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HbA1c / Creatinine Ratio as an Index of Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus (DM) is a genetic and/or lifestyle disease which had wide ramifications affecting the functioning of several organs. As of now, approximately 35% of Indian population are with DM. Uncontrolled DM will lead to many other diseases, the first being the alterations in kidney function followed by cardiac and liver diseases. About 45% of kidney diseases are caused by uncontrolled DM. HbA1c and serum creatinine are the two gold standards for the monitoring and control of DM and kidney disease and there must exist some association between them. This research article presents an association found between these analytes and depicts HbA1c/ Creatinine ratio as an Index to assess the progression and control of DM in a group of patients with T2DM. Very good association was found between HbA1c and creatinine as well as HbA1c to the ratio, both for controls and patients ($p < 0.0001$). The outcome of this study strongly suggests that all patients undergoing treatment for T2DM be investigated for serum creatinine to ascertain kidney function.

Keywords: DM, HbA1c, Creatinine, Obesity, CKD

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INTRODUCTION

Uncontrolled DM will lead to many complications and the organ first affected is kidney. There are many contributing factors for the development of T2DM among which modern life style, junk food and obesity play a major role. HbA1c is the gold standard to monitor Diabetic Control during the preceding 2 to 3 months and its persistent elevation will cause kidney failure and the two markers used to evaluate it are serum creatinine and urinary excretion of proteins. Hence there must exist a relationship between HbA1c and creatinine. The aim of this study is to find out the association between them in a group of T2DM patients as well as normal controls.

Obesity and excessive inflammation/oxidative stress are pathophysiological foctors associated with kidney dysfunction. Treatment with hemin reduced renal histo-pathological lesions including glomerular-hypertrophy, tubular-cast, tubular-atrophy and mononuclear cell-infiltration in Hemin treated Zucker-Fatty rats. Importantly, the concomitant potentiation regeneration proteins and podocyte cytoskeletal proteins are novel mechanisms by which hemin rescue nephropathy in obesity[1] The worldwide prevalence of obesity and its associated metabolic and cardiovascular disorders has risen dramatically within the past 2 decades. There is a growing awareness of the renal consequences of obesity, and considerable progress is being made in understanding its pathophysiology. Weight reduction results in lowered proteinuria. Aside from low sodium diet and exercises, more widespread use of renoprotective therapy (e.g., ACE inhibitors and statins) in treatment of hypertension in obese subjects should be advocated. Renal protection should result in reducing the cardiovascular complications of obesity.[2] Current evidence suggests that excess weight gain may be responsible for 65-75% of the risk for essential hypertension. Abnormal renal pressure natriuresis, due initially to increased renal tubular sodium reabsorption, is a key factor linking obesity with hypertension. Excess visceral adipose tissue may physically compress the kidneys, increasing intrarenal pressures and tubular reabsorption. Sustained obesity eventually causes structural changes in the kidneys and loss of nephron function, further increasing arterial pressure and leading to severe renal disease in some cases.[3]

Abnormal kidney function is an important cause as well as a consequence of obesity. Excess renal sodium reabsorption, probably in the loop of Henle, and a hypertensive shift of pressure natriuresis play a major role in initiating increased blood pressure associated with weight gain. Obesity is the main cause of T2DM and an important cause of human essential hypertension, it seems likely that obesity is also one of the most important risk factors for

End-Stage Renal Disease (ESRD).[4] Obesity increases renal sodium reabsorption and impairs pressure natriuresis by activation of the renin-angiotensin and sympathetic nervous systems and by altered intrarenal physical forces. Chronic obesity also causes marked structural changes in the kidneys that eventually lead to a loss of nephron function, further increases in arterial pressure, and severe renal injury in some cases. Although there are many unanswered questions about the mechanisms of obesity hypertension and renal disease, this is one of the most promising areas for future research, especially in view of the growing, worldwide "epidemic" of obesity.[5] Excess weight gain is a major risk factor for essential hypertension and for ESRD. Obesity raises blood pressure by increasing renal tubular sodium reabsorption, impairing pressure natriuresis, and causing volume expansion because of activation of the sympathetic nervous system and renin-angiotensin system and by physical compression of the kidneys, especially when visceral obesity is present. Weight reduction is an essential first step in the management of obesity, hypertension, and kidney disease. Special considerations for the obese patient, in addition to adequately controlling the blood pressure, include correction of the metabolic abnormalities and protection of the kidneys from further injury.[6]

Obesity-induced hypertension, like all forms of experimental and human hypertension studied thus far, is associated with renal dysfunction characterized by the resetting of pressure natriuresis. In obese subjects, this resetting is primarily a result of increased renal tubular reabsorption as Glomerular Filtration Rate (GFR) and renal blood flow are markedly reduced. Obesity may also be attributable to altered intrarenal forces caused by histologic changes in the renal medulla that may compress the loops of Henle and vasa recta, increase tubular sodium reabsorption, and activate the renin-angiotensin system. The quantitative importance of these intrarenal changes and their interrelationship with neurohumoral activation in obesity is an important area for further investigation.[7] Recent studies show that adipose tissue is a complex organ with functions far beyond the mere storage of energy. Indeed, it has recently been shown that fat tissue secretes a number of adipokines - including leptin, adiponectin and retinol-binding protein, as well as cytokines such as resistin, visfatin, tumor necrosis factor and interleukin-6. Adipokine serum levels are furthermore markedly elevated in Chronic Kidney Disease (CKD), likely due to a decreased renal excretion. Evidence suggests that these pluripotent signaling molecules may have multiple effects modulating insulin signaling, endothelial health and putatively Cardio Vascular Disease (CVD). As fat tissue is also a storage depot for energy, much needed in the catabolic milieu of uremia, further research is still needed to elucidate the likely complex interactions between these signaling networks, vascular health and outcome in this high-risk population[8] The incidence and prevalence of obesity has risen markedly in the last decade, and this epidemic

represents a serious health hazard with significant morbidity and mortality. In conditions of chronic hyperleptinemia, such as obesity, leptin may function pathophysiologically for the development of hypertension as well as cardiac and renal disease. Thus, in addition to weight control, reduction of circulating leptin may confer cardiovascular and renal protective effects in patients with obesity induced hypertension.[9]

Close correlation seems to be between the worsening of renal functions and the decrease of thrombocyte sensitivity in DM: The hypercholesterinemia observed in nephropathic diabetes did not lead to the hyper aggregability known in familial hypercholesterinemia. Thus it appears likely that the increase in cholesterine level in the serum does not influence directly, but rather by the effects in connection with its origin, differently the thrombocyte reactivity.[10]

Statistically significant differences were observed in the Hemoglobin (Hb) concentrations when comparing individuals classified with different stages of CKD in the younger and elderly groups. In the younger group, there was no significant difference in the Hb concentrations between the stage 3a and 3b CKD patients. However, in the elderly group, the Hb concentrations were significantly higher in patients classified with stage 3a CKD when compared with those with stage 3b, whose GFR cutoff point was <60 ml/min/1.73 m^2, indicating that Hb levels may be used to discriminate stages of CKD in elderly patients; thus, Hb may be used as a biomarker to assess the severity of CKD.[11]

Systematic assays of glycosylated haemoglobin (HbA1c) were performed to verify that pregnant women with glycosuria and normal fasting blood glucose and glucose tolerance tests had no disturbances in glycoregulation . On the third trimester, HbA1c levels were significantly higher in glycosuric women of normal weight than in controls. They were also significantly higher in obese glycosuric women than in controls of the same weight and exceeded normal limits, highlighting better detection (by glucose tolerance test) and better supervision of women with "renal" diabetes.[12] Both T1DM & T2DM accounts for 60% of the ESRD attributed to diabetes in the United States, yet little is known about glomerular function or the development of renal disease in this type of diabetes. The Diabetic Renal Disease Study (DRDS) is designed to provide new information on the functional determinants of renal disease in both forms of DM and will serve as the basis for designing intervention strategies.[13]

Studies of glomerular structure and hemodynamic function in diabetic Pima Indians indicate that glomerular hyperfiltration often develops at the onset of T1DM and remains elevated until after overt nephropathy appears. Structurally, the glomeruli in subjects with microalbuminuria are not clearly distinguishable from those in subjects with normoalbuminuria, but macroalbuminuria is characterized by extensive glomerular sclerosis,

mesangial expansion, and widening of epithelial cell foot processes that together lead to a rapid decline in GFR. The decline in glomerular function in subjects with macroalbuminuria is due both to a loss of ultrafiltration surface area and to reduction in glomerular hydraulic permeability.[14] Patients with CKD have significant changes in serum and urinary concentration of several amino acids and changes in renal clearance of some specific amino acids. Normalization of cortisol levels restored the amino acid profile.[15]

Disturbed amino acid metabolism may be a more important causative factor in the etiology of diabetic microangiopathy than hitherto recognized and, in addition, that this may affect the therapeutic approach in both T1DM & T2DM patients.[16] In both cirrhotic patients and control subjects, combined hyperinsulinemia/hyperaminoacidemia elicited a similar stimulation of non-oxidative leucine disposal (an index of protein synthesis) and leucine oxidation while causing a greater suppression of endogenous leucine flux than observed with insulin alone. Thus the suppressive effect of insulin on protein degradation and the stimulatory effect of insulin/amino acid infusion on protein synthesis are not impaired in cirrhotic patients, demonstrating a clear-cut dissociation between the effects of insulin on protein and glucose metabolism.[17]

The use of angiotensin-converting enzyme inhibitors, which has been reported to be associated with an inhibition of erythropoiesis, does not seem to have a clinically significant effect on haemoglobin levels. In order to address all the independent risk factors in diabetic ESRD, optimal management of these patients should involve interdisciplinary care (diabetologist and nephrologist) and consideration of correction of anaemia.[18] Co-incubation with glucose and hydrogen peroxide synergistically increased Carboxy Methyl Valine-Hb (CMV-Hb) formation. The CMV-Hb level was higher in the diabetic group than the non-diabetic group, and CMV-Hb was correlated with the plasma total cholesterol and serum creatinine levels. The CMV-Hb level was decreased by antioxidant therapy, whereas HbA1c did not change. These results demonstrate that CMV-Hb may be a useful marker for accumulation of oxidative stress in diabetic patients.[19]

MATERIALS AND METHOD

25 male patients and an equal number of controls in the age group of 30-80 years were selected for this study. For control patients attending Master Health Checkup (MHC) were enrolled and for patients, those attending the Diabetic Clinic were selected. The main objective of this study was to find out the association between HbA1c and Creatinine as well as to HbA1c/Creatinine ratio both for Controls and Patients with T2DM.

Diuri CS 1300 B analyser and Dialab reagents were used to measure Creatinine and Biorad D10 analyser and the kit supplied by that company was used to measure HbA1c. The

accuracy of these analytes were validated by the use of Bio-Rad accuracy controls at two levels.

Inclusion criteria

Patients who attended the Endocrine Clinic and whose HbA1c >6.5% and Creatinine >1.3mg/dL were included.

25 patients who attended the routine Master Health Checkup and whose HbA1c and creatinine levels were normal served as controls.

Exclusion criteria

Patients who attended the Diabetic Clinic and whose HbA1c values <6.5% and Creatinine values <1.3mg/dL were excluded.

For statistical analysis of data, a software downloaded from the website http://www.graphpadquickcalcs.com was used to calculate, students 't' distribution (t) and probability (p) between the group of analytes studied for both controls and between controls and patients.

RESULTS AND DISCUSSION

Table I: Mean & SD for Control & Patient groups (n=25)

Group	n	Analytes					
		HbA1c		Creatinine		HbA1c/Creatinine ratio	
		Mean	SD	Mean	SD	Mean	SD
Controls (n=25)	25	5.5	0.297	0.8	0.147	6.83	1.136
Patients (n=25)	25	8.6	1.653	2.17	1.058	4.57	1.557

Table II: Statistical Parameters (t & p) for Controls & Patients groups

Groups compared	t	p
Controls		
HbA1c vs Creatinine	70.91	<0.0001
HbA1c vs ratio	5.66	<0.0001
Creatinine vs ratio	26.32	<0.0001
Patients		
HbA1c vs Creatinine	16.38	<0.0001
HbA1c vs ratio	8.87	<0.0001
Creatinine vs ratio	6.37	<0.0001

Table I presents the Mean & SD for HbA1c and creatinine for both controls and patients. It is clear from this Table that significant increases are observed for patients HbA1c & Creatinine and HbA1c/Creatinine ratio compared to controls and a visual inspection certainly reveals an excellent association may exist between these groups for the three analytes studied.

Table II shows the statistical parameters viz t & p between HbA1c & Creatinine and also to the ratio for both Controls & patients. A highly significant association ($p<0.0001$) was observed between HbA1c and Creatinine as well as to the ratio, both for controls and

patients. This strongly suggests that creatinine will indeed be altered in all uncontrolled T2DM patients.

Numerous studies have been done in the field of laboratory diagnosis related to DM, especially T2DM. While HbA1c serves as the reliable marker to monitor diabetic control during the preceding 2-3 months, serum creatinine is the most important test to evaluate kidney function. Studies done in the past have linked uncontrolled DM to kidney diseases and hence there must exist an association between these markers and obesity induced DM will induce progression of kidney diseases [4]. A close relationship has also been observed between the severity of DM and worsening of kidney diseases [10,11]. Further Hemoglobin levels are also directly linked to HbA1c. Based on these previous observations, this study outcome has established a close link between DM and Kidney Function by finding an association between the Diabetic control marker HbA1c to Kidney function marker Creatinine.

CONCLUSION

In many previous studies done in the past linking DM to CKD, no correlation between HbA1c and Creatinine was done, and hence this study was undertaken to link these two diseases based on the laboratory diagnostic indices HbA1c and Creatinine. The outcome this study has strongly established an association ($P< 0.0001$) between HbA1c and Creatinine and the ratio between Hba1c to Creatinine, both for controls and patients. The outcome this study strongly suggests that all patients undergoing treatment for T2DM be investigated for serum creatinine to ascertain kidney function.

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