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RESEARCH ARTICLE

STUDY OF GLYCEMIC BIOMARKERS IN DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Background: Diabetic nephropathy is the most common aetiology of end stage kidney disease (ESKD). Strict glycemic control reduces the development and progression of diabetes-related complications, and there is evidence that improved metabolic control improves outcomes in diabetic subjects with chronic kidney disease (CKD). **Materials and Methods**: The present study has been conducted on 150 diagnosed & clinically established patients of Diabetes mellitus with nephropathy,who attended OPD and wards of Medicine and Department of Urology, J.L.N. Medical College and Associated group of Hospitals, Ajmer. These patients were compared with 150 Diabetic without nephropathy subjects. Anthropometric measurements and biochemical estimations were performed. Ethicalclearance was obtained before start of the study. **Results**: The Mean ± SD values of blood glucose (Fasting & PP), serum creatinine, serum fructosamine, GHb and serum glycated albumin were observed statistically highly significant ($p<0.0001$) in CKD-3 subjects as compared with non CKD subjects.**Conclusion:** Prospective studies testing pre-specified diabetes control targets based on glycated albumin and continuous glucose measurement remain to be performed in order to determine whether morbidity and mortality would be reduced with intensive glycemic control using these measurements as reference target.

Introduction:

The global incidence of diabetes mellitus is rising exponentially and diabetic nephropathy is now the predominant cause of chronic kidney disease (CKD) [29]. Diabetic nephropathy causing end-stage kidney disease (ESKD) accounts for 30– 50% of all new patients commencing renal replacement therapy (RRT) [6, 27]. Overall, there is evidence in the general diabetic population implying that tight glycaemic control may reduce the development and progression of diabetic complications and there are suggestive data that metabolic control improves outcomes in the CKD population. Current guidelines recommend achieving and maintaining normoglycemia by implementing intensive treatment in people with CKD [20]. However, there is suggestive data that in ESKD patients with comorbidities and malnutrition, higher Glycated haemoglobin (HbA1c) target values might be favourable [16]. Glycaemic control in the presence of CKD is complicated by altered glucose and insulin homeostasis. Decrease in renal metabolism and clearance results in a prolonged duration of insulin action [17]. Blood glucose concentrations may decline with progressive nephropathy due to malnutrition and reduced renal gluconeogenesis [11]. Furthermore, glucose and insulin levels are influenced by the HD procedure by increased clearance [1] and equally, the high-

glucose concentrate dialysate used in PD impacts on serum glucose levels substantially [18]. Glycated proteins, Other glycated plasma proteins include fructosamine (FA) and glycated albumin (GA) which are also formed non-enzymatically when proteins react with glucose in a similar manner to the formation of HbA1c [4, 10]. However, the turnover of plasma proteins is much shorter than haemoglobin (half life ~2–3 weeks), thus the degree of glycated plasma proteins provide an index of glycaemia over a shorter period of time. Measurements of glycated serum proteins show a good correlation with HbA1c and plasma glucose concentrations in diabetic subjects without renal disease and therefore have been suggested as alternative methods to assess metabolic control in diabetes [7, 14]. Glycated albumin, Similar to fructosamine, GA provides a short-term index of glycaemic control and is not influenced by albumin concentration, as the glycation component is calculated as a ratio of total albumin concentration [10, 22]. In addition, GA is not affected by RBC lifespan or rHuEpo administration [13, 21] and other limitations affecting HbA1c and fructosamine values. In diabetic subjects, GA has strong correlations with glucose and provides a reliable index of glycaemic control over the preceding 2–3 weeks [23]. GA concentrations increase and decrease more rapidly with fluctuations in overall glucose compared to HbA1c, allowing rapid changes to be detected at an earlier stage [24]. It has been revealed that increased levels of GA are linked to both the presence and severity of cardiovascular disease and impaired kidney function. Observations of the biological properties of GA have been related to the pathogenesis of diabetic vascular complications [3]. As such, GA is perhaps a more reliable measure of glycaemic control as well as a predictor of developing vascular complications, in people with diabetes and nephropathy.

Materials and Methods:

The present study has been conducted on 150 diagnosed & clinically established patients of Diabetes mellitus (type-I & type-II) with nephropathy,who attended OPD and wards of Medicine and Departement of Urology, J.L.N. Medical College and Associated group of Hospitals, Ajmer. These patients were compared with 150 Diabetic (type-I & type-II) without nephropathy subjects. They were divided according to the classification of chronic kidney disease (eGFR-MDRD) into CKD stage 1, 2 and 3 (eGFR>90, 89-60 and 59-30 ml/min/1.73 m^2, respectively) .The study was carried out in the department of Biochemistry at J.L.N. Medical College, Ajmer over a period of two year. The study was approved by the Ethics committee of our college. All the anthropometric measurements including height, weight, body mass index (BMI) and blood pressure (BP) were performed. Blood sample collection was done by aseptic technique and subjected to the biochemical estimations. The glycemic profile which consisted of fasting blood glucose (FBG), post prandial blood glucose (PPBG) (by Enzymatic GOD-POD End point method), HbA1c (by Cation–exchange resin method), serum fructosamine (By Nitro Blue Tetrazolium method) and serum Glycated Haemoglobin (Enzyme Linked Immunosorbent Assay.) and serum creatinine (Jaffe's colorimetric kinetic method) were estimated / calculated in the groups. Patients on treatment for any thyroid dysfunction and taking medication due to thyroid disorder , uncontrolled hypertension, renal tumor, renal replacement therapy, non-diabetic CKD, polycystic kidney disease, renal malformation or agenesis, cancer, patient on glucocorticoids therapy, HIV positive case and pregnant women were excluded. Statistical significance is tested by assuming mean ranks in the test. P values < 0.05were considered significant.

Results:

The present study had been concluded on 300 subjects with age group (18-70 years). These were further divided into 2 groups. Group I comprised of 150 subjects who were Diabetic without Nephropathy (control), Group II comprised of 150 subjects who were Diabetic with Nephropathy patients.

Table:1 Distribution of the subjects studied in relation to Diabetes

S. No.	Group Studied	No. of subjects		Total
		Type I Diabetes	Type II Diabetes	
1	DiabetesWithout Nephropathy	27	123	150
2	Diabetes with Nephropathy	35	115	150
	Total	62	238	300

Table:2 Comparison of parameters of the subjects studied

S.	Parameters	Group I	CKD-1(n=60)	CKD-2(n=70)	CKD-3(n=20)

No.		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
1	Blood Sugar (F) (mg/dl)	111.22±12.88	106.98±12.84	112.77±11.39	123.33±9.45*
2	Blood Sugar (PP) (mg/dl)	158.54±24.63	158.54±24.63	148.83±16.77	172.69±50.36*
3	Serum Creatinine (mg/dl)	0.75±0.08	0.78±0.09	1.07±0.16	1.34±0.14*
4	SerumFructosamine (µmol/L)	291.56±9.55	287.75±13.71	291.34±14.29	279.2±8.46[@]
5	Glycated Haemoglobin (%)	8.01±0.97	6.84±0.43[#]	7.65±1.03	6.67±0.48[#]
6	Glycated Albumin (%)	21.33±2.73	19.31±2.35*	21.94±2.56	5.33±2.55[@]

*Highly Significant as compared to diabetic without nephropathy (non-CKD) (P value <0.0001)
[@] Highly Significant as compared to non-CKD or CKD-1 or 2 (P value <0.0001)
[#] Highly Significant as compared to non-CKD or CKD-2 (P value <0.0001)

Table:2 illustrates the mean value of Bood Glucose (Fasting & PP) and Serum creatinine levels were elevated in the CKD-3, even with lower serum fructosamine levels. Serum fructosamine was observed statistically highly significant (p<0.001) in CKD-3 subjects when compared with non CKD or CKD 1 or 2 subjects. GHb value in CKD stage 1 **(6.84±0.43)** and CKD stage 3 **(6.67±0.48)** is highly significant (p<0.0001) as compared to non CKD **(8.01±0.97)**, CKD stage 2 **(7.65±1.03)** and serum glycated albumin in CKD stage 3 **(25.33±2.55)** is highly significant (p<0.0001) as compared to non CKD **(21.33±2.73)**, CKD stage 1 **(19.31±2.35)** and CKD stage 2 **(21.94±2.56)**.

Discussion:

Diabetes is a major health problem among CKD patients and is the leading cause of end stage renal disease (ESRD). National kidney foundation has defined chronic kidney disease (CKD) as either kidney damage or glomerular filtration rate (GFR) below 60 ml/min/1.73m2 for three or more months with or without evidence of kidney damage, irrespective of the cause.[19] Improved glycemic control slows the progression of CKD. We also found significant change in haemoglobin concentrations (Table-2) with change in eGFR. Haemoglobin was found to be significantly reduced in group 2 subjects compared to group 1 subjects. CKD is associated with erythropoietin (EPO) deficiency and normochromic normocytic anemia. EPO deficiency is because of transformation of peritubular fibroblasts into myofibroblasts. Therefore haemoglobin cannot be produced. In early stages of CKD, there is inverse relation between Hb and EPO release. Increase EPO compensates for decrease in Hb. As disease advances a direct relation is seen between Hb and EPO. Therefore in advanced stages of renal failure HbA1c levels may not predict the glycemic status of individual. There was no significant differences in gender, age or Body Mass Index (BMI) between diabetic without nephropathy and diabetic with nephropathy subjects. **Vijay vishwanathan et al. (2009)**, **JP Rivelie et al. (2009)** and **Harn-Shen-Chen et al. (2010)** this study also support that sex, age or BMI were similar between the diabetic CKD and diabetic non-CKD patients. No significant differences were observed in mean blood glucose, glycated albumin and fructosamine between both diabetic without nephropathy and diabetic with nephropathy subjects. **Frederick E Vos et al. (2011)** also stated that no significant differences were observed in average blood glucose obtained by CGM (continuous glucose monitoring), Glycated albumin and Fructosamine between both study groups. **Frederick E Vos et al. (2012)** show that albumin is glycated in a similar manner as haemoglobin but is not affected by RBC lifespan, or Erythropoietin stimulating agents (ESA) administration. As such GA is suggested to be more appropriate measure of glycations in CKD due to diabetes. GA appears to be superior in accuracy as a marker of glycaemic control compared with fructosamine and HbA1c in patients with diabetic nephropathy. The results of the present study are in accordance to the previous studies done by Schleicher E et al. (1989), E Lamb et al. (1993), Mai-Szu Wu et al. (1997), Takahashi S. et al. (2007) , Peacock TP et al. (2008) , Vijay Viswanthan et al. (2009), Satyavani K et al. (2011) and Agarwal R et al. (2011),

Conclusion:

Prospective studies testing pre-specified diabetes control targets based on glycated albumin and continuous glucose measurement remain to be performed in order to determine whether morbidity and mortality would be reduced with intensive glycaemic control using these measurements as reference target.

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