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Research Article

Effect of Hypertriglycridemia on the Frequency of Albuminuria in Saudi Populaion with Type 1 Diabetes Mellitus

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1. Key words

Type 2 diabetes; Albuminuria and hypertriglycridemia

2. Abstract

2.1. Background

Diabetic nephropathy is the main reason for the increase in the number of patients with end stage renal disease worldwide, including in Saudi Arabia. The development of albuminuria in type 1 diabetes (T1DM) might be induced by hypertriglycridemia. In this study we report the effect of hypertriglyceridemia on the frequency of albuminuria in patients with T1DM attending the diabetes centre in Saudi Arabia.

2.2. Methods

The study was retrospective conducted at the diabetes centre Clinics at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. A total of 278 Saudi with T1DM were randomly selected.

2.3. Results

Total of 278 patients with T1DM included in this study; 92 (33.1%) male and 186 (66.9%) female with mean age 25.9 ± 3.3 years (minimum 13.5, maximum 29.7 years). Hypertension was present in 105(38.2%). Mean BMI 31.5 ± 6.1, HbA1c was 7.8 ± 2.4, mean TG was 1.8 ± 1.1 mmol/l and mean albumin excretion rate was 60.9 ± 234.3. Albuminuria was present in 83 (29.9%) and was not significantly more prevalent in female (67.5%) with female predominance (sex ratio female:male) 2.1:1. Cases with albuminuria have significantly higher HbA1c compared to normalbuminuria, 8.6±2.6 vs. 7.5±2.2 respectively, p=0.001. HTN with albuminuria was more frequent in 42(50.6%) of albuminuria group with odd ratio 2.1 (1.2-3.6), p=0.008. The mean TG is non-significantly higher in age group 20-24 and 25-29 years compared to age group <20 years with non-significant male predominant across age groups.

2.4. Conclusion

We conclude that hypertriglyceridemia in patients with T1DM should be considered as a potential risk factor and as a diagnostic biomarker to be used in conjunction with other biochemical markers for early diagnosis, assessment, and follow-up of albuminuria.

2. Introduction

Diabetic nephropathy is the main reason for the increase in the number of patients with end stage renal disease worldwide including in Saudi Arabia and Europe [1,2]. Patients with Type 1 diabetes (T1DM) and incipient renal disease (micro albuminuria) have a three-fold increase, patients with overt renal disease (macro albuminuria) a nine-fold increase, and patients with end stage renal disease an 18-fold increase in all-cause mortality, but patients without renal disease show no excess mortality beyond that of the general population. 3 The occurrence of albuminuria in a patient with T1DM is clearly indicative of an enhanced risk of nephropa-

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thy and cardiovascular disease [4,5].

T1DM patients with nephropathy have an altered lipid profile [5]. Plasma lipids are a risk factor for the development and progression of diabetic nephropathy [6]. The results of animal studies suggested that lipids may play a role in the development and progression of diabetic nephropathy [7]. 7 A recent microarray analysis showed that the genes involved in lipid metabolism are overex- pressed in the kidneys of rats with streptozotocin-induced diabetes [8]. It is difficult to demonstrate convincingly that serum lipids play a primary role in the development and/or progression of diabetic nephropathy and to exclude the possibility that lipid changes be secondary to nephropathy as glomerular disease may cause changes in lipoproteins [9].

In T1DM patients with nephropathy and overt albuminuria, elevated plasma levels of triglycerides are observed [10]. In the European Diabetes Prospective Complications Study Group Complications study (EURODIAB-IDDM), macro albuminuria was associated with significantly increased plasma triglycerides in both sexes [11]. It is well known that lipid abnormalities are associated with diabetic renal disease and already present at an early stage [12]. Severe renal insufficiency may lead to secondary changes in the lipid profile by several mechanisms [13]. Whether lipid abnormalities are also involved in the pathogenesis of renal disease, is still a matter of debate.

Although T1DM is common in Saudi Arabia, very little is known about complications and their risk factors in Saudi Arabia. There have been few studies on the influence of hypertriglyceridemia on albuminuria in Saudi populations. The identification of such individuals is an important challenge to care providers. In this study we report the effect of hypertriglyceridemia on the frequency of albuminuria in patients with T1DM attending the diabetes centre in Saudi Arabia.

4. Methods

The study is a retrospective conducted at the diabetes centre Clinics at King Fahad Armed Forces Hospital. A total of 278 Saudi with T1DM were randomly selected. The demographic data and medical history were documented. Blood Pressure readings were within a gap of 15 minutes using a mercury sphygmomanometer by palpation and auscultation method in right arm in sitting position. Two readings, 15 min apart, were taken and the average of both the readings was taken for analysis. Hypertension (HTN) was also diagnosed based on anti HTN medications or having a prescription of antihypertensive drugs and were classified as Hypertensive irrespective of their current blood pressure reading or if the blood pressure was greater than 140/90 mmHg i,e systolic BP more than 140 and diastolic BP more than 90 mm of Hg – Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [14]. HbA1c was expressed as percentage. High performance liquid chromatography was used. Albuminuria was assessed by measurement of mean albumin excretion rate (AER) on timed, overnight urine collections. We use a polyclonal radioimmunoassay for albumin measurement. Albuminuria was defined as AER ≥30 g/min in overnight urine collections (equivalent to ≥30 mg/g creatinine in a random spot sample) [15]. The method used for determining TG levels in the laboratory was the Enzmatic method.

Statistical Analysis Univariate analysis of baseline demography and clinical laboratory were accomplished using unpaired t-test. Chi square(X2) test were used for categorical data comparison. The independent relationship between risk factors and the odds ratio of having albuminuria were analyzed using logistic regression. All statistical analyses. Were performed using SPSS Version 22.0. All P values were based on two-sided tests. P<0.05 was considered to be significant.

5. Results

Total of 278 patients with T1DM included in this study; 92 (33.1%) male and 186 (66.9%) female with mean age 25.9 ± 3.3 years (minimum 13.5, maximum 29.7 years) , **Table 1**.

Table 1: Demographic parameters of patients with type 1 diabetes [mean±standard deviation or number (%).

Parameters		Total
n (%)		278
Age (years)		25.9 ± 3.3
Gender	Male	92 (33.1)
	Female	186 (66.9)
Body mass index (kg/m²)		31.5 ± 6.1
Hypertension		105 (38.2)
HbA1c		7.8 ± 2.4
Serum triglyceride (mmol/L)		1.8 ± 1.1
Serum creatinine (µmol/L)		64.3 ± 15.9
Urine albumin (g/min)		60.9 ± 234.3

Table 2: Comparison of features between albuminuria groups in patients with type 1 diabetes [mean±standard deviation or number (%).

P value	Normoalbuminuria			
	1065(70.1)	Albuminuria	Parameters	
		83(29.9)		
0.9	195(33.3)	27(32.5)	Male	Gender
	130(66.7)	56(67.5)	Female	
0.4	25.8±3.3	26.2±3.1	Age(years)	
0.8	31.5±6.0	31.7±6.6	Body mass index (kg/m²)	
0.005	63(32.8)	42(50.6)	Hypertension	
0.001	7.5±2.2	8.6±2.6	HbA1c	
0.04	1.7±1.0	2.1±1.4	Serum triglyceride (mmol/L)	
0.9	64.3±15.4	64.4±17.0	Serum creatinine (µmol/L)	
<0.0001	10.4±7.1	179.7±406.2	Urine microalbumin (g/min)	

Hypertension was present in 105(38.2%). Mean BMI 31.5 ± 6.1, HbA1c was 7.8 ± 2.4, mean TG was 1.8 ± 1.1 mmol/l and mean albumin excretion rate was 60.9 ± 234.3. Albuminuria was present in 83 (29.9%) and was not significantly more prevalent in female (67.5%) with female predominance (sex ratio female: male) 2.1:1, **Table 2**. Cases with albuminuria have significantly higher HbA1c compared to normalbuminuria, 8.6±2.6 vs. 7.5±2.2 respectively, p=0.001. HTN with albuminuria was more frequent in 42(50.6%) of albuminuria group with odd ratio 2.1 (1.2-3.6), p=0.008, **Table 2** and **3**. **Figure** for the mean TG according to age groups stratified by gender in patients with albuminuria showed the mean TG is non-significantly higher in age group 20-24 and 25-29 years compared to age group <20 years with non-significant male predominant across age groups.

Table 3: Odd ratio of hypertension, HbA1c and triglyceride level and Frequency of albuminuria in Saudi adults based on regression analysis.

Parameters	Odd ratio (95% CI)	P value
Hypertension	2.1 (1.2-3.6)	0.008
HbA1c	1.2 (1.1-1.3)	0.003
Serum triglyceride (mmol/L)	1.1 (0.9-1.4)	0.2

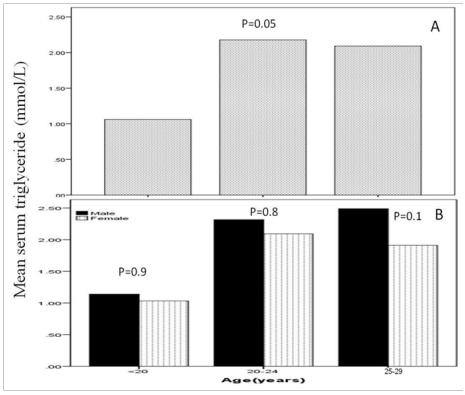

Figure: Mean serum triglyceride according to age groups (years) stratified by gender (A and B) in patients with type 1 diabetes and albuminuria

6. Discussion

The prevalence of T1DM had increased in Saudi Arabia and most European populations and it may also be rising among US youth [16,17]. The prevalence, incidence and mortality of end stage renal disease and from all forms of cardiovascular disease are strikingly increased in persons with diabetes compared to those without diabetes. 18,19 The cumulative incidence of microalbuminuria in patients with T1DM was 12.6% over 7.3 years according to EURODIAB and 33% in an 18-year follow-up study in Denmark [20,21].

A large body of evidence implicates poor metabolic control with the risk of developing microalbuminuria. Elevated levels of glucose increase the risk, not only for the short term, through the generation of advanced glycated proteins, activating an isoform of the protein kinase C and increasing the sensitivity to angiotensin II. What is controversial is whether or not there is a glycemic threshold for risk. Data coming from cross-sectional, follow-up and intervention studies has not supported the existence of a threshold, and efforts to reduce HbA1c should, therefore, be continued at all levels [20]. Clinical trials have consistently demonstrated that A1c levels<7% are associated with decreased risk for clinical and structural manifestations of diabetic nephropathy in T1DM patients. In the Diabetes Control and Complications Trial, intensive treatment of diabetes reduced the incidence of microalbuminuria by 39% [22].

HbA1c has been shown to be independently correlated with TG levels, indicating that this disorder was mostly observed in patients with poor glycemic control [23]. In a British follow-up study of 229 children with T1DM, TG was positively correlated with HbA1c and around 10% of the patients had TG values outside recommendations [24]. Data from the Coronary Artery Calcification in type 1 diabetes study, which examined 652 patients with T1DM, have shown, in patients not using hypolipidemic agents, that a higher HbA1c was associated with significantly higher levels of TG [25]. 25 In that study, 1% change in HbA1c was associated with an increase of 0.052 mmol/l (4.5 mg/dl) for TG. In a other study, performed in 512 young patients with T1DM and in 188 healthy age-matched controls, patients with suboptimal control (HbA1c >7.5%) had much more lipid quantitative disorders than patients with optimal control (HbA1c<7.5%). 26 All these data suggest that quantitative lipid abnormalities are more frequent, when type 1diabetes is not well controlled. In addition, some patients with T1DM may have insulin resistance and greater dyslipidemia [27]. In a recent study performed in 60 young type 1 diabetic patients and 40 adults with T1DM, it has been shown that lower glucose infusion (more insulin resistance) was associated with higher levels of TG in both youths and adults [28]. These data indicate that insulin resistance may be an additional factor that could induce quantitative lipid abnormities in some T1DM patients with a background of insulin resistance (abdominal obesity, family history of type 2 diabetes).

Patients with treated T1DM may show quantitative lipid disorders. In a prospective study performed in 895 young subjects with T1DM, 20.1% had plasma TG above 1.7 mmol/l. 23 The control of blood lipids is one of the cornerstones in the treatment of T1DM. Apart from effects on macrovascular outcomes, dyslipidemia potentially contributes to micro vascular disease [29, 30]. Prospective studies have confirmed a link between serum lipids and nephropathy, although lipid fractions measured in these studies have been limited, and parameters associated with kidney disease have not been consistently identified [31,32]. In T1DM patients with nephropathy and overt albuminuria, elevated plasma levels of TG are observed [33]. 33 In the EURODIAB IDDM Complications study, macro albuminuria was associated with

significantly increased plasma TG in women. 11 It may be that different lipid variables are important at different stages of diabetic kidney disease. For example, TG appeared to have different effects on the progression of nephropathy, depending upon the duration of diabetes [34]. The mechanisms responsible for these lipoprotein abnormalities in T1DM patients with microalbuminuria remain unclear.

A clinic based study introduces referral bias, is one of the limitations of this study. This could have introduced some degree of referral bias. However the prevalence of albuminuria is similar to that reported in other studies. A single urine spot collection with semi quantitative dipstick determinations was used to detect albuminuria. The American Diabetes Association guidelines stated that this technique has acceptable sensitivity and specificity, but recommend that several collections should be done in a 3 to 6 month period before diagnosing a patient as having albuminuria [32]. We conclude that hypertriglyceridemia in patients with T1DM should be considered as a potential risk factor and as a diagnostic biomarker to be used in conjunction with other biochemical markers for early diagnosis, assessment, and follow-up of albuminuria.

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