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Impact of Initiation of Insulin Therapy on Serum Prolactin and Cortisol Levels in Type 2 Diabetic Male Patients

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ABSTRACT

Background: Starting insulin therapy significantly improves overall glycemic control in type 2 diabetes mellitus (T2DM) patients who had not been able to meet their target glycemic control objectives with oral anti-diabetic medication therapy. **Objective:** To assess impact of initiation of insulin therapy on serum prolactin and cortisol levels in T2DM male patients.

Patients and methods: The study was conducted on 30 male T2DM patients attending diabetes clinic at Ain Shams University Hospitals. All patients were subjected to the following investigations at the time of initiation of insulin therapy: Fasting plasma glucose (FBG). 2 hours post prandial plasma glucose (2HPPBG), Hemoglobin A1c (HbA1c), serum cortisol (9 a.m.) and serum prolactin.

Results: On studying the correlation between cortisol and prolactin with other laboratory findings showed that there were no significant correlations between cortisol and prolactin, and FBS, 2HPPBG and HbA1C in the first and third visits in group I. No significant correlations between cortisol and prolactin with FBS and 2HPPBG in the second visit in group I. However, there was a significant positive correlation between cortisol with FBS (P=0.028) and HbA1C (P=0.033) in group II. Also, a significant positive correlation between cortisol with FBS (P=0.034) and 2HPPBG (P=0.041) in group III. There was a highly significant positive correlation between cortisol and FBS (P=0.001) in group III. Also, there was a highly significant positive correlation between prolactin and 2HPPBG (P=0.008) in group II.

Conclusion: The present study suggests that initiation of insulin therapy in poorly controlled T2DM patients achieves a highly significant reduction in blood glucose level. Also, insulin therapy in T2DM patients has impact on other hormones regulating blood glucose level as it reduces serum prolactin and cortisol levels.

Keywords: Type 2 diabetes mellitus, adrenocorticotropic hormone, fasting plasma glucose. 2 hours post prandial plasma glucose, Hemoglobin A1c, serum cortisol, serum prolactin.

INTRODUCTION

A prevalent metabolic condition called type 2 diabetes mellitus (T2DM) is characterized by a loss in insulin sensitivity and hyperglycemia brought on by relative insulin insufficiency [(1)]. Starting insulin treatment significantly improved overall glycemic control in T2DM patients whose target glycemic control objectives had not been met on oral anti-diabetic medication therapy [(2)]. In critical illness, intensive insulin treatment was linked to reduced blood cortisol levels [(3)].

The postpartum period's prolactin hormone function is to get the breasts ready for breastfeeding. Other organs and cells, including lymphoid cells, adipocytes, and pancreatic cells, also express the prolactin receptor. A significant trigger for cells to adjust to increasing metabolic demands has been identified as a physiological rise in prolactin levels during pregnancy [(4)].

On the opposite end of the prolactin spectrum, high levels, as those found in prolactinoma patients, are linked to a greater risk of hyperglycemia, obesity, and insulin resistance [(5)]. Glucagon levels can be lowered by insulin treatment. After therapy, non-obese T2DM patients were found to have lower glucagon levels than T2DM patients who were fat [(6)].

The aim of the present study was to assess impact of initiation of insulin therapy on serum prolactin and cortisol levels in T2DM male patients.

PATIENTS AND METHODS

The present study was conducted on 30 male patients who were diagnosed to have type 2 diabetes attending diabetes clinic at Ain Shams University Hospital from 1 January to 1 July 2018. Their ages range from 40 to 60 years old. The purpose of the study was explained to all participants.

All patients were subjected to the following:

A) Full medical history taking including (age, duration of diabetes and drug history including total daily dose of insulin therapy, last oral antidiabetic drug therapy and history of corticosteroid and bromocriptine drug therapy).
B) Detailed clinical examination including (systolic and diastolic blood pressure, body weight and height, BMI and diabetes complications).
C) Laboratory Investigations: All patients were subjected to the following investigations at the time of initiation of insulin therapy: fasting plasma glucose (FBG). 2 hours post prandial blood glucose (2HPPBG), Hemoglobin A1c (HbA1c), serum cortisol (9 a.m.) level by ELISA (enzyme immunoassay for the quantitative measurement of human Cortisol), and serum prolactin level by ELISA (enzyme immunoassay for the quantitative measurement of human Prolactin).

Thereafter, the patients were divided into 3 equal groups (10 patients in each group): Group I

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was investigated again in the third day. Group II was investigated again in the tenth day. Group III was investigated again in the twentieth day. All the previous investigations were repeated to all patients 3 months after initiation of insulin therapy.

Exclusion criteria include Type 1 diabetes mellitus, morbid obesity, chronic kidney disease, chronic liver disease, patients with hyperprolactinemia and Cushing syndrome, history of bromocriptine therapy at last 3 months before the study, history of cortisol therapy at last 3 months before the study, and malignancy.

Methods:

1. **Fasting and postprandial blood glucose:** Glucose estimation was carried out according to Trinder kinetic using a colorimetric enzymatic method.**It was Carried out by using GLUCOSE KIT (GOD-POD Method),** Shenzhen Mindray, medical electronic Co., (China).
2. **HBA1C:** Random blood samples were withdrawn from the patients.

   It was carried out by using TRUEchemie HbA1c kit, Athenese-Dx (India). The reference range of HbA1C is (2.8%-4.9%) in a non-diabetic population **[8].**
3. **Cortisol: It was carried out by using VIDAS cortisol S (CORS) Kit, bioMerieux Inc., (France). The normal range of cortisol level by ELISA is (50-230 ng/ml) [9].**
4. **Prolactin: It was carried out by VIDAS PROLACTIN (PRL) KIT, bioMerieux Inc., (France). The mean prolactin concentration in males is (2-6 ng/ml) and in females is (2-15 ng/ml) [10].**

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Sciences (IBM SPSS) version 20 and the following analyses were done: Qualitative data were presented as number and percentages. Quantitative data were presented as mean, standard deviations and ranges.

The comparisons between groups with qualitative data were done by using: Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found to be less than 5. Repeated measures ANOVA test was used to compare means across one or more variables that are based on repeated observations. Paired t- test was used to compare two means that are from the same patient. Pearson correlation coefficients were used to assess the correlation between two studied parameters in the same group. Receiver operating characteristic (ROC) curve was used to assess the best cut off point with its sensitivity, specificity, positive predictive value and negative predictive value. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P-value $\leq$0.05 was considered significant, P-value <0.01 was considered as highly significant, and P-value >0.05 was considered insignificant.

RESULTS

There was significant positive correlation between cortisol with FBS, 2HPPBG and HbA1C in group II and III and highly significant positive correlation between cortisol and FBS in group III (Tables 1, 2, 3).

Table (1): Comparison between the three visits in Group I regarding laboratory results.

Variable		Group I			Test value	P-value	Sig.
		1st visit	2nd visit	3rd visit			
FBS	Mean ± SD	264.3 ± 65.96	129.1 ± 31.94	108.8 ± 12.61	65.486•	0.001	HS
2H PPBG	Mean ± SD	353.3 ± 96.57	196.7 ± 45.55	161 ± 33.33	37.037•	0.001	HS
HbA1c	Mean ± SD	10.62 ± 1.37	–	7.44 ± 0.55	7.163••	0.001	HS
Cortisol a.m. (50-230ng/ml)	Mean ± SD	195.1 ± 11.37	174.1 ± 16.29	131.5 ± 19.49	33.052•	0.001	HS
Prolactin (2-6 ng/ml)	Mean ± SD	4.39 ± 1.04	4.23 ± 0.96	3.98 ± 0.97	12.410•	0.002	HS

Post hoc analysis			
Variable	**1st visit vs 2nd visit**	**1st vs 3rd visit**	**2nd visit vs 3rd visit**
FBS	0.000	<0.001	0.175
2H PPBG	0.000	0.000	0.192
Cortisol a.m. (50-230ng/ml)	0.000	0.000	0.007
Prolactin (2-6 ng/ml)	0.324	**0.008**	0.002

P-value >0.05: Non-significant; P-value $\leq$0.05: Significant; P-value <0.01: Highly significant

•: Repeated measures ANOVA test; ••: Paired t-test

Table (2): Comparison between the three visits in group II regarding laboratory results.

Variable		Group II			Test value	P-value	Sig.
		1st visit	2nd visit	3rd visit			
FBS	Mean ± SD	200.7 ± 40.74	121.9 ± 24.98	114.7 ± 37.55	18.655•	0.001	HS
2H PPBG	Mean ± SD	359 ± 70.28	191.5 ± 26.9	179.3 ± 55.95	37.696•	0.001	HS
HbA1c	Mean ± SD	10.36 ± 0.91	–	7.7 ± 0.92	8.043••	0.001	HS
Cortisol a.m. (50-230ng/ml)	Mean ± SD	195.8 ± 13.64	128.4 ± 21.12	102.5 ± 24.38	143.335•	0.001	HS
Prolactin (2-6 ng/ml)	Mean ± SD	4.09 ± 1.01	3.99 ± 0.69	3.91 ± 0.93	8.578•	0.007	HS

Post hoc analysis			
Variable	1st visit vs 2nd visit	1st vs 3rd visit	2nd visit vs 3rd visit
FBS	0.002	0.003	1.000
2H PPBG	0.000	0.001	1.000
Cortisol a.m. (50-230ng/ml)	0.000	0.000	0.001
Prolactin (2-6 ng/ml)	0.096	0.030	0.110

P-value >0.05: Non-significant; P-value ≤0.05: Significant; P-value <0.01: Highly significant

•: Repeated measures ANOVA test; ••: Paired t-test

Table (3): Comparison between the three visits in group III regarding laboratory results.

		Group III			Test value	P-value	Sig.
		1st visit	2nd visit	3rd visit			
FBS	Mean ± SD	207.20 ± 44.01	134.00 ± 31.28	109.50 ± 16.08	33.349•	0.001	HS
2H PPBG	Mean ± SD	370.30 ± 85.83	202.60 ± 31.46	175.00 ± 49.42	31.586•	0.001	HS
HbA1c	Mean ± SD	10.40 ± 1.20	–	7.75 ± 0.72	5.426••	0.001	HS
Cortisol a.m. (50-230ng/ml)	Mean ± SD	195.40 ± 14.40	113.40 ± 13.10	94.20 ± 17.86	1094.63•	0.00	HS
Prolactin (2-6 ng/ml)	Mean ± SD	4.35 ± 0.96	4.22 ± 0.84	4.13 ± 0.95	17.114•	0.001	HS

Post hoc analysis			
Variable	1st visit vs. 2nd visit	1st vs. 3rd visit	2nd visit vs. 3rd visit
FBS	0.002	0.000	0.080
2H PPBG	0.000	0.000	0.590
Cortisol a.m. (50-230ng/ml)	0.000	0.000	0.000
Prolactin (2-6 ng/ml)	0.028	0.003	0.012

P-value >0.05: Non-significant; P-value ≤0.05: Significant; P-value <0.01: Highly significant

•: Repeated measures ANOVA test; ••: Paired t-test

There were no significant correlations between cortisol a.m. and prolactin with FBS, 2HPPBG and HbA1C (Table 4).

Table (4): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group I	Cortisol a.m. (50-230ng/ml) 1st visit		Prolactin (2-6 ng/ml) 1st visit	
	R	P-value	R	P-value
FBS 1st visit	0.036	0.920	0.182	0.614
2H PPBG 1st visit	0.207	0.567	0.116	0.751
HbA1c 1st visit	0.571	0.084	0.383	0.275

There were no significant correlations between cortisol a.m. and prolactin with FBS and 2HPPBG (Table 5).

Table (5): Correlations between cortisol a.m. and prolactin with FBS and 2H PPBG.

Group I	Cortisol a.m. (50-230ng/ml) 2nd visit		Prolactin (2-6 ng/ml) 2nd visit	
	R	P-value	R	P-value
FBS 2nd visit	0.280	0.434	0.432	0.213
2H PPBG 2nd visit	0.018	0.960	0.076	0.834

There were no significant correlations between cortisol a.m. and prolactin with FBS, 2HPPBG and HbA1C (Table 6).

Table (6): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group I	Cortisol a.m. (50-230ng/ml) 3rd visit		Prolactin (2-6 ng/ml) 3rd visit	
	R	P-value	R	P-value
FBS 3rd visit	0.467	0.174	0.086	0.813
2H PPBG 3rd visit	0.128	0.725	0.133	0.715
HbA1c 3rd visit	0.325	0.359	0.623	0.054

There were no significant correlations between cortisol a.m. and prolactin with FBS, 2HPPBG and HbA1C (Table 7).

Table (7): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group II	Cortisol a.m. (50-230ng/ml) 1st visit		Prolactin (2-6 ng/ml) 1st visit	
	R	P-value	R	P-value
FBS 1st visit	0.085	0.815	0.085	0.815
2H PPBG 1st visit	0.098	0.789	0.389	0.266
HbA1c 1st visit	0.182	0.614	0.067	0.855

There were no significant correlations between cortisol a.m. and prolactin with FBS. No significant correlation between cortisol a.m. with 2HPPBG. Highly significant positive correlation between prolactin with 2HPPBG (Table 8).

Table (8): Correlations between cortisol a.m. and prolactin with FBS and 2H PPBG.

Group II	Cortisol a.m. (50-230ng/ml) 2nd visit		Prolactin (2-6 ng/ml) 2nd visit	
	R	P-value	R	P-value
FBS 2nd visit	0.040	0.913	0.071	0.846
2H PPBG 2nd visit	0.274	0.444	**0.781****	**0.008**

There was no significant correlation between prolactin with FBS. No significant correlations between cortisol a.m. and prolactin with 2HPPBG and no significant correlation between prolactin with HbA1C. There was significant positive correlation between cortisol a.m. with FBS. There was significant positive correlation between cortisol a.m. with HbA1C (Table 9).

Table (9): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group II	Cortisol a.m. (50-230ng/ml) 3rd visit		Prolactin (2-6 ng/ml) 3rd visit	
	R	P-value	R	P-value
FBS 3rd visit	**0.689***	**0.028**	0.122	0.738
2H PPBG 3rd visit	0.255	0.476	0.018	0.960
HbA1c 3rd visit	**0.673***	**0.033**	0.268	0.454

There are no significant correlations between cortisol a.m. and prolactin with FBS, 2HPPBG and HbA1C (Table 10).

Table (10): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group III	Cortisol a.m. (50-230ng/ml) 1st visit		Prolactin (2-6 ng/ml) 1st visit	
	R	P-value	R	P-value
FBS 1st visit	**0.669***	**0.034**	0.14	0.699
2H PPBG 1st visit	0.413	0.236	0.183	0.613
HbA1c 1st visit	0.344	0.331	0.183	0.613

There are no significant correlations between cortisol a.m. and prolactin with FBS and 2HPPBG (Table 11).

Table (11): Correlations between cortisol a.m. and prolactin with FBS and 2H PPBG.

Group III	Cortisol a.m. (50-230ng/ml) 2nd visit		Prolactin (2-6 ng/ml) 2nd visit	
	R	P-value	R	P-value
FBS 2nd visit	**0.872****	**0.001**	0.073	0.841
2H PPBG 2nd visit	**0.652***	**0.041**	0.517	0.126

There were no significant correlations between cortisol a.m. and prolactin with FBS, 2HPPBG and HbA1C (Table 12).

Table (12): Correlations between cortisol a.m. and prolactin with FBS, 2H PPBG and HbA1C.

Group III	Cortisol a.m. (50-230ng/ml) 3rd visit		Prolactin (2-6 ng/ml) 3rd visit	
	R	P-value	R	P-value
FBS 3rd visit	0.332	0.348	0.150	0.679
2H PPBG 3rd visit	0.437	0.207	0.264	0.461
HbA1c 3rd visit	0.252	0.482	0.129	0.723

DISCUSSION

Insulin antagonistic properties of cortisol are apparent. The beta cells in the pancreas produce less insulin as a result. Contrarily, the central impact of glucocorticoids causes them to augment the vagal stimulation for insulin release.

The balance between these effects has the potential to result in compensatory hyperinsulinemia and blood sugar elevations as well as insulin resistance. As a result, the blood glucose level rises and the liver's production of glycogen increases [(11)].

Prolactin influences eating habits, weight gain, and insulin resistance by preventing the formation of adiponectin and Interleukin-6 in adipose tissue, which may result in type 2 diabetes mellitus [(12)]. However, experimental research have shown that prolactin influences pancreatic cell development and lowers the threshold for insulin production induced by glucose, suggesting that prolactin has a preventive impact against type 2 diabetes mellitus [(13)].

In the present study it was found that, after insulin therapy, there was a highly significant reduction in FBS, 2HPPBG and HbA1C between the three visits in the three groups. These results are in agreement with **Andayani *et al.*** [(14)] and **Pandit** [(15)] who studied the comparative effectiveness of multi oral anti diabetic drugs versus insulin therapy for glycemic control in type 2 diabetes mellitus and found that addition of insulin in poorly controlled type 2 diabetic patients on metformin and sulfonylurea treatment achieved a significantly greater reduction in HbA1c, fasting plasma glucose, and postprandial plasma glucose versus those treated with three-drug combination therapy. And also agree with the result reported by **Suzuki *et al.*** [(16)] who studied the effectiveness of Basal-supported Oral Therapy (BOT) using insulin glargine in patients with poorly controlled type 2 diabetes and found that it is a useful strategy that can

achieve good glycemic control without causing serious hypoglycemia and the introduction of this therapy before exhaustion of pancreatic β cells may increase its effectiveness.

Also our study found that there was significant positive correlation between cortisol with FBS, 2HPPBG and HbA1C in group II and III and highly significant positive correlation between cortisol and FBS in group III.

It is similar to that found in **Dias *et al.*** [17] who studied the longitudinal association of changes in diurnal cortisol features with fasting glucose and suggested a detrimental role of cortisol contributing to glycaemia among individuals with diabetes. Also similar to **Kamba *et al.*** [18] who studied the association between higher serum cortisol levels and decreased insulin secretion in a general population and found that high serum cortisol levels are significantly associated with decreased β cell function, even in the physiological cortisol range and higher serum cortisol levels are a risk factor for future incidence of diabetes. And also similar to **Ortiz *et al.*** [19] who studied the association of morning serum cortisol with glucose metabolism and diabetes and found that higher morning serum cortisol was associated with higher FBS and lower β-cell function among participants without T2D and higher FBS and HbA1c in participants with diabetes.

Our study proposal was to approve that when initiating insulin therapy in type 2 diabetic patients, there would be initial increase in cortisol (as anti-insulin hormone) and prolactin levels as a response to the state of stress experienced by a newly insulin treated diabetic patient trying to keep certain blood glycemic level that the body was adapted to before insulin therapy, then their levels would decrease due to the adaptation of the body to the newly controlled glycemic level.

However, our results revealed that after initiation of insulin therapy, there was highly significant reduction in cortisol level between the three visits in the three groups without initial surge in its level which is similar to that found in **Vanhorebeek *et al.*** [3] who studied the cortisol response to critical illness: Effect of intensive insulin therapy and found that intensive insulin therapy was associated with lower serum cortisol levels in critical illness. This effect, which was independent of binding capacity, related to the improved outcome with this intervention. This contradiction may be because hyperglycemia itself is considered a stressful condition that increases cortisol level which declines after correction of this hyperglycemia by insulin therapy.

Also, our study found that there was highly significant reduction in prolactin level after insulin therapy between the three visits in the three groups also without initial surge in its level. It may be also due to the correction of hyperglycemic state by insulin therapy.

The present study found a highly significant positive correlation between prolactin with 2HPPBG in group II. Verifying that prolactin is a diabetogenic hormone. This is in agreement with **Daimon *et al.*** [20] who studied the association between serum prolactin levels and insulin resistance in non-diabetic men and found that the associations between serum prolactin levels within the physiological range and insulin resistance were found to be positive for men and higher serum prolactin levels within the physiological range seem to be associated with insulin resistance in non-diabetic men.

Also, it agrees with the results reported by **Al–Fartosy and Mohammed** [21] who studied the comparison of insulin resistance, prolactin and HbA1C with relation to obesity in men and women of healthy control and diabetic patients and found that increased obesity leads to increased insulin resistance which affected on levels of HbA1c and prolactin in men and women type 2 diabetic patients and these strong association between insulin resistance and levels of HbA1c and prolactin could be considered as good biomarkers of the risk of T2D and obesity in men and women type 2 diabetic patients. And also agree with **Chamarthi and Cincotta** [22] who studied the effect of bromocriptine therapy on glycemic control in subjects with type 2 diabetes mellitus whose dysglycemia is inadequately controlled on insulin and found that bromocriptine therapy improves glycemic control in T2DM patients whose glycaemia is poorly controlled on metformin plus insulin. This glycemic impact occurred without significant change in FPG, suggesting a postprandial glucose lowering mechanism of action. And also similar to **Aranda *et al.*** [23] who studied the influence of bromocriptine plus metformin treatment on glycaemia and blood pressure in patients with type 2 diabetes mellitus and found that the ability of combined therapy with bromocriptine and metformin to control hyperglycemia and reaffirmed its advantages for controlling T2DM.

However, these results disagree with **Wang *et al.*** [24] which was the first study to investigate the association between circulating prolactin and glucose regulation and found that a high circulating prolactin level was significantly associated with a lower risk of prevalent diabetes and impaired glucose regulation in men and postmenopausal women. The difference in **Wang *et al.*** [24] results may be due to a large sample of community based men and women and the cross-sectional nature of the study make the observed associations cannot deduce any causality.

Our study disagrees with **Chahar *et al.*** [4] who studied the association of serum prolactin level with impaired glucose regulation and diabetes and found that lower prolactin levels were associated with

prediabetes and diabetes, higher prolactin levels were found to associate with lower HbA1c and fasting plasma glucose and decreasing relative risk for both prediabetes and diabetes were found in males and females with increasing prolactin levels. This difference in results may be explained by the difference in the characteristics of the participants (as it included males and females divided into diabetics, prediabetics and normal groups), large sample size and the cross sectional nature of the study make no causal inference can be drawn so prospective studies are better to clarify their precise relationship.

CONCLUSION

Our results suggest that initiation of insulin therapy in poorly controlled diabetic patients achieves a highly significant reduction in blood glucose level. Also, insulin therapy in diabetic patients has impact on other hormones regulating blood glucose level as it reduces serum prolactin and cortisol levels. Our findings suggest a diabetogenic effect of prolactin.

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Author contribution: Authors contributed equally in the study.

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