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Evaluation the Effect of Glyburide and/or Metformin on Testosterone Levels in Men Patients with Type 2 Diabetes Mellitus

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Abstract: Low testosterone serum levels have been linked with pathogenesis of type 2DM. Type 2DM pharmacotherapy may also affect the testosterone levels since; metformin decreases testosterone levels, whereas glyburide might increase the testosterone levels. Sixty-one men patients with type 2DM were selected: 22 of patients were treated with metformin, 20 of patients were treated with glyburide and 19 patients were treated with glyburide plus metformin the duration of disease was 3-6 years, compared with 20 normal healthy volunteers. Total testosterone, free testosterone and other biochemical measures as well as anthropometric variables were evaluated in each treated group. In glyburide or metformin treated patients, there were significant reduction in testosterone serum levels regarding the total and free testosterone $p<0.01$whereas patients that were treated with combined glyburide plus metformin there was an insignificant reduction in both total and free testosterone $p>0.5$. *Conclusion:* Combined therapy of metformin plus glyburide in type 2DM lead to a significant increment in the testosterone levels, which may play an important role in the amelioration of metabolic complications that are induced by type 2 DM.

Keywords: Testosterone, Metformin, Glyburide, Type 2DM

1. Introduction

Type 2DM is a metabolic and endocrine disorder due to defects in insulin secretion and/or action characterized by polyuria, polyphagia, polydepsia and progressive weight loss [1]. Low testosterone serum levels have been linked with pathogenesis of type 2DM since; endogenous testosterone is responsible for reduction of insulin resistance and prevent the development of type 2 DM, whereas; exogenous testosterone leads to significant endocrine and metabolic disorders that favoured the induction of dyslipidemia and insulin resistance [2, 3].

Recently, patients with type 2DM are characterized by low sex drive and impotence due to low endogenous testosterone levels that are resulted from secondary hypogonadism induced by metabolic consequences of insulin resistance [4].

Type 2DM pharmacotherapy may also affect the testosterone levels since; metformin decreases testosterone levels in women with polycystic ovary [5], metformin is extensively used in the management of type 2DM through inhibition of hepatic gluconeogenesis and glycogenolysis [6], additionally; glucose lowering effect of metformin may be via inhibition of free fatty acids releasing from adipose tissue [7]. Moreover, metformin inhibits leptin secretion from adipose tissue and improve insulin sensitivity with significant reduction in caloric intake [8].

On the other hand, glyburide is an oral hypoglycemic agent related to sulfonamide antibiotics is widely used in the treatment of type 2DM, it acts through activation of sulfonylurea receptor 1 at the pancreatic beta cell that causing inhibition of ATP-sensitive potassium channels causing membrane depolarization and opening of voltage-gated calcium channels with subsequent insulin secretions [9]. Glyburide might increase the testosterone levels [10].

Therefore, the aim of the present study was evaluation the effect of glyburide and/or metformin on testosterone levels in patients with type 2 diabetes mellitus.

2. Subjects and Methods

2.1. Subjects

This cross-sectional study involved sixty-one men patients with type 2DM, with age rang 40-60 years that were selected according to the American diabetic association criteria, from Iraqi Endocrinology Center, 22 patients treated with metformin 850mg three times daily, 20 patients treated with glyburide 5mg/day, 19 patients treated with glyburide 5mg/day plus metformin 850mg/day, the duration of disease was3-6 years, those patients compared with 20 normal healthy volunteers.

2.2. Anthropometric Measures

Height (m) and body weight (kg) were calculated then body mass index BMI was estimated by specific equation BMI=weight (kg)/height (m^2) [11].

2.3. Biochemical and Hormonal Assay

10 ml of venous blood sample from each patient was aspirated and then centrifugated at 2500rpm and stored at -20 Ċ. Fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) were calculated by specific kit methods. Lipid profile was estimated by Friedwald formula [12].

Total testosterone and free testosterone were estimated by a specific ELISA kit method (AD-901-065, enzo immunoassay).

2.4. Statistical Analysis

SPSS version 20 was used for analysis of data, the data expressed as mean± SD, one way ANOVA test and unpaired t test were used to detect the significance of differences among the selected group regarding *P* is significant when it less than 0.05

3. Results

Results of the present study showed that all recruited patients were male (100%), 22 (36.06%) of them treated with metformin, 20 (32.78%) of them treated with glyburide and 19 (31.14%) of them treated with metformin plus glyburide. Additionally; 34 (55.73%) of the selected patients were smokers. Moreover; there is an associated disease in addition to type 2DM 33 (54.09%) with hyprtension, 14 (22.95%) with ischemic heart disease, 13 (21.31%) with dyslipidemia and 22(36.06%) with cerebro-vasular accidents. On the other hand, 30 (49.18%), 31 (50.81%), 33 (54.09%) and 13 (21.31%) of patients received ACEI, ant-platelets, calcium channel blockers and diuretics respectively table 1.

Table 1. *Clinical criteria of diabetic patients.*

Criteria	Mean± SD, n (%)
Age (years)	40-60
Number	61
Gender	100% male
Disease duration	
Diabetic pharmacotherapy	
Metformin	22(36.06%)
Glyburide	20(32.78%)
Metformin+glyburide	19(31.14%)
Smoking	34(55.73%)
Associated diseases	
Hypertension	33(54.09%)
Ischemic heart disease	14(22.95%)
Dyslipidemia	13(21.31%)
Cerebro-vascular accident	22(36.06%)
Associated medications	
ACEI	30(49.18%)
Anti-platelets	31(50.81%)
Calcium channel blockers	33(54.09%)
Diuretics	13(21.31%)

Data presented as Mean± SD, n (%), ACEI: angiotensin converting enzyme inhibitor

In glyburide or metformin treated patients, there were significant reduction in testosterone serum levels regarding the total and free testosterone $p<0.01$whereas patients that were treated with combined glyburide plus metformin there was an insignificant reduction in both total and free testosterone $p>0.5$, table 2.

Table 2. *Effect of glyburide and/or metformin on anthropometric and biochemical measures regarding testosterone serum levels in patients with type 2DM.*

Variables	Control(n=20)	Glyburide(n=20)	Metformin(n=22)	Combination(19)	Fstatistic	ANOVA
Total T(nmol/L)	18.54±3.77	11.64±4.84*	6.33±2.56!	16.56±4.34^{ns}	40.27	<0.01
Free T(nmol/L)	0.345±0.11	0.174±0.10*	0.295±0.13!	0.297±0.12^{ns}	7.92	<0.01
FBG(mg/dL)	99.77±8.84	123.56±12.63*	133.43±11.99!	110.23±11.64†	35.008	<0.01
HbA1c (%)	5.55±1.22	7.55±2.66*	7.99±2.88!	6.94±2.63††	3.87	0.012
TG(mg/dL)	112.62±11.69	185.54±13.64*	155.69±12.75!	144.52±11.39†	117.71	<0.01
TC(mg/dL)	133.69±12.52	239.56±15.88*	199.16±11.45!	166.43±13.81†	226.28	<0.01
VLDL(mg/dL)	22.52±5.69	37.11±6.76*	31.14±6.64!	28.91±7.33†	16.58	<0.01
HDL(mg/dL)	55.76±5.85	43.63±5.44*	48.89±6.62!	51.73±4.99††	15.50	<0.01
LDL(mg/dL)	55.40±6.34	158.83±13.38*	119.13±9.23!	85.80±8.44†	420.45	<0.01
BMI(kg/m^2)	21.53±2.63	24.64±3.64*	23.69±3.45!!	23.62±3.22†	3.23	0.027
SBP(mmHg)	125.54±11.43	144.54±11.32*	147.39±12.52!	146.53±10.48	16.40	<0.01
DBP(mmHg)	74.53±3.56	90.53±8.53*	92.12±9.22!	90.11±8.11	32.002	<0.01

Results are expressed as mean±SD, Total T: total testosterone; Free T: free testosterone; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; TG: total triglyceride; TC: total cholesterol; VLDL: very low density lipoprotein; HDL: high density lipoprotein; LDL: low density lipoprotein; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure, Unpaired t test = *$p<0.01$ compared to control, !p<0.01 and !!$p<0.05$ compared to control,†$p<0.01$ and ††$p<0.05$, ns: insignificant $p>0.05$

Therefore, total testosterone levels were higher in patients treated with combined glyburide plus metformin compared to metformin or glyburide alone figure 1.

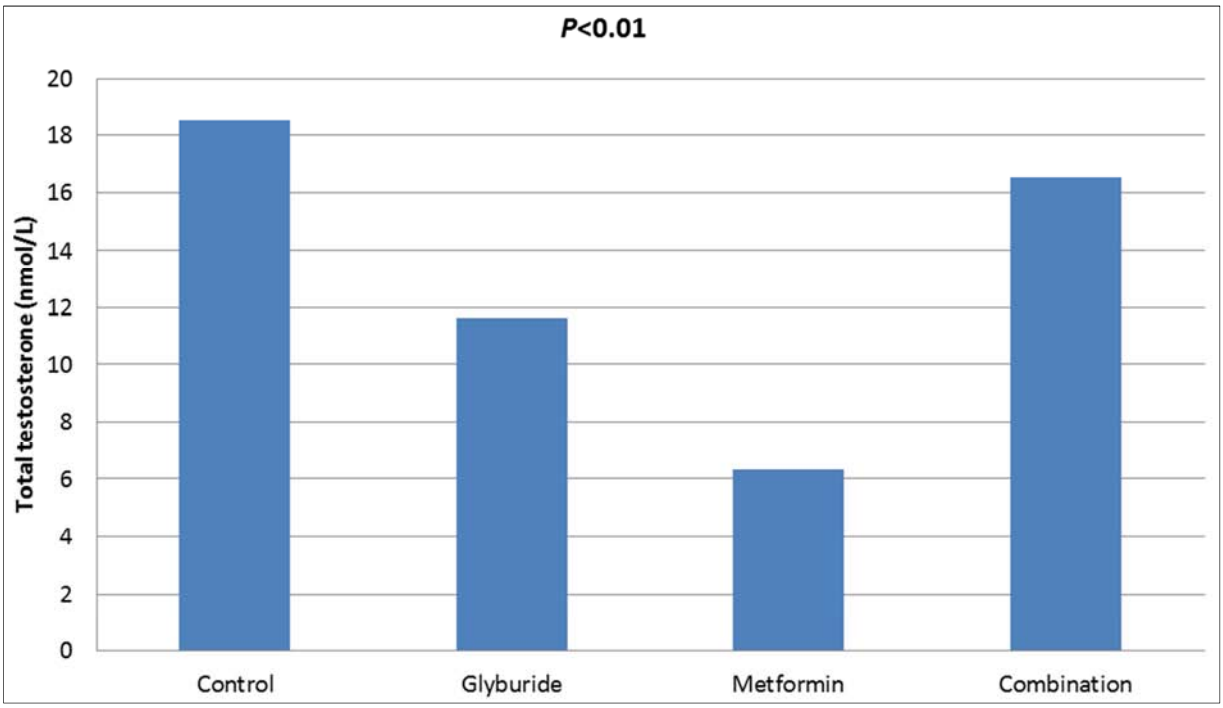

Figure 1. *Testosterone serum levels in patients with type 2DM that are treated with metformin and/or glyburide.*

Moreover, total testosterone levels were negatively correlated with fasting blood glucose figure 2

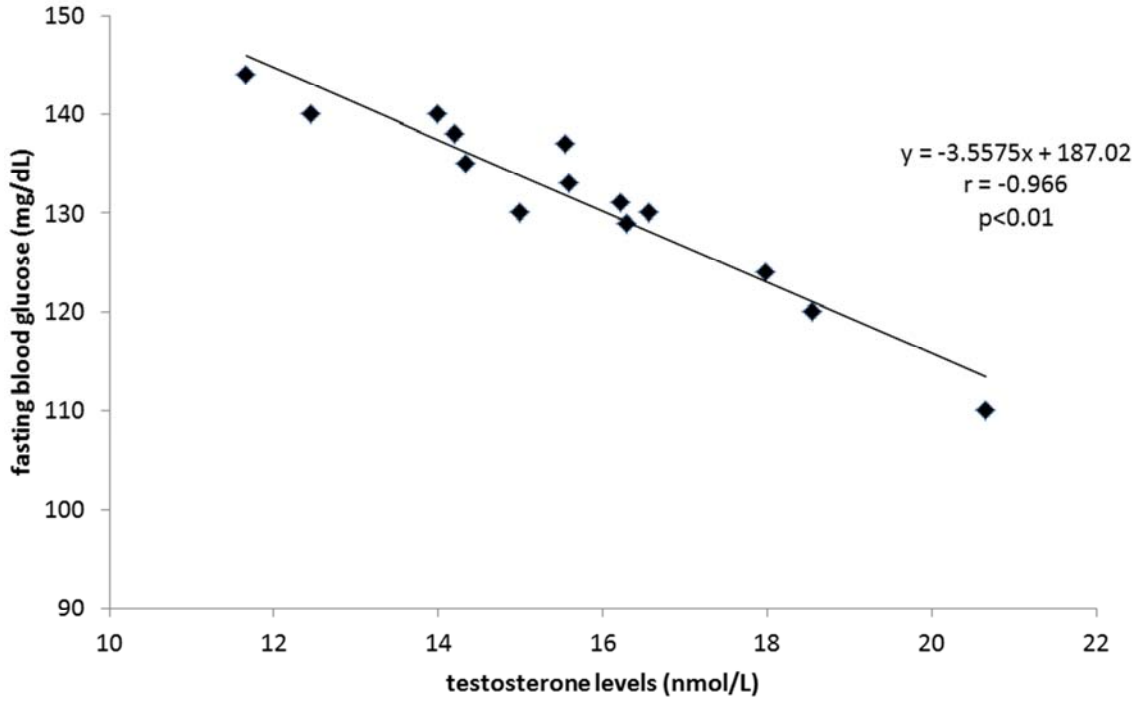

Figure 2. *Negative correlation between total testosterone and high fasting blood glucose.*

4. Discussion

The present study revealed a significant reduction in the testosterone serum levels in patients with type 2DM compared with normal healthy, non-diabetic men which correspond with Nirmali *et al.* study that demonstrated low testosterone serum levels in patients with type 2DM which is linked to alterations in lipid profile [13].

Low levels of testosterone in patients with type 2DM may be due to diabetic induced-oxidative stress that causing a significant reduction in testicular and adrenal androgen productions [14]. Moreover, Yen *et al,* study showed that metabolic changes induced by type 2DM attenuated the chemical responsiveness of testicular Leydig cells and then inhibit basal and stimulated testosterone secretions [15].

Additionally, most diabetic patients in the current study are associated with dyslipidemia and hypertension, which may have detrimental effects on the testosterone production since; these metabolic changes are negatively correlated with testosterone serum levels [16].

Indeed, 34 (55.73%) of our patients were active smokers this may affect testosterone serum levels since; chronic nicotine smoking leads to activation of testosterone secretion and inhibit peripheral conversion of testosterone into estrogen [17] this may explain the elevation in the testosterone serum levels in the present study.

In metformin-treated patients there was significant reduction in the testosterone levels compared with healthy control since; metformin leads to significant diminution in the testosterone levels through inhibition of pituitary luteinizing hormone secretion and key enzymes in the synthesis of testosterone hormone [18], whereas; in glyburide-treated patients also there was significant reduction in the testosterone levels compared with control that is not compatible with other study that revealed significant elevation in the testosterone levels, low levels of testosterone in glyburide treated patients in the present study may be due to small sample size, sever metabolic alterations and age of patients herein most of patients were not younger.

On the other hand, diabetic patients in the current study that were treated by metformin plus glyburide showed significant raising in the testosterone serum levels which may be due to amelioration of metabolic alterations or due to direct effects on the testosterone production in view of the fact that; chronic glyburide administration in type 2DM lead to raising in total and free testosterone due to indirect stimulation of testosterone production through modulation of glucocorticoid secretion, insulin sensitivity and testicular function [19], thus glyburide modulates metformin effect on the testosterone levels.

Therefore, combined therapy of metformin plus glyburide in type 2DM lead to a significant increment in the testosterone levels, which may play an important role in the amelioration of metabolic complications that are induced by type 2DM [20].

5. Conclusion

Combined therapy of metformin plus glyburide in type 2DM lead to a significant increment in the testosterone levels, which may play an important role in the amelioration of metabolic complications that are induced by type 2DM.

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