Interaction of Insulin Hormone with Microalbuminuria and Blood Pressure in Type 2 Diabetic Patients.

Israa Harjan Mohsen **Haider Kamil Zaidan** **Ali Hmood Al-Saadi**
Collage of Science/Kufa University   *Collage of Science/Babylon University*
profali_alsaadi@yahoo.com

Abstract

This study aimed to evaluate the interaction between insulin hormone with microalbuminuria and blood pressure in type 2 diabetic patients. The results of this study showed that patients with diabetic of both male and female have significant elevation ($p \leq 0.05$) in insulin hormone levels, insulin resistance ,fasting blood glucose (FBG) and microalbuminuria than control group. Insulin sensitivity show significant decrease in diabetic group when compared with control group. There are no significant differences in blood pressure in diabetic group when compared with control group. According to the duration of disease the results showed that microalbuminuria exert significant elevation in the fourth duration (> 15) years of disease when compared with other duration and with the increase in the duration of diabetic , the fasting blood glucose (FBG) values showed a significant increase than the lower duration of diabetic.Insulin sensitivity values showed a significant decrease in the fourth duration (> 15) years of disease when compared with other duration . The correlation analysis showed that there were positive significant correlation between insulin and microalbuminuria in both genders in diabetic group , while there is an positive correlation between insulin and systolic pressure in males.
Conclusions: In diabetic patients ,hyperinsulinemia cause elevation in microalbuminuria and this increase the risk of development of nephropathy and progression of cardiovascular disease.
Key words: Insulin , Microalbuminuria , Blood pressure , Insulin Resistance ,Insulin Sensitivity , Nephropathy.

الخلاصة

هدفت الدراسة الحالية الى تقييم مدى التداخل بين هرمون الانسولين والالبومين البولي المجهري وضغط الدم لدى مرضى السكري من النوع الثاني . اظهرت نتائج هذه الدراسة ان المرضى الذين يعانون من داء السكري النوع الثاني لكلا الذكور والاناث ارتفاع معنوي في ($p \leq 0.05$) في مستويات هرمون الانسولين ومقاومة الانسولين وسكر الدم الصيامي والالبومين البولي المجهري مقارنة بمجموعة السيطرة بينما انخفضت مستويات حساسية الانسولين معنويا في مجموعة مرضى السكري من النوع الثاني بالمقارنة مع مجموعة السيطرة . اظهرت نتائج التحليل الاحصائي حسب مدة المرض وجود ارتفاع معنوي في مستويات الالبوين البولي المجهري بينما انخفضت مستويات حساسية الانسولين في المدة التي يكون فيها المرض اكثر من 15 سنة مقارنة مع مدد المرض الاخرى في حين تزداد مستويات السكر الصيامي بزيادة مدة المرض .واوضحت تحليلات الارتباط وجود ارتباط ايجابي بين الانسولين والالبومين البولي المجهري في كلا الجنسين بينما كانت العلاقة موجبة مع ضغط الدم الانقباضي في الذكور فقط.
الكلمات المفتاحية: انسولين، الالبومين البولي المجهري، ضغط الدم، مقاومة الانسولين، حساسية الانسولين، اعتلال كلوي.

Introduction

The type 2 diabetes represent complex disease which is results from the combination between genetic , environmental and behavioral factors (Chen *et al.,*2011).It is characterized by insulin resistance that's it inability of the body to effectively use insulin and inadequate insulin secretion from pancreas resulting in high blood glucose levels(hyperglycaemia) (Das and Elbein 2006; ADA,2013).

Type 2 diabetes is commonly associated with obesity ,physical inactivity,hypertension, blood lipid levels distortion and a tendency to develop thrombosis(CDC,2004).It is estimated 90-95% of diabetic patients and approximately 350 million of people in the world have diabetes . Diabetes was the direct cause of some 1.5 million deaths, in 2012 ,with more of

them occurring in low- and middle-income countries. WHO projects that diabetes will be the important condition that leading cause of death by 2030 (WHO,2015).

For several years type 2 diabetes may remain undiagnosed because of the developing hyperglycemia is appear gradually and chronic complication of diabetes are already present at the time of diagnosis (Fong *et al.,*2004 ;Gross *et al.,*2005). Hyperglycemia exert its direct and indirect effect on vascular vessels which represent the important source of morbidity and mortality in type 2 diabetes, and this complication include macrovascular complication and microvascular complications which is include diabetic nephropathy , neuropathy and retinopathy (Bloomgarden,2004;Holt *et al.,*2010).

Microalbuminuria is a term that describe the rate of urinary albumin excretion .It is reflect the integrity of microvascular and function of glomerular endothelial. The elevation of microalbuminuria indicate kidney disease development   (Heinig and   Johnson *,2006)*.Abnormalities in metabolism and blood pressure accompanied with diabetes and there are some researches suggested that that hypertension lead to increase the development of nephropathy disease especially in diabetic patients (Kannel *et al*.,1991; Peralta *et al.,*2006). So this study is designed to evaluate the interaction between insulin hormone with microalbuminuria and blood pressure in type 2 diabetic patients.

Materials and methods

The study subjects comprised from 80 patients with type 2 diabetes without any complications selected from AL-Sader Teaching Hospital (male and female) with different duration of disease range from (1-20 years), the control group study included 40 people apparently healthy and this group matched with patient group. All subjects in this study were taken consent before participation in this study.Venous blood samples were drawn from patient and control subjects by using disposable syringes (5mL) in the sitting position. Five ml of blood were obtained from each subject by vein puncture pushed slowly into disposable tubes containing separating gel was allowed to clot at room temperature for 10-15 minutes and then centrifuged at $2000 \times g$ for approximately 10-15 minutes then the sera were obtained and stored at -20˚C until analysis (hormonal assayed).

Urine samples are collected in the first morning from patients and control groups in special container for this purpose and the test was conducted as soon as possible. The COMBINA 13 Strips kit was used to determine microalbuminuria levels in urine. It is based on the "protein error" principle of the indicator, which is caused by the presence of albumin. Sulfonephthalein has a high sensitivity for albumin (Thomas, 2008).

Measurement of arterial blood pressure for each patient in the sitting position by using Mercury sphygmomanometer two additional times, waiting a five minutes between measurements and then take the reading rates.

Determination of fasting blood glucose (FBG)
The RanDox kit was used to determine serum Glucose levels. It is based on the PAP enzymatic determination of glucose (Barham and Trindoer method,1972).
Hormonal assay
Insulin hormone is assayed by using the Monobind ELISA Kit which was based on standard sandwich enzyme-linked immune-sorbent assay technology
Determination of insulin resistance and **insulin sensitivity**
Insulin resistance is evaluated by determination of homeostasis model assessment of insulin resistance (HOMA-IR) (Mathews *et al.,* 1985 ; Stumvoll and Gerich ,2001) and calculate by using the following equation
$IR_{HOMA} = (I_0 \times G_0) / 22.5$
Were : IR_{HOMA} : insulin resistance according to homeostasis model assessment.
I_0: Fasting insulin level. G_0: Fasting glucose level.
The **quantitative insulin sensitivity check index** (*QUICKI*) is derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose (Katz *et al.,* 2000).
1 / (log(fasting insulin µU/mL) + log(fasting glucose mg/dL)

7. Statistical Analysis

All statistical analysis were performed by using SPSS version 17. Data were expressed as (mean ± SD) by using T-test. The normality of the distribution of all variables was assessed by the student′s ANOVA test and Pearson correlation analyses that have been used to determine the significant difference between the groups (Al-Mashhadni and Al-Mashhadni, 1989).

Results

The levels of hormone and physiological parameters in both gender of patients with type 2 diabetic and control groups

The statistical analysis of this study shows significant differences between patients with diabetic and control groups. Patients with diabetic of both male and female have significant elevation ($p \leq 0.05$) in insulin hormone levels, insulin resistance ,fasting blood glucose (FBG) and microalbuminuria than control group. Insulin sensitivity show significant decrease in diabetic group when compared with control group. There are no significant differences in blood pressure in diabetic group when compared with control group as shown in table (1).

Table(1) The levels of hormone and physiological parameters in both gender of patients with diabetic and control group

Group parameters	Control Mean ± SD		Diabetic only Mean ± SD		P value of gender	P value of group
	Male	Female	Male	Female		
Insulin (µIU/ml)	8.46±3.40	8.39±2.97	13.81±2.49	13.34±2.209	0.62	0.05*
FBG(mg/dl)	93.25±5.11	89.42±6.21	263.25±9.92	201.33±6.97	0.3	0.01*
Insulin resistance	2.2±0.49	2.27±0.6	8.69±2.81	6.42±2.53	0.06	0.02*
Insulin sensitivity	0.39±0.02	0.41±0.1	0.15±0.06	0.17±0.09	0.11	0.03*
Microalbuminuria (mg/l)	11.41±0.52	14.03±0.86	48.73±4.52	42.03±7.38	0.64	0.008*
Systolic pressure (mm Hg)	128.16±1.33	111.32±3.76	129.78±8.21	130.42±6.98	0.76	0.12
Diastolic pressure (mm Hg)	71.94±2.83	74.52±1.77	86.00±0.74	79.16±5.71	0.78	0.41

t-test at $P \leq 0.05$
(Mean ± SD): Mean± Standard Deviation

Correlation between Insulin hormone and some physiological parameters in type 2 diabetic patients and control subjects

According to the correlation analysis there were positive significant correlation between insulin and microalbuminuria in both genders in diabetic group , while there is an positive correlation between insulin and systolic pressure in males. The other parameter show no significant correlation with insulin as shown in table (2) .

Table (2) Correlation analysis between Insulin (µIU/ml) hormone and some parameters of type 2 diabetic and control group

Group parameters	Insulin (µIU/ml) hormone Diabetes group			
	Male		Female	
	r	P value	r	P value
FBG(mg/dl)	0.49	0.21	0.27	0.35
Microalbuminuria (mg/l)	0.52	0.03*	0.31	0.02*
Systolic pressure(mm Hg)	0.41	0.04*	0.18	0.07
Diastolic pressure(mm Hg)	0.24	0.11	0.28	0.09

Correlation coefficient (r)   * significant $P \leq 0.05$

The levels of insulin hormone and physiological parameters in patients with Type 2 diabetic among duration of disease and between gender

The statistical analysis of some hormonal and physiological parameters in diabetic patients according to the duration of disease showed that microalbuminuria exert significant elevation($p \leq 0.05$) in the fourth duration (> 15) years of disease when compared with other duration and with the increase in the duration of diabetic , the fasting blood glucose (FBG)

values showed a significant increase($p \leq 0.05$) than the lower duration of diabetic.Insulin sensitivity values showed a significant decrease($p \leq 0.05$) in the fourth duration (> 15) years of disease when compared with other duration while other parameters show no significant differences with the progress of the duration as shown in table (3) .

Table(3) The levels of insulin hormone and physiological parameters in patients with Type 2 diabetic among duration of disease and between gender

Groups	Diabetic only group (Mean ± SD)							
	1-5 (years)		> 5 (years)		> 10 (years)		> 15 (years)	
parameters	Male	Female	Male	Female	Male	Female	Male	Female
Insulin (µIU/ml)	12.4±1.84	13.39±2.68	14.34±0.24	12.24±0.76	11.22±3.71	12.65±2.73	15.29±2.92	14.63±1.98
FBG(mg/dl)	188±6.64	158.25±5.42[b][cd]	218.33±4.48	201.4±6.54[ad]	266±7.21	229.1±6.75[a]	238±10.53	359±7.01[ab]
Insulin resistance	6.4±2.00	5.22±2.41	7.04±3.61	6.63±0.01	8.44±2.35	7.15±1.64	8.82±3.67	8.68±2.87
Insulin sensitivity	0.23±0.08	0.24±0.05[d]	0.19±0.07	0.21±0.05	0.11±0.06	0.18±0.08	0.05±0.01	0.01±0.002[a]
Microalbuminuria (mg/l)	39.6±5.09	40.16±2.06[d]	40.77±7.00	45.11±2.21	45.6±1.77	46.99±3.52	48.77±5.33	50.98±0.97[a]
Systolic pressure(mm Hg)	128.19±4.27	122.28±8.07	125.32±4.91	134.77±5.32	136.4±10.98	126.65±2.76	124.56±5.43	136.07±12.03
Diastolic pressure(mm Hg)	96.98±0.65	74.87±4.54	75.6±7.665	79.34±7.15	81.28±	82.13±5.04	87.05±3.87	76.47±1.48

a : significant difference with first duration   ; b : significant difference with second duration
c : significant difference with third duration ; d : significant difference with fourth duration

Discussion

The results of the present study show that patients with type2 diabetes ,whether males or females , have significantly higher insulin hormone levels than control group as shown in table (1) and this result is in agreement with the study of (Mamza *et al.,*2013) were they found elevation of insulin hormone levels in patients with type2 diabetes and this elevation associated with insulin resistance status.Also, (the global diabetes community,2015) explain the role of insulin resistance in developing of hyperinsulinemia with the compensating of pancrease in producing more insulin and this will lead to development of type 2 diabetes and reported that hyperinsulinemia associated with several risks such as atherosclerosis, high levels of triglycerides and uric acid ,hypertension and obesity.

The purification of blood from insulin depend on receptors of insulin and enzyme that degrading it and deficient of these two molecules will lead to impaired in insulin purification and then hyperinsulinemia and this will lead to development of insulin resistance(Farris *et al.,*2003; Farris *et al.,*2004). The levels of insulin were determined by the balance between the production and clearance of insulin (Ye,2007; Corkey,2012).

Several studies found that impairment of insulin sensitivity may result from hyperglycemia and hyperinsulinemia themselves (Yki-Jarvinen ,1992 ; Mandarino *et al.,*1984). Insulin Resistance is defined as a condition in which target tissues have decreased sensitivity to insulin, leads to elevated both blood insulin and glucose levels [Nan *et al.,*2012].

The body become more resistant to insulin as the duration of disease are increase , so that high or normal levels of insulin but the available insulin is insufficient (Mathews *et al.,*1985) and this agreed with our finding as shown in table (3)

The results of this study showed significant elevation of FBG in type 2 diabetic group than control as shown in table (1) and this agreed with the former studies of (Hamaddi,2012;Mohamed,2014).

Hyperglycemia is the main feature of diabetic and its elevation may associated with the elevation of glucagon level which involve in hepatic glucose production ,the major factor that participate in fasting and postprandial hyperglycemia (Lefebvre,2006) .

According to the duration of disease the levels of FBG was significantly higher as the duration increase as shown in table (3) and this may be due to increase of insulin resistance and impaired the glycemic control and this related with longer duration of diabetes (Escobdo *et al.,*2010 ; Khattab *et al.,*2010; Verma *et al.,*2006).

The results of this study showed significant elevation of Microalbuminuria in type 2 diabetic group than control as shown in table (1) and this agreed with the studies of (Basi *et*

*al.,*2008 ; CAI Xiao *et al,*2011) who found elevation of microalbuminuria in diabetic patients and suggest that elevation of microalbuminuria represent an indicator of the early stages of diabetic kidney disease.

Elevation of microalbuminuria may result from hyperglycemia that stimulate increase the activity of protein kinase C in renal endothelial cells that participate in alteration the permeability of vascular cells and the response to angiotensin II and cause the accumulation of microabuminuria(Way *et al.,*2001) and this mean the impaired in glycemic control may lead to development of diabetic nephropathy(Iseki *et al.,*2004).Moreover,other studies found the prescence of relationship between oxidative stress and the severity of renal injury that result from the glyco- and lipo-oxidation products which lead to the mesangial matrix and nodular lesions (Vasavada and Agarwal,2005; Forbes *et al.,*2008).These evidence suggest that pathophysiology of diabetic nephropathy may result from disturbance in different enzymes and metabolic pathways (Luis-Rodríguez *et al.,*2012).

Several researches indicate the prescence of relationship between microalbuminuria and high blood pressure may be related to an association between essential hypertension and renal hemodynamic and these events may be accountable for, the promoting of atherosclerosis and nephrosclerosis resulting in microalbuminuria.(Diamond and Karnovsky,1988) The changes direct transmission of increased systemic pressure to the glomeruli, increased glomerular filtration, reduced tubular reabsorption of albumin, and structural damage to the glomeruli and arterioles(Hostetter *et al.,*1981 ;Rodicio *et al.,*1998).Other studies indicate that main risk factors that causing elevation of microalbuminuria are hypertension and long term diabetes (Salah *et al.,*2002 ; El-Wakf *et al.,*2011).

According to the duration of disease the levels of microalbuminuria was significantly higher as the fourth duration as shown in table(3) and this agreed with the study of **(Rathore et al.,2015)** who found the presence of an association between duration of type 2 diabetes and microalbuminuria i.e duration of diabetes is represent predictor for microalbuminuria via predisposition of hyperglycemia-induced advanced glycosylation end products .Moreover, other studies indicate that microalbuminuria associated with long duration of diabetes and related with dietary status and it represent markr for complications of diabetes(Behradmanesh *et al.,*2013 **;** Suryawanshi *et al.,*2015).

The results of this study showed no significant differences in systolic and diastolic blood pressure in type 2 diabetic group than control as shown in tables (1)and this agreed with the study of (Hammadi,2012) who found the elevation of blood pressure appear only in patients who have higher levels of microalbuminuria.

Several research indicated the presence of an association between blood pressure elevation and endothelial dysfunction which is correlated with insulin resistance and this lead to use non significant elevation of blood pressure as a marker for insulin resistance which represent a main feature of diabetes and cardiovascular disease (Ferrannini *et al.,*1987; Julius *et al.,* 1991).

The correlation analysis in this study showed that the correlation between insulin and FBG is non-significant in patients with type 2 diabetes as shown in table (2). Previous studies have been found that hyeperglycemia and hyperglucagonemia may result from increased in hypersensisitivity to circulating norepinephrine and consequently lead to increased in the increased in beta cell insulin secretory in mice and this mean that fasting and postprandial hyperglycemia of diabetic patient has destructive effect on dynamic insulin secretion (Liang and Cincotta ,2001; Xu *et al.,*2003).

On the other hand , there were positive correlation between insulin and microalbuminuria.Several researches indicating that hyperinsulinemia in type 2 diabetic patients has the ability to cause an elevation in glomerular hydrostatic pressure ,increase permeability of the vascular of renal,and enhance reabsorption of renal sodium(Tucker *et al.,*1992 ;Catalano *et al.,*1997). Several researches have been found that insulin participate indirectly in elevation of microalbuminuria by causes increase in uric acid levels which lead to elevation of microalbuminuria and it has been found that both are elevated in diabetic patients (Kodama *et al.,*2009;Bandaru and Shankar,2011).

The correlation analysis showed the presence of positive correlation between insulin and blood pressure and this agreed with the several researches that found an association between hypertension and insulin resistance and blood pressure improved in diabetic patients when regulating insulin secretion (Goutham,2001; Hettihewa *et al.*,2008). In the state of insulin resistance, the insulin-stimulated NO pathway is selectively impaired and the compensatory hyperinsulinemia may activate MAPK pathway, resulting in enhancement of vasoconstriction, proinflammation, increased sodium and water retention and the elevation of blood pressure(Muniyappa *et al.*,2007; Zhou *et al.*,2010).

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