

Variation of Glycosylated Hemoglobin (HbA1C) Cutoff among type-2 diabetic nephropathy Patients

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Abstract

Objectives: The aim of the study was to determine glycosylated hemoglobin (HbA1c) cut-off and lipid correlation, duration of diabetes with level of proteinuria.

Materials And Methods: Cross sectional study was done on 250 patients with type-2 diabetes mellitus subjects attending medicine clinic, King George's medical university (KGMU) Lucknow, India. Subjects were screened for diabetic nephropathy depending on the base line parameter, clinical history of disease and documented in pre-tested proforma. Routine blood parameters, HbA1C and 24 hrs urine microalbumin level were carried out in department of pathology.

Result: The level of HbA1c was higher among the patients of nephropathy (8.54±0.97) compared with non-nephropathy (7.32±0.84, 95%CI=7.17-7.47). Increased HbA1c was found among both 5-10 and >10 years diabetic duration. However, HbA1c was similar among all duration of diabetes groups within non-nephropathy. The total cholesterol (TC), HDL cholesterol (HDL-c), LDL cholesterol (LDL-c) and VLDL cholesterol (VLDL-C) were almost similar in HbA1c range <7, 7-8.9 and 9-10.9 and without insignificant differences (p>0.05). Although, Triglyceride (TG) level was significantly higher in HbA1c 9-10.9 (174.20±48.95mg%) than 7-8.9 (159.66±31.47mg%) and <7 (158.82±29.67mg%). High prevalence of nephropathy was found among HbA1c range 9-10.9 (Urine albumin :246.35±126.29mg/d) compared with 7-8.99 (Urine albumin :159.89±70.16mg/d) and <7 (Urine albumin :132.80±90.33mg/d) respectively.

Conclusion : HbA1c cut-off >7 % should be considered as an index of glycemic control as well as important tool for over all metabolic derangement and target organ damage among diabetes population. Hence, establishment of HbA1c cut-off value with long duration of diabetes might be useful for prediction of treatment control and prevention of renal failure.

Keywords; Diabetic Nephropathy; Glycosylated Hemoglobin; Triglyceride; Renal failure

Introduction

Diabetes Mellitus (DM) is a metabolic disorder associated with micro- and macro-vascular complications. Microvascular complications include neuropathy, retinopathy, and nephropathy. Macrovascular complications are coronary artery and peripheral artery disease. In large major complication is linked with all major organ damage leads to morbidity and mortality.[1,2]

Diabetic nephropathy (DN) is leading cause of end stage renal disease (ESRD) associated with high rates of morbidity and mortality.[3] Early identification and treatment of nephropathy complication can reduce the medical and economic burden of major damage.[4] Although microalbuminuria is a widely used indicator for diabetic nephropathy, its diagnostic accuracy is limited by the fact that structural damage might precede albumin excretion.[5]

Numerous guidelines have defined HbA1c as marker of mean blood glucose levels and as a priority therapeutically.[6] Chronic hyperglycemia is responsible for the development of complications in diabetes patients. Furthermore, glucose variability could be a predictor of complications. Glucose variability could be defined in several ways: within-day variability, between-day variability and long-term variability expressed using changes in HbA1c. [7] Diabetes Control and Complications Trial (DCCT) evidenced that HbA1c variability, similar to mean A1c levels, could predict the development of nephropathy and retinopathy in T1DM patients. [8] Intra-person standard deviation in HbA1C was an independent risk factor for the development of microalbuminuria in T2DM Tsukuba Kawai Diabetes Registry. [9]

Although numerous prevalence and incidence risk factors studies have been carried out to rule out correlation for diabetic nephropathy but limitation of prognostic as well as biomarker of glycemic control was not emphasized properly in previous studies. Aim of this study to determine association of HbA1c cut-off variation in nephropathy complication with relation to duration of diabetes and dyslipidemia.

Material & Methods

The cross sectional study designs were used for risk factors for nephropathy. The study has been carried out in type-2 diabetic mellitus subjects attending medicine clinic, KGMU, had been screened for nephropathy. Institutional Ethical Committee of KGMU granted ethical clearance for study in 2014. Diabetic in the age group of 40 - 69 years, with fixed OHA dosage and receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for screening of microalbuminuria were recruited.

Diabetic subjects with other concurrent acute illness including infectious disease, malignancy, active immunological diseases, medical history of clinical cardiovascular disease, tuberculosis, pregnancy, lactation, using corticosteroids or other medicines such as statins, or vitamins, or mineral supplements in the past 3 months, severe uncontrolled hypertension (> 140/90 mmHg) or renal insufficiency (serum creatinine > 1.5 mg/dl), who were receiving insulin preparations as a part of diabetes management, individuals with hematuria/pyuria/urinary tract infections/ketonuria at the time of screening, who had performed strenuous physical exercise and smoking history were excluded from the study.

The risk of nephropathy among type-2 diabetes was being reported to be 15-20%.10(Vishwanathan et.al, 1998). Assuming 80% power and 5% significance level, the sample size was calculated by using the formula for risk factor objective, the calculated sample size was 246. Therefore, total of 250 patients were enrolled in the study for risk factor of nephropathy.

Routine Blood Parameter and HbA1c was estimated in ethylenediaminetetraacetic acid anti coagulated whole blood by ion exchange chromatography. TC, TG, HDL-c were measured by enzymatic methods using Hitachi 917 auto analyzer with its original reagent. (Accurex Biochemical Pvt. Ltd, Mumbai, India).

24 hrs Urine albumin estimation was done after persistent proteinuria detection by dipstick methods a gap of one week and urine microscopic examination to rule out any infection, then 24-h quantitative determination of microalbumin in urine by turbid metric immunoassay based on antigen- antibody reaction in measurement by the end point method (Erba Diagnostics Mannheim GmbH, Mallastrasse Mannheim / Germany.).

Statistical analysis

The data collected was entered in Microsoft Excel program and was checked for any inconsistency. A one - sample Kolmogorov - Smirnov test was used to investigate whether the variables were normally distributed. The unpaired t- test was used to investigate the differences at the baseline values among two groups. The statistical significance was accepted at a probability level of less than 0.05. Analyses were performed by using SPSS software package (WINDOWS version 15.0: SPSS Inc., Chicago, IL,USA).

Result

Mean age was almost similar among both groups. Long duration of diabetes 11.57±3.58 years was found in nephropathy. Blood pressures were significantly (p<0.0001) higher among nephropathy (systolic: 133.52±6.81, diastolic: 81.09±4.74 mmhg) as compared to non-nephropathy ((systolic: 129.12±4.58, diastolic: 77.24±7.36). Fasting blood glucose (FBG) was higher among nephropathy (153.37±34.24) than non-nephropathy (123.54±51.78) and post-prandial blood glucose (PPBG) similar difference was observed. (Table-1) The level of HbA1c was higher among nephropathy (8.54±0.97, 95%CI=8.37-8.71) than non-nephropathy (7.32±0.84, 95%CI=7.17-7.47). (Fig:1).

Table 1: Comparison of baseline characteristics of Type-2 Diabetic subjects

Characteristics	Non-nephropathy (n=120)	Nephropathy (n=130)	p-value
Age in years	54.86±8.48	57.37±6.21	0.06
Duration of diabetes (years)	7.22±1.83	11.57±3.58	0.001
BMI (kg/m ²)	24.76±2.22	27.14±2.06	0.0001
Systolic blood pressure (mmHg)	129.12±4.58	133.52±6.81	0.0001
Diastolic blood pressure (mmHg)	77.24±7.36	81.09±4.74	0.0001
Fasting blood sugar	123.54±51.78	153.37±34.24	0.0001
Post-prandial blood sugar	171.06±37.70	208.09±51.38	0.0001
HbA1c	7.17±0.84	8.37±0.97	0.0001
Serum urea	22.55±6.84	30.10±6.56	0.0001
Serum creatinine	0.92±0.31	1.14±0.28	0.0001

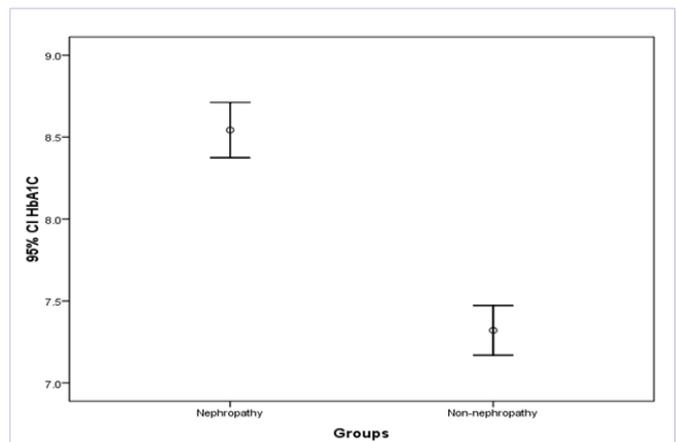


Figure 1: HbA1c level between nephropathy and non-nephropathy patients

The HbA1c was significantly (p=0.008) higher among nephropathy (7.90±0.45) patients of duration <5 years than non-nephropathy (7.17±0.75) patients. Similar observation was found for duration of diabetes of 5-10. The HbA1c was significantly (p=0.03) different between duration of diabetes <5 vs 5-10 (p=0.04) and <5 vs >10 (p=0.02) years within nephropathy patients. However, HbA1c was similar among all duration of diabetes groups within non-nephropathy patients (Fig 2).

TC, HDL-c, LDL-c and VLDL-c were almost similar in HbA1c <7, 7-8.9 and 9-10.9 without insignificant difference (p>0.05). However, TG level was significantly higher in HbA1c 9-10.9 (174.20±48.95) than 7-8.9 (159.66±31.47) and <7 (158.82±29.67) (Table 2).

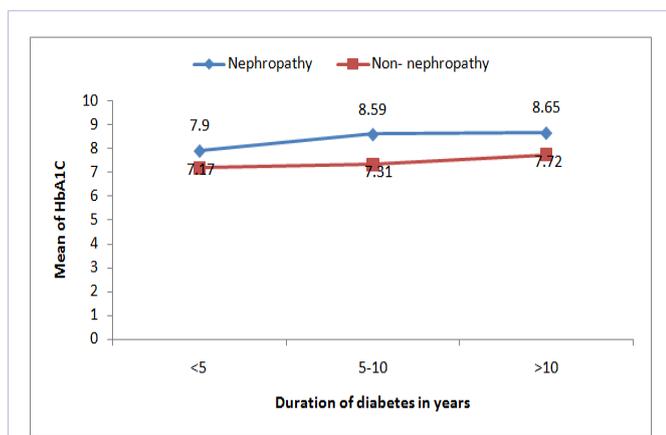


Figure 2: HbA1c level by duration of diabetes between nephropathy and non-nephropathy patients

Table 2: Comparison of lipid profile by level of HbA1c levels among nephropathy patients

Lipid profile (mg/dl)	HbA1c %			Significance
	<7 (n=5)	7-8.9 (n=83)	9-10.9 (n=42)	
Total cholesterol	151±30.94	152.33±20.64	156.16±25.83	F=1.85, p=0.17
TG	158.82±29.67	159.66±31.47	174.20±48.95	F=5.60, p=0.002*
HDL-c	26.40±4.92	25.78±7.27	24.57±4.69	F=0.35, p=0.71
LDL-c	96.60±20.25	97.28±19.43	99.88±28.00	F=1.15, p=0.85
VLDL-c	36.60±7.16	37.89±6.33	38.99±11.04	F=0.44, p=0.64

Table 3: Comparison of microalbumin by level of HbA1c among nephropathy patients

HbA1c %	No. of patients	No. with nephropathy	% with nephropathy	Urine microalbumin among nephropathy
<7	42	5	11.9	132.80±90.33 ¹
7-8.9	158	83	52.5	159.89±70.16 ¹
9-10.9	50	42	84.0	246.35±126.29 ¹

F=12.04, p=0.001, p=0.0001 (Multiple comparison tests)

The urine microalbumin level was also significantly (p=0.001) higher among the patients of nephropathy of HbA1c 9-10.9 (246.35±126.29) compared with 7-8.99 (159.89±70.16) and <7 (132.80±90.33) (Table 3).

Discussion

Persistent Hyperglycemia beyond the limit of renal threshold leads development of diabetic kidney diseases and HbA1c variability. [11] In our study, HbA1c were significantly higher among nephropathy than non-nephropathy and increased with diabetes duration although all receiving oral hypoglycemic agents (OHA), similar finding in previous studies.[12-15] Moreover, significant differences were observed in duration of diabetes cut-off between <5 and 5-10 (p=0.04), <5 and >10 (years) among nephropathy, similar association were observed diabetes duration and higher HbA1C values in recent studies.[16-17] Variation may be sensitivity of HbA1c for detecting glycemic variability,18 cellular metabolic memory.[18-20] Predominantly, signal of previous poor glycemic control manifests development of microvascular complication.[21-22] Therefore, HbA1c cut-off variation for nephropathy associated with duration of diabetes due to glucose fluctuations might enhances oxidative stress.[23]

In present study, comparison of lipid levels among nephropathy patients observed that TG significantly altered with increased level of glycosylation which is accordance in previous long term indian observation study.[24]

Dyslipidemia is one of the common conditions associated with a poor glycemic control in type -2 DM. The pathogenesis of dyslipidemia in type -2 DM is a decrease in activity of lipoprotein lipase due to insulin deficiency or resistance. Under the action of insulin, enzyme lipoprotein lipase metabolizes lipids in a healthy individual. In type 2 DM, the relative insulin deficiency and decreased adiponectin causes decrease lipoprotein lipase activity resulting in high LDL-c, TG and low HDL-c. Qualitative defects in LDL are also seen in type 2 diabetes including atherogenic, glycated or oxidized LDL further amplifying the risk of Atherogenesis.[25-26] Lebovitz et. Al mentioned the lipotoxic mechanism by triglyceride which interferes with gastric or neural pathway which regulates glycemic control.[27] In another study, positive HbA1c correlation with triglycerides as prognostic indicator for the target organ damage.[28]

Increased urine microalbumin was found among HbA1c 9-10.9 and high prevalence of nephropathy observed between HbA1c 9-10.9 and 7-8.99 compared to HbA1c <7.00. Similar results reported by Parving et al. [29] observed that HbA1c cut-off of 7.5%, microalbuminuria (39%) and overt albuminuria in 9.8% of the patients while other remained normoalbuminuric. Cummings et.al.[30] suggested that Hba1c cut-off should be <7% for renal protection. In light of our interpretation, HbA1c range 7.0-7.5% considered as good glycemic control to retard long term damage.

Conclusion

Recently global norms for glycemic control by American college of physician target HbA1c level between 7-8% in most patients with type-2 diabetes as against the traditional 6.5-7%, which has been followed over decades. Recommendation is leading conflict among the diabetologist, nephrologist to achieve target blood glucose level for management of diabetes complication. Therefore, Indian Asian ethnicity, race, age

,diabetes duration ,diet and drug choice are the major dependent factor for determining HbA1c target. In our research concluded that vascular complication was more prominent in long duration of diabetes and HbA1c variability observed among nephropathy group and high prevalence of nephropathy in type -2 diabetes patients receiving fixed oral hypoglycemic drugs along with ACE inhibitors regimen since known diabetic duration.

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