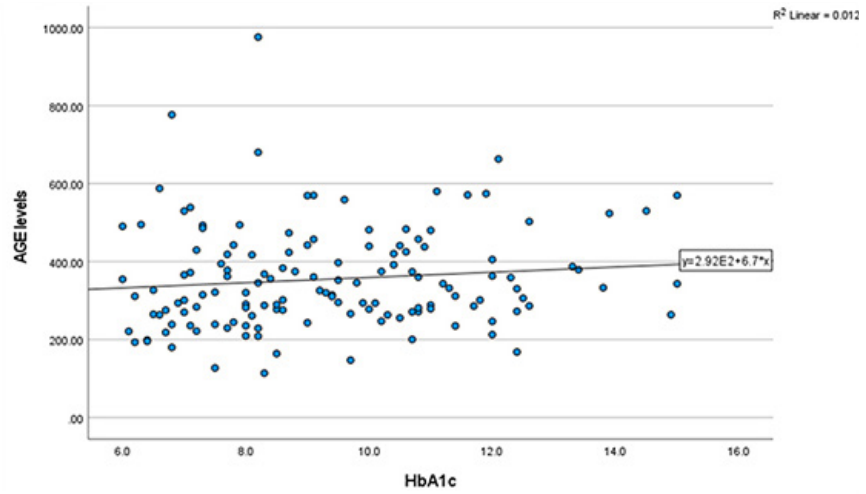

Supplementary Figure 1 Scatter diagram for correlation of advanced glycation end products (AGE) levels with HbA1c