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Full Length Research Paper

Biochemical parameters among type 2 diabetic patients complaining of erectile dysfunction

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Patients with type 2 diabetes mellitus (DM) have more disturbances of sexual and reproductive functions. The consequences of type 2 DM may include dyslipidemia, insulin resistance (IR), cardiovascular disease (CVD) and low testosterone level. The main objective of this study is to determine the value of various biochemical parameters in relation to erectile dysfunction (ED) in type 2 DM patients in Gaza city, Palestine. A total of 160 males between the age of 35 – 60 years were recruited; 80 type 2 DM patients and 80 as controls. Anthropometric, demographic, sexual and clinical data were obtained by questionnaire. Increased prevalence of high BMI and HOMA-IR were observed among type 2 DM patients, while high incidence of low testosterone was found in the same group ($p < 0.05$). Testosterone was correlated negatively and significantly with BMI and duration of type 2 DM ($p < 0.05$). ED was correlated significantly and directionally with dyslipidemia, duration of type 2 DM, and complications of diabetes mainly retinopathy ($p < 0.05$). While, nocturnal/early morning erection (NEME) was correlated significantly but inversely with duration of type 2 DM ($p < 0.05$). In addition, fasting blood glucose (FBG), duration of type 2 DM and low level of testosterone were predictor factors associated with ED ($p < 0.05$), while increased BMI was a predictor factor associated with low testosterone level ($p < 0.05$). In the present study, high incidence of low testosterone and increased prevalence of ED among type 2 DM patients could be attributed to uncontrolled type 2 DM, obesity, IR, dyslipidemia, long duration of type 2 DM and its complications.

Key words: Type 2 diabetes mellitus, erectile dysfunction, insulin resistance, testosterone, Gaza, Palestine.

INTRODUCTION

Type 2 DM comprises an array of dysfunctions resulting from the combination of resistance to insulin action and inadequate insulin secretion. Its disorders are characterized by hyperglycemia and associated with microvascular, macrovascular, and neuropathic complications. It is a common disorder with a prevalence that rises markedly with increasing degree of obesity (Salem et al, 2011). One of the complications of type 2 DM is the disturbance of sexual and reproductive functions. Low circulating testosterone concentration is frequently found in men with metabolic syndrome (MS) and type 2 DM (Arver, 2008 and Jones, 2008). ED is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance (Al-Adl et al., 2011). The inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse is a distressing and common symptom, affecting up to one-third of adult men. The prevalence of ED increases with age, and it is common in men with systemic disorders such as hypertension, ischemic heart disease, or DM (McCulloch, 2013). Among diabetic men, the prevalence varies from 35 to 90% (Giugliano, 2010). Many factors are associated with ED, among these are depression, hormonal changes, and vascular or neurologic damage after trauma or surgery. ED is also associated with different endocrine-metabolic disorders like type 2 DM, and dyslipidemia (Knoblovits et al., 2010). Whitsel et al. (2001) reported that testosterone reduced total cholesterol and Low density lipoprotein-cholesterol (LDL-C), while Roger et al. (2007) reported a positive

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association between high density lipoprotein-cholesterol (HDL-C) and testosterone in men with type 2 DM. In addition, ED appears to arise about 10 years earlier in diabetic patients than in the general population, and decreases the health-related quality of life (Phe and Roubret, 2012). A study showed that hypogonadism is frequently associated with type 2 DM, at least in the 6th decade, type 2 DM associated with hypogonadism might exacerbate sexual dysfunction by reducing libido and mood and further compromising penile vascular reactivity (Corona et al., 2006). Other researchers found a significantly lower concentrations of testosterone and HDL-C, but higher concentrations of glucose in patients suffering from MS and type 2 DM compared with controls ($p < 0.05$). Testosterone correlated positively with libido and NEME but inversely with ED in type 2 DM ($p < 0.05$). Deficient glucose uptake by the pituitary and the gonads and low circulating HDL-C are consequences of IR which could lead to hypogonadism (Davies et al., 2010).

The objective of this study is to investigate biochemical parameters in relation to ED in type 2 DM patients, evaluate the presence of obesity and IR in type 2 DM patients, determination of testosterone level and its relationship with obesity and IR, and determine the relationship between the duration of type 2 DM and the levels of FBG and testosterone. This study is the first to investigate glucose, HbA1c, insulin, testosterone and lipid profile levels in blood and its relation to ED in type 2 DM patients in Gaza City-Palestine.

MATERIALS AND METHODS

This study is case control one which was conducted in Gaza city-Palestine from April to October, 2013.

Inclusion criteria (for cases and controls)

A total of 160 males aged 35 – 60 years were recruited for this study; 80 type 2 DM patients were recruited by consultant physicians from the diabetes clinic in Primary Health Care Centers (Al-remal and Sabha clinic). While an apparently healthy 80 eugonadal (testosterone level >3.0 ng/ mL), non-diabetic male subjects were recruited as controls.

Exclusion criteria (controls)

Fasting blood glucose (FBG), insulin, HbA1c, lipid profile and testosterone levels were determined to exclude type 2 DM and ED.

Characteristics of the subjects

Demographic indices (age, parity, duration of diabetes and family history of type 2 DM) were obtained through questionnaires (face to face interview). Sexual characteristics (libido, ED, and NEME) were recorded through questionnaires using international index for erectile function (IIEF-5) scores. Anthropometric indices (weight and height) were measured using DETECTO Scale (USA). Body mass index (BMI) was calculated according to the following formula:

$$BMI = \text{weight (Kg)} / (\text{height (m)})^2$$

Biochemical investigations

10 ml of venous blood were collected aseptically by vein puncture from each subject in morning (8:00 – 10:00 AM) while fasting for at least 12 h, 3 mL of the blood were collected and placed in vacuum blood collection tube containing ethylene-di-amine tetra acetic acid (EDTA.K3) as anticoagulant for the determination of HbA1c. The remaining 7 mL of blood were delivered into vacuum blood collection tube without additives, samples were allowed to clot at room temperature for 15 min and serum was separated after centrifugation at 5000 rpm for 10 min using Thermo Scientific HERAEUS LABOFUGE 200 Centrifuge. Serum was analyzed for the determination of glucose, total cholesterol, triglycerides, and HDL-C, insulin and testosterone levels. LDL-C was calculated by using Fried Wald's formula (Friedewald et al., 1972). An homeostasis model assessment for insulin resistance (HOMA-IR) index was calculated according to the formula of HOMA-IR calculator version 0.3 http://www.hcvsociety.org/files/HOMACalc.htm, where IR was defined as a HOMA-IR of 3.0 or greater. All biochemical tests were carried out at Nebras Medical Laboratory, Gaza -Palestine. A written permission was obtained from the local Helsinke committee for the purpose of observing ethical considerations. Statistical package for social sciences (SPSS) software version 18 was used for analysis of data.

RESULTS

Age and body mass index of subjects

Table 1 compares the mean ± SD of age and BMI in type 2 DM patients and controls. The mean age was the same in both type 2 DM and control subjects, (50.73 ± 7.13) years, as controls were selected and matched with cases according to age. Type 2 DM patients are presented with statistically significant higher BMI ($P < 0.05$) than controls (31.28 ± 6.43 vs. 27.41 ± 3.44).

Comparison of biochemical indices among type 2 DM patients and controls

Table 2 shows the mean values of FBG, cholesterol, triglycerides, HDL-C, LDL-C, HbA1c, insulin,

Table 1. Age and BMI of type 2 DM patients and controls.

	Participant	N	Mean	SD	SE	P - value
Age	Type 2 DM	80	50.7375	7.13299	0.79749	
	Control	80	50.7375	7.13299	0.79749	1.00
BMI	Type 2 DM	80	31.2888	6.43869	0.71987	
	Control	80	27.4100	3.44944	0.38566	0.000*

N = number of subjects, SD = Standard deviation, SE = Standard error, P = probability, * = Significant, BMI = Body mass index, Type 2 DM = Diabetes Mellitus type 2.

Table 2. Comparison of biochemical indices among Type 2 DM patients and controls.

	Type 2 DM (N = 80)	Control (N = 80)	P-value
	Mean ± SD	Mean ± SD	
FBG (mg/dL)	202.1 ± 87.0	80.3 ± 10.8	0.000*
HbA1c (%)	9.2 ± 1.7	5.7 ± 0.4	0.000*
Insulin level (µIU/mL)	25.7 ± 38.5	12.8 ± 6.6	0.004*
HOMA-IR	13.4 ± 23.9	2.5 ± 1.4	0.000*
Cholesterol (mg/dL)	203.6 ± 51.2	195.7 ± 36.0	0.258
Triglycerides (mg/dL)	198.8 ± 76.1	160.2 ± 65.6	0.001*
HDL-C (mg/dL)	37.5 ± 9.4	40.7 ± 8.2	0.022*
LDL-C (mg/dL)	126.5 ± 47.1	122.1 ± 35.5	0.511
Testosterone (ng/mL)	4.3 ± 1.9	6.3 ± 2.1	0.000*

HOMA-IR = Homeostasis Model Assessment – Insulin Resistance, FBG = Fasting blood glucose, HDL-C = High density lipoprotein-cholesterol, LDL-C = Low density lipoprotein-cholesterol, HbA1c = Glycohemoglobin A1c, N = number of subjects, SD = Standard deviation, SE = Standard error, P = probability, * = Significant, Type 2 DM = Diabetes Mellitus type 2.

testosterone, and HOMA-IR among subjects. Comparison shows a statistically significant difference in FBG, triglycerides, HDL-C, HbA1c, insulin level, testosterone, and HOMA-IR. Significantly higher FBG, triglycerides, HbA1c, insulin level, and HOMA-IR ($P < 0.05$) were observed in type 2 DM patients. However, significantly lower HDL-C and testosterone ($P < 0.05$) were observed in the same group. There was no significant difference in cholesterol and LDL-C between type 2 DM patients and controls ($P > 0.05$).

Correlation of biochemical indices in type 2 DM patients

Table 3 shows the correlations among biochemical indices. FBG was correlated positively and significantly with HbA1c, and HOMA-IR ($P < 0.05$). In addition, insulin level was directionally and significantly correlated with HOMA-IR, ($P < 0.05$). Cholesterol was significantly correlated with triglycerides and LDL-C in the positive direction ($P < 0.05$). In addition, there was a significant positive correlation of triglycerides with LDL-C, but inversely with HDL-C ($P < 0.05$). All other correlations were not significant ($P > 0.05$).

In addition, Table 3 shows that HbA1c was correlated significantly with BMI, and duration of type 2 DM in the positive direction ($P < 0.05$). Insulin level was correlated positively and significantly with BMI, also HOMA-IR was correlated positively and in a significant manner with BMI ($P < 0.05$). In addition, cholesterol was significantly correlated with duration of type 2 DM in a positive direction ($P < 0.05$). However, there was a significant positive correlation of triglycerides with BMI ($P < 0.05$). LDL-C was positively and significantly correlated with duration of type 2 DM ($P < 0.05$). All other correlations were not significant ($P > 0.05$).

Relationship of anthropometric and demographic indices with testosterone in subjects

Table 4 shows that there was a significant negative correlation between testosterone and BMI ($p < 0.05$). Also, in type 2 DM patients a negative significant correlation was found between testosterone and duration of type 2 DM ($p < 0.05$). In addition, for control group testosterone was correlated positively and significantly with sport practicing ($p < 0.05$). All other correlations were not significant ($p > 0.05$).

Table 3. Correlation of biochemical indices (lipids profile, FBG, HbA1c, insulin level, and HOMA-IR) with anthropometric indices in Type 2 DM patients.

Indices		FBG	HbA1c	Insulin level	HOMA-IR	Cholesterol	Triglycerides	HDL-C	LDL-C
FBG (N=80)	R	1.0	0.323*	0.069	0.269*	0.125	0.138	0.048	0.081
	P-Value	-	0.004	0.544	0.016	0.269	0.222	0.669	0.473
HbA1c (N=80)	R	0.323*	1.0	-0.100	-0.090	0.059	0.156	-0.140	0.040
	P-Value	0.004	-	0.377	0.428	0.601	0.168	0.214	0.724
Insulin	R	0.069	-0.100	1.0	0.941*	0.160	0.080	-0.044	0.157
Level (N=80)	P-Value	0.544	0.377	-	0.000	0.156	0.482	0.697	0.165
HOMA	R	0.269*	-0.090	0.941*	1.0	0.169	0.088	-0.036	0.162
-IR (N=80)	P-Value	0.016	0.428	0.000	-	0.135	0.436	0.752	0.152
Cholest-erol	R	0.125	0.059	0.160	0.169	1.0	0.421*	-0.057	0.967*
(N=80)	P-Value	0.269	0.601	0.156	0.135	-	0.000	0.613	0.000
Triglyc-erides	R	0.138	0.156	0.080	0.088	0.421*	1.0	-0.502*	0.237*
(N=80)	P-Value	0.222	0.168	0.482	0.436	0.000	-	0.000	0.035
HDL-C (N=80)	R	0.048	-0.140	-0.044	-0.036	-0.057	-0.502*	1.0	-0.100
	P-Value	0.669	0.214	0.697	0.752	0.613	0.000	-	0.378
LDL-C (N=80)	R	0.081	0.040	0.157	0.162	0.967*	0.237*	-0.100	1.0
	P-Value	0.473	0.724	0.165	0.152	0.000	0.035	0.378	-
BMI (N=80)	R	0.019	0.256*	0.263*	0.283*	0.180	0.301*	-0.132	0.126
	P-Value	0.865	0.022	0.018	0.011	0.109	0.007	0.242	0.266
Duration of Type	R	0.108	0.355*	0.009	-0.030	0.279*	-0.022	-0.028	0.316*
2 DM (N=80)	P-Value	0.340	0.001	0.934	0.790	0.012	0.848	0.803	0.004

FBG = Fasting blood glucose, HbA1c = Glycohemoglobin A1c, HOMA-IR = Homeostasis model assessment – Insulin resistance, HDL-C = High density lipoprotein-cholesterol, LDL-C = Low density lipoprotein-cholesterol, N = number of subjects, P = probability, r = Pearson's correlation coefficient, * = Significant, Type 2 DM = Diabetes mellitus type 2, BMI = Body mass index.

Table 4. Correlation of anthropometric and demographic indices with testosterone.

Indices	Testosterone	
	Type 2 DM (N = 80), (r, P – Value)	Control (N = 80), (r, P – Value)
NEME	0.052, 0.650	-0.204, 0.069
Duration of Type 2 DM	-0.209, 0.032*	-
Smoking	0.108, 0.342	-0.033, 0.769
BMI	-0.370, 0.001*	-0.239, 0.032*
Age	0.024, 0.831	-0.131, 0.246
Sport practicing	0.125, 0.271	0.283, 0.011*

NEME = Nocturnal/Early morning erection, Type 2 DM = Diabetes mellitus type 2, BMI = Body mass index, N = number of subjects, P = probability, r = Pearson's correlation coefficient, * = Significant.

Relationships of biochemical, anthropometric and demographic indices with ED and NEME in type 2 DM

In type 2 DM patients, there was a significant positive correlation between ED and cholesterol, triglycerides, and LDL-C respectively ($p < 0.05$), but there was a significant correlation between ED and HDL-C in the negative direction ($p < 0.05$). Correlation of other indices was not significant ($P > 0.05$). In addition, there was no statistically significant correlation between NEME and biochemical indices ($p > 0.05$) (Table 5).

In men with type 2 DM, there was a significant positive correlation of ED with duration and complications (mainly retinopathy) of type 2 DM ($p < 0.05$). Correlation of other indices were not significant ($p > 0.05$). However, NEME was correlated significantly but inversely with age and duration of type 2 DM ($p < 0.05$) (Table 5).

Discussion

Sexual health may be a window into men's health. Testosterone plays a critical role in male reproductive and metabolic functioning as well as improving life quality. Low testosterone is associated with a variety of comorbidities, including type 2 DM, IR, obesity, MS, and

Table 5. Correlation of biochemical indices, anthropometric and demographic indices with ED and NEME.

Indices	ED	NEME
	Type 2 DM (N = 80), (r, P – Value)	Type 2 DM (N = 80), (r, P – Value)
FBG	-0.139, 0.109	-0.041, 0.717
Cholesterol	0.365, 0.001*	-0.166, 0.141
Triglycerides	0.195, 0.041*	-0.119, 0.292
HDL-C	-0.208, 0.032*	0.152, 0.178
LDL-C	0.379, 0.001*	-0.173, 0.125
HbA1c	0.141, 0.105	-0.052, 0.649
Insulin level	0.012, 0.458	0.022, 0.844
HOMA-IR	-0.028, 0.401	0.045, 0.690
Testosterone	0.009, 0.470	0.052, 0.650
Age	0.075, 0.254	-0.230, 0.040*
BMI	0.040, 0.361	-0.054, 0.633
Duration of Type 2 DM	0.794, 0.000*	-0.266, 0.044*
Complications of Type 2 DM	0.272, 0.015*	-0.013, 0.910

ED = Erectile dysfunction, NEME = Nocturnal/Early morning erection, FBG = Fasting blood glucose, HDL-C = High density lipoprotein-cholesterol, LDL-C = Low density lipoprotein-cholesterol, HbA1c = Glycohemoglobin A1c, HOMA-IR = Homeostasis model assessment – Insulin resistance, N = number of subjects, P = probability, r = Pearson's correlation coefficient, * = Significant, Type 2 DM = Diabetes mellitus type 2, BMI = Body mass index.

CVD (Rice et al., 2008). The prevalence of hypogonadism increases with age, and most men diagnosed with type 2 DM are older than 40 years. However, it remains unclear whether decreased testosterone levels are related to aging or diabetes and its complications (Ding et al., 2006; Corona et al., 2006; and Selvin et al., 2007). In the present study, testosterone was significantly lower in type 2 DM patients compared with control group ($p < 0.05$). The mean age of type 2 DM patients and controls was the same (50.73 ± 7.132 years), which mean that the observed low testosterone in this study may be attributed to type 2 DM, and its complications, as all subjects had the same age. In addition, a high percentage (67.5 %) of type 2 DM patients did not experience NEME. Although NEME decreases by age, there was a negative correlation between NEME and duration of type 2 DM ($p < 0.05$) that could be attributed to the decreased level of testosterone among type 2 DM patients.

Testosterone levels vary inversely with waist circumference and BMI in men with MS. Contrarily, a direct and significant relationship was observed between BMI and testosterone in men with type 2 DM (Davies et al., 2010). Another study evaluated the effect of obesity on serum testosterone levels and penile duplex ultrasonography variables in men with ED, obesity was associated with lower testosterone levels and disturbances of penile haemodynamics (Zohdy et al., 2007). According to the present results, prevalence of high BMI and obesity was significantly higher in type 2 DM patients compared with controls ($p < 0.05$). In addition, testosterone was correlated significantly but inversely with BMI ($p < 0.05$). This could be attributed to the difference in the mean BMI for type 2 DM patients in Palestinian people compared to other populations. However, BMI correlated significantly and positively with HbA1c, insulin level, HOMA-IR, and triglycerides ($p < 0.05$). These correlations may be due to uncontrolled diabetes, which was observed clearly by the high level of FBG and HbA1c in type 2 DM patients compared with controls. In addition, high calorie diet and sedentary life style which lead to obesity and may cause hypogonadal state that disrupts the endocrine system, as its normal function is critical for maintaining erection.

Bansal et al. (2005) evaluated the prevalence of IR, measured by the quantitative insulin sensitivity check index, in 154 men with ED. They reported a 79.2% incidence of IR in patients with ED but without comparing them with a control group, and a negative correlation was observed between HOMA and international index for erectile function (IIEF-5). In the present study, a statistically significant higher degree of IR in type 2 DM patients was found compared with controls ($p < 0.05$). In addition, a positive statistically significant correlation between BMI and HOMA-IR was observed ($p < 0.05$). However, the observed results coincided with those of Bansal et al. (2005) regarding the high incidence of IR among diabetic ED patients, which in our study could be attributed to high prevalence of BMI and long duration of type 2 DM, as 44 (55%) of type 2 DM patients have had the disease for more than eight years.

Among patients with ED, type 2 DM is associated with

hypogonadism, at least in the 6th decade (Corona et al., 2004). The reduction of total testosterone in type 2 DM patients could be theoretically due to a reduction of sex hormone binding globulin (Van Dam et al., 2003). In fact, among those patients in whom measurements of free testosterone were available, diabetes was associated with low hormone levels (Corona et al., 2006). The present finding indicates that duration of type 2 DM was correlated significantly but inversely with testosterone ($p < 0.05$), which affirm the hypothesis of increased prevalence of ED in type 2 DM patients due to the high prevalence of low testosterone in type 2 DM patients than in control group.

Dyslipidemia characterizes individuals with MS and type 2 DM (Ashraf –Sohail et al., 2006). In hypogonadal men with type 2 DM, testosterone was correlated negatively with total cholesterol, but had no effect on other components of the lipid profile (Malkin et al., 2004). While others found a positive association between HDL-C and testosterone (Roger et al., 2007 and Stanworth et al., 2007). In the present study, there was no correlation between testosterone and lipid profile among type 2 DM patients ($p > 0.05$), this could be attributed to small sample size in this study. In addition, cholesterol and LDL-C were correlated positively and significantly with duration of type 2 DM, but testosterone was correlated inversely and significantly with duration of type 2 DM and BMI ($p < 0.05$), this could be explained on the basis that long duration of type 2 DM and prolonged elevation of glucose may lead to IR and dyslipidemia which in turn causes reduced utilization of glucose by pituitary gland cells. Pituitary dysfunction leads to decreased secretion of LH and FSH which control testosterone secretion. However, ED was correlated significantly and positively with cholesterol, triglycerides, and LDL-C, but inversely with HDL-C ($p < 0.05$). These results coincide with previous studies in that dyslipidemia is a risk factor of ED and is linked to it. In addition, ED was correlated with duration of type 2 DM and its complications ($p < 0.05$), this may be attributed to endothelial dysfunction which characterizes diabetic patients.

In a study of Sharifi et al. (2012), they found that age and administration of calcium channel blockers in type 2 DM men were the only independent predictors of ED, while other previously published risk factors including BMI, blood pressure, HbA1c, impaired lipid profile, high creatinine, testosterone level, and even history of smoking did not have predictive value for ED risk in type 2 DM patients (Sharifi et al., 2012). On the other hand, other studies reported that long duration of type 2 DM and poorer glycemic control in diabetic men were significant predictors of ED (Mijares et al., 2010; Yang et al., 2010; and Giugliano et al., 2010). However, other studies reported no correlation between ED and BMI (Ziaei-Rad et al., 2010). In the present study, duration of type 2 DM, FBG, and testosterone were the only predictor risk factors associated with ED ($P < 0.05$). Data is not shown.

Incidence of low testosterone in the present study was higher in type 2 DM patients than controls. As a result ED is common among type 2 DM patients and they probably were affected earlier than non-diabetic men. In addition, low testosterone among type 2 DM patients may be a result of increased prevalence of obesity. Increased prevalence of IR among type 2 DM patients could lead to decreased glucose uptake by the pituitary and gonads leading to hypogonadism and low testosterone level. High incidence of dyslipidemia among type 2 DM patients is considered as one of the important risk factors that increases incidence of ED. Long duration of type 2 DM and prolonged elevation of glucose lead to IR, dyslipidemia, and low testosterone level. In addition, high level of blood glucose and long duration of type 2 DM, in addition to low testosterone level were determined to be of the leading independent predicting risk factors associated with ED.

It is recommended to inform type 2 DM patients with its complications including ED, and provide relevant information, and increase clinician awareness of the need to address men's sexual health and implement appropriate strategies. Continuous monitoring of FBG, HbA1c, testosterone, and lipid profile for type 2 DM patients for the purpose of early detection of ED. Restricted diet and changing life style in addition to therapeutic agents may be beneficial for type 2 DM patients.

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