THE RELATION BETWEEN HBA1C AND URINE ALBUMIN EXCRETION IN TYPE 2 DIABETES MELLITUS PATIENTS

Solak İbrahim[*], Bulgurlu S.S.[**], Demirtunç R.[***]
[*]Health Sciences University Konya Education and Research Hospital Department of Family Practice, Konya, Turkey - [**]Health Sciences University Haydarpaşa Numune Education and Research Hospital Department of Family Practice, Istanbul, Turkey - [***]Health Sciences University Haydarpaşa Numune Education and Research Hospital Clinic of Internal Diseases, Istanbul, Turkey

ABSTRACT

Introduction: Hyperglycemia and duration of diabetes are known risk factors for diabetic nephropathy, and the presence of microalbuminuria is a strong indicator of nephropathy. We aimed to examine the relation between Hemoglobin A1c (HbA1c) and urine albumin excretion (UAE) in this study.
Material and methods: The association between HbA1c and UAE was evaluated in 57 patients with diabetes mellitus, who had at least 8 years of disease history and 5 years of follow-up.
Result: Hb1Ac levels were above the target levels, and UAE levels were significantly increased with duration of disease, which was also associated with diabetic nephropathy.
Conclusion: According to the findings of this study, severe glucose control may inhibit progression of diabetic nephropathy.

Keywords: Hemoglobin A1c, Urine Albumin Excretion, Type 2 Diabetes Mellitus, Nephropathy, Microalbuminuria.

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Introduction

The World Health Organization has declared diabetes mellitus is the second disease after HIV that requires a global combat strategy. The underlying reason is the high morbidity and mortality rate due to micro-macro vascular complications and economical load for the economy of countries. There were 382 million diabetic patients as of 2013 globally, and 592 million cases are expected in 2035 with an increase rate of 55%[1].

Independent risk factors in development of diabetic neuropathy are hyperglycemia, hypertension, smoking, advanced age, insulin resistance, male gender (the risk is low in women before menopause), black origin, high protein diet, family history cardiovascular diseases, and genetic factors[2-7].

There is strong evidence regarding the relation of diabetic microangiopathy with duration and severity of hyperglycemia. Nephropathy frequency increases with extended diabetes duration. Diabetic

nephropathy progresses in 30%-40% of Type-1 diabetes over 20-40 years, and 50% of Type-2 diabetes over 20 years of disease history. Also, end stage renal disease (ESRD) develops in 8-10 years after onset of proteinuria[8].

Microalbuminuria is the earliest clinical manifestation of diabetic nephropathy. The appearance of microalbuminuria indicates the existence of structural damage in kidney and subsequently apparent nephropathy with macroalbuminuria, significant decrease in glomerular filtration rate, and a progression towards renal impairment/insufficiency at the final stage[9].

If HbA1c levels are below 7,1% for prolonged periods, the percentage of microvascular complications such as retinopathy, neuropathy, and nephropathy decreases up to 50%-70%[10]. And regardless of duration of diabetes, the risk of microalbuminuria increases with increased HbA1c levels above 10.1%[11].

A diabetic patient is diagnosed with obvious diabetic nephropathy in case of an albuminuria ≥ 300 mg at least twice a day, or proteinuria ≥ 500 mg daily in the urine test throughout a 3 - 6 months' period. If these patients do not receive appropriate treatment and follow-up, proteinuria often proceeds to nephrotic stage and renal functions deteriorate over time. Hypertension accompanies frequently this syndrome. Microalbuminuria is the decisive factor in terms of increased cardiovascular disease (CVD)[12, 13].

In this retrospective study, changes in UAE and HbA1c levels and the relationship of these two parameters with each other were examined and evaluated in type-2 diabetes mellitus patients who have been followed up in the polyclinic regularly for urine albumin excretion (UAE) and HbA1c in 24 hours' urine at least once a year.

Materials and methods

Fifty-seven diabetes mellitus patients that treated at the outpatient 3th Internal Medicine Service Diabetes Polyclinic of Haydarpaşa Numune Education and Research Hospital and followed-up regularly (at least once in a year) between 2004 and 2008 were enrolled in the present study. Only those patients whose HbA1c and UAE levels were measured simultaneously were included. If these were measured several times throughout a year, only the maximum values were considered.

Patients were evaluated individually regardless of their treatment. All cases were treated and followed-up for diabetes, hypertension, and dyslipidemia. Moreover, those diagnosed with nephropathy were followed up by nephrology polyclinic. All cases had a diabetes history of 8 years and more.

Exclusion criteria were presence of chronic kidney diseases except diabetes mellitus, malignancy, use of steroids, third degree heart failure, and presence of infection at the time of urination for microalbuminuria.

Biochemical analysis

UAE in 24-hour urine was analyzed using Roche/Hitachi modular analytics P800/D 2400 module device. HbA1c was determined using HPLC (high-performance liquid chromatography) device. 30-300 mg/day excretion of albumin in the urine is determined as microalbuminuria, more than 300 mg/day is determined as macroalbuminuria.

Blood Sampling Method

Patients' blood samples for HbA1c analyses were obtained after a 12 hour of overnight fasting.

24-Hours Urine Collection Method

A urine collection container was given to patients. After wasting their first urine by pouring it, they were asked to collect all the subsequent urinations in urine collection container including their first one the next day. In order to understand whether the patients collected enough urine, the level of creatinine correspondence according to body weight was controlled. Hence, creatinine excretion according to the total body weight it was supposed to be minimum 15 mg in women and 20 mg in men.

Statistical Analyses

NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) program was used for statistical analyses. During the analyses of the data obtained, besides the descriptive statistical methods (mean, standard deviation) in the comparison of quantitative data in the analysis of the parameters with normal distribution according to the years for the evaluation of the repeated measures variance analysis, paired sample t-test were employed. Parameters without normal distribution according to the years were

evaluated using Friedman test and for pair-wise comparisons Wilcoxon signed rank test was used. Comparison of qualitative data was made using Chi-square test. Spearman's rho correlation test was applied for the comparison of relationship between the parameters. Results were evaluated at 95% confidence interval and the $p < 0.05$ statistical significance level.

Results

The present study was conducted with 57 participants aged between 37 and 80, out of whom 22 (38.6%) were female and 35 (61.4%) male, followed-up between the years 2004 - 2008. The mean age of patients was 60.7±10.1 years (table 1).

	UAE (mg /day)		+p
	Ort±SD	Median	
2004	126,07±252,23	16,2	
2005	84,12±137,64	21,3	
2006	146,35±271,71	31,5	0,001**
2007	171,82±335,99	35	
2008	168,01±402,86	28	
2004-2005 ++p	0,981		
2004-2006 ++p	0,029*		
2004-2007 ++p	0,020*		
2004-2008 ++p	0,049*		
2005-2006 ++p	0,002**		
2005-2007 ++p	0,001**		
2005-2008 ++p	0,005**		
2006-2007 ++p	0,698		
2006-2008 ++p	0,334		
2007-2008 ++p	0,157		

Table 1: Changes in UAE levels between 2004 and 2008.
+*Friedman Test;* ++*Wilcoxon test;* *p<0.05;* **p<0.01*

UAE levels of the patients according to the years showed statistically significant differences ($p < 0.01$). Whereas there were no statistically significant changes in the UAE level between 2004 and 2005 ($p > 0.05$), the level of changes in the subsequent years 2006, 2007, and 2008 ($p < 0.05$) were statistically significant. Compared to the 2005 UAE level the increase witnessed in 2006, 2007, and in 2008 was statistically significant ($p < 0.01$).

However, there was no statistically significant difference in the other years ($p > 0.05$) (fig. 1).
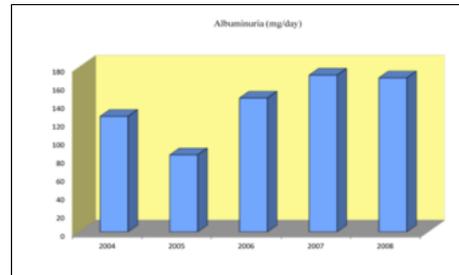

Fig. 1: Changes in UAE levels between 2004 and 2008.

There were no statistically significant differences in the HbA1c levels according to the years ($p > 0.05$) (table 2).

	HbA1c (%)	+p
	Ort±SD	
2004	7,72±1,46	
2005	7,80±1,54	
2006	7,80±1,31	0,399
2007	8,04±1,48	
2008	8,02±1,50	
2004-2005 ++p	0,654	
2004-2006 ++p	0,533	
2004-2007 ++p	0,079	
2004-2008 ++p	0,179	
2005-2006 ++p	1,000	
2005-2007 ++p	0,219	
2005-2008 ++p	0,251	
2006-2007 ++p	0,072	
2006-2008 ++p	0,181	
2007-2008 ++p	0,895	

Table 2: Changes in HbA1c between 2004 and 2008.
+*Variance Analysis of Repeated Measurements;* ++*Paired sample t test*

There was no statistically significant relation between HbA1c and UAE levels according to the years ($p > 0.05$) (fig. 2, table 3).
There was no statistically significant difference in the HbA1c levels of patients with macro level albuminuria and with micro level albuminuria over the years ($p>0.05$).
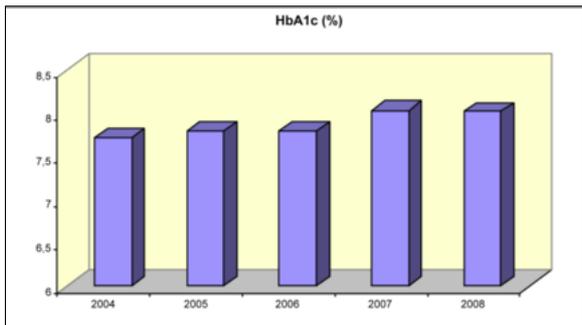
HbA1c (%)

Fig. 2: HbA1c changes between 2004 and 2008.

	HbA1c (%)- UAE (mg / day)	
	R	P
2004	0,190	0,158
2005	0,084	0,534
2006	0,026	0,846
2007	-0,069	0,608
2008	0,123	0,363

Table 3: Correlation between UAE and HbA1c levels between 2004 and 2008.
r: Spearman's rho correlation test

Discussion

The course of renal function in type 2 diabetes patients is heterogeneous[14]. The transition from normoalbuminuria to microalbuminuria is less obvious in Type 2 diabetes when compared to Type 1 diabetes. Although microalbuminuria is less specific in low-level nephropathy, it is an independent risk factor for atherosclerotic diseases and premature deaths. Insufficient glycemic control and duration of diabetes have a serious impact on the prognosis of diabetic nephropathy treatment[10, 15].

Hypertension treatment in Type 2 diabetes patients is a very important method for protection from nephropathy[16]. However, blood pressure monitoring is not within the scope of the present study. There are a lot of think tank groups suggesting microalbuminuria scanning as a prevention strategy in type 2 diabetes patients[17]. Although the significant increase in the years compared to the first 2 years disappears in the subsequent years, this could be explained with the increase in patients' compliance and intensity of the treatment, which could be the subject of another research.

There was no statistically significant difference in HbA1c levels during 2004 and 2008. In diabetes cases with diabetes over 8 years, mean HbA1c levels were 7.72%, 7.8%, 7.8%, 8.04%, and

8.02% respectively. These levels are not different from the results of other studies conducted.

In the NHANES III study in the USA, the average diabetes duration was 11.5 years and average HbA1c level was above 8%. 65.8% of the cases had normoalbuminuria and 34% had macroalbuminuria. Mean HbA1c levels were determined as 7.6% in specific diabetes clinics in the USA[18].

The DETECT study in Germany[19] has determined that mean HbA1c levels of diabetic patients with a disease history of 10 years was 8.2%, and microalbuminuria incidence was 81%.

In a joint US - Canada study, the ACCORD study, that conducted with 10.250 cases with a mean diabetes period of 10 years, a decrease in the mean HbA1c levels was observed from 8.1% to 7.9% after 3,5 years[20].

Mean HbA1c levels are varying in Europe. Although the mean HbA1c level is 7.4%, it ranged between 7.0% in Sweden and 7.8% in UK. The EUCID project was conducted in Europe to reach the targets in diabetes treatment, and showed that the proportion of diabetes patients with HbA1c above 7% is around 50% in 11 countries[21].

Over the years, there was no significant relationship between the UAE and HbA1c levels (Table 4).

		Microalbuminuria>30mg/day	Normoalbuminuria<30mg/day	p
		n (%)	n (%)	
2004	HbA1c >7	17 (%70,8)	19 (%57,6)	0,306
	HbA1c<7	7 (%29,2)	14 (%42,4)	
2005	HbA1c> 7	17 (%68,0)	19 (%59,4)	0,503
	HbA1c<7	8 (%32,0)	13 (%40,6)	
2006	HbA1c >7	21 (%70,0)	17 (%63,0)	0,574
	HbA1c<7	9 (%30,0)	10 (%37,0)	
2007	HbA1c >7	23 (%74,2)	21 (%80,8)	0,556
	HbA1c<7	8 (%25,8)	5 (%19,2)	
2008	HbA1c >7	19 (%67,9)	22 (%75,9)	0,501
	HbA1c<7	9 (%32,1)	7 (%24,1)	

Table 4: Distribution of albuminuria according to year of follow-up and HbA1c levels
Chi-square test

A previous study that conducted in Japan has evaluated the HbA1c levels and microalbuminuria presence in 33 patients that followed-up for 6 years, and found that mean HbA1c level was 7.9% in patients with microalbuminuria, and 8.6% in

patients with macroalbuminuria. The researchers claimed that the presence of microalbuminuria is a strong indicator of nephropathy presence and HbA1c levels above the target values are associated with nephropathy[22].

In the present study, the mean HbA1c levels were above the target value and though it leaded to an increase in microalbuminuria levels at last three years, this increase was not statistically significant.

Another risk factor in diabetic nephropathy development is the duration of diabetes. There were strong and statistically significant differences in the patients' baseline and 5 years later UAE levels. Other studies in the world have revealed that an increase in UAE cannot be prevented despite the mean HbA1c levels are kept consistent.

In order to reduce diabetes mellitus complications such as nephropathy, which pose a significant economic burden on the country and afflicted patients, nationwide policies should be developed to prevent the disease, and effective strategies should be developed for early diagnosis and follow-up.

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Corresponding author
SOLAK İBRAHIM*
Health Sciences University Konya Education and Research Hospital Department of Family Practice
Konya
(Turkey)