EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 6 (June-2015) pp. 451-462

www.ijcrar.com

Evaluation of microalbuminuria and urine beta 2 microglobulin in patients with type 1 and 2 diabetes

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KEYWORDS

Diabetes,
Nephropathy,
Beta2-macroglobulin,
Microalbumin,
Hemoglobin A1C

A B S T R A C T

Diabetes is disorder of metabolism so that the body cannot use sugar completely. Due to this disorder there is low or lack of excretion of insulin or lack of insulin action properly. Diabetes' outbreak is so that it is called a universal challenge with diverse late side effects such as nephropathy. In this research, the urine beta2-microglobulin and microalbumin; that are important in the diagnosis of renal involvement in diabetic patients were investigated. This cross sectional study was conducted in Endocrine Research Center of Tabriz University of Medical Sciences and Biology Department of Islamic Azad University, Ahar Branch on 24 patients with type 1 diabetes and 76 patients with type 2 diabetes referred to the Endocrinologist in 2013. After collection of urine sample and blood sample, the levels of microalbumin and beta2-microglobulin and creatinine in urine were measured and level of hemoglobin A1C, creatinine, Cholesterol, Triglyceride and blood sugar were measured. In this study the level of beta2-microglobulin in urine of the patients with diabetes was higher than normal but its level in type 1 compared to type 2, showed significant increase ($p<0.05$) and increase of urine microalbumin has significant changes in the patients with type 2 diabetes. In type 1 diabetes, significant correlation was found between level of microalbumin with length of diabetes, blood sugar and hemoglobin A1C level and also significant correlation was observed between urine beta2-microglobulin with age of patients. In type 2 diabetes, significant correlation was found between level of microalbumin and urine beta2-microglobulin with length of diabetes and serum and urine creatinine. Significant correlation and changes was not found between microalbumin and urine beta2-microglobulin with cholesterol, triglycerides, BMI and systolic and diastolic blood pressure. According to this fact that preservation of the blood sugar in normal range and also control of the dyslipidemia and hemoglobin A1C level are important in control of diabetes and prevention of short term and long term side effects diagnosis and on time control of blood sugar in diabetes patients play an import role in prevention of complications. So, tests of urine beta2-microglobulin and microalbumin can be used for early diagnosis of renal failure in type 1&2 diabetes.

Introduction

Diabetes mellitus is a chronic metabolic disorder which reduces the speed of glucose consumption and proper metabolism of glucose. As a result of this condition, the level of blood sugar escalates. Diabetes is a disease as a result of which either the body suffers from insulin shortage or the produced insulin is not properly distributed among the cells. Insulin is a hormone that is necessary for the entrance of glucose to most body cells (Cracken, 1997; Tipton, 2008; Moran, 2004; Basevi and Mario, 2011).

In the past, diabetes mellitus was classified into the following two groups by National Diabetes Data Group (NDDG) in 1979: insulin-dependent and non insulin-dependent diabetes mellitus. In the 80s and 90s the classification was employed widely, but it caused treatment problems as a result of which the following classification was presented in 1997 by the American Diabetes Association: type 1 diabetes, type 2 diabetes, gestational diabetes, and others. Although this classification has defects, it is still in use (Maraschin, 2012).

About 25.8% of the children and adults in the United States (i.e. approximately 8.3% of the American population) suffer from diabetes mellitus (Moran, 2004). According to the expectations the global prevalence of diabetes mellitus is increases and the number of diabetics will be 366 million people in 2030. Therefore, this disorder is introduced as a major health challenge (Ahmed et al., 2012). Diabetes mellitus is a chronic disease which calls for medical care and patient training to prevent its acute complications and reduce the risk of development of long-term complications (Beth, 2009). Problems may occur in diagnosing children, adolescents and adults with diabetes while an accurate diagnosis contributes to the treatment and prevention of this disease (Basevi and Mario, 2010).

One of the late complications of diabetes mellitus is nephropathy. Studies indicated that the increased excretion of urinary protein can be a clinical complication caused by diabetes nephropathy and generally leads to nephropathy (Sacks et al., 2011).

Beta2-microglobulin and microalbumin are among the excretory urinary proteins which are of great significance in terms of prognosis and diagnosis.

Beta2-microglobulin is an indicator of renal performance variations. The presence of albumin in urine of a diabetic patient reflects the late complications of diabetes and the patient's potential for renal diseases (Asim et al., 2010; Rheeder et al., 2012; Hruby and Mayer, 2008; Jerums and MacIsaac, 2002; Pant et al., 2009).

Microalbuminuria is one of the early signs of diabetic kidney diseases. It is observed before persistent proteinuria and shows a potentially reversible phase of diabetic nephropathy (Alleyn et al., 2010).

In this research, the differences and similarities of type 1 and type 2 diabetes were examined with regard to the changes in beta2-microglobulin and microalbumin. Moreover, blood sugar, BMI, age, gender, and illness duration of the patients were examined and the significance of each of the parameters was shown separately or together.

The objective of this research was to examine and compare the changes of beta2-microglobulin and microalbumin in the urine of patients with type 1 and 2 diabetes.

Materials and Methods

In a descriptive study that was performed in Endocrine Research Center of Tabriz University of Medical Sciences and Biology Department of Islamic Azad University, Ahar Branch On diabetic patients were examined to observe the changes of beta2-microglobulin and microalbumin in the urine of patients with type 1 and 2 diabetes.

Samples studied in this research were selected from patients who visited the endocrinology clinic due to diabetes. The patients were included in the study after obtaining their informed consent.

In this study, members of the control group were not compared with diabetics and the bases for comparison were the natural standard values.

Morning urine samples of the patients were obtained randomly. After macroscopic observations and centrifuge operations with a frequency of 2800 and duration of 4 minutes, it was tried to determine whether the level of bacteria and white globules exceeded 5 to 6 globules in microscopic terms. Next, the levels of beta2-microglobulin and microalbumin were measured and the levels of protein were tested using the test-type. When the protein level was lower than 1+ the level of microalbumin was measured and when protein level was over 1+ the level of urinary albumin was measured instead of microalbumin.

Test method

In order to measure creatinine the Jaffe method was used and blood sugar was measured using the glucose oxidase method. Beta2-microglobulin was also measured using the ELISA method and microalbumin was measured using the immunometric method. Hb A1c was also assayed using the Boromate affinity assay method.

Statistical analysis

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Results and Discussion

In the present study, 100 patients with type 1 and type 2 diabetes were enrolled into the study. The patients' age varied from 16 to 71 years. Moreover, 24% and 76% of the patients were suffering from type 1 and type 2 diabetes.

The changes of beta2-microglobulin in patients with type 1 and 2 diabetes were significantly different ($P<0.05$). The changes of the aforementioned parameter for patients with type 1 and 2 diabetes are shown in chart 1 and 2.

The changes of beta2-microglobulin in patients with type 1 and type 2 diabetes were significantly different ($P=0.018$). In other words, the levels microalbumin of patients with type 2 diabetes were higher than patients with type 1 diabetes. The levels of microalbumin in the patients with type 1 and 2 diabetes are shown in chart 3and 4.

Diabetes is a metabolic disorder caused by different reasons and is accompanied by different levels of insulin shortage or lack of response to insulin. This definition shows the important role of insulin and important changes caused its shortage to human

metabolism. Type 2 diabetes accounts for almost 85-90% of all diabetic patients (Cracken, 1997).

This disease has a less lethal image with the recent advancements, but it is still the major cause of blindness and renal failure and usually leads to amputation of hands and feet. Although no method has been found for the treatment of diabetes, it is possible to control it successfully. One of the objectives for controlling diabetes is to control blood sugar, blood pressure, and dyslipidemia. A balanced diet, weight controls, adherence to a healthy lifestyle, consumption of prescribed drugs and supervision of the conditions (if necessary) are of great importance (Moran, 2004; Maraschin, 2012).

The FBS test is the best test for the diagnosis of diabetes in children and non-pregnant adults, but it is not possible to easily determine the type of diabetes (Maraschin, 2012; Ross, 2006).

In this study, results of some parameters such as levels of microalbumin, urinary beta2-microglobulin, cholesterol, TG, serum creatinine, and BMI were significantly different for patients with type 1 and 2 diabetes ($P<0.05$). Therefore, these can be used as the indicators for distinguishing different types of diabetes.

Results of examining the levels of microalbumin and urinary beta2-microglobulin indicated that the highest level of microalbumin changes is seen in patients with type 2 diabetes as compared to patients with type 1 diabetes.

The highest level of beta2-microglobulin changes is also observed in patients with type 1 diabetes as compared to patients with type 2 diabetes. These findings comply with the results of several studies reporting the increase in microalbumin in diabetes and renal diseases. The findings, however, do not comply with the results of some studies. However, no study has been carried for comparing the status of these variables in type 1 and 2 diabetics.

In the study by Rheeder et al. (2012), the glomerular filtration method was used to examine 117 fifty year old samples. More than 50 of the patients had diabetes. In this study, the level of beta2-microglobulin was measured in diabetic patients with peripheral arterial disease and peripheral non-arterial disease and no significant difference was observed (Rheeder et al., 2012). However, the level of beta2-microglobulin in our study was significantly higher in the diabetics.

In the study by Pant et al. (2009), the relationship of microalbuminuria with age, gender, weight, creatinine excretion, and BMI was examined. The level of serum creatinine was also measured in all of the patients. The results of this study demonstrated that BMI and patient's gender had no significant effect on microalbuminuria whereas age and duration of diabetes treatment were directly related to Microalbuminuria (Pant et al., 2009). The type of diabetes was not determined in this study, but the results of our study comply with the results of the research by Pant et al. In the study by Alleyn et al. (2010), the urine samples were randomly obtained from 471 patients with type 1 diabetes who aged from 8 to 18 years. The results of this study demonstrated that persistent microalbuminuria is significantly related to the duration of diabetes in children, but was not significantly related to the age of patients (15). In this study, patients with youth diabetes or type 1 diabetes were examined and the results of this study comply with the results of our research in the case of type 1 diabetes.

Daousi et al. (2008) carried out a study to investigate the relationship of hyperglycemia with increased albuminuria in the long run in 400 patients with type 1 diabetes. The patients aged over 50 years and research results indicated that there was a significant relationship between blood sugar and urinary albumin (Daousi et al., 2008). This finding complies with the finding of our study in the case of type 1 diabetes.

In 1979, Viberti et al. conducted a study to examine the effect of controlling blood sugar on the levels of urinary albumin and beta2-microglobulin in patients with insulin-dependent diabetes. In this study, 17 non-diabetic patients and 43 patients with insulin-dependent diabetes were studied to investigate the effect of improved blood sugar control on glomerular indices and tubular function of kidneys. Based on the findings of this study it can be concluded that the level of urinary albumin excreted during the insulin injection declined considerably but no significant changes were observed in excretion of beta2-microglobulin (Viberti et al., 1979).

In the study by Murussi et al. (2007) high levels of albuminuria predicting the extent of micro- and macro-albuminuria as well as the increased mortality rate were measured and examined in patients with type 2 diabetes in Brazil. In this research, 193 patients with type 2 diabetes, who showed excretion of microalbumin within 8 years, were studied and the levels of GFR were measured in such patients.

Results of this study revealed the persistent development of micro- and macro-albuminuria as well as the relationship of the development of micro and macro-albuminuria with duration of diabetes and mortality (Murussi et al., 2007). Results of this study comply with the results of our study regarding the level of microalbumin and duration of diabetes in the case of type 2 diabetes.

Aksun et al. conducted a study in 2004 to measure the levels of beta2-microglobulin and cystatin in 68 patients with type 2 diabetes. The patients had or lacked urinary excretion of albumin. In patients with Microalbuminuria, serum C cystatin and glucose concentration were considerably higher than the patients that did not suffer from Microalbuminuria. However, no significant changes were observed in excretory levels of beta2-microglobulin (Aksun et al., 2004). In our study, in patients with type 2 diabetes no significant relationship was observed between microalbumin and blood sugar while a significant relationship was observed between excretory levels of beta2-microglobulin and microalbumin.

In the study by Djukanovic et al. (2013) samples of urinary proteins were examined for 74 patients with nephropathy, 50 healthy participants and 22 patients with glomerulonephritis. Urinary excretion of beta2-microglobulin, albumin, and G immunoglobulin was examined in patients with nephropathy, glomerulonephritis, and healthy individuals and urinary excretion of all of them was higher than the normal levels in patients with nephropathy. In patients with glomerulonephritis an increase in microalbuminuria was observed. In half of the patients with glomerulonephritis an increase in beta2-microglobulin was observed and in 11 patients an increase in IgG was observed (Djukanovic et al., 2013). However, in our study, no distinction was made between patients with glomerulonephritis and nephropathy.

In 1989, Hosoi et al. carried out a study on 41 patients with insulin-dependent diabetes and found a significant difference in the

levels of beta2-microglobulin and microalbumin in the diabetic patients and participants in the control group (Hosoi et al., 1989). This finding complies with our findings in the case of type 1 diabetes.

In the study by Shahjahan et al. (2011) a total of 88 patients were studied. The patients ranged from 30 to 60 years and 50 were male and 38 were female. The patients showed different levels of renal performance and were randomly selected from the patients visiting the Sheikh Zayed Hospital in Lahore, Pakistan. Clearance of creatinine, 24-hour creatinine and serum creatinine was prepared for the patients and the patients were classified into 4 groups based on their creatinine clearance results. The levels of urinary and serum beta2-microglobulin were measured in all groups and it was found out that the aforementioned levels of beta2-microglobulin increased in parallel.

Table.1 Frequency and percent of patients with Diabetes

			Diabetes Type		Total
			Type 1	Type 2	
Gender	Male	Frequency	10	30	40
		Percent	41.7%	39.5%	40%
	Female	Frequency	14	46	60
		Percent	58.3%	60.5%	60%
Total		Frequency	24	76	100
		Percent	24%	76%	100%

Table.2 Laboratory finding of patents with type 1&2 Diabetes

	Diabetes type	Mean ± Std	CI 95%	P
Microalbumin *mg/l*	1	17.29 ± 25.97	6.32-28.26	0.018
	2	60.46 ± 86.21	40.76-80.16	
Beta2-microglobulin µg/ml	1	0.52 ± 0.41	0.347-0.695	0.014
	2	0.34 ± 0.26	0.282-0.402	
Age	1	22.33 ± 4.18	20.57-24.1	0.0001
	2	52.7 ± 10.83	49.59-54.54	
HbA1C	1	7.19 ± 1.3	6.64-7.74	0.5
	2	6.97 ± 1.2	6.72-7.27	
BS *mg/dl*	1	133.8 ± 24.75	137.37-144.28	0.767
	2	135.9 ± 31.36	128.75-143.08	
TG *mg/dl*	1	138 ± 22.46	128.52-147.52	0.0001
	2	176.6 ± 33.42	169.31-184.58	
Cholesterol *mg/dl*	1	139.33 ± 21.16	130.40-148.27	0.0001
	2	163.34 ± 24.96	157.18-169.50	
Serum Cr *mg/dl*	1	1.24 ± 0.43	1.05-1.42	0.0001
	2	0.93 ± 0.22	0.87-0.97	
Urine Cr *mg/dl*	1	81.33 ± 22.48	71.83-90.82	0.33
	2	58.98 ± 20	81.41-90.55	
BMI	1	22.79 ± 1.55	22.13-23.45	0.0001
	2	30.13 ± 4.54	29.09-31.17	
SBP *mmHg*	1	132.38 ± 12.65	127.03-137.72	0.585
	2	130.81 ± 11.32	128.9-133.47	
DBP *mmHg*	1	78.62 ± 7.6	75.40-81.84	0.158
	2	76.46 ± 6.11	75.06-77.85	

Table.3 Correlation of studied parameters in patients with type 1 Diabetes

		Beta2-microglobulin	Microalbumin
Microalbumin	Correlation	0.391	-
mg/l	P_Value	0.059	-
Age	Correlation	0.393	0.47
	P_Value	0.57	0.20
Disease duration	Correlation	0.313	0.678
	P_Value	0.136	0.0001
HbA1C	Correlation	0.249	0.672
	P_Value	0.243	0.0001
BS	Correlation	0.167	0.447
mg/dl	P_Value	0.436	0.029
TG	Correlation	-0.148	0.243
mg/dl	P_Value	0.491	0.252
Cholesterol	Correlation	-0.091	0.386
mg/dl	P_Value	0.673	0.062
Serum Cr	Correlation	0.466	0.644
mg/dl	P_Value	0.022	0.01
Urine Cr	Correlation	-0.441	-0.293
mg/dl	P_Value	0.031	0.164
BMI	Correlation	-0.148	0.028
	P_Value	0.489	0.895
SBP	Correlation	0.082	0.206
mmHg	P_Value	0.702	0.335
DBP	Correlation	-0.108	0.012
mmHg	P_Value	0.616	0.954

Table.4 Correlation of studied parameters in patients with type 2 Diabetes

		Beta2-microglobulin	Microalbumin
Microalbumin	Correlation	0.398	-
mg/l	P_Value	0.0001	-
Age	Correlation	0.075	0.274
	P_Value	0.52	0.015
Disease duration	Correlation	0.355	0.510
	P_Value	0.002	0.0001
HbA1C	Correlation	0.088	0.293
	P_Value	0.451	0.010
BS	Correlation	-0.020	0.212
mg/dl	P_Value	0.863	0.066
TG	Correlation	0.108	-0.081
mg/dl	P_Value	0.352	0.489
Cholesterol	Correlation	-0.026	-0.103
mg/dl	P_Value	0.352	0.489
Serum Cr	Correlation	0.322	0.474
mg/dl	P_Value	0.005	0.0001
Urine Cr	Correlation	-0.203	-0.499
mg/dl	P_Value	0.078	0.0001
BMI	Correlation	0.009	0.119
	P_Value	0.941	0.306
SBP	Correlation	-0.216	-0.054
mmHg	P_Value	0.061	0.641
DBP	Correlation	-0.123	0.05
mmHg	P_Value	0.291	0.966

Chart.1 Frequency of Beta2-microglobulin in patients with Type 2 Diabetes

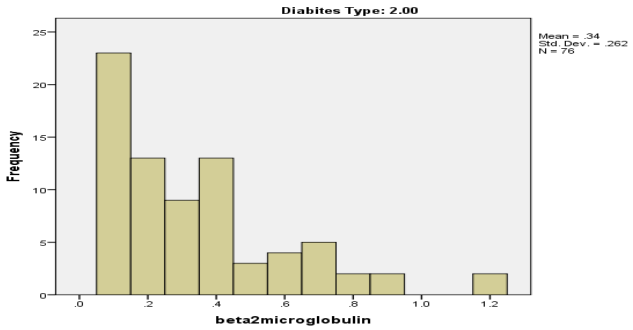


Chart.2 Frequency of Beta2-microglobulin in patients with Type 1 Diabetes

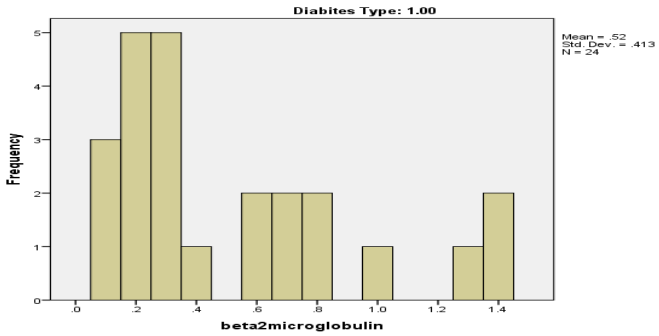


Chart.3 Frequency of microalbumin in patients with Type 2 Diabetes

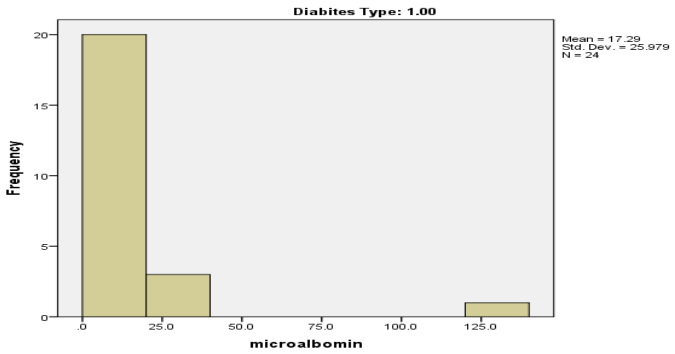


Chart.4 Frequency of microalbumin in patients with Type 1 Diabetes

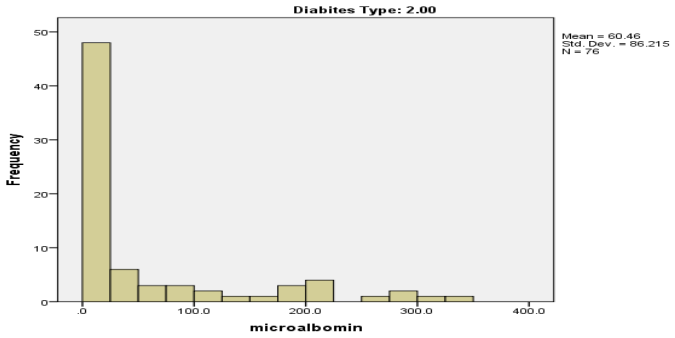


Chart.5 Correlation of microalbumin and Beta2-microglobulin

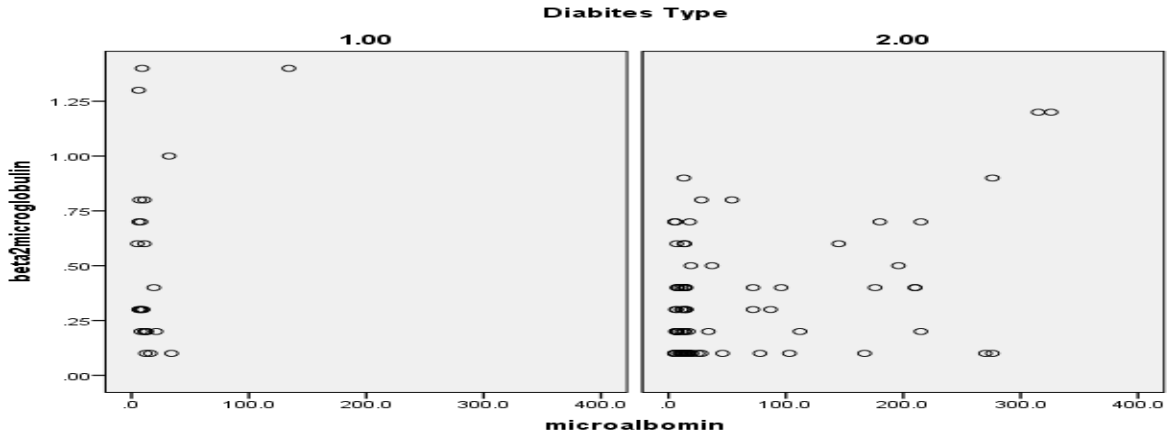


Chart.6 Correlation of Beta2-microglobulin and HbA1C

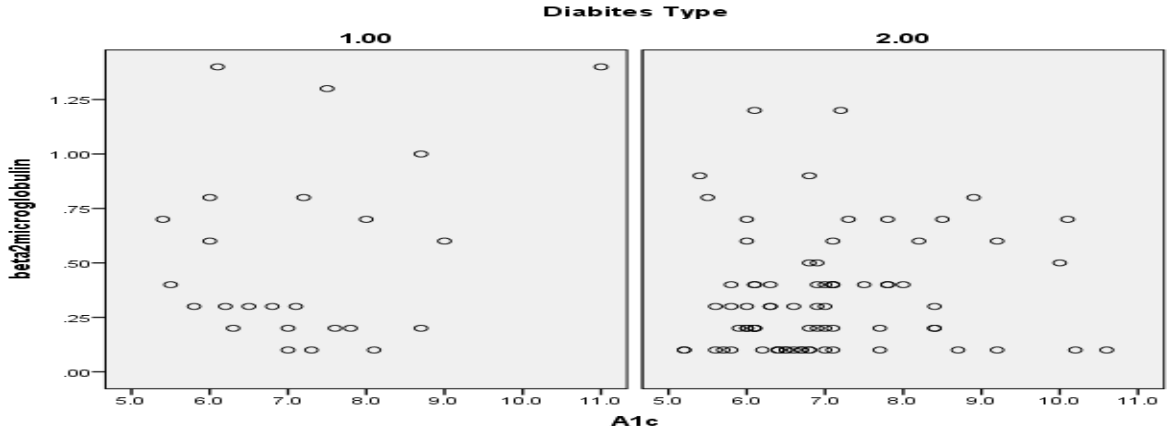
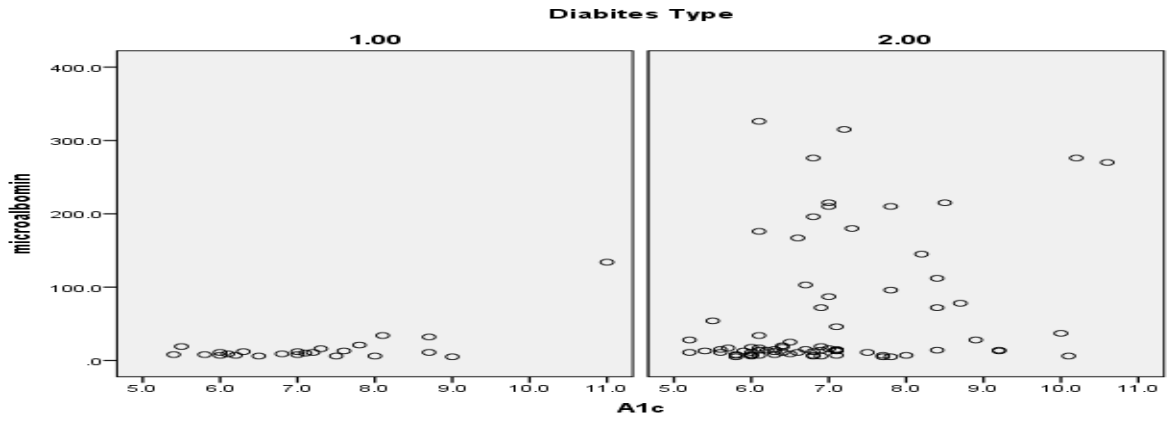


Chart.7 Correlation of microalbumin and HbA1C



Although serum creatinine and beta2-microglobulin showed a positive correlation in all groups, there was a negative correlation between beta2-microglobulin and creatinine clearance in all groups (Shahjahan et al., 2011). In this study, type 1 and type 2 diabetes were not differentiated but our results comply with the findings of Shahjahan et al. overall.

In 1982, Poortmans et al. conducted a study to examine the relationship between protein excretion and early signs of renal function disorders in adolescents with diabetes. In this research, the levels of albumin, beta2-microglobulin, creatinine, and total urine protein were measured in 21 diabetic adolescents before and after the exercise test.

The urinary creatinine levels in the diabetic and non-diabetic patients were almost equal but in resting, the total outputs of urinary protein, albumin, and beta2-microglobulin were significantly higher in diabetics than members of the control group (Poortmans et al., 1982). In this study, although the exercise test was used, the overall results concerning the increase in urinary beta2-microglobulin comply with our results.

Conclusion

In the case of diabetes mellitus, with type 2 diabetes as its most common form, prevention is the best solution. Control of blood sugar, blood pressure and dyslipidemia is one of the most important solutions for controlling diabetes.

Complications of diabetes usually develop before the patient is informed of the disease. If signs of diabetes are diagnosed before development of the disease, it is possible to prevent the irreversible consequences of diabetes to the possible extent.

The level of beta2-microglobulin increases with destruction of the kidney tubules and the level of microalbumin increases with renal glomerular damage. Hence, controlling the level of urinary beta2-microglobulin and microalbumin in diabetics is the most important way of controlling the progress of diabetes. By controlling these variables and correcting the lifestyle of patients, it is possible to control the complications of diabetes including nephropathy.

Suggestions

The changes of microalbumin and beta2-microglobulin in gestational diabetes shall be compared to the changes in type 1 and 2 diabetes.

The changes in urinary beta2-microglobulin should be compared to the changes in serum beta2-microglobulin in diabetics. The changes in microalbumin and beta2-microglobulin shall be examined depending on the geographic locations using a control group at a greater statistical level.

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