Effects of diabetic pharmacotherapy on prolactin hormone in patients with type 2 diabetes mellitus: Bane or Boon

Huda Abdulbaki Rasheed,
Hayder M. Al-Kuraishy[1],
Ali I. Al-Gareeb[1],
Nawar Raad Hussien,
Marwa S. Al-Nami

Department of Clinical Pharmacology,
Medical Faculty, College of Medicine,
Al-Mustansiriya University,
[1]Department of Pharmacology,
Toxicology and Medicine, College of
Medicine, Al-Mustansiriya University,
Baghdad, Iraq

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Abstract

Prolactin is a polypeptide hormone secreted from the anterior part of the pituitary gland which was implicated as a diabetogenic factor in the pathogenesis of type 2 diabetes mellitus (T2DM). Therefore, the aim of the present study was to evaluate prolactin serum levels in patients with T2DM regarding the effect of diabetic pharmacotherapy. Eighty patients with T2DM compared with 25 male healthy controls were recruited and divided into four groups: Group I – 29 patients with T2DM treated with metformin, Group II – 30 patients with T2DM treated with glyburide, Group III – 21 patients with T2DM treated with glyburide plus metformin, and Group IV – 25 control male healthy patients. Prolactin serum levels were high in patients with T2DM compared with controls ($P < 0.01$). Prolactin serum levels were higher in glyburide-treated patients compared with metformin-treated patients ($P < 0.01$). This study concludes that high prolactin levels in patients with T2DM are linked with diabetic complications and regarded as a beneficial phenomena to overcome IR and diabetic complications. Metformin but not glyburide reduced prolactin levels due to the improvement of insulin resistance.

Key words: Metformin, prolactin, type 2 diabetes mellitus

INTRODUCTION

Prolactin is a polypeptide hormone secreted from the anterior pituitary gland which is responsible for lactation in women and reproduction, metabolism, behavior, and immune function in both males and females.[1] Normally during pregnancy prolactin serum levels are increased to hold of insulin resistance (IR).[2] As well, prolactin is involved in regulation of glucose metabolism, since high prolactin levels are associated with low incidence of type 2 diabetes mellitus (T2DM).[3]

Previously, prolactin hormone was implicated as a diabetogenic factor in the pathogenesis of T2DM, since hyperprolactinemia led to IR and impairs islet β-cell function.[4]

Recently, prolactin has a potential role in the regulation of glucose metabolism; it stimulates insulin secretion through specific prolactin receptors (PRLRs) on the β-cell of the pancreas.[5] In addition, prolactin inhibits lipogenesis at high level, but at low physiological level, it inhibits lipolysis due to the specific effect of prolactin on the

Address for correspondence:
Dr. Hayder M. Al-Kuraishy,
Department of Pharmacology, Toxicology and Medicine,
College of Medicine, Al-Mustansiriya University,
P.O. Box: 14132, Baghdad, Iraq.
E-mail: hayderm36@yahoo.com

adipocyte differentiation through activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ). Therefore, PRLR knockout mice showed a reduced mass of the pancreatic islet of the pancreas and blunted insulin function in a previous experimental study.[6]

On the other hand, pathological hyperprolactinemia and high physiological levels of prolactin may be a compensatory mechanism against T2DM induced-glucotoxicity and inflammatory changes.[7]

Furthermore, diabetic pharmacotherapy may affect prolactin serum levels in patients with T2DM, since metformin is an effective adjuvant therapy in reducing prolactin in antipsychotic induced-hyperprolactinemia,[8] whereas glyburide induces failure in the glucose counter-regulatory response in the secretion of glucagon and anterior pituitary hormones.[9]

Therefore, the aim of the present study was to evaluate prolactin serum levels in patients with T2DM regarding the effect of diabetic pharmacotherapy.

MATERIALS AND METHODS

This case-controlled cross-sectional study was approved by the specific Scientific Ethical Committee under ethical clearance number RTD123YR 4/1/2018 in respect to the Declaration of Helsinki.[10]

Study design
This was a single-center, randomized, and open-label study. A total number of 80 male patients with T2DM were recruited from a diabetic center who were divided into three groups: Group I – 29 patients with T2DM treated with metformin 1500 mg/day, Group II – 30 patients with T2DM treated with glyburide 10 mg/day, and Group III – 21 patients with T2DM treated with glyburide 5 mg/day plus metformin 1500 mg/day. In addition, 25 male healthy controls matched with patients for age were involved in this study as a control group (Group IV) who are recruited from medical staff at a diabetic center.

All patients and enrolled participants gave informed verbal consent for their participation in this study.

Inclusion criteria included male patients with T2DM with an age range of 40–55 years on metformin and/or glyburide therapy for at least 5 years of duration.

Exclusion criteria included psychological diseases, neurological diseases, hypothyroidism, end-stage kidney disease, hepatic dysfunctions, connective tissue disorders, history of intake of dopamine receptor agonist or antagonist agents, malignant disorders, and sexual dysfunctions.

Anthropometric measurements
Body mass index (BMI) was estimated by specific equation: BMI = weight (kg)/height (cm^2), whereas waist–hip ratio (WHR) was calculated by dividing waist circumference on hip circumference in centimeter.[11] Blood pressure measurements were done at supine position from the left arm by digital automated blood pressure monitoring 2 h apart. Pulse pressure = systolic blood pressure (SBP) − diastolic blood pressure (DBP) and mean arterial pressure (MAP), MAP = SBP + 2DBP/3.[12]

Biochemical measurements and hormonal assay
After an overnight fasting, 10 mL of venous blood was taken from antecubital area from each patient and enrolled subjects, and the blood samples were centrifugated at 3000/rpm and stored at −20° Ċ for later analysis. Fasting blood glucose (FBG) was determined by glucose oxidase method.[13] Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) were measured by colorimetric ELISA kits method (abcam, 65390, USA). Low-density lipoprotein (LDL) was estimated by the Friedewald equation.[14] Very LDL = TG/5 and atherogenic index (AI) =log (TG/HDL) were estimated by specific equations.[15]

Fasting insulin was measured by the enzyme-linked immunosorbent assay (ELISA) method (insulin human ELISA kit, catalog number: KAQ1251). IR and β-cell function were determined by the homeostatic model assessment (HOMA-2) that measures HOMA-IR (IR), HOMA-β% (β-cell function), and HOMA-S% (insulin sensitivity).[16] Glycated hemoglobin (HbA1c) was measured by a specific kit (human HbA1c AIi1c, GHbA1c, MBS702379). Human C-reactive protein (CRP, mg/dL) was measured by the ELISA method (CRP ab99995). Prolactin serum level (ng/ml) was estimated by the ELISA kit method (human prolactin quantikine and solid-phase sandwich ELISA 5617). All kit procedures were done according to the kit instructions.

Statistical analysis
Data analysis was performed using the SPSS (IBM SPSS Statistics for Windows version 20.0, 2014 IBM, Corp., Armonk, NY, USA). The data presented as mean ± standard deviation, and unpaired Student's *t*-test was used to determine the significance of differences. Analysis of variance was followed by Bonferroni *post hoc* test. $P < 0.05$ was considered as statistically significant.

RESULTS

In this study, all of the recruited patients and controls showed insignificant differences in age ($P = 0.33$). Body weight and BMI of diabetic patients demonstrated a significant difference from controls ($P = 0.003$), whereas WHR showed insignificant difference between diabetic patients and controls ($P = 0.06$). Besides, most of the

diabetic patients were associated with other concomitant illnesses as 86.25% and 96.25% of them were hypertensive and dyslipidemic, respectively. Furthermore, 36.25% of the diabetic patients were on metformin therapy, whereas 37.5% and 26.25% of them were on glyburide and metformin plus glyburide therapy correspondingly, and other agents are shown in Table 1.

Table 1: Demographic characteristics of the present study

Variables	T2DM	Control	P
n	80	25	
Gender: Male	80 (100)	25 (100)	
Age (years)	44.71±3.63	43.98±3.21	0.33
Body weight (kg)	99.85±9.53	81.77±8.83	<0.0001
Height (m)	179.34±3.21	179.77±3.88	0.57
BMI (kg/m²)	31.05±1.66	25.30±1.55	<0.0001
WHR (cm)	1.34±1.04	0.95.1±0.11	0.06
Concurrent diseases			
Hypertension	69 (86.25)	…………	
Dyslipidemia	77 (96.25)	…………	
Peripheral vascular diseases	11 (13.75)	…………	
Asthma	5 (6.25)	…………	
COPD	9 (11.25)	…………	
IHD	75 (93.75)	…………	
Current therapy			
Metformin	29 (36.25)	…………	
Glyburide	30 (37.5)	…………	
Metformin + glyburide	21 (26.25)	…………	
Other drugs			
Statins	78 (97.5)	…………	<0.0001
Omga-3 fatty acid	73 (91.25)	…………	
Antiplatelets	74 (92.5)	……………	
Anticoagulants	5 (6.25)	……………	
Theophylline	9 (11.25)	……………	
ACEI	44 (55)	……………	
CCBs	12 (15)	……………	
Trimetazidine	39 (48.75)	……………	
Tonics	72 (90)	6 (7.5)	

Data are expressed as mean±SD, *n* (%). BMI: Body mass index, WHR: Waist–hip ratio, COPD: Chronic obstructive pulmonary disease, IHD: Ischemic heart disease, ACEI: Angiotensin-converting enzyme inhibitor, CCBs: Calcium channel blockers, SD: Standard deviation, T2DM: Type 2 diabetes mellitus

Anthropometric parameters were statistically differed among treated groups compared with controls ($P < 0.01$) except for height ($P = 0.9$) and WHR ($P = 0.28$). In the metformin-treated group, systolic, diastolic, and MAP pressures were low compared with the glyburide-treated group ($P < 0.05$). MAP was low in the metformin plus glyburide-treated group compared with the glyburide-treated group ($P < 0.05$) [Table 2].

Biochemical and hormonal changes in the present study showed significant differences among diabetic patients regarding specific diabetic pharmacotherapy compared with controls ($P < 0.01$).

Combination therapy (glyburide plus metformin) in patients with T2DM showed a better effect on most of the glycemic indices and lipid profile than glyburide or metformin monotherapy ($P < 0.05$).

AI and CRP level were ameliorated in metformin and metformin plus glyburide-treated diabetic patients compared with glyburide-treated patients ($P < 0.05$).

Prolactin serum levels were high in patients with T2DM compared with healthy controls ($P < 0.01$), and it was 10.66 ± 2.45 (ng/ml), 32.88 ± 5.85 (ng/ml), 38.71 ± 6.79 (ng/ml), and 35.89 ± 6.51 (ng/ml) for controls, metformin-treated patients, glyburide-treated patients, and metformin plus glyburide-treated patients, respectively. Prolactin serum levels were higher in glyburide-treated patients compared with metformin-treated patients and metformin plus glyburide-treated patients ($P < 0.03$) [Table 3].

Prolactin levels were positively correlated with FBG, HbA1c, insulin levels, HOMA-IR, and CRP levels [Table 4].

Moreover, prolactin levels were significantly correlated with BMI ($r = 0.56$, $P = 0.001$), TG levels ($r = 0.82$, $P = 0.001$), and TC levels ($r = 0.65$, $P = 0.001$), but it negatively correlated with HDL levels ($r = 0.54$, $P = 0.001$) [Figure 1].

Regarding the difference in prolactin serum levels between diabetic patients and healthy controls, Prolactin serum

Table 2: Anthropometric and blood pressure changes in patients with type 2 diabetes mellitus

Anthropometric parameters	Control (*n*=25)	Metformin (*n*=29)	Glyburide (*n*=30)	Combination (*n*=21)	F	P
Body weight (kg)	81.77±8.83	96.82±7.84	99.71±6.11	97.89±6.45	32.14	0.000*
Height (m)	179.77±3.88	179.36±3.21	179.34±3.56	179.39±3.92	0.08	0.9
BMI (kg/m²)	25.30±1.55	30.10±3.81	31.45±3.66	30.40±2.98	19.004	0.000*
WHR (cm)	0.95±0.11	1.14±1.01	1.39±1.05	1.33±1.03	1.273	0.28
SBP (mmHg)	123.65±6.78	145.79±4.64	150.75±5.90#	146.79±4.48	125.41	0.000*
DBP (mmHg)	79.44±6.84	88.95±7.67	95.11±5.22#	90.39±5.29	28.09	0.000*
MAP (mmHg)	94.19±5.62	107.89±6.68	113.65±5.83#	109.19±4.81$	53.87	0.000*

#*P*<0.05 (glyburide vs. metformin), $*P*<0.05 (combination vs. glyburide), **P*<0.01. BMI: Body mass index, WHR: Waist–hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Table 3: Biochemical and hormonal changes in type 2 diabetes mellitus regarding the effect of diabetic pharmacotherapy

Biochemical and hormonal variables	Control (*n*=25)	Metformin (*n*=29)	Glyburide (*n*=30)	Combination (*n*=21)	F	P
FBG (mg/dl)	81.77±8.83	144.52±7.65	141.22±6.11	133.11±5.22[#,$]	438.09	0.000
HbA1c (%)	5.77±1.71	8.6±2.32	9.99±2.56	7.11±2.12[#]	18.15	0.000
Fasting insulin (mIU/l)	8.64±2.55	16.81±3.22	19.33±3.66[¶]	17.84±3.11	58.03	0.000
HOMA-IR	1.09±0.11	2.39±1.01	2.72±1.05	2.49±1.01	17.29	0.000
HOMA-β%	125.0±6.89	66.4±4.95	76.4±7.95[¶]	80.3±5.29[$]	419.94	0.000
HOMA-S%	91.6±5.35	41.8±4.81	36.7±4.64[¶]	40.2±4.56	739.18	0.000
TG (mg/dl)	112.89±9.62	188.24±12.5	201.63±13.85[¶]	182.71±12.63[#]	270.80	0.000
TC (mg/dl)	129.11±11.80	191.61±11.8	207.12±13.92[¶]	199.73±13.43	200.44	0.000
LDL (mg/dl)	49.80±5.61	110.14±9.71	126.83±10.49[¶]	114.44±9.47[#]	368.66	0.000
HDL (mg/dl)	56.73±3.63	43.82±7.83	39.96±5.53[¶]	48.74±4.12	43.43	0.000
VLDL (mg/dl)	22.60±4.89	37.64±5.56	40.32±6.39	36.54±3.47	57.92	0.000
AI	0.06±0.001	0.27±0.01	0.34±0.02[¶]	0.214±0.01[#,$]	233.93	0.000
CRP (mg/L)	1.21±0.72	2.61±1.82	3.96±1.94[¶]	2.33±0.41[$]	19.56	0.000
Prolactin (ng/ml)	10.66±2.45	32.88±5.85	38.71±6.79[¶]	35.89±6.51	128.99	0.000

[#]$P<0.05$ (combination vs. glyburide), [$]$P<0.05$ (combination vs. metformin), [¶]$P<0.05$ (glyburide vs. metformin). FBG: Fasting blood glucose, HbA1c: Glycated hemoglobin, HOMA: Homeostatic model assessment, IR: Insulin resistance, β%: β-cell function, S%: insulin sensitivity, TG: Triglyceride, TC: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very LDL, AI: Atherogenic index, CRP: c-reactive protein

Table 4: Correlation between prolactin levels and glycemic and inflammatory indices in patients with type 2 diabetes mellitus

Variables	Metformin		Glyburide		Combination	
	r	P	r	P	r	P
FBG (mg/dl)	0.84	0.001[#]	0.81	0.001[#]	0.99	0.0001[#]
HbA1c (%)	0.81	0.001[#]	0.92	0.0001[#]	0.73	0.001[#]
Insulin mIU/l	0.99	0.001[#]	0.99	0.0001[#]	0.96	0.001[#]
HOMA-IR	0.98	0.001[#]	0.99	0.0001[#]	0.69	0.001[#]
HOMA-β%	−0.49	0.01*	−0.99	0.0001[#]	−0.84	0.001[#]
HOMA-S%	−0.57	0.001[#]	−0.98	0.0001[#]	−0.95	0.001[#]
CRP (mg/L)	0.99	0.001[#]	0.89	0.01*	0.89	0.001[#]

[#]$P<0.01$, *$P<0.05$. FBG: Fasting blood glucose, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment, IR: Insulin resistance, β%: β-cell function, S%: Insulin sensitivity, CRP: C-reactive protein

levels were high in 20% (with 0.2 rate and 0.25 odd) of control participants and 86.25% (0.86 rate and 6.27 odd) in diabetic patients, but normal prolactin levels were observed in 80% and 13.75% for controls and diabetic patients, respectively (*P* = 0.001) [Table 5].

DISCUSSION

T2DM is a metabolic disorder associated with cardiovascular morbidity and mortality due to hyperglycemias, dyslipidemia, and inflammatory changes.[17] These findings are in corresponding with results of the present study, since most of the recruited patients were hypertensive, obese, and dyslipidemic.

Furthermore, the chief finding of the present study was high prolactin serum levels in patients with T2DM as reported by Daimon *et al.*'s study which confirms a link between high prolactin levels and IR.[18] Besides, prolactin is also produced from adipose tissue and act as a cytokine in regulation of body metabolism. Adipose tissue-derived prolactin level appears to be proportional with body fat.[19] These phenomena coincide with our results, since all of the enrolled patients were with high BMI. As well, adipose tissue macrophages are shown to produce prolactin in response to hyperglycemia and diabetic-induced inflammation[20] seeing as CRP levels, FBG, and HbA1c were elevated in our patients. CRP levels reflect the inflammatory changes in patients with T2DM as supported by Hwang *et al.*'s study that illustrated a link between diabetic complications and high CRP levels.[21] Moreover, elevated prolactin levels in T2DM may be a compensatory mechanism against hyperglycemia, since prolactin plays a vital role in the enhancement of pancreatic β-cell function to overcome IR as confirmed by Ruiz-Herrera *et al.*'s study which showed that administration of prolactin via osmotic mini-pumps into rodent adipose tissue leads to improvement in the insulin sensitivity, reduces inflammatory cytokine expression in visceral fat, prevents adipocyte hypertrophy, and increases expression of GLUT4.[22]

Normally, prolactin hormone leads to noteworthy biological action on β-cell of the pancreas through activation of protein kinase and phosphatidlinositol-3 kinase that modulates islet density and insulin sensitivity.[23] Furthermore, prolactin activates peroxisome PPAR-γ at adiposity leading to reduction of blood glucose and lipids. As well, prolactin activates paroxonase-1 gene which improves endothelial dysfunction in T2DM.[24] On the other hand, hyperprolactinemia adversely affects body metabolism leading to hyperglycemia and metabolic disorders; therefore, administration of bromocriptine or other D2
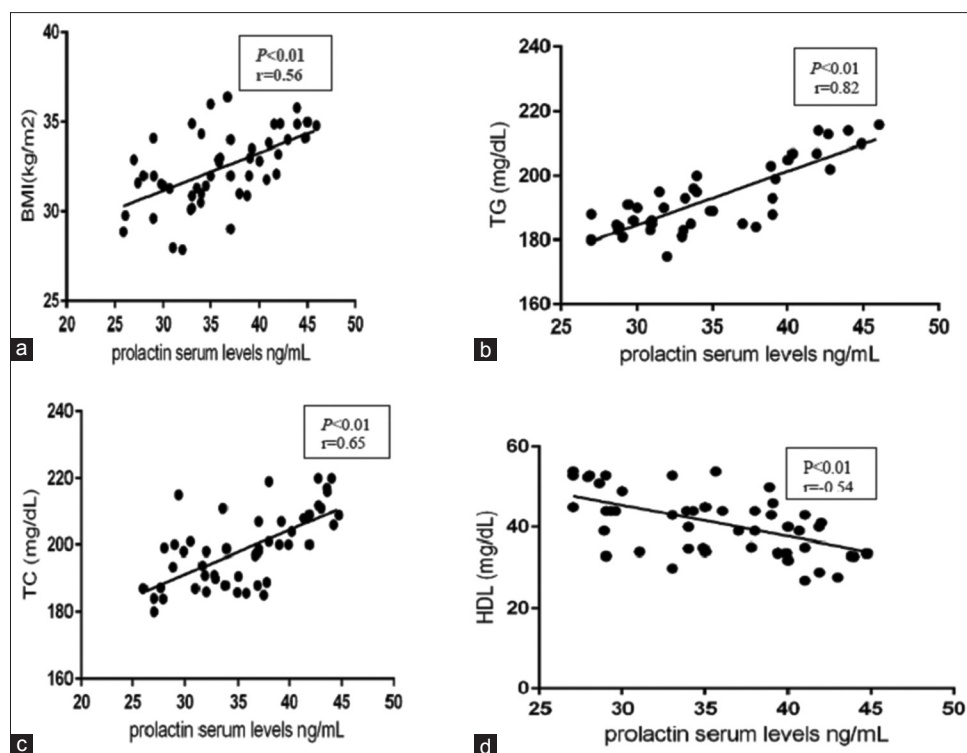
Figure 1: Correlation of prolactin serum levels: (a) With body mass index, (b) with triglyceride levels, (c) with total cholesterol levels, (d) with high-density lipoprotein levels

Table 5: The differences in prolactin levels between diabetic patients and healthy controls

Prolactin levels (ng/ml)	Control (*n*=25)	Diabetic patients (*n*=80)
High	5 (20)	69 (86.25)
Normal	20 (80.0)	11 (13.75)
Rate	0.2	0.86
Odds	0.25	6.27
Risk ratio (95% CI)	0.23 (0.105–0.510)	
Odd ratio (95% CI)	0.033 (0.012–0.128)	
Fisher's exact test (*P*)	<0.0001	

CI: Confidence interval

agonists ameliorates IR and metabolic complications through central inhibition of prolactin secretion.[25]

Indeed, prolactin in the present study was positively correlated with TG and TC levels, but it negatively correlated with HDL as documented by Perić *et al.*'s study.[26]

Regarding the effect of diabetic pharmacotherapy in the present study, glyburide-treated patients showed higher IR and prolactin levels compared with the metformin-treated group or their combination, since glyburide increases appetite and body weight causing worsening of IR which correlated positively with high prolactin levels. Furthermore, glyburide may increase prolactin secretion from the anterior pituitary gland through antagonizing effect of somatization.[27]

Besides, in the metformin-treated group, there was low prolactin and low IR compared with the glyburide group which might be due to relatively low IR or due to metformin effect. Ortega-Gonzalez *et al.*'s study showed that metformin improves endogenous hypothalamic dopaminergic tone which inhibits endogenous prolactin secretion and ameliorates IR in obese women with polycystic ovary syndrome.[28]

Combination of metformin plus glyburide produced better glycemic control than either metformin or glyburide monotherapy, but prolactin serum levels were not decreased more than the metformin-treated group, since glyburide antagonizes metformin effect on prolactin secretion.[29]

Alongside, high prolactin levels in T2DM might be due to low dopaminergic activity seeing as dopamine receptors are decreased in obese and hyperinsulinemic status.[30]

Therefore, a high prolactin level in patients with T2DM is regarded as beneficial phenomena to overcome IR and diabetic complications.

Limitations of the present study were relatively small sample size, single center, and newly diagnosed patients with T2DM who were not included, and gender differences were not evaluated in this study.

In spite of these limitations, this study is regarded as a preliminary step for large-scale study to observe

the association between prolactin levels and T2DM induced-complications.

CONCLUSION

High prolactin levels in patients with T2DM are linked with diabetic complications. Metformin but not glyburide reduced prolactin levels due to the improvement of IR. Also, high prolactin level in patients with T2DM is regarded as beneficial phenomena to overcome IR and diabetic complications.

Conflicts of interest
There are no conflicts of interest.

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