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To Evaluate the Role of HbA1C as a Predictor for the Development of Diabetic Nephropathy in Type 1 Diabetic Patients

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Abstract- *Aim:* The aim of this study to evaluate the role of HbA1C as a predictor for the development of diabetic nephropathy in type 1 diabetic patients.

Methods: This prospective observational study was carried out by involving 120 patients. The ‘‘fluctuations” in HbA1C over time was assessed. HbA1C fluctuation was defined as an increase in HbA1C of more than 2% between two consecutive measurements, or an increase of more than 1% at 2 points in time.

Results: There was no association between gender and the development of diabetic nephropathy ($p = 0.95$). There were no significant group differences in the ‘‘age at onset of diabetes” or ‘‘time period from the onset of diabetes till admission to the chronic care center” ($p = 0.48$ and $p = 0.81$, respectively). The association between fluctuations in HbA1C and diabetic nephropathy is shown in Table 1.

Keywords: *type 1 diabetic, diabetic nephropathy, glycosylated hemoglobin (HbA1C).*

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Conclusion: We concluded that the T1D patients who have a similar mean HbA1C may progressively behave differently in terms of developing nephropathy, depending on the fluctuations in HbA1C.

Keywords: type 1 diabetic, diabetic nephropathy, glycosylated hemoglobin (HbA1C).

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I. Introduction

The proportion of patients with end-stage renal disease (ESRD) caused by diabetes has progressively increased during the last few decades and diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) in the world. Diabetic nephropathy is defined by persistent albuminuria, declining glomerular filtration rate (GFR) and progressive rise in blood pressure. Approximately 40-50% of patients with type 1 diabetes and 20-30% of patients with type 2 diabetes develop diabetic nephropathy.[1] Based on studies in type 1 diabetes, it had been generally considered that once overt diabetic nephropathy, manifesting as persistent proteinuria, is present, it was only possible to slow, but not halt, the progression toward ESRD.[2-4] This led investigators during the early 1980s to search for early predictors of diabetic nephropathy. Most investigators now agree that diabetic nephropathy result from the interaction of multiple metabolic, genetic and other factors of which chronic hyperglycemia is one of the most significant factor in both the initiation and progression of the disease.[5] Different randomized controlled trials and observational studies have strongly suggest that hyperglycaemia or closely associated factors of poor glycaemic control, like HbA1c is a good predictor of diabetic nephropathy[5-9], and is highly correlated with fasting blood glucose (FBG) and does not require measurement in the fasting state.[10] One study showed that increasing HbA1c categories had a higher prevalence of chronic kidney disease (CKD) and micro or macro-albuminuria. In the multivariable models, HbA1c categories above 7.0% were significantly associated with increased prevalence of diabetic nephropathy compared with the lowest category.[11] Another study demonstrated that HbA1c >6.5% predicts a future risk of kidney disease. Above the threshold point with the increasing of HbA1c levels the risk of kidney diseases also increases sequentially.[12] It indicates that HbA1c may be used as a useful marker for nephropathy along with other risk factors. The ADVANCE trial documented that (in subjects with type 2 diabetes mellitus) strict glycaemic control (mean HbA1c: 6.5%) in comparison with standard control

(mean HbA1c: 7.3%) is associated with a significant reduction in renal events, including onset of or worsening of nephropathy [hazard ratio (HR) 0.79; P = 0.006], new-onset microalbuminuria (HR 0.91; P = 0.02), and, in particular, development of macro-albuminuria (HR 0.70; P <0.001).[13] There are several other predictors[14-18] of diabetic nephropathy including advanced age, longer duration of diabetes, body weight, smoking, diabetic ketoacidosis, mild to moderate nonproliferative diabetic retinopathy, proliferative diabetic retinopathy (the most prevalent predictor), proteinuria, hypertension, dyslipidaemia, physical inactivity etc. Both sexes are vulnerable to diabetic nephropathy, although there is an unexplained male preponderance of diabetic nephropathy. Ethnicity and family history also affect the risk of diabetic nephropathy. The burden of nephropathy will increase in future as the incidence of diabetes increases and the age of onset declines, although the effects may be lessened by the use of emerging therapies.[19] Therefore, we attempted to do a clinical study on relation of HbA1c and other risk factors with nephropathy.

II. Material and Methods

This prospective observational study was carried out by involving 120 patients after taking the approval of the protocol review committee and institutional ethics committee.

Type 1 diabetic patients are followed up regularly at least every 3 months. At each visit, HbA1C is measured; body weight and the average dose of total insulin required per day are measured. Height is documented once a year. Blood pressure is systematically measured at diagnosis, and recorded at least once a year. Eye examination, for the presence of diabetic retinopathy, is done by an ophthalmologist at the first visit to the center then followed up a yearly basis. Microalbuminuria is tested in each patient 5 years after the diagnosis of type 1 diabetes, as recommended by ADA[20], and then yearly.

Patients with type 1 diabetes, as defined by ADA[21], admitted to the chronic care center were studied. Only patients admitted to the chronic care center within 12 months of diagnosis of type 1 diabetes mellitus were included, since structural renal abnormalities due to diabetes usually occurs afterward.[22]

Patients were excluded from the study if the duration of diabetes was less than 5 years, since diabetic nephropathy is known to occur after at least 5 years of the disease.[20] Patients were also excluded from the study if they suffered from wolfram syndrome, or had thalassemia or other hemoglobinopathy. Two hundred and ten patients met the inclusion criteria, and 90 patients were excluded. The final sample size was 120 patients.

The following information was obtained: age, gender, date of birth, date of onset of diabetes, date of admission to the center, family history for diabetes, results of microalbuminuria after 5 years of diagnosis, the dates and the results of HbA1C at each visit, BMI at baseline and blood pressure. Patients (micro-albuminureavs non-microalbuminurea) were selected based on a cutoff point of 24 h urine microalbumin of >30 mg/24 h on more than two occasions.

Acceptable metabolic control was defined as having a mean HbA1C <8% and a poor metabolic control denoted a mean HbA1C P8%. Although the definition of poor vs acceptable metabolic control is not standardized, our definition was based on our assay methodology. Results were considered significant at the 5% critical level ($p < 0.05$).

III. Results

The sample analyzed consisted of 120 type 1 diabetic patients, 67 females and 53 males, aged 10–30 years were included in this study. 20 among 120 (16.67%) developed nephropathy after 5 years of onset of diabetes.

As shown in Table 1, there was no association between gender and the development of diabetic nephropathy ($p = 0.95$). There were no significant group differences in the ‘‘age at onset of diabetes” or ‘‘time period from the onset of diabetes till admission to the chronic care center” ($p = 0.48$ and $p = 0.81$, respectively). BMI at first visit for those who developed nephropathy was not significantly different from the BMI at first visit for those who did not have evid ence of nephropathy ($p = 0.41$). There was no significant difference in the outcome between those with and without family history of diabetes. Hypertension was omitted, because of no variability, as patients were not hypertensive.

Table 1: Main characteristics of the study population in relation to the development of diabetic nephropathy

Parameter	Nephropathy N = 20	No nephropathy N = 100	p- value
Gender [n (%)]a			
Male	9 (45)	44 (44)	0.95
Female	11 (55)	56 (56)	
Age at onset (years)	11.95 ± 5.6	11.13 ± 4.10	0.48

Time period from onset of diabetes to admission to CCC (years)	3.97 ± 4.3	3.73 ± 4.3	0.81
BMI at baseline (kg/m2)	19.85 ± 5.3	19.05 ± 3.5	0.41
Family history of diabetes [n (%)]b			
Positive	10 (50)	58 (58)	
Negative	10 (50)	42 (42)	0.36
Mean HbA1C (%)	9.5 ± 1.7	8.6 ± 1.2	0.004
Fluctuations in HbA1C [n (%)]			
Present	12 (60)	54 (54)	
Absent	8 (40)	46 (46)	0.05

Data are means ± SD unless otherwise specified. a [n (%)] indicates the number in each category and (percentage). b Totals do not add up to 120 due to missing data.

The mean HbA1C per individual was 8.65 ± 1.3 in the whole sample. As shown in Table 1, mean HbA1C was 9.5 ± 1.7% among those who developed nephropathy compared to a mean of 8.6 ± 1.2% for those who did not develop nephropathy, and was statistically significant between the two groups (p = 0.004).

The association between fluctuations in HbA1C and diabetic nephropathy is shown in Table1. Among those who developed nephropathy, 10 of 20(60%) had fluctuations in HbA1C; compared to those who do not develop nephropathy 54 of 100 (54%) had fluctuations in HbA1C (p = 0.05).

In order to identify the predictors for diabetic nephropathy, we performed a multivariate analysis, by entering all risk covariates into a multiple logistic regression analysis (Table 2). Results from the full model (referred to as Model 1) revealed that mean HbA1C was the only significant predictive factor; all other variables were not significant. Since our hypothesis is to test whether the presence of fluctuations in HbA1C predicts the development of nephropathy adjusting for the mean HbA1C, we further studied three other models one including the two covariates the mean and the ''fluctuations" in HbA1C (referred to Model 2), another model including only mean HbA1C as a covariate (referred to as Model 3) and the last model including the fluctuations in HbA1C (Model 4). The Model 2 leads to a smaller BIC than Model 3 (BIC dropped from 101.4 to 104.7), indicating positive evidence for a better fit. We also noticed that the odds ratio of the mean HbA1C decreases from 1.76 to 1.56 when the covariate ''fluctuations" is added to the model and becomes closer to 1. Considering Model 4, the odds ratio of the fluctuations in HbA1C is 4.18; however when adjusting for the mean HbA1C (Model 2), the odds ratio dropped to 2.35 and the fluctuations in HbA1c was no more a significant predictor factor.

Table 2: Multivariate analysis for the prediction of diabetic nephropathy

Parameter	Odds ratio Model 1	(95%CI)	Model 2	Model 3	Model 4
Average mean of HbA1C	1.67 (1.04;	2.69)	1.56 (1.02; 2.39)*	1.76 (1.19; 2.60)*	
Fluctuations in HbA1C	1.90(0.43;	8.42)	2.35 (0.57; 9.78)		4.18 (1.14; 15.32)*
Gender	0.86(0.28;	2.64)			
Family history	1.33 (0.43;	4.14)			
Age at onset	1.07(0.89;	1.27)			
Time between onset of diabetes till admission to CCC	0.94 (0.81;	1.09)			
Baseline BMI	0.94 (0.76;	1.15)			
BIC	—123.41		—104.72	—101.41	—104.23

IV. Discussion

WHO multicentric study of vascular disease in diabetes, observed a wide geographic variation in prevalence of nephropathy i.e. 2.4% from Hong Kong, 23% from Delhi to 37% from Oklahoma, USA21. These geographical and population variation in prevalence of diabetic nephropathy could be due to real ethnic variation in the susceptibility to diabetic nephropathy i.e. genetics, poor glycaemic control, hypertension or other socioeconomic, cultural and environmental factors. Several studies indicated that HbA1c may show a glycaemic threshold with micro and macro-vascular complications of diabetes, suggesting it may

additionally be useful biomarker to identify individuals at risk for different vascular complications.[23,24,25] However, in our study, the duration of diabetes was set to 5 years after diagnosis. Our finding that the age at onset of diabetes is not associated with the development of diabetic nephropathy is com- mensurate with recent data[26]; however, as in their study, we did not account for pubertal staging.[27]

The results of our study, like many other reports, did not show an association between gender and the development of diabetic nephropathy. This contrasts with a previousfinding by Holl et al., showing an impact of female gender on the development of insidiousnephropathy.[28] Any association between gender and nephropathy should take into consideration the pubertal stage since the hormonal effects could be at the base of this difference. Data on the association between BMI, an index of metabolic state, and the development of diabetic nephropathy, is scarce.[28] In our study, BMI was measured at the first visit to the center, when most of the patients had poor metabolic control that might have negatively affected the weight. Although the baseline BMI was found to be associated with the development of microvascular complications[29], the impact of BMI was apparent only at higher values. Follow- ing BMI longitudinally and accounting for pubertal changes would help in establishing the associations between BMI and diabetic nephropathy.

Metabolic control was the only established and consistent predictor for the development of diabetic nephropathy. In reviewing the literature, different measures have been used in order to study the association between metabolic control and diabetic nephropathy. The mean HbA1C is repeatedly used[30,27]; the median has also been used as a summary measure.[31] Based on the results of our study, the mean HbA1C remains the only significant predictor for the development of diabetic nephropathy in type 1 diabetic patients, even after adjusting for ''fluctuations''. The use of ''fluctuations'' in HbA1C as a longitudinal measure for the change in the metabolic state is original. It may better reflect the changes in ambient glycemia within one individual. This latter was found to be the culprit in the development of diabetic nephropathy through activation of the proteinase C[32], upregulating the heparanase expression[33], enhancing sensitivity to TGF beta 1[34] and increasing VEGF (vascular endothelial growth factor) expression.[35] Our data showed that ''fluctuations'' in HbA1C predicted the incidence of nephropathy, based on the positive evidence that the model including fluctuations fits the data better. This may have many implications: first, these findings may help to achieve a better understanding of the pathophysiology of diabetic nephropathy, since they suggest that, although this latter is accelerated by the chronic hyperglycemia (manifested as mean HbA1C), it is much worse during acute increases in glycemia which is reflected by fluctuations in HbA1C. Second, our data highlight the issue that a single jump in HbA1C have a durable effect, this agrees with the hypothesis of ''long time- glycemic memory'' and supported by findings from DCCT on microvascular complications. Third, as diabetic nephropathy has an insidious onset, one large increment in HbA1C during the first 5 years, would be an indicator of a development of nephropathy well before the appearance of microalbuminuria.

Nevertheless, our data were unable to establish the association between fluctuations in HbA1C and the development of nephropathy in diabetics with acceptable control. The sample size was small to permit the comparison between the different groups; this was well seen by the wide confidence intervals. Interestingly, taking the whole model, the mean HbA1C explains 10% the prediction for the development of diabetic nephropathy. Other factors, such as genetic predisposition, have been known to be associated with the development of nephropathy. Family history of hypertension[36], kidney disease and other cardio-vascular risk factors[37], were used as a measure for genetic predisposition.

V. Conclusion

We concluded that the type 1 diabetic patients who have a similar mean HbA1C, in the long run, may behave differently in terms of developing nephropathy, depending on the fluctuations in HbA1C and more precisely, depending on the frequency of the acute jumps in the HbA1C.

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