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Original Article

An investigation of the association between the level of prolactin in serum and type II diabetes

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ABSTRACT

As a hormone secreted from the pituitary gland, prolactin (PRL) plays an important role in increasing beta cell proliferation, stimulating the secretion of insulin, preventing the activities of caspases on pathways that cause apoptosis in the Langerhans' islands, and moderating the immune system in regulating the whole body's sensitivity to insulin. Therefore, PRL level changes in type II diabetes and it can be concluded that PRL can play an important role in metabolic disorders of glucose. The present study is carried out in order to investigate the association between serum levels of PRL and type II DM. Blood samples were taken from 64 females affected by type II diabetes and 70 healthy ones, whose PRL level was measured using electrochemiluminescence (ECL) technique. It was a case-control study, and based on the definition dedicated to each group, subjects were assigned to two groups. The patient group included the subjects with type II diabetes while the control group included healthy samples. Data were analyzed using SPSS software (Mann-Whitney test, *t*-test, and spearman's rho correlation test). According to the results, PRL concentration in the serum of people affected by type II diabetes (5.32 ± 0.36) was significantly ($P^{<}0.05$) lower than that of control group (18.38 ± 2.3). The results also showed that in type II diabetes, the level of PRL changes so that the concentration of PRL in the serum of the patients was lower than that of healthy ones. Therefore, PRL concentration in the blood can be related to diabetes.

1. Introduction

DM is a metabolic disease which is recognized by chronic hyperglycemia together with metabolic deficiency of carbohydrates, lipoproteins, lipids, and proteins. DM is one of the oldest human diseases known [1]. The difference between diabetes type I and II was well identified in 1936 [2]. In 1988, type II diabetes was introduced as a major component of metabolic syndrome [3]. There are many causes of DM but it is always caused by insulin secretion defect or failure to respond to insulin or both. Most patients with type II diabetes also have type I diabetes (mainly due to immune system or something apart from it). DM type II is more common compared to the one caused by hyperglycemia, resistance to insulin, and relative insufficiency of insulin [4]. DM type II is caused by genetic reactions and environmental and behavioral risk factors [5,6]. Also it can be related to pregnancy hormones, genetic deficiencies, infections, and special medications [7]. There is a direct relationship between blood glucose increase and behavioral and physiological responses of the body. Anyway, the brain identifies blood glucose increase and sends neural signals to pancreas and other organs to reduce the effects of blood glucose increase [8]. It is very important to proliferate beta cells for research on diabetes type I and II. Signals pathway specification among cells which have a significant role in induction of beta cell proliferation can help to solve this problem. To this end, important data on signal pathways activated by foods or growth factors such as epidermal growth factors, growth factors derived from plackets and wingless-type MMTV integration site family (WNT) and hormones such as

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leptin, estrogen and progesterone related to proliferation of human and rodent beta cells were collected. Proliferation of human beta cells is essential for prevention and treatment of diabetes type I and II [9]. The pathway of intracellular signals which connects the receptors and existing channels on the surface of the cells to the mechanism of the proliferation of beta cells is very complicated. Interestingly, signals pathway can well connect the some pathways that activate cyclin-dependent kinase (CDK), the primary and end cyclins and the cell cycle inhibitors and accordingly, the mechanisms of cell cycle multiply are increased [9]. One of the most important features of signal pathways is the crossover compounds between and within the pathways of the signal. For instance, glycogen synthase kinase-3 (GSK3) beta is a kinase which acts structurally and is found in both Wnt-B-Catenin and phosphatidylinositol-3 kinase (PI3K)/AKT pathways. Perhaps, insulin receptor substrate (IRS) maybe exists in PI3K and Ras/MAP kinase pathways. Receptor signal of PRL may not only act at the end of JAC-STAT5 pathway but is also able to act at PI3K and 5′-prime-AMP-activated protein kinase (AMPK) pathways. Anyway, these pathways are full of automatic multiplier and suppressor materials. Therefore, insulin and Insulin-like growth factor 2 (IGF2) activates the pathways of PI3K/mammalian target of rapamycin (mTOR) kinase by IRS2 which prohibits the function of IRS2 as the feedback to weaken its signal. The above mentioned small molecules such as glucose and growth factors, etc. can activate the proliferation of beta cells, which are appropriate purposes for these challenging topics [9]. Fewer researches have been done about these pathways on mature human beta cells. While there are many similarities between mature human beta cells and those of juvenile rodents, significant differences are noticed between the details of this pathway. Finding these differences may be the key answer to the question of why mature human beta cells show more resistance to proliferation and therapeutic opportunities for induction of proliferation. Development of the purification techniques of human beta cells creates a great opportunity to describe and define unique details about the anatomy of proliferation of human beta cells. Therefore, regarding the human beta cells, we are still moving ahead in the darkness without light [9]. PRL is made up of 198 amino acids and its molecular weight is 23 KD. This hormone has little similarity to growth hormone (GH) and human placental lactogen (HPL) which indicates the duplication and divergence of a common predecessor gene GH-PRL-HPL. PRL is made in lactotrope cells which comprises 20% of anterior pituitary cells. Normal PRL serum level in mature individuals is about 10–25 μg/dl in females and 10–20 μg/dL in males. Thyrotropin-releasing hormone (TRH) ((Pyro)Glu-His-Pro (NH2)) is a hypothalamic tripeptide that releases PRL within 15–30 min of intravenous injection. The physiological relationship between TRH and PRL adjustment is not known yet, since it seems that TRH generally plays a role in adjusting thyroid stimulating hormone (TSH). Vasoactive intestinal peptide (VIP) causes the induction of PRL secretion while glucocorticoids and thyroid hormone prohibit PRL secretion to some little extent. The serum level of PRL rises transiently after exercise, eating, sexual intercourse, minor surgical operations, general anesthesia, chest damage, acute myocardial infarction, and other forms of harmful stress. During pregnancy, PRL level increases remarkably (approximately 10 times) and decreases rapidly 2 weeks after childbirth. If breastfeeding begins, the PRL base level remains high. Sucking nipples stimulates the reflexive increase of PRL level which lasts 30–45 min. It also activates the neurosecretory cells or afferent nerve pathways in hypothalamus which inducts PRL secretion. Over time, the reaction to nipple sucking decreases and the level of PRL among lactation promises goes back to normal [10]. The global outbreak of diabetes is spreading incredibly. In 2011, there were 1.5 million patients with diabetes in Iran [9,10]. Since PRL increases the proliferation of beta cells, stimulates insulin secretion, prohibits the activities of caspases in the pathways leading to Langerhans islands apoptosis, and moderates the function of immune system in adjusting the sensitivity of the whole body to insulin, the importance of studying the relationship between levels of PRL in serum and type II diabetes becomes more obvious. The purpose of the present study was to investigate the relationship between levels of PRL in serum and type II diabetes within the studied population.

2. Material and methods

2.1. Reagents

Phenol, Phosphate buffered saline (PBS), 4-aminopyridine, glucose oxidase, sodium phenothiazine salt, fructosyl peptide oxidase, pre-treatment lubricant solution, sodium hydroxide (NaOH), picric acid, tris, 2-oxoglutarate, urea, NADH (reduced form of nicotinamide adenine dinucleotide), glutamate dehydrogenase (GLDH), cholesterol esterase, cholesterol oxidase, catalase, ethylenediaminetetraacetic acid (EDTA), sodium azide, and H-DAOS were purchased from Sigma, USA. PRL kit was purchased from DiaSorin, Italy. The kits for measuring fasting blood sugar (FBS), blood glucose, triacylglyceride (TG), low-density lipoprotein (LDL), high-density lipoproteins (HDL), hemoglobin A1c (HbA1c), urea, creatinine, cholesterol, and other materials were provided with high quality and purity.

2.2. Apparatus

For measuring PRL, an auto-analyzer was used (model CL2A, Lauzon, Italy). Also, alpha classic AT plus (SEAL analytical, USA) was applied to measure blood glucose, cholesterol, triglyceride urea, creatinine, LDL, HDL, FBS, and HbA1C. A centrifuge (Eppendorf 5417 R, Germany), was used to prepare plasma for measuring urea and creatinine.

2.3. Sampling

The samples for this study were selected from among the people referring to the laboratory of Shahid Fayyazbakhsh Hospital in Tehran. They were healthy or diagnosed to have type II diabetes. With the sample size based on $\alpha = 0.05$, the prevalence can be generalized to type II diabetes with 19.7. The sample size was 70 people in each group.

α = type I error
β = type II error
1-β = power, 80%
p = the percentage with which the sample size was calculated (equation (1)).

$$n_1 = n_2 = \frac{2\left(Z_{1-\alpha'2} + z_{1-\beta}\right)2 + [P_1\,(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2} = 70$$
$$\propto = 0.05,\ P_1 = 0.197, P_2 = 0.5,\ \beta = 0.2 \quad (1)$$

According to the sampling formula, in order to compare the two ratios at 95% confidence level, the test power was 80%, and the desired outcome ratios in the case and control groups were 19.7% and 50% for 70 patients and 70 healthy samples, respectively. Blood Sugar, FBS, urea, creatinine, LDL, HDL, cholesterol, and TG were tested using the provided kits. The patient group included 70 diabetic samples of whom 4 were omitted because of hyper

prolactinemia and 2 because of pregnancy. Finally, n = 64 female samples with type II diabetes were selected. Based on world health organization (WHO) criteria, patients with diabetes are considered as:

- double-repeat fasting plasma glucose higher than 126 mg/dl, or
- Two-hour postprandial plasma glucose (2hpp) higher than 200 mg/dl.

In this study, the patients' group included females whose diabetes was confirmed by physicians, majority of whom were treated with glucose control drugs, insulin, except those who controlled their blood glucose with a diet. In the control group (n = 70), the subjects did not have any diabetes-affected person among their first grade relatives. They were taken a fasting blood sugar and a 2hpp to ensure that they did not have impaired fasting glucose (IFG) or impaired glucose test (IGT); the samples with 2hpp normal were considered as control. And since this study was a case-control, the samples in both case and control groups were selected with the same sex, race, etc.

2.4. The inclusion criteria for entering in the study

The subjects included in this study were people with type II diabetes symptoms, confirmed by double-repeat fasting plasma glucose higher than 126 mg/dl, or 2hpp higher than 200 mg/dl as patient group, and 70 healthy people as control group.

2.5. Criteria for being excluded from study

Smoking individuals, pregnant and lactating women, people with thyroid disorders (hypothyroidism), pituitary hypnotics, those using PRL suppressants, chronic renal failure, chest surgery or herpes zoster disease were excluded from the study. Data about the subjects were collected using a questionnaire and their written consent for getting blood tests was taken, too. 4CC venous blood was taken from every subject in control and case groups, of which 2CC was injected in venoject tubes with EDTA anticoagulant, and 2CC in tubes without EDTA.

2.6. Preparing samples for measuring PRL level

In this study the auto-analyzer device was used to measure serum PRL. Also, 250 ʎ serum from control and case groups was used.

2.7. Measuring serum PRL using ECL technique

ECL is a process in which the stable precursors on the surface of an electrode in a cyclic oxidation-reduction reaction, the highly reactive species followed by light are produced. In this technique, Ru(BPY)3, Ruthenium-tris(2,2′-bipyridyl) together with tripropylamine (TPA) is used. During oxidation reactions, the two substances are oxidized by losing electrons and produce Ru $(bpy)_3^{+3}$ and TPA^{++}, respectively. Then TPA^{+} changes to TPA· radical. By giving an electron to Ru $(bpy)_3^{+3}$ changes it to excited Ru $(bpy)_3^{+2}$. Its restoration to basic Ru$(bpy)_3^{+3}$ is together with emission at 620 nm. Therefore, the light by Ru$(bpy)_3^{+2}$ is produced when it is on the surface of electrode and at the presence of TPA [11]. In this study, after calibration of the auto-analyzer device, the amount of PRL in sample serums was measured using ECL technique.

2.8. Statistical analysis

Data were analyzed using SPSS software version 22, and the two-way P value less than 0.05 indicates a significant difference statistically. The normality of the population was tested using Kolmogorov-Smirnov Test. T-test, Mann-Whitney, and Spearman rho correlation methods were used to statistical analysis.

3. Results

3.1. Studying the biochemical and demographic factors and their comparison between the case and control groups

T-test was applied in order to compare the mean of biochemical factors such as FBS, blood glucose, TG, LDL, HDL, cholesterol, HbA1C, urea, and creatinine between the case and control groups. Standard deviation (SD) for each is stated. Table 1 shows the comparison of biochemical and demographic factors between the case and control groups using *t*-test. As it is observed, due to the nature of diabetes, a significant different exists between the two groups (except LDL) which was expected (p-value ≤0.05).

3.2. Studying the mean of PRL density and its comparison between case and control groups

In order to compare the mean of PRL concentration between case and control groups, Mann-Whitney test was used. SE stands for standard error. Table 2 shows the mean of PRL density in both case and control groups using Mann-Whitney test. As it is seen, there is a significant difference (p<0.001) between two studied groups.

As Fig. 1 shows, PRL mean in control group is 18.38 while it is 5.39 in case group. Mann-Whitney test for two groups had a significant difference statistically (*p-value* ≤0.0001).

3.3. Investigation of the correlation between biochemical and demographic factors and serum PRL level in control group

The correlation between biochemical and demographic factors and PRL level in serum was studied in case and control groups. As it is seen, there is a correlation between cholesterol and serum PRL level in control group. But in the diabetic group, there was no correlation between biochemical factors and serum PRL level. Table 3 shows the correlation using Spearman rho in control group.

Table 1
Comparison between Mean, Standard Deviation, and Significance Level in Biochemical Factors of Blood Using *t*-test.

Parameters	Groups	N	Mean (SD)	*P*-Value
FBS mg/dl	Control (Health)	70	93.5 (17.8)	<0.001
	Diabetics	64	184.2 (66.7)	
Blood Sugar mg/dl	Control (Health)	70	126.3 (35.9)	<0.001
	Diabetics	64	270.9 (89.6)	
Urea mg/dl	Control (Health)	70	22.2 (6.8)	<0.001
	Diabetics	64	32.0 (10.9)	
Creatinine mg/dl	Control (Health)	70	0.8 (0 .1)	0.035
	Diabetics	64	0.9 (0.1)	
TG mg/dl	Control (Health)	70	97.8 (60.1)	<0.001
	Diabetics	64	184.8 (75.2)	
Cholesterol mg/dl	Control (Health)	70	164.5 (32.2)	0.007
	Diabetics	64	188.2 (44.5)	
LDL mg/dl	Control (Health)	70	99.7 (21.8)	0.643
	Diabetics	64	102.8 (36.5)	
HDL (mg/dl	Control (Health)	70	58.1 (42.0)	0.022
	Diabetics	64	45.3 (10.0)	
HbA1C (%)	Control (Health)	70	4.8 (0.3)	<0.001
	Diabetics	64	7.7 (1.4)	
Age (Year)	Control (Health)	70	40.3 (12.6)	<0.001
	Diabetics	64	54.3 (10.8)	

Table 2
Mean of PRL concentration in both Case and Control Groups Using Mann-Whitney Test.

Groups	Concentrations of PRL (SE)	N (%)	*P*-Value
Control (Healthy)	18.38 (13.9)	70 (52.2)	<0.0001
Case (Diabetics)	5.39 (2.9)	64 (47.8)	

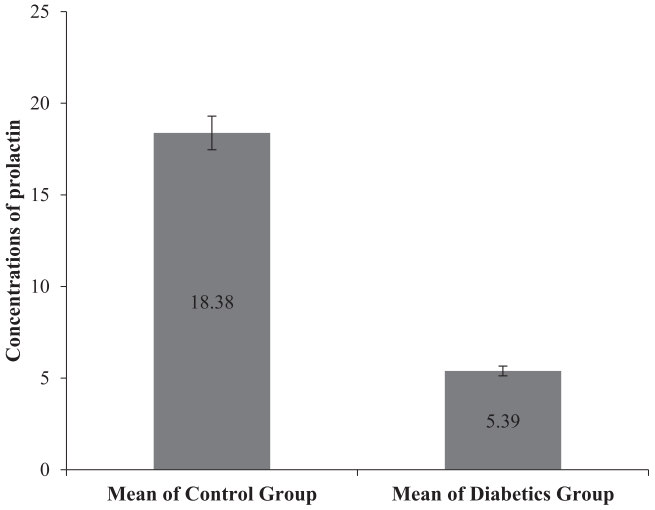

Fig. 1. Comparison of the mean of PRL concentration between case and control groups.

3.4. Investigation of the correlation between biochemical and demographic factors and serum PRL level in diabetic group

At this step, the correlation between biochemical and demographic factors and serum PRL level in diabetic group was studied. Table 4 shows the results of correlation test between biochemical, demographic factors and serum PRL level using Spearman rho in the diabetic group. As it is observed, there was no correlation between biochemical factors and serum PRL level.

4. Discussion

Diabetes is a widely spreading disease in communities imposing a heavy financial cost on treatment and life of individuals affected by this disease. The number of people affected by this illness is increasing but there are many that are not identified yet. The prevalence of this disease and the injuries that it brings in the quality of individuals' lives, and related cost are very important. It is essentials for all countries to take important steps to prevent and treat this disease [5]. A study by Wang et al., in 2013 showed that after menopause in men and women, the increase of blood PRL had a remarkable relationship with the lower prevalence of diabetes and impaired glucose regulation (IGR). This was the first study for the evaluation of the relationship between blood PRL and glucose adjustment in many men and women [12]. The results of Wang et al. study are in accordance with results of the previous studies. During pregnancy, the number of PRL and PRL receptors increases parallelly with the increase of beta cells mass and stimulation of insulin secretion for adjusting additive function of Langerhans islands and following that the adjustment of glucose homeostasis increases normally [13–15]. In non-pregnant models, PRL increases beta cells proliferation, insulin secretion stimulation, and prohibits the activities of caspases in the pathways that cause apoptosis of Langerhans islands, and plays an important role in adjusting the sensitivity of the whole body to insulin [16,17]. The previous study showed that human fat tissues make PRL and also the PRL receptors are expressed in them. It confirms the results that indicate PRL acts as a cytokine. PRL directly adjusts the fat acids synthesis and the decreasing adjustment of lipoprotein lipase in fat tissues [18,19]; as a result, the lipogenesis are inhibited and the biological activity of adipokinase such as adiponectin, interleukin-6 and probably leptin are adjusted [20,21]. All in all, these studies claimed that PRL acts as an adipokine and plays an important role in the emergence of resistance against insulin and adjusting energy [22]. In fact, the role of PRL in adjusting glucose and resistance to insulin depends on its concentration in blood. Destruction of PRL or deficiency of PRL receptors with hyperplasia of beta cells (decreased amount of pancreas insulin mRNA) has retarded insulin secretion in response

Table 3
Significance level and correlation coefficient of blood factors in control group using spearman rho.

Parameter		FBS (mg/dl)	Blood Sugar (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	TG (mg/dl)	Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	HbA1c (%)	Age (year)	PRL (ng/dl)
FBS (mg/dl)	r^{**}	1	0.935	0.54	0.337	.4730	0.057	−0.121	−0.256	0.743	0.266	−0.208
	P^{*}		<0.001	<0.001	0.038	0.003	0.734	0.468	0.121	<0.001	0.1	0.210
Blood Sugar (mg/dl)	r^{**}		1.00	0.591	0.362	0.452	0.124	−0.133	−0.318	0.77	0.143	−0.144
	p^{*}			<0.001	0.025	0.004	0.457	0.427	0.052	<0.001	0.392	0.389
Urea (mg/dl)	r^{**}			1.00	0.221	0.465	0.324	0.096	−0.2	0.498	0.373	−0.129
	p^{*}				0.183	0.003	0.047	0.568	0.229	0.001	0.021	0.44
Creatinine (mg/dl)	r^{**}				1.00	−0.103	0.008	−0.199	−0.226	0.27	0.163	−0.313
	p^{*}					0.539	0.962	0.232	0.172	0.1	0.327	0.056
TG (mg/dl)	r^{**}					1.00	0.268	0.468	−0.517	0.167	0.353	−0.025
	p^{*}						0.103	0.003	0.001	0.317	0.03	0.884
Cholesterol (mg/dl)	r^{**}						1.00	0.638	−0.432	0.014	0.492	0.47
	P^{*}							<0.001	0.007	0.935	0.002	0.003
LDL (mg/dl)	r^{**}							1.00	−0.431	−0.172	0.241	0.346
	P^{*}								0.007	0.302	0.145	0.033
HDL (mg/dl)	r^{**}								1.00	−0.102	−0.451	0.059
HbA1C (%)	P^{*}									0.542	0.005	0.725
	r^{**}									1.00	0.026	−0.109
Age (year)	P^{*}										0.878	0.513
	r^{**}										1.00	−0.109
PRL (ng/dl)	p^{*}											0.513
	r^{**}											1.00
	p^{*}											

FBS= Fast Blood Sugar; TG = Triglycerides; LDL = Low Density Lipoprotein; HDL= High Density Lipoprotein; HbA1C = Hemoglobin A1C; r^{**} = Spearman rho Correlation Coefficient; $P^{*}<0.05$ = Considered as statistically significant.

Table 4
Significance level and correlation coefficient of blood factors in diabetic group using Spearman's rho.

Parameter		FBS (mg/dl)	Blood Sugar (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	TG (mg/dl)	Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	HbA1C (%)	Age (Year)	PRL (ng/dl)
FBS (mg/dl)	r^{**}	1.00	0.794	0.349	0.348	0.673	−0.17	−0.091	−0.394	0.842	0.261	0.334
	p^{*}		0.006	0.323	0.324	0.033	0.638	0.8	0.26	<0.01	0.467	0.345
Blood Sugar (mg/dl)	r^{**}		1.00	0.208	0.174	0.467	0.128	0.176	−0.345	0.879	0.442	0.365
	p^{*}			0.564	0.631	0.174	0.725	0.627	0.328	0.001	0.2	0.3
Urea (mg/dl)	r^{**}			1.00	−0.132	0.116	−0.337	−0.257	0.086	0.416	0.532	−0.288
	p^{*}				0.717	0.749	0.34	0.474	0.814	0.232	0.113	0.419
Creatinine (mg/dl)	r^{**}				1.00	0.696	0.567	0.261	0.087	0.348	0.348	0.262
	p^{*}					0.025	0.087	0.466	0.811	0.324	0.324	0.465
TG (mg/dl)	r^{**}					1.00	0.353	0.188	−0.212	0.564	0.236	0.377
	p^{*}						0.318	0.6	0.556	0.09	0.511	0.283
Cholesterol (mg/dl)	r^{**}						1.00	0.766	0.389	0.006	0.462	0.052
	p^{*}							0.001	0.266	0.987	0.179	0.887
LDL (mg/dl)	r^{**}							1.00	0.224	−0.139	0.273	−0.085
	p^{*}								0.533	0.701	0.446	0.815
HDL (mg/dl)	r^{**}								1.00	−0.37	0.394	−0.59
	p^{*}									0.293	0.26	0.073
HbA1c (%)	r^{**}									1.00	0.047	−0.204
	p^{*}										0.714	0.106
Age (Year)	r^{**}										1.00	−0.286
	p^{*}											0.424
PRL (ng/dl)	r^{**}											1.00
	p^{*}											

FBS= Fast Blood Sugar; TG = Triglycerides; LDL = Low Density Lipoprotein; HDL= High Density Lipoprotein; HbA1C = Hemoglobin A1C; r^{**} = Spearman rho Correlation Coefficient; $P^{*}<0.05$ = Considered as statistically significant.

to glucose and lacks the average tolerance of glucose [23]. The physiological increase of PRL by increasing mass of beta cells and sensitivity of liver to insulin [24,25] increases insulin secretion through glucose, and by increasing dopamine synthesis, hypothalamus has a direct impact on the regulation of glucose and improvement of energy [25,26]. The impact of the increase of PRL physiologically, and the increase of PRL pathologically is different on the metabolism of glucose. In diabetic mice, high level of PRL excites the whole body, increases the resistance of liver cells to insulin, and weakens the secretion capacity of insulin [25]. It causes prolactinemia in patients with hyperprolactinemia [27]. Generally, patients with pituitary prolactinemia probably had hyperglycemia with obesity and resistance to insulin. To return these complications, treatment with bromocriptine (dopamine Agonist) is suggested [27–29]. Wang et al. proved that the increase of PRL in serum physiologically is together with desirable metabolism of glucose which included lower amount of fasting plasma glucose (FPG), postprandial glucose (PPG), and HbA1C. By comparing the first, third and fourth quarter of PRL with high HOMA-B index they found that there is a relationship between PRL and activities of beta cells. Anyway, no linear relationship was observed between PRL quarters. Based on Wang et al. findings, it is concluded that the difference in serum PRL level has a relationship with the change of glucose metabolism in non-pregnant humans, which indicates that PRL plays an important role in defective metabolism of glucose. It is essential to carry out more research to know about the probable potential of PRL in pathogenicity by means of diabetes [12]. Although studies about PRL effects on type II diabetes and its complications are very few, the presented experimental studies show that PRL affects type II diabetes through metabolic effects on fat tissues [22,30], evolution and growth of pancreas beta cells [31,32], resistance to insulin [30,33], and fat metabolism [30,34]. PRL's ability in insulin stimulation, adiponectin suppression and reloading interleukin-6, show that PRL plays an important role in emergence of insulin resistance (HOMA-IR) [22]. Although these studies strengthen the idea that PRL stimulates the growth and life of beta cells in pancreas [31,32]. Other studies showed that there was no relationship between PRL and metabolic disorders [35]. Data from a cross sectional study on schizophrenic patients showed that high amount of dopamine and following that the low concentration of PRL have no relationship with the increase of the risk of type II diabetes, resistance to insulin, and IFG [36,37]. Therefore, it might be considered that the clozapine (an anti-psychotic) prevents the attack and development of type II diabetes by increasing the concentration of PRL through prohibiting type II diabetes receptor [38]. Anyway, as the previous studies were cross-sectional, identification of the factor and the effect of the relationship between PRL and type II diabetes is difficult in them [36,39,40]. In a study, it was proved that insulin secretion is the main sign of PRL increment [34]. In some studies on the changes of serotonergic pathways, it was proved that by decreasing the concentration of PRL MetS diseases increase [41,42]. Also it was shown that deficiency in PRL receptors in mice results in evolution of imperfect pancreatic beta cells and accordingly retarded reaction to insulin, and the moderate tolerance of glucose in those mice [32]. Contrary to our findings, studies on increase of PRL due to tumors secreting PRL (prolactinemia) showed that after treatment with dopamine agonists, the decrease of dopamine increases sensitivity to insulin [43,44]. However, the results were obtained from a statistical population including few patients with prolactinemia whose PRL concentration was out of normal range. Thus, the results cannot be generalized to the whole population. On the other hand, HOMA-IR as a criterion of resistance to insulin does not change after treatment with dopamine agonists [43], and the concentration of PRL has no relationship with HOMA-IR variations or decrease of glucose. It is worth mentioning that a cross-sectional study was performed on fat patients without prolactinemia, and the results showed that there was no relationship between concentration of PRL, insulin, HOMA-IR, and the amount of glucose [33,35]. The laboratory studies showed that PRL affects secretion of beta cells through increasing the activities of glucokinase [45], improves the viability of beta cells [46,47], and prevents the normal apoptosis of beta cells [48]. Balbach et al., in 2013 proved that the low concentration of PRL has a relationship with the high risk of type II diabetes in both sexes. Despite the variable relationship between PRL and type II diabetes, and not the relationship of PRL and MetS,

together with lack of longitudinal relationship with the two results, Balbach et al. findings did not prove that PRL as a cardiac-metabolic risk factor acts causatively. Therefore, it is supposed that PRL acts mostly as a marker for a set of variables engaged in attack and progress of type II diabetes. So it is essential to do more observations and interference studies to investigate the interaction of PRL on related risk factors [49].

5. Conclusion

Having selected the population in this study, blood sugar, FBS, HbA1C, cholesterol, triglyceride, LDL, HDL, Urea, and creatinine tests were performed. Then PRL was tested using ECL technique. As the physiological increase of PRL increases the secretion of insulin, it has an indirect impact on adjusting glucose and improving energy through increasing the synthesis of dopamine in hypothalamus. In the presented study, there was a reverse relationship between PRL level in serum and diabetes in women, and the relationship was statistically significant. In summary, the findings of this study are in accordance with findings of previous studies and it can be concluded that PRL can cause important glucose metabolic disorders and calls on more comprehensive studies to determine the potential effect of PRL in development of diabetes.

Conflicts of interest

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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