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Research Article

Correlation between microalbuminuria and glycosylated haemoglobin and cardiovascular disease in diabetic patients: a case-control study

Jayaprakash Subramani*, Prabhusamy

Department of General Medicine, Velammal Medical College & Research Institute, Madurai, Tamil Nadu, India

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***Correspondence:**
Dr. Jayaprakash Subramani,
E-mail: drjp2010@gmail.com

ABSTRACT

Background: Microalbuminuria is an independent risk factor for cardiovascular mortality in both diabetic and non-diabetic individuals. Our aim was to assess the incidence of elevated glycosylated haemoglobin and cardiovascular disease in relation to microalbuminuria in diabetic patients.
Methods: Diabetic patients with or without microalbuminuria were assigned into two groups. Each group consisted of 100 patients. Patients with co-morbid conditions which contribute to microalbuminuria were excluded from this study. Data on clinical features, fasting and postprandial blood glucose, HbA1C (glycosylated haemoglobin) level, urine microalbumin levels, renal parameters, cardiovascular events, diabetic retinopathy changes were collected for both groups and compared.
Results: Majority of patients were in 5th and 6th decade with male to female ratio of 2.5:1 in microalbuminuria group and 1:1.1 in non-microalbuminuria group. Mean duration of diabetes was 4.3 yrs in patients with microalbuminuria; and 3.5 yrs in patients without microalbuminuria. Incidence of elevated glycosylated haemoglobin (HbA1c $\geq$ 6.5%) in microalbuminuria group was 69%; in patients without microalbuminuria was 43%. Incidence of coronary artery disease (CAD) was 32% in microalbuminuria group; 16% in patients without microalbuminuria. These differences were statistically significant. Diabetic retinopathy was observed in 23% of patients in microalbuminuria group; 19% in patients without microalbuminuria.
Conclusions: Microalbuminuria in diabetic patients was significantly associated with poor glycaemic control. It was strongly associated with longer duration of diabetes. Incidence of cardiovascular events was higher in patients with microalbuminuria compared to patients without microalbuminuria.

Keywords: Microalbuminuria, Glycosylated haemoglobin, Cardiovascular disease

INTRODUCTION

Diabetes is rising globally, driven both by population growth and ageing and by increasing age-specific prevalence. The number of people with diabetes increased from 153 million in 1980, to 347 million in 2008. Mean FPG and diabetes prevalence in 2008 were also high in south Asia, Latin America and the Caribbean, and central Asia, North Africa, and the Middle East. Mean FPG in 2008 was lowest in sub-Saharan Africa, east and Southeast Asia, and high-income Asia-Pacific.[1]

According to the WHO-2016 report, prevalence of diabetes in India is 7.8% in general population. Diabetes contributes to 2% of total deaths in India.[2] The WHO Consultation report released in 2011 concluded that HbA1c can be used as a diagnostic test for diabetes, provided that stringent quality assurance tests are in place. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. HbA1c reflects average plasma glucose over the previous eight to 12 weeks.[3] The risk of vascular complications increases exponentially as the mean HbA1c level increases[4]. Furthermore, it has been suggested that

HbA1c variability, which is also an independent risk factor for the development of diabetic complications in individuals with type 1 diabetes.

It is recognized that the presence of microalbuminuria, in addition to being a marker of incipient renal disease in diabetic patients, seems to be also a marker of large vessel disease, and is associated with increased cardiovascular disease mortality, especially coronary heart disease.[5-7] The presence of microalbuminuria possibly reflects the process of generalized vascular damage, affecting simultaneously glomeruli, the retina and the intimal layer of large vessels. This has been demonstrated by studies of markers of endothelial dysfunction and measurements of trans-capillary protein leakage.[8]

Our aim is to correlate glycosylated haemoglobin values with microalbuminuria and detect the incidence of cardiovascular events in relation to microalbuminuria. Even though other reports in the literature stress that CAD is associated mainly with macro-albuminuria and not microalbuminuria, we tried to investigate the relation between CVD and microalbuminuria.[9-11] We have retrospectively conducted this study to find out whether the development of microalbuminuria is strongly associated with abnormal HbA1C.

METHODS

Retrospective analysis of diabetic patients, who attended health screening check-up in Velammal medical college hospital, Madurai, a tertiary care hospital from Jan, 2015 to Dec, 2015 was done. Patients with following criteria were enrolled for the study:

Inclusion criteria

Diabetic patients were identified according to WHO-2006 criteria as follows:

Fasting plasma glucose ≥ 126 mg/dl or.

2 hour post prandial glucose ≥ 200 mg/dl.

Microalbuminuria (MA) is defined as the presence of albumin in the urine above the normal range of less than 30 mg per day but below the detectable range with the conventional dipstick methodology.

Diabetic patients were divided into 2 groups.

100 patients with microalbuminuria were assigned as "cases".

100 patients without microalbuminuria were assigned as "controls".

Exclusion criteria

Diabetic patients with following features were excluded from the study to eliminate confounding errors.

- Elderly (age > 65 years)
- Smoking
- Alcohol use
- Hypertension
- Dyslipidemia
- Obesity (Body mass index ≥30 kg/ m^2)
- Anaemia
- Chronic kidney disease
- Chronic liver disease
- HIV infection
- Rheumatoid arthritis

Methodology

Out of 300 patients with diabetes attended health screening check-up, 100 patients with microalbuminuria & 100 patients without microalbuminuria were identified. Factors known to influence the development of microalbuminuria other than diabetes were eliminated. Clinical features, blood sugar values (FBS, PPBS), HbA1C, renal profile, urine analysis (including urine for micro albuminuria) data and fundus examination reports were collected and analysed. Above data was compared with diabetic patients without microalbuminuria to find out the relation of microalbuminuria with HbA1c, duration of diabetes, occurrence of retinopathy and cardiovascular events with statistical significance. Statistical analysis was done using SPSS software.

RESULTS

Clinical characteristics of patients in both groups were analysed with respect to age & gender distribution, duration of diabetes, glycosylated haemoglobin levels, occurrence of retinopathy and cardiovascular events. Table 1 illustrates demographic characteristic of both study group.

Maximum numbers of patients in both groups were in 5^{th} and 6^{th} decade. Male to female ratio was 2.5: 1 in microalbuminuria group; 1:1.1 in patients without microalbuminuria. Mean duration of diabetes in microalbuminuria group was 4.3 years. Mean duration of diabetes in patients without microalbuminuria was 3.5 years. This difference is statistically significant (p value = 0.02). Incidence of elevated glycosylated haemoglobin (HbA1c ≥ 6.5%) in microalbuminuria group was 69%; in patients without microalbuminuria was 43%. This difference was statistically significant (p value <0.05). Incidence of coronary artery disease (CAD) was 32% in microalbuminuria group; 16% in patients without microalbuminuria. This difference in occurrence was statistically significant (p value = 0.001). Incidence of cerebro vascular accident (CVA) in microalbuminuria group was 9%; incidence was 2% in patients without microalbuminuria. This difference is statistically significant (p value <0.05).

Table 1: Clinical characteristics of both study groups.

Characteristics	DM with microalbuminuria (Total-100)	DM without microalbuminuria (Total-100)	P value
Mean age (years)	48.7	50.2	
Gender distribution Male Female	 72 28	 54 46	
Mean duration of diabetes (years)	4.3	3.5	0.02
Incidence of elevated level of HbA1C (≥ 6.5%)	69%	43%	0.0001
Cardiovascular events CAD CVA	 32% 9%	 16% 2%	 0.001 <0.05
No. of patients with diabetic retinopathy changes Total Mild NPDR Moderate NPDR Severe NPDR PDR	 23% 14% 6% 3% 0	 19% 13% 6% 0 0	 0.37
P value <0.05 - significant			

DM- Diabetes Mellitus, CAD - Coronary artery disease, CVA - Cerebro vascular accident, NPDR - Non-proliferative diabetic retinopathy, PDR - Proliferative diabetic retinopathy

Diabetic retinopathy was observed in 23% of patients in microalbuminuria group. Proportion of patients found in various stages of retinopathy in microalbuminuria group as follows: Mild Non-proliferative diabetic retinopathy (NPDR) (14%), Moderate NPDR (6%), severe NPDR (3%). Retinopathy was seen in 19% patients without microalbuminuria. Proportion of patients with various stages as follows: mild NPDR (13%), moderate NPDR (6%). Correlation between abnormal HbA1C level and retinopathy is significant in both groups. Severe NPDR was seen in patients with microalbuminuria with HbA1C > 10 %. Incidence of diabetic retinopathy in both groups was statistically insignificant (p value =0.37).

DISCUSSION

Glycosylated haemoglobin or haemoglobin A1C (HbA1c) has been adopted by the World Health Organization into its recommended criteria for diagnosis of diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that tight glycaemic control, quantified by lower blood glucose and A1C levels, reduced the risk of the development of complications from diabetes. HbA1c continues to be fundamental for the clinical management of diabetes. It has been demonstrated that mean glycaemia in the 30 days prior to sampling for HbA1c contributes approximately 50% to the final result, whereas the levels from around 90 to 120 days earlier contribute only around 10%.

Microalbuminuria is an early marker for diabetic nephropathy and risk factor for cardiovascular disease. MA predicts the development of ischemic cardiovascular events related to development of atherosclerosis. Numerous clinical studies in individuals with either type 1 or type 2 diabetes with MA demonstrate higher cardiovascular disease mortality. Based on the data from large single and multi-centre clinical trials, including the Heart Outcomes Prevention Evaluation (HOPE) study, it is clear that the presence of microalbuminuria is a signal from the kidney that cardiovascular risk is increased and that vascular responses are altered.[12,13] The single most significant determinant that initiates the development of diabetic vasculopathy as well as nephropathy is the resultant advanced glycosylation end products and related moieties that are created by hyperglycemia.[14]

In individuals with MA who do not have diabetes, both endothelial dysfunction and alterations in the extracellular matrix contribute to the increase in vascular permeability and ultimately promote the atherosclerotic process.[15] Defective endothelial permeability permits lipid influx into the vessel wall causing atherosclerotic changes. MA is associated with a higher prevalence of diabetic complications, metabolic and non-metabolic risk factors, target organ damage as well as adverse CVD in both diabetic and non-diabetic people.

In our study, patients with factors which contribute to the development of microalbuminuria and cardiovascular disease (mentioned in exclusion criteria) other than diabetes were eliminated during selection of cases. This was done to avoid confounding errors in analysing data. It is clearly evident from our study that longer duration of diabetes and elevated glycosylated haemoglobin levels

were significantly associated with development of microalbuminuria. In our study, cardiovascular events were higher among diabetic patients with microalbuminuria which is a marker for endothelial dysfunction.

In a similar study from Chennai (Tamil Nadu) conducted in 2001, showed the prevalence of microalbuminuria was increased with the increase in duration of diabetes.[16] This finding was similar to our study. In a study conducted in north India showed elevated HbA1c to be associated with microalbuminuria.[17] Similar finding was observed in our study too. The association of glycaemic control with microalbuminuria has been well established by various studies conducted in western world.[18,19]

Recently, studies have shown that microalbuminuria reflects an increased risk for cardiovascular disease in T2DM and was implicated as a marker of increased cardiovascular morbidity and mortality for patients with T2DM. The cumulative risk of MAU in T2DM is estimated at 20-40% in the DM period of 5-10 years, with most dying due to cardiovascular disease.[20] Our study showed significant increase in cardiovascular events in diabetic patients with microalbuminuria, which was reported from western studies.

Epidemiological studies have shown that diabetic retinopathy and nephropathy are closely associated and that this correlation can be explained by a common mechanism involving tissue damage by the factors mentioned above such as HbA1c level, hypertension, dyslipidaemia, duration of diabetes, age of onset, and cigarette smoking.[21] In contrast, our study showed diabetic retinopathy was not significantly associated with microalbuminuria.

A limitation of this study was retrospective design of data analysis with medium number of patients. The results of this study need to be confirmed by randomised controlled trial conducted in large population.

CONCLUSION

Microalbuminuria in diabetic patients was strongly associated with elevated glycosylated haemoglobin (HBA1C), which is an index of glycaemic control. Duration of diabetes was longer in patients with microalbuminuria compared to patients without microalbuminuria which was statistically significant. Microalbuminuria in diabetic patients was strongly associated with higher incidence of cardiovascular events compared to diabetic patients without microalbuminuria. But incidence of diabetic retinopathy was not significantly higher in relation to microalbuminuria. It is concluded that incidence of microalbuminuria is higher among diabetic patients with poor glycaemic control and it is a significant marker for cardiovascular disease.

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