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Assessment of Glycated Hemoglobin (HbA1c) and Serum Fructosamine as Predictors of Microvascular Complications in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Obesity is widely recognized as a serious worldwide health issue, with a clear relationship to metabolic abnormalities including insulin resistance and high blood pressure. Leptin and adiponectin, two adipose-derived hormones, serve conflicting roles in regulating vascular and metabolic activities. However, few studies have looked at their link with cardiometabolic risk in South Asian populations. The purpose of this study was to look at how serum leptin and adiponectin affect blood pressure and insulin resistance in obese Pakistani adults.

Methods: Cross-sectional study was carried out at three tertiary care facilities from January 2024 to June 2025. A total of 120 obese people (BMI ≥30 kg/m²; ages 25-60) were recruited. Demographic, anthropometric, and clinical data were gathered. Blood pressure was assessed using established methods, and fasting blood samples were tested for glucose, insulin, leptin, and adiponectin. Insulin resistance was evaluated using the homeostasis model assessment (HOMA-IR). Correlation tests and multivariate regression were used in the statistical analysis, which controlled for age, gender, and BMI.

Results: The study population's mean BMI was 33.8 ± 3.9 kg/m2, and its mean age was 44.5 ± 9.8 years, with 57.5% of the participants being female. The mean values of leptin and adiponectin were 21.5 ± 9.3 ng/mL and 6.2 ± 2.1 µg/mL, respectively. When compared to those with normotension, hypertensive participants showed considerably greater levels of leptin (25.2 ± 8.7 vs. 18.3 ± 7.2 ng/mL, $p<0.01$) and significantly lower levels of adiponectin (5.1 ± 1.8 vs. 7.2 ± 2.3 µg/mL, $p<0.01$). Systolic pressure and HOMA-IR were favorably connected with leptin ($r=0.38$ and $r=0.42$, $p<0.001$), but adiponectin was inversely correlated ($r=–0.32$ and $r=–0.39$, $p<0.01$). Both adiponectin and leptin were validated by regression models as independent predictors of insulin resistance and hypertension.

Conclusion: Obese Adults from Pakistan show a clear imbalance between leptin and adiponectin, with greater levels of leptin and lower levels of adiponectin being independently associated with insulin resistance and high blood pressure. These adipokines might guide preventative and intervention plans and act as early markers of cardiometabolic risk.

Keywords: Obesity; Leptin; Adiponectin; Hypertension; Insulin resistance

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INTRODUCTION

The hallmarks of type 2 diabetes mellitus (T2DM) are insulin resistance, reduced insulin production, and chronic and persistent hyperglycemia as a chronic progressive metabolic disease. It causes approximately 90 percent of all cases of diabetes worldwide and is among the significant health problems in the world in the twenty-first century. According to the estimates made by the International Diabetes Federation (IDF), more than 460 million individuals in the world currently have diabetes and the numbers will keep growing tremendously within the coming few decades [1]. The burden of type 2 diabetes is particularly worrying in the country as one of the highest prevalence rates of the disease are observed in South Asia and Pakistan is not an exception, as per the recent study. The primary problem of diabetes, other than the dysregulation of the metabolism, is its chronic effects, especially microvascular like diabetes retinopathy, nephropathy and neuropathy. These problems place a substantial burden on the health care systems and are the primary reason of morbidity, disability and lower life quality [2,3].

Persistent hyperglycemia is the key causative factor of such problems. Therefore, glucose control remains the cornerstone of diabetes treatment. Precise glycemic condition biomarkers are needed to monitor the treatment and predict the possibility of future problems [4]. Here, the glycated hemoglobin (HbA1c) has traditionally been considered as the gold standard. It is well associated with development of microvascular complications as shown by seminal studies such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), and is an average blood glucose level in the past 8-12 weeks. Subsequently, HbA1c is commonly recommended in diagnosing and monitoring diabetes [5].

There are however some major disadvantages of HbA1c. It may be affected by conditions which affect the longevity of red cells in the body, including anemia, hemoglobinopathies or chronic renal disease. In addition, HbA1c fails to provide any satisfactory information about the short-term change or glycemic variability that is highly considered to be the common root cause of microvascular damage. Other biomarkers have since been suggested to redress the shortcomings of serum fructosamine; they include serum galactose [6,7].

The serum fructosamine gives the indication of the average of glycemia within a two to three weeks period since the reflection of glycated plasma proteins predominantly derivative of albumin is given. It may also be especially helpful when HbA1c is inaccurate due to nondependence on red cell turnover [8]. Alongside, fructosamine has been proposed as a complement to HbA1C in clinical practice and is better responsive in explicating the short-term changes in the glycemic situation. Its usefulness as a predictor of microvascular complications in diabetes type 2 is yet to be firmly determined yet the usefulness of its utility in diabetes monitoring has been a subject of several studies [9].

The comparative and joint predictive ability of fructosamine and HbA1c in association with diabetes complications is vital since it is needed due to the following reasons. A deeper comprehension of the respective advantages is capable of improving clinical judgments and help to assess the risks of individuals with type 2 diabetes more personally [10]. Thus, the objective behind the ongoing study was to assess the association between microvascular complications such as retinopathy, nephropathy, and neuropathy and HbA1c and serum fructosamine levels in type 2

diabetes patients. This study intends to provide light on whether fructosamine may be used in conjunction with HbA1c to identify individuals who are more likely to have difficulties by comparing their predictive capacities [11].

MATERIALS AND METHODS

This study was designed as a multicenter, cross-sectional observational study that was conducted over 1 year, between February 2024 and February 2025, in numerous tertiary care hospitals in Pakistan. It was based on the involvement of both governmental and business organizations, which provided a diverse group of patients reflecting the clinical range of type 2 diabetes mellitus (T2DM) across the country. Ethical permission was obtained by the Institutional Review Boards of the sites involved in the study prior to the commencement of the study and prior to recruitment, all subjects signed the informed consent form.

A successive non-probability selection method was used to sample 100 individuals with known type 2 diabetes, who were at the internal medicine department and endocrinology department of the outpatient department. The age bracket of the patients was 35 to 70 years and they had to be on regular antidiabetic medication at least three months prior to participation and their illness must have lasted at least five years. Cancer patients, people with chronic liver diseases, thyroid troubles, type 1 diabetes or gestational diabetes were excluded. Because of potential interference with the accuracy of the HbA1c, persons with hemoglobinopathies, anemia, or recent blood transfusion were not included. Also excluded were pregnant or nursing women, and patients with severe renal impairment, which is determined as less than estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73m 2.

Demographic variables, including age, sex, body mass index, duration of diabetes, and type of therapy had been entered in a standardized proforma. Comorbid conditions such as dyslipidemia and hypertension were noted and blood pressure measure taken. Venous blood samples of all persons were collected following 810 hrs of an overnight fast. Fasting blood glucose levels were determined by the glucose oxidase-peroxidase enzymatic method. Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography that was certified to the National Glycohemoglobin Standardization Program (NGSP) and comparable to the Diabetes Control and Complications Trial (DCCT) reference. The serum fructosamine levels in the serum were measured using the nitroblue tetrazolium colorimetric test which was then reported in terms of micromoles per liter. The kidney functionality was determined through the determination of serum creatinine and the calculus of the eGFR using CKD-EPI formula. Spot urine sample was used to calculate albumin to creatinine ratio, which is the content of albumin in the urine.

All the participants had their micro-vascular issues examined. A qualified ophthalmologist examined diabetic retinopathy using a dilated fundus examination and categorized it into proliferative and non-proliferative groups using the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Diabetic nephropathy was seen through the presence of microalbuminuria; an albumin-to-creatinine ratio of above 30 mg/g or reduced eGFR of below 60 mL/min/1.73 m 2. The diabetic neuropathy was evaluated using clinical symptoms such as numbness, burning, and paresthesia. Others signs were low temperature discrimination, protective feeling loss on monofilament testing, and low vibration sensibility. A sample of people was used to

carry out nerve conduction studies in order to establish the presence of neuropathy.

All the data was inputted into and analyzed using version 26.0 of the Statistical Package of Social Sciences (SPSS). Categorical variables were provided in percentages and frequencies, and mean and standard deviation were used to provide continuous variables. The correlation coefficient of Pearson was used to determine the association between microvascular issues and HbA1c and serum fructosamine. The comparison of groups was calculated using the independent t-test/Mann-Whitney U test of continuous variables and the chi-square test of categorical data. Logistic regression analysis was applied in order to identify independent predictors of retinopathy, nephropathy, and neuropathy. To investigate the diagnostic performance of the biomarkers, Receiver Operating Characteristic (ROC) curves were generated and the area under the curve calculated with the use of HbA1c and fructosamine as well as a combination of the two. The variable was determined as statistically significant when the p-value was below 0.05.

RESULTS

Baseline Characteristics of the Study Population:

The study comprised one hundred participants with type 2 diabetes mellitus. There were 44 female participants and 56 male participants, with an average age of 55.2 ± 8.6 years. Diabetes lasted an average of 10.1 ± 4.3 years. The study group's mean body mass index (BMI) was 27.8 ± 3.5 kg/m². The majority of patients (48%), followed by oral treatment alone (36%), were receiving mixed therapy consisting of insulin and oral hypoglycemic medications. A lower percentage (16%) were receiving insulin alone. The mean fasting blood glucose level was 164.5 ± 38.7 mg/dL, the mean HbA1c was 8.2 ± 1.5%, and the mean serum fructosamine concentration was 321.6 ± 68.4 µmol/L, according to the baseline biochemical data (Table 1).

Table-1: Baseline demographic and biochemical characteristics of the study population (n = 100).

Variable	Mean ± SD / n (%)
Age (years)	55.2 ± 8.6
Gender (Male/Female)	56 (56%) / 44 (44%)
Duration of diabetes (years)	10.1 ± 4.3
Body Mass Index (kg/m²)	27.8 ± 3.5
Fasting Blood Glucose (mg/dL)	164.5 ± 38.7
HbA1c (%)	8.2 ± 1.5
Serum Fructosamine (µmol/L)	321.6 ± 68.4
Treatment (OHA / Insulin / Both)	36% / 16% / 48%

Table 1 demonstrates that the enrolled patients were predominantly middle-aged with long-standing diabetes, uncontrolled glycemic status, and a mean HbA1c value well above the recommended target range. The elevated fructosamine levels similarly reflected poor short-term glycemic control across the study population.

Prevalence of Microvascular Complications:

Out of the 100 patients, diabetic retinopathy was observed in 42% of participants, diabetic nephropathy in 36%, and diabetic neuropathy in 49%. Among retinopathy cases, 30% had non-proliferative and 12% had proliferative retinopathy. Nephropathy was predominantly in the form of microalbuminuria, although 8% of cases showed macroalbuminuria with significant reduction in eGFR. Neuropathy presented most frequently with sensory symptoms including paresthesia, numbness, and burning sensations in the lower limbs, and was confirmed in 15 patients through nerve conduction studies (Table 2).

Table-2: Distribution of microvascular complications among the study population.

Complication	Frequency (n=100)	Percentage (%)
Diabetic Retinopathy	42	42%
• Non-Proliferative	30	30%
• Proliferative	12	12%
Diabetic Nephropathy	36	36%
Diabetic Neuropathy	49	49%

As illustrated in Table 2, neuropathy emerged as the most frequent complication, followed by retinopathy and nephropathy. The prevalence pattern highlights that nearly half of the patients had neuropathic involvement, emphasizing the clinical importance of early detection strategies for this disabling condition.

Association of HbA1c and Fructosamine with Microvascular Complications:

Patients with microvascular complications had significantly higher HbA1c and serum fructosamine levels compared to those without complications. The mean HbA1c among patients with retinopathy was 9.1 ± 1.3% versus 7.5 ± 1.2% in those without ($p < 0.001$). Similarly, patients with nephropathy had a mean HbA1c of 8.9 ± 1.4% compared to 7.7 ± 1.1% in those without ($p < 0.01$). Fructosamine levels were also higher among patients with neuropathy (mean 348.7 ± 66.1 µmol/L) compared to those without neuropathy (294.3 ± 59.4 µmol/L, $p < 0.01$). These findings indicate that HbA1c correlates more strongly with retinopathy and nephropathy, whereas fructosamine shows a closer association with neuropathy (Table 3).

Table-3: Comparison of HbA1c and serum fructosamine levels in patients with and without complications.

Complication	HbA1c (%) With / Without	p-value	Fructosamine (µmol/L) With / Without	p-value
Retinopathy	9.1 ± 1.3 / 7.5 ± 1.2	<0.001	334.6 ± 70.4 / 310.2 ± 62.5	0.07
Nephropathy	8.9 ± 1.4 / 7.7 ± 1.1	<0.01	329.1 ± 68.3 / 317.6 ± 65.7	0.18
Neuropathy	8.6 ± 1.5 / 7.9 ± 1.4	0.08	348.7 ± 66.1 / 294.3 ± 59.4	<0.01

As shown in Table 3, HbA1c provided statistically significant associations with retinopathy and nephropathy, while fructosamine was a better marker for neuropathy. This reinforces the complementary role of both markers in evaluating risk across different types of microvascular complications.

Predictive Accuracy of HbA1c and Fructosamine:

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the predictive accuracy of HbA1c and serum fructosamine for the detection of microvascular complications. For retinopathy, HbA1c showed an area under the curve (AUC) of 0.83, while fructosamine demonstrated a lower AUC of 0.71. For nephropathy, HbA1c again outperformed fructosamine with an AUC of 0.80 versus 0.68. Interestingly, for neuropathy, fructosamine showed better predictive performance with an AUC of 0.76 compared to HbA1c with an AUC of 0.70. When HbA1c and fructosamine were combined in the predictive model, the overall diagnostic accuracy improved with an AUC of 0.87, suggesting that the dual-marker approach provided superior sensitivity and specificity (Table 4).

Table 4. Receiver Operating Characteristic (ROC) curve analysis of HbA1c and fructosamine.

Complication	HbA1c (AUC)	Fructosamine (AUC)	Combined (AUC)
Retinopathy	0.83	0.71	0.86
Nephropathy	0.80	0.68	0.84
Neuropathy	0.70	0.76	0.81

Table 4 clearly shows that HbA1c had superior predictive accuracy for retinopathy and nephropathy, while fructosamine provided better prediction of neuropathy. Importantly, the combination of both markers yielded the highest AUC values across all complications, supporting their complementary role in clinical practice.

Overall, the findings of this multicenter study of 100 patients with diabetes mellitus type 2 were in favor of a heavy load of microvascular complications and almost half of the patients had neuropathy and over a third of them had retinopathy and nephropathy. The HbA1c proved to be the most predictive of diabetic retinopathy and nephropathy thus it is an indication that HbA1c is the gold standard of long-term glycemic monitoring. Certificates of serum fructosamine were however more closely linked with diabetic neuropathy possibly due to its ability to report dynamic changes in glycemic variations that lead to nerve damage. As compared to markers individually, when markers were analysed together the predictive value was more impressive and therefore the twofold method of the clinical evaluation and the stratifying of the danger is fundamental.

DISCUSSION

The study was conducted in Pakistan and included tertiary care hospitals; it provides useful information regarding the predictability of the fructosamine level in serum (HbA1c) and serum (fructosamine) in developing the microvascular complications in patients with T2DM [12]. The results reinforce the view that although HbA1c still remains the strongest predictor of long-term complications which include retinopathy and nephropathy, serum fructosamine has a supplementary role, especially in the determination of neuropathic

status. The findings are of importance in a South Asian setting where the prevalence of diabetes is one of the highest worldwide and the scarcity of resources leads to the necessity of cost-effective but accurate biomarkers of risk stratification [13].

Our findings prove that HbA1c has close correlations with diabetic retinopathy and nephropathy. Patients with retinopathy were found to have a mean HbA1c of 9.1 percent vs. the 7.5 percent in those without and the patients with nephropathy had a mean of 8.9 percent vs. 7.7 percent [14]. They are similar to the findings of the UK Prospective Diabetes Study (UKPDS) where HbA1c was determined as a key determinant of microvascular risk with each 1 percent lowering in HbA1c being associated with a significant reduction in the rates of retinopathy and nephropathy. Our results are consistent with this landmark trial in strengthening the use of HbA1c as the gold standard biomarker of long-term glycemic burden [15].

Surprisingly, serum fructosamine was also reported to have a greater correlation with diabetic neuropathy compared to HbA1c. Fructosamine level was significantly higher among patients with neuropathy (348.7 μmol/L) as compared to those without neuropathy (294.3 μmol/L, $p < 0.01$). The given observation can be justified by the heightened awareness of the fact that not only short-term changes in glycemic can have an independent pathogenic effect in the development of neuropathy but also through the mechanism of oxidative stress, mitochondrial dysfunction, and microvascular ischemia [16]. HbA1c attempts to average glycemia over 8-12 weeks and therefore is prone to averaging variability but fructosamine attempts to average glycemic status over 2-3 weeks and is therefore very sensitive to changes. This could be the explanation as to why fructosamine has proved to be a more predictive factor of neuropathy in our cohort [17].

This explanation was also augmented by receiver operating characteristic (ROC) curve analysis. The area under curve (AUC) of HbA1c of retinopathy (0.83) and nephropathy (0.80) was observed to be large as compared to fructosamine (0.76 compared to 0.70 respectively) [18]. It is worth mentioning that combination of HbA1c and fructosamine had the greatest diagnostic ability with a 0.87 AUC, which indicates that a dual-marker kind of study is more sensitive and specific in identifying patients who are at risk of developing microvascular complications. Clinical implications of this finding are high and they can be interpreted as that serum fructosamine cannot be ignored despite HbA1c despite the fact that high GV or conditions affecting the red cell turnover therefore result in less predictability of HbA1C [19,20].Other advantages of fructosamine to a healthcare system with resource limits such as Pakistan include patients with complicated cases reporting late and the distribution of the laboratory resources may not be even [21].

It is cheap, technically less complex, and does not depend on hematological problems, as is typical of the local population, caused by nutritional deficiencies and comorbidities. Although it is not a substitute to HbA1c, its value as a supplementary marker is more likely to be recognized and incorporated into the guidelines of diabetes care and especially in low- and middle-income countries [22,23].

There are a number of strengths in this study. It was done in several tertiary care hospitals and, in this way, enhances the generalizability and the representation of a heterogeneous population of clinical cases. It used standardized assays of the HbA 1c and fructosamine and validated clinical and laboratory diagnoses of the complications.

However, one must admit limitations. Allowing identification of causality but not causal is the only way to remove the causality in cross-sectional design [15,18]. The adopted sample was appropriate to conduct a primary examination but it was quite small and a prospective investigation of more scale is needed to establish the verdicts. In other variables including postprandial hyperglycemia, continuous glucose monitoring(CGM) measurements, and fine-grained variability indices were unmeasured and this would have given more mechanistic understanding [19,22].

These shortcomings of take place, the results demonstrate the paradigm in which Hb A1c can be insufficient to signify the spectrum of glycemic threat. Fructosamine demonstrates a few additions of information especially in the prediction of neuropathy and clinical states with no predeterminations of HbA1c. The fact that a combination of those biomarkers is more complex is a more advanced method of monitoring glycemia and stratifying the risk of complications in patients with T2DM [23-25].

CONCLUSION

In conclusion, HbA1c was found to be the most reliable predictor of diabetic retinopathy and nephropathy and can be used to mention that HbA1c is the gold standard of long-term assessment of the glycemic indices. Nonetheless, serum fructosamine is also useful complementary data, and is particularly applicable in the prediction of diabetic neuropathy which in all likelihood can be attributed to the fact that it records short term fluctuations of the glycemia. Integrating HbA1c and fructosamine is a better predictor of overall accuracy and can be a stronger approach to the early identification of the microvascular complications. The combination of these two markers into general clinical practice, particularly in healthcare facilities with limited resources, might be helpful in further risk stratification, allow taking necessary interventions earlier, and eventually warrant better patient outcomes with type 2 diabetes mellitus.

Conflict of Interest:

The authors report no conflicts of interest.

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Authors' contributions:

ZH1: Conceptualization, study design, data collection, drafting.

TH: Data acquisition, clinical input, manuscript review.

ZHq: Biochemical analysis, data interpretation.

SA: Statistical analysis, results compilation.

SUSZ: Literature review, critical revision.

ZH2: Clinical supervision, final approval.

All authors read and approved the final manuscript.

Data Availability Statement:

The data used in this study are available upon reasonable request from the corresponding author, subject to ethical and institutional guidelines.

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