Association of Microalbuminuria with Glycemic Status

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Abstract

Glycosylated hemoglobin (HbA1c) is an established marker of glycemic status in diabetic subjects. In this cross-sectional study we aimed to determine the association of microalbuminuria with glycemic status and to determine the predictive value of HbA1c for elevated microalbuminuria in diabetic subjects. Serum creatinine, urinary creatinine, microalbumin and HbA1c were measured by standard methods. Urine albumin creatinine ratio (ACR) was calculated from urinary microalbumin and urinary creatinine. Multivariate linear regression model was applied to determine the association of ACR with HbA1c. The likelihood of relative risk and odds ratio of elevated ACR were also determined for HbA1c. Elevations of ACR between subjects with HbA1c level above the median value and below the median value of HbA1c were compared to explore HbA1c as a predictor of elevated microalbuminuria. It is observed that, ACR is positively associated with HbA1c (β=0.2063, P= 0.000038) after adjustment for age, sex and serum creatinine in a multivariate linear regression analysis. The relative risk of elevated microalbuminuria was 1.39 (95% CI: 1.15 to 1.67) and OR was 2.39 (95% CI: 1.29 to 4.42) for HbA1c above the median (8.5%) compared to that with HbA1c below the median value. The study revealed that, elevation of microalbuminuria is positively associated with glycemic status and elevated HbA1c predicts the elevation of microalbuminuria in diabetic subjects.

Introduction

Diabetic nephropathy is the leading cause of premature deaths in diabetic patients, with deaths related to cardiovascular disease (CVD) as well as renal failure[1]. Microalbuminuria is a marker of diffuse endothelial dysfunction associated with widespread vascular abnormalities, including impaired arterial reactivity and elevated levels of markers of endothelial activation[2,3]. The excretion of small amount of albumin in the urine has been documented to predict renal failure and cardiovascular morbidity as well as mortality in diabetics[4,5]. HbA1c and albumin creatinine ratio (ACR) are significantly increased in diabetic patients[6]. Glycosylated hemoglobin (HbA1c) is commonly used as a marker of glycemic status. HbA1c has been proposed as a dual marker for glycemic control and CAD risk factor[7]. It has also been estimated that each percentage point increase in HbA1c correspond to a 35% increase in the risk of microvascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal)[8]. The ACR is a validated, reliable single-sample measure of urinary albumin excretion that is highly correlated with albumin excretion rates assessed by 24-h urine collection[9,10]. Microalbuminuria may be a modifiable risk factor of CVD and diabetic nephropathy. If proper intervention is not given in time, microalbuminuria is related to the development of IHD and nephropathy[11]. Early detection of microalbuminuria may help to prevent diabetic nephropathy as well as other microvascular complications. In this study we aimed to explore the association of microalbuminuria with glycemic status and to evaluate HbA1c as a predictor of elevated microalbuminuria in diabetic subjects in a tertiary healthcare center.

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Materials and Methods

Four hundred specimens obtained during January 2011 to August 2011 from confirmed diabetic subjects were analyzed. Blood specimens were collected in blood collection tubes (BD vacutainer® containing 3.6 mg K2EDTA; BD, Franklin Lakes, NJ USA) and spot urine specimens were collected in clean glass tubes. HbA1c was measured by high-pressure liquid chromatography (HPLC) method using D-10™ glycosylated hemoglobin testing system (Bio-Rad Laboratories, Inc., Hercules, CA, 94547, USA). Urine microalbumin level was measured by a particle-enhanced turbidimetric inhibition immunoassay method using Dimension RxL max automated analyzer (Siemens Healthcare Diagnostics Ltd.) and urine creatinine concentration was measured by modified Jaffe´'s method using Dimension RxL max automated analyzer. Urine ACR was calculated as ratio of microalbumin concentration and creatinine concentration in urine and results were expressed in mg/g unit. Results are expressed as mean±SD and the Pearson correlation coefficient of ACR with HbA1c, age and serum creatinine was determined by linear regression analysis. To test the significance of association of ACR with HbA1c, multivariate linear regression model was used. Statistical analyses were performed by using STATISTICA version 8 and GraphPad software version 5.04 for Windows.

Results

The mean age of the study subjects was 51.9±12.7 years. Of the total subjects, 53% were male and 47% were female. The mean values of urine ACR, HbA1c and serum creatinine were 69.8±135.5 mg/gm, 8.9±2.25% and 1.04±0.33 mg/dL respectively.

The Pearson correlation coefficients of ACR with HbA1c, age and serum creatinine were 0.2002 (P=0.00006), 0.0195 (P=0.6985) and 0.1882 (P=0.0002). The correlation coefficient of serum creatinine with age was 0.3689 (P<0.0001). Multivariate linear regression analysis showed that ß value of ACR is statistically significant for HbA1c (ß=0.2144, P=0.00003) when adjusted for age and sex. The result of coefficient (ß) of UACR for HbA1c after adjustment for age, sex and serum creatinine by multiple regression analysis is shown in table I. After adjustment for age, sex and serum creatinine, the ß value of ACR was 0.2063 (P= 0.000038).

Table I: Multiple linear regression analysis of variables with urine ACR

Effect	Parameters	t	P	ß	− 95% CL	+ 95% CL
Intercept	− 125.85	− 2.86	0.00446			
HbA1c	12.32	4.16	0.000038	0.2063	0.1089	0.3037
Age	− 0.07	− 0.13	0.89742	− 0.0069	− 0.1121	0.0983
Sex	− 10.02	− 1.46	0.14595	− 0.0739	− 0.1737	0.0258
S Creatinine	86.49	3.98	0.000083	0.21195	0.1072	0.3167

Elevation of microalbuminuria was higher in subjects with HbA1c above the median value (8.5%) compared to those with HbA1c below the median value. Fisher's exact test showed that microalbuminuria is significantly associated with HbA1c (P<0.0044). The relative risk of elevated microalbuminuria was 1.39 (95% CI: 1.15 to 1.67) and OR was 2.39 (95% CI: 1.29 to 4.42).

Discussion

In this study, urine ACR correlated significantly and positively to HbA1c (r=0.2002, P=0.00006) and serum creatinine (r=0.1882, P=0.0002) but not significantly related to age (r=0.0195, P=0.6985). The association of urine ACR with HbA1c remained statistically significant (ß=0.2063, P=0.000038) after adjustment for age, sex and serum creatinine.

Urine albumin creatinine ratio is the early detection marker of renal dysfunction and is affected by factors such as hypertension, duration of diabetes, smoking, body mass index, exercise, oxidized LDL etc. We observed no significant association of urine ACR with age, which is the major confounder of impaired kidney function and found significant association with serum creatinine, the surrogate marker of kidney function. But serum creatinine showed significant positive correlation with age. So the significant positive association of urine ACR with HbA1c in diabetic subjects may reflect the facts that the risk of microvascular complications is associated to diabetic status. This finding is consistent with the findings of other researchers[11,12,13]. Moreover, the significant odds ratio and relative risk of elevated microalbuminuria in subjects with the higher HbA1c (above the median) compared to lower HbA1c (below the median) indicates the predictive value of HbA1c for the elevation of microalbuminuria in diabetic subjects. HbA1c reflects the glycemic status of the previous three months. In the case of overt hyperglycemia for a long time, basement membrane proteins are glycosylated with the loss of charge selectivity and increased glomerular perfusion and filtration[14,15,16]. The result indicates that HbA1c reflects the microvascular dysfunction in diabetic subjects.

Microalbuminuria is positively associated with glycemic status and elevated HbA1c predicts the deterioration of microalbuminuria in diabetic subjects.

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