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Association of Glycated Haemoglobin with Urea And Creatinine In Patients With Type 2 Diabetes Mellitus

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Abstract
Background*: Glycated haemoglobin (HbA1c) is considered a gold-standard measure of chronic glycaemia in diabetic patients. Changes in renal profile is also well related with severity of DM as ruled by HbA1c.Serum creatinine and serum urea are recognised as ideal markers to co-relate the progression of diabetic nephropathy*
Aims and objectives: *To investigate the association of serum urea and creatinine with glycosylated Haemoglobin in type 2DM patients.*
Materials and Methods: *A cross-sectional study was conducted among the patients with a history of type 2 Diabetes mellitus for the past 10 years who were attending diabetic clinic at MES Medical College and hospital, Perinthalmanna, Malappuram district, Kerala. Anthropometric measures, blood pressure, fasting serum blood glucose (FBPS), postprandial blood glucose (PPBS), HbA1c, fasting serum urea and creatinine were registered for both cases and controls.*
Results: *FBS, PPBS, HbA1C were significantly high in case group. Levels of serum urea was significantly high in case as compared to control group. Ratios of HbA1C /serum urea, HbA1C /serum creatinine showed statistically significant higher values in cases when compared to controls.HbA1c is significantly associated with serum urea and creatinine of diabetic patients.*
Conclusion*: Proper and timely regulation of blood glucose level will prevent the progression of diabetes to renal impairment*
Key words*: Association, HbA1c, serum creatinine, serum urea, Type2 DM*

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I. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycaemia due to derangement in carbohydrate, fat, and protein metabolism. It is associated with absolute or relative deficiencies in insulin secretion, insulin action or both that can lead to severe cardiovascular, renal, neurological and retinal complications.[1, 2] This serious debilitating and deadly disease has now reached epidemic proportion and the prevalence rates are expected to go even higher in the future.[3] India has a high prevalence of diabetes mellitus and the numbers are increasing at an alarming rate. In India alone, diabetes is expected to increase from 40.6 million in 2006 to 79.4 million by 2030. Studies have shown that the prevalence of diabetes in urban Indian adults is about 12.1%, the onset of which is about a decade earlier than their western counterparts and the prevalence of Type 2 diabetes is 4-6 times higher in urban than in rural areas.[4]

Reductions in β-cell mass and abnormalities of β-cell function can both be demonstrated in patients with type 2 DM and individuals at increased risk for diabetes The metabolic disease has been identified with some disorders such as mild kidney disease, endothelial dysfunction and oxidative stress. In both developed and developing countries, chronic kidney disease (CKD) is one of the main causes of morbidity and mortality. [5, 6, 7, 8] It has been suggested that in lifetime 25-45% of the diabetic patients would be developing clinically evident diabetic nephropathy. Glycosylation of tissue proteins may contribute to diabetic nephropathy apart from other microvascular complications. In diabetes mellitus, hyperglycaemia causes the excess of glucose to combine with free amino acids on circulating or tissue proteins. This non-enzymatic process initially forms reversible early glycosylation products and later irreversible advanced glycosylation end-products (AGEs) via an Amadori rearrangement. The tissue accumulation of AGEs, by crosslinking with collagen, can contribute to the associated renal and microvascular complications. Diabetic patients may reach End Stage Renal Disease (ESRD) if

diabetes mellitus is not adequately controlled. In most countries diabetic nephropathy has become the single most frequent cause of ESRD.[3]

Glycated haemoglobin (HbA1c) is formed by a non-enzymatic, irreversible process of addition of glucose to haemoglobin. The glycated haemoglobin stays in the RBCs throughout the lifespan of RBCs, and represents average glycaemia over the last 12-16 weeks. The International Diabetes Federation recommends HbA1c values below 6.5%, whereas the American Diabetes Association recommends that the HbA1c to be below 7.0% for most patients Good glycaemic control can reduce the incidence of diabetic nephropathy.[10,11] The earliest detectable abnormality of nephropathy is microalbuminuria followed by decrease in glomerular filtration rate (GFR) and increase in serum creatinine concentrations.[12]Many studies have reported nephropathy as a complication due to the long standing duration of diabetes and correlated it with microalbuminuria, hypertension,[13,14,15] but there are scarcity of studies which have assessed the relation between levels of serum creatinine and urea with glycaemic index. Thus this study was undertaken to investigate the association of glycated haemoglobin with serum urea and creatinine in patients with type 2 diabetes mellitus.

II. Materials and Methods

Data were obtained from the subjects with history of type 2 DM for the past 10 years (including male and female) who were attending diabetic clinic at MES Medical College and hospital, Perinthalmanna, Malappuram district, Kerala. A patient based cross-sectional study was conducted from December 2020 to May 2021. Patients including both individuals who were willing to participate with an age limit of 30-55, without any serious illness such as liver diseases, kidney diseases, endocrine diseases and malignancy were included for this study. All the subjects were matched according to the age and sex. Healthy subjects with an age limit of 30-55 without any clinical evidence of major diseases based on the baseline investigations were selected as controls. Written informed consent were obtained from each subject. Anthropometric measurements like, blood pressure, fasting serum blood glucose (FBPS), postprandial blood glucose (PPBS), HbA1c, serum urea and creatinine were registered.

Sampling Procedure

To determine the required sample size

$$n = \frac{r+1}{r} \frac{SD^2 (Z\beta + Z\alpha/2)^2}{d^2}$$

SD – Taken from previous studies, d = Expected mean difference between case and control
r = ratio of case and control, Z (α/2) =1.96 (5 % alpha error), Zβ = 0.84 (20% beta error)
SD – 0.65, d = 0.29, r = 2, Z (α/2) =1.96 (5 % alpha error),Zβ = 0.84 (20% beta error
The calculated sample size was 89.

Sample Collection:

Anthropometric measurements – Age, Sex, Body Mass Index (BMI), Waist Hip ratio (WHR) and blood pressure were registered. 5ml of venous blood with overnight fasting were collected in the next morning (before breakfast) for blood sugar estimation and serum lipid profile. Fasting blood sample for serum separation was collected in a clot activator tube under aseptic conditions and serum was separated. Fasting blood glucose, serum urea and creatinine were estimated using J &J Vitros 5.1FS autoanalyzer and HbA1c using whole blood were analyzed using – Immunoturbidimetric method.

Ethical Approval

The protocol was approved by Ethical Review Committee of MES Medical College on 10 October 2019 with IEC No. IEC/MES/09/2019). Research participation, confidentiality, and consent were followed as per Helsinki declaration, with local adaptation to allow both verbal and written instructions.

Statistical Analysis:

Data were examined by using the Statistical Package of Social Sciences (SPSS-IBM) version 22.0. Descriptive statistics were computed for the variables. Unpaired t test was used to establish the association between variables 'P' value was less than 0.05 was used to indicate statistical significance.

III. Results

Demographic details of the cases and controls were shown in Table 1. Statistically significant difference was obtained for the anthropometric measurements such as systolic, diastolic blood pressure, BMI and WHR among two groups ($P < 0.05$).Variations in FBS, PPBS & HbA1c levels among cases and controls were depicted in Table 2.There is increase in all three parameters in cases compared to controls which was statistically significant ($p<0.05$).

Table 1: Demographic details of cases and controls

Variables	Cases	Controls	P value
Age	48.66±6.57	47.27±2.42	0.06
Males	45	55	0.183
Females	45	35	
Body Mass Index	24.99 ±4.54	23.81±2.675	<0.05*
Waste Hip Ratio	0.91±0.002	0.89±0.005	<0.05*
SBP	128± 16.5	113.11± 8.02	<0.05*
DBP	82.7± 8.8	73.66 ± 6.94	<0.05*

***Denotes statistical significance**

Table 2: Distribution of diabetic parameters among cases and controls

Diabetic Parameters	Cases	Controls	P value
FBS	166.9±51.9	85.32 ±8.4	<0.05*
PPBS	216.25±69.1	114.34±12.33	<0.05*
HbA1c	7.91±2.14	5.13± 0.244	<0.05*

***Denotes statistical significance**

Table 3 described the results of serum urea and creatinine levels among cases and controls. Statistically significant increase in serum urea levels were seen in cases compared to controls, whereas levels of serum creatinine showed an increase among cases which was statistically insignificant. The association between serum urea and creatinine with HbA1c was depicted in Table 4. HbA1c / Urea, HbA1c /creatinine ratios were significantly higher in cases when compared to controls.

Table 3: Distribution of urea and creatinine among cases and controls

Parameters	Cases	Controls	P value
Urea	23.45± 8.1	19.1± 4.18	<0.05*
Creatinine	0.72 ±0.2	0.70± 0.16	.399

***Denotes statistical significance**

Table 4: Association of HbA1C with urea and creatinine among cases and control

Parameters	Cases	Controls	P value
HbA1c/Urea	0.36±0.13	0.28±0.06	<0.05*
HbA1c/Creatinine	11.52±3.9	7.7±1.9	<0.05*

***Denotes statistical significance**

IV. Discussion

Diabetes mellitus is a major cause of morbidity and mortality. An international study has reported that diabetes control worsened with longer duration of the disease, with neuropathy as the most common complication followed by cardiovascular complications, renal complications, retinopathy, and foot ulcers. Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. Measurement of serum urea and creatinine are easily available tests for this purpose which can assist in detection and prevention diabetic kidney disease at an early stage and can limit the progression to ESRD.[16,17] Hence, this study was undertaken to study the levels of serum creatinine and urea in Type 2 diabetes mellitus and their association with HbA1c levels.

As mentioned earlier diabetic nephropathy is the considered the commonest complication of Type 1 and Type 2 diabetes gradually leading to ESRD. Hence it is important to detect diabetic nephropathy to keep a check on the presence and thereafter progression of impaired renal function.[3] Diabetic nephropathy is clinically diagnosed with the decrease in Glomerular filtration rate (GFR), probability of hypertension, cardiovascular diseases and morbidity or mortality caused due to it. Therefore increased level of urea and creatinine with hyperglycaemia especially in patients with uncontrolled diabetes may lead to severe renal failure. Creatinine is released by the skeletal muscle as the breakdown of creatinine phosphate. GFR increases in patient with early onset of diabetes which specifies progressive loss of kidney function. Serum creatinine and serum urea are conventional markers of GFR. Serum creatinine is a more profound index of renal function test as compared to serum urea. This is because serum creatinine accomplishes most of the requirements of a perfect filtration marker. Estimation of renal damage in diabetic patients can be efficiently completed by analysing the serum urea and creatinine levels as they have proved to be useful as prognostic markers and predictors of renal damage.[18, 19]

In current study, significantly elevated mean serum level of urea and clinically elevated mean creatinine levels were figured out in patients with diabetes, which are well-identified threat causes for renal disease.HbA1c is done to monitor the control of blood glucose in diabetes mellitus. Several studies have shown

the positive correlation of HbA1c with duration of DM and as a strong predictor of risk for diabetes complications. According to a study conducted by Chutani et al. [9] Type 2 diabetic patients with high level of Hb1Ac were at a higher risk of developing kidney diseases in future. Unnikrishnan et al.[20] in his study in the Indian diabetic population had observed that poor glycaemic control is a key factor which is responsible, for micro- and macrovascular changes that occur in diabetes, predisposing diabetic patients to complications.

Mohan et al.[21] in his study had reported that although there is scarce data on the prevalence on diabetic complications in India, there is increase in number of early-onset diabetes cases which is also responsible for various diabetic complications due to longer disease duration. Hyperglycaemia may directly cause mesangial expansion and injury by increasing the mesangial cell glucose concentration. Initially, glomerular mesangium expands by cell proliferation and later by cell hypertrophy. Transforming growth factor β (TGF-β) is important in the mediation of expansion and later fibrosis by the stimulation of collagen and fibronectin.[22, 23] Glucose can bind reversibly and finally irreversibly to proteins in the kidneys and circulation to form advanced glycosylation end-products (AGEs). Due to long standing hyperglycaemia, AGEs can form complex cross-links over years and contribute to renal damage. Furthermore, TGF-β, platelet-derived growth factor and vascular endothelial growth factor are elevated in diabetic nephropathy thereby acting as mediators of proliferation and expansion, contributing to further renal and microvascular complications.[24]

In this present study, we had found a statistically significant increase in mean levels of serum urea among the diabetic patients which was in accordance with the study conducted by Bamanikar et al.[1] where diabetic individuals had significantly high level of serum urea in comparison to non-diabetic and normal control individuals. We have observed a significant difference in HbA1c / urea and HbA1c /creatinine ratios which was in line with study conducted by Chutani et al.[9] where a statistically significant association was obtained in the levels of HbA1c with serum urea and creatinine. Mishra et al.[25] in study on diabetic subjects reported that serum urea and serum creatinine in diabetic patients were significantly increased with increasing duration of diabetes and thereby concluded that increase in duration of diabetes was the risk factor for the kidney damage progression. Over a time high blood sugar level damage millions of nephron, the tiny filtering units in each kidney.[26]

The elevated levels of HbA1c can be lowered by intensive treatment plan, but the elevated levels of serum urea and creatinine which are set on increase due to permanent damage to the kidneys would be difficult to reverse because damage to the kidneys in diabetes mellitus is a permanent phenomenon. The only way to control this progressive glomerular damage and thereby elevated levels of serum urea and creatinine would be early detection and intervention. Effective control of blood glucose levels can stop progression to diabetic nephropathy and remarkably reduce the morbidity and mortality associated with this metabolic disorder.

V. Conclusion

It was concluded that elevated levels of serum urea and creatinine were seen in patients with type 2DM which are the direct markers of kidney damage. HbA1c can be considered as an indirect predictor for kidney diseases in addition to as a biomarker for glycaemic control. Thus this present study suggested the importance of glycaemic control in early prevention of diabetic nephropathy.

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