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Research Paper

Association of Glycation Gap with Renal Complication

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ABSTRACT
Aim of the study: *Insulin resistance, decreased insulin secretion, and increased glucose production is all symptoms of Type 2 Diabetes Mellitus. Blood proteins are non-enzymatically conjugated with glucose as a result of elevated blood glucose levels. HbA1c and fructosamine are produced and indicate the average blood sugar level. The difference between HbA1c and the HbA1c value anticipated from the fructosamine value is calculated as the Glycation Gap. The emergence of renal complications is linked to the glycation gap. The study's goal is to determine the link between Glycation Gap and renal complications.*
Material & Method: *A total of 59 diabetic patients with no renal complications, 60 diabetic patients with renal complications, and 64 healthy controls were included in the study. The urine albumin excretion rate (UAER) and other biochemical parameters were calculated and compared.*
Result: *In both diabetes with and without renal complications, HbA1c, fructosamine, and the Glycation Gap are significantly higher. In diabetes mellitus with complications, urine albumin excretion is significantly higher than in diabetes without complications. The Glycation Gap and urine albumin excretion rate have a favourable relationship. In diabetes, there is a link between the Glycation Gap and the occurrence of renal complications.*
Conclusion: *Glycation Gap can reflect the presence of disease and diabetic complications.*
KEYWORDS: *fructosamine, Glycation Gap, HbA1c, UAER*

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I. Introduction

Type 2 Diabetes Mellitus (DM) is a set of disorders marked by varying degrees of insulin resistance, decreased insulin secretion, and increased glucose production. Hyperglycemia is a condition caused by a genetic and metabolic impairment in insulin action and/or secretion. [1]

In 2014, the global prevalence of Type 2 diabetes was 8.5 percent. Over the last few decades, the incidence rate has risen quicker in developing and impoverished countries. [2] In 2016, India was ranked third, with a prevalence rate of 9 percent in males and 8.3 percent in females. [3] The American Diabetes Association (ADA) has proposed the following criteria for the diagnosis of DM. [4]

HbA1c ≥ 6.5% FPG ≥ 126 mg/dl
2 hours≥ 200 mg/dl

Presence of clinical symptoms of hyperglycemia or crisis, random blood sugar ≥ 200 mg/dl. Diabetic problems are known to be caused by prolonged exposure to high glucose levels. Blood glucose control is essential for such a long time. Protein glycation is thought to be a marker for the progression of diabetes complications as well as the underlying cause of the most serious complications. [5]

Glycated derivatives are formed when proteins react spontaneously with glucose. The glycation of proteins is influenced by the amount of glucose in the blood. Non-enzymatic glycation affects a wide range of proteins. In diabetes mellitus, the number of glycated proteins increases, which contributes to problems. [6-9] As the half-life of red blood cells is 12-16 weeks, HbA1c indicates the circulating plasma glucose level with a normal red blood cell life span [10] and average glycemia over the past 12-16 weeks. [11]

HbA1c is modified haemoglobin in which glucose is connected to the -chain's N-terminal valine. [12] Glucose attaches to haemoglobin in a non-enzymatic manner. [13] This is accomplished by first forming the labile adduct aldimine (Schiff base), which is then converted to the more stable ketimine form. [11] The American Diabetes Association and the World Health Organization recently proposed that HbA1c levels below 6.5 percent be used to diagnose diabetes mellitus. [14]

The DCCT (Diabetes Control and Complication Trial) found that a 1% increase in HbA1c implies a 36 mg/dl increase in blood glucose and is linked to microvascular complications. [15]

In 1982, the term "fructosan" was first used in the clinical chemistry literature to describe a generic type of glycated protein. [16] Glycation occurs in albumin, just like it does in other proteins. [17] The major Amadori adduct generated is fructolysine, which is formed when glucose reacts with albumin's lysine (59th position). Glycated albumin is the most abundant fructosamine, accounting for approximately 80% of total glycation in plasma. [18]

The gap between observed glycated haemoglobin (HbA1c) and HbA1c predicted from fructosamine is known as the Glycation Gap (GG). The difference between the observed HbA1c and the HbA1c predicted from the measured fructosamine based on the HbA1c-fructosamine regression equation, according to Cohen et al. [19] According to Ananth U. Nayak's research, a positive GG is linked to micro and macrovascular problems in diabetes. [20] Thus, the study was undertaken to evaluate the correlation of GG with renal complications.

II. MATERIAL AND METHOD

The Department of Medicine collaborated with the Department of Endocrinology at Medical College to perform this case-control study.The participants in the study gave their written consent.

The study enrolled a total of 183 participants. They were divided into three categories. Group-1 (64 numbers) was chosen as the euglycemia control group. Groups 2 and 3 (59 and 60, respectively) were diabetics without renal complications and diabetics with renal complications. The following criteria for inclusion and exclusion were chosen.

Inclusion criteria

Patients between 30-80 years of age are clinically diagnosed as cases of Diabetes Mellitus without & with renal complications.

Exclusion criteria

- Any other endocrinal disorder
- Hemoglobinopathy
- Chronic inflammatory disease
- Hypertensive patients

Collection of samples

A total of 5 mL of fasting venous blood was taken. Two millilitres were preserved in a simple vacutainer for biochemical analysis, two millilitres were transferred to an EDTA vacutainer for HbA1c measurement, and one millilitre was kept for fasting blood sugar estimation. 2 mL blood was taken after 2 hours for postprandial glucose assessment. For urinary albumin estimation, 5 mL of urine was collected.

Statistical Analysis

All the data were expressed in mean ± SD. The statistical significance was found by one-way ANOVA (post hoc test) version 20. The ‘p-value of < 0.05 was taken as significant. Pearson correlation was done to find out the correlation. A Chi-square test was used to find out the association.

III. RESULT

Demographic character & BMI

The demographic & BMI of all groups is shown in table-1. There was no observed significant difference in age,male to female ratio and BMI between all groups.

Table 1. Demographics

Parameter	Control (group-1) n=64	DM without renal complication (group-2) n=59	DM with renal complication (group-3) n=60	‘p’ value
Age in year	55.34 ± 11.09	55.83 ± 12.11	55.18 ± 11.24	**0.849**
M:F Ratio	39:25	39:20	43:20	**0.675**
BMI (kg/m^2)	**24.96 ± 3.5**	**26,87 ± 4.23**	**25.61 ± 5.17**	**0.058**

Biochemical Parameters

When comparing group -2 and group-3 study populations to group-1 study population, fasting blood sugar was considerably higher ($p<0.001$). In comparison to the group-2 population, group-3 showed a substantial increase ($p<0.001$) in fasting blood sugar. With a 'p-value of 0.05, the PPBS revealed a similar tendency.

The UAER value in the group-3 study population increased significantly ($p<0.001$) when compared to the group-2 study population. When comparing group-2 and group-3 study populations to group-1 study populations, serum creatinine levels were considerably higher ($p<0.001$), however, there was no significant

difference between group-2 and group-3 study populations.

Table 2. Comparison of the biochemical parameters

PARAMETERS	CONTROL(GROUP-1)N=64	DM WITHOUT RENAL COMPLICATION (GROUP-2) N=59	DM WITH RENAL COMPLICATION (GROUP-3) N=60	'P' VALUE
FBS (MG/DL)	85.95 ± 9.96	130.27 ± 8.12	168.4 ± 10.9	**<0.001**
PPBS (MG/DL)	94.54 ± 9.07	192.22 ± 18.08	219.34 ± 33,55	**<0.001**
UAER (MG/MIN)	-	8,8 ± 4.19	154.48 ± 63.26	**<0/001**
SERUM CREATININE (MG/DL)	**0.5 ±0.12**	**0.6 ±0.12**	**0.67 ± 0.13**	**0.232 (GR-3 VS GR-2), <0.001 GR-3 VS GR-1**

Special biochemical parameters

Table 3. Comparison of the special parameters

PARAMETER	CONTROL (GROUP-1)N=64	DM WITHOUT RENAL COMPLICATION (GROUP-2) N=59	DM WITH RENAL COMPLICATION(GROUP-3) N=60	'P' VALUE
HBA1C (IN %)	5.0 ± 0.33	8.26 ± 0.97	10.55 ± 1.7	**<0.001**
FRUCTOSAMINE (MMOL/L)	1.64 ± 0.34	2.58 ± 0.4	3.05 ± 0.4	**<0.001**
ESTIMATED HBA1C (IN %)	7.22 ± 1.0	10.05 ± 1.22	11.51 ± 1.21	**<0.001**
GLYCATION GAP (GG)	**-2.22 ± 1.08**	**-1.79 ± 1.39**	**- 0.88 ± 2.03**	**<0.001**

Table 3 shows that HbA1c levels in group-2 and group-3 study populations were substantially higher (p0.001) than in group-1 study population, with a similar significant rise in group-3 compared to the group-2 study population.

In comparison to the group-1 study population, the values of fructosamine and estimated HbA1c revealed a significant increase (p0.001) in group-2 and group-3 study populations. When compared to the group-2 study population, there was a considerable increase in group-3. When compared to group-2 and group-1 study populations, the Glycation Gap was much higher in group-3. However, as complications arise, the negative of the Glycation Gap decreases, and it becomes positive.

IV. DISCUSSION

Type 2 Diabetes Mellitus is characterised by insulin resistance, decreased insulin secretion, and increased glucose production. [1] Type 2 diabetes can cause retinopathy, nephropathy, neuropathy, myocardial infarction, and stroke. Lowering HbA1c concentrations has been shown to greatly lessen the development and progression of microvascular problems. [15,22] Glycated haemoglobin, which represents the average glucose concentration over the previous 8-12 weeks [23,24], is linked to the risk of micro and macrovascular complications. [25,26]

Because albumin in the blood has a half-life of 14-20 days, the fructosamine concentration indicates the average glucose concentration over 10-14 days, a much shorter period than HbA1c. [27]

In contrast to the study of Garber AJ et al., we found no significant differences between the study groups in terms of BMI. [28] Both diabetes mellitus without issue and diabetes mellitus with renal complication had a significant increase in HbA1c, which was consistent with Rahber et al findings [29]. In Type 2 Diabetes Mellitus, poor glycemic control is a well-known factor in the development and progression of microalbuminuria. The importance of increasing HbA1c was proven by Middleton RJ et al, [30].

Urinary albumin excretion (UAER) was found to be higher in diabetics with renal complications. A similar finding was made by Pedlersen EB et al. [31] In our research, we discovered that diabetes mellitus with

renal complications has a significantly higher fructosamine level than diabetes mellitus without renal issues. Our findings are consistent with Chen HS et al research [32] We detected a positive GG in 21 individuals with renal complications and three positive GG in patients without renal difficulty in the study. In Type 2 diabetes, GG predicts the advancement of nephropathy. The study undertaken by Rodri' guez-Segade backs this up. [32]

V. CONCLUSION

The presence of diabetes complications is indicated by the level of serum fructosamine and the Glycation Gap. As a result, a large-scale study is required.

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