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ASSOCIATION OF SERUM PROLACTIN CONCENTRATIONS WITH RENAL FAILURE IN DIABETIC PATIENTS

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Abstract

Background and aims: *Diabetes is one of the causes of end-stage renal disease, so that about 70% of all diabetic patients have nephropathy. Prolactin is a hormone that is affected by diabetes but the interaction between diabetes and prolactin has not been understood properly. This study aimed to evaluate the relationship between changes in serum prolactin levels in diabetic patients with renal failure.* ***Material and methods:*** *In this study 223 individuals were participated and after assessment of inclusion/ exclusion criteria 189 individuals were evaluated. Finally, the individuals were divided into three groups: Control (C), Diabetic (D), and Diabetic Nephropathy (DN). Blood samples were collected between 8.00 a.m. and 12.00 a.m. for measurement of prolactin levels and biochemical analysis.* ***Results:*** *The results showed that sodium, potassium, urea, creatinine and prolactin significantly increased in DN group compared to control individuals (P< 0.001). The prolactin levels were significantly decreased in the group of patients with diabetes (P< 0.001).* ***Conclusion:*** *The results of the current study indicated that serum prolactin level decreased in diabetes while it increased in diabetic nephropathy.*

key words: *prolactin, diabetes, nephropathy, hemoglobin A1c*

Background and aims

Diabetes is one of the causes of end-stage renal disease, so that about 70% of all diabetic patients have nephropathy [1]. Diabetic nephropathy is one of the most important factors determining the severity of diabetes. Physiopathology of diabetes is complex and not fully identified. Evidence shows that endocrine system is altered in diabetes. Previous studies show that the overall performance of the endocrine system including hypothalamus, pituitary, thyroid, adrenal, and parathyroid and adipose tissue hormones impaired [2]. Prolactin

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(PRL) is a protein hormone that plays important role in the production of milk. PRL is not only important for lactation, but also involved in reproduction, growth and development, and plays a role in the regulation of osmolality and metabolism [3]. Many studies have been done about changes in PRL levels in diabetes but the results are somewhat contradictory. Induced diabetes in rats after delivery reduces the secretion of PRL followed by decreased milk production [4] and also reduces the secretion of PRL in response to breastfeeding [5]. Human studies have shown that in men with type one and two diabetes, PRL levels are normal [6] or increased [7] whereas the level is decreased in women with type one diabetes (T1DM) [8]. In some previous studies, there have not been differences between serum PRL levels in type one and two diabetes [7,9]. No correlations between PRL levels were observed with duration of diabetes and HbA1c level [9]. The results of some studies on type 2 diabetes (T2DM) suggest that PRL is effective on adipose tissue development and growth of pancreatic beta cells, insulin resistance and lipid metabolism [10,11]. Several studies have shown that PRL, regulates the transfer of ions and water from the cell membrane. Preliminary observations suggest that PRL reduces the transfer of sodium and increases potassium transport in epithelial cells in mammals [12]. In addition, other studies have shown that PRL regulates renal excretion of sodium; however, the results are inconsistent [13-15]. PRL receptors are present in many tissues, including the kidneys [16,17]. Dopamine plays an important role in the regulation of salt homeostasis. The PRL tyrosine kinase classic receptor carrying out regulatory effects of dopamine [18,19].

Altogether the interaction between diabetes and PRL, and the effect of renal failure in diabetic patients on PRL levels have not been understood properly. In this study, the relationship between changes in serum PRL levels in diabetic patients with renal failure has been evaluated.

Material and Methods

Study population:

This study was approved by the Ethics Committee of the Urmia university of medical sciences. In this study, 223 individuals from Mahabad city of west Azarbayjan province, a region in northwest Iran, were enrolled; after assessment of inclusion/ exclusion criteria 189 individuals were evaluated (66 men and 123 women, aged 19–87). Of the 223 baseline participants, we excluded participants due to: PRL not measured (n=15), pregnancy (n=4), hormone therapy (n=2), thyroid and liver disorders (n=6) and missing data (n=7).

After collecting precise information on medical history, female menstruation status, hormone replacement therapy (HRT), age and sex, in the final study sample of 189 individuals were divided to three groups: Control group (C), Diabetic group (D) and Diabetic Nephropathy group (DN). More information of the subjects in each of the groups is illustrated in Table 1.

Table 1. Data regarding gender and age in studied groups.

Study Groups	Total (M&F)	Male	*Female*	*Age (Mean ±SE)*	Age (Lower-Upper)
Control (C)	70	16	*54*	*40.11±1.4*	19-73
Diabetic (D)	74	21	53	54±1.1	21-74
Diabetic Nephropathy (DN)	45	29	16	64±1.9	33-87
Total	189	66	123	51.4±1	19-87

Biochemical analysis. Serum BUN, Creatinine, Na, K, Glucose and HbA1c measurement:

The concentrations of plasma urea and creatinine were measured using autoanalyzer (Selectra- XL, Netherland). Serum sodium and potassium were assessed by flame photometer (Corning 480). Serum glucose concentration was determined using the kit and autoanalyzer (Selectra- XL). HbA1c was determined by assay kit and the method of automated high-performance liquid chromatography analyzer chromatography (Eppendorf ECOM 6125, Germany).

Serum PRL Measurement:

Blood samples were drawn from the cubital vein between 8.00 a.m. and 12:00 a.m. and centrifuged at 3000 g at 5 ˚C for 10 min to separate sera then stored at 20 C until biochemical analysis. Serum PRL was determined from frozen sera of participants using chemiluminescent Immunoassay on an ELISA reader (Anthos 2020). Serum control was used for low, normal and high hormone level (Monobind, USA, Lot: MCA1A2, MCB1A2 and MCC1A2, respectively). For determination the deviation of the results before and after serum storage and for stability verification of PRL measurement, we randomly selected and measured PRL concentrations in fresh serum samples of some male and equal number of female participants after serum extraction. We retested PRL concentrations in the same samples. The laboratory reference range of PRL was 3.31–19.80 ng/mL for adult men and 5.4–24.2 ng/mL for adult women.

Statistical analysis

Distribution of data was checked by Kolmogorov–Smirnov test. Since distribution of data was normal, parametric test was used to analyze the data. Group differences were compared using a one-way analysis of variance followed by Tukey's test to determine differences between groups. Results were expressed as the mean ± S.E. of the mean. Differences were considered statistically significant at $p<0.05$.

Results

Table 2 shows the results of serum Sodium, Potassium, Urea and Creatinine. Sodium was significantly increased in diabetic nephropathy (DN) group compared with control subjects ($p<0.001$).

Table 2. Serum levels of Sodium, Potassium, Urea and Creatinine in study groups.

Study Groups	Na (mEq L^{-1})	K (mEq L^{-1})	Urea (mg dL^{-1})	Cr (mg dL^{-1})
Control (C)	136.7±0.39	4.30±0.03	24.52±0.86	0.84±0.01
Diabetic (D)	135.5±0.59	4.66±0.05*	29.36±0.95	0.92±0.01
Diabetic Nephropathy (DN)	139.9±0.80*†	5.13±0.1*†	85±22±6.30*†	2.51±0.25*†
** and † show significance differences with Control and Diabetic groups respectively. The results are in Mean ±SE and p < 0.001*				

There was no significant difference on sodium level between diabetic (D) and control(C) group. Potassium was significantly increased in diabetic nephropathy (DN) group compared with control and diabetic groups ($p<0.001$), and there was significant difference on potassium level between diabetic and control group ($p<0.001$). Urea level was non-

significantly higher in diabetic group compared with control subjects. Also, urea was significantly higher in diabetic nephropathy (DN) group compared with control and diabetic groups ($p<0.001$). The changes of creatinine in study groups were similar to urea changes. In diabetic nephropathy (DN) group creatinine was increased significantly in comparison with control and diabetic groups ($p<0.001$).

The results of blood glucose, hemoglobin A1c and PRL are presented in Table 3. Blood glucose level in diabetic (D) and diabetic nephropathy (DN) groups was significantly higher than that of control (C) group ($p<0.001$). Changes in hemoglobin A1c (HbA1c) in any groups was similar and in line with changes in glucose.

Table 3. Serum levels of Glucose and Hemoglobin A1c in study groups.

Study Groups	Glucose (mg dL^{-1})	Hemoglobin A1c (%)	
Control (C)	83.72±1.11	5.09±0.03	
Diabetic (D)	227.13±6.88*	9.21±0.20*	
Diabetic Nephropathy (DN)	217.62±15.53*	9.05±0.46*	
** shows significance differences with Control group* *the results are in Mean ±SE and p < 0.001*			

Table 4. Serum PRL concentration in study groups by individuals' gender.

Study Groups	Sex	Individuals	PRL(ng mL^{-1})
Control (C)	Male Female Total	16 54 70	8.66±0.86 12.62±1.09 11.72±0.89
Diabetic (D)	Male	21	7.12±1.43
	Female total	53 74	6.76±0.43 6.86±0.50*
Diabetic Nephropathy (DN)	Male Female total	29 16 45	13.31±1.05 18.09±3.23 15.01±1.35*†
** and † show significance differences between Control and Diabetic groups respectively.* *All data are in Mean ±SE and p < 0.05*			

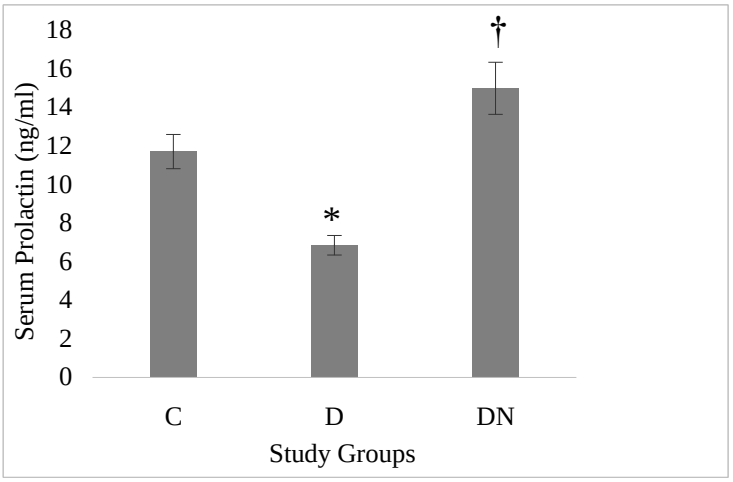

Figure 1. *Mean of Serum Prolactin levels (Control = C, Diabetic = D and Diabetic Nephropathy =DN)*
** and † shows a significant difference between C (P< 0.001) and D (p < 0.05) respectively.*

Evaluating the results of serum PRL levels showed that PRL was significantly lower in diabetic (D) group compared with control and diabetic nephropathy groups ($p<0.001$). Elevation of PRL level in diabetic nephropathy (DN) was significant compared with control and diabetic groups ($p=0.036$ and $p<0.001$ respectively, Figure 1 & Table 4). In healthy control group, serum PRL concentrations in females were higher than those of males (Table 4).

Discussions

The overall results of present study showed that serum sodium, potassium, urea, creatinine, blood glucose, hemoglobin A1c and PRL were significantly increased in diabetic Nephropathy (DN) patient. Also, the results show significant decrease in serum PRL level in diabetic patient.

As mentioned before altogether the interaction between diabetes and PRL, and the effect of renal failure in diabetic patients on PRL levels have not been understood properly. In this study, the changes in serum PRL levels in people with diabetes and diabetic nephropathy were assessed. As expected, blood glucose levels, glycosylated hemoglobin and potassium were significantly higher in diabetic patients than the control group. In the diabetic group compared with the healthy control group and diabetic nephropathy serum PRL significantly reduced. This study confirms the results of previous studies that have suggested plasma PRL decreases in early diabetes [4,8]. The decline may be due to pituitary damage and destruction of lactotroph cells in early stages of diabetes [20]. Tiange Wang et al have reported that a high circulating PRL level was significantly associated with a lower risk of prevalent diabetes in men and postmenopausal women [21]. With the assumption that PRL levels in normal subjects are influenced by sex, previous studies and literature suggest that the average blood PRL levels in females are slightly higher than males [22,23]. In this study, we also observed that a PRL level in healthy females was higher than healthy males. In current study, serum PRL level in patients with diabetic nephropathy was significantly increased compared with diabetic patients; this finding is a little more complicated.

In this study, we observed that blood levels of urea, creatinine, potassium and sodium in patients with diabetic nephropathy was significantly higher than those in people with diabetes and these findings suggest kidney damage in individuals. Another finding that the mean age of patients with diabetic nephropathy was higher than that of diabetic patients without nephropathy suggesting that diabetes has led to nephropathy over the time. Assessment of changes in PRL levels in patients with diabetic neuropathy was the main objective of this study and the results showed a significant increase of serum PRL levels in diabetic nephropathy compared with diabetic patients without nephropathy. The main finding of this study is that it increases blood PRL levels in diabetic patients with nephropathy. According to the influence of sex on PRL levels, PRL is normally higher in healthy female subjects. Despite the twice as much the number of females than males in diabetic group, a significant decrease in serum PRL was seen in this study, in turn, represents the lack of influence of individual's gender and confirms that diabetes itself was PRL-lowering condition. Moreover, in the diabetic nephropathy group the number of females was far less than males. So, high PRL levels in this group can not only be affected by sex, but PRL has been increased due to severe kidney damage or may be another factor. Our results are similar to the results of previous study that reported Cirrhosis and chronic renal failure cause hyperprolactinemia [24]. These abnormalities

may be inducing an increased level of PRL secretion and a decreased metabolic clearance rate [25]. PRL is normally metabolized in the kidneys and liver; and in case of diabetic nephropathy, it is likely that excessive accumulation of PRL in the blood cannot be discharged effectively and consequently leads to buildup of PRL in the blood.

Conclusions

The results of present study showed that serum PRL levels increases in diabetic patients with nephropathy. A probable mechanism can be either over production of PRL from its natural sources or low clearance of it in diabetes-induced damaged kidneys. Further detailed studies should be conducted to evaluate the precise mechanisms of increase of PRL in these patients.

Conflicts of interest. Authors have no conflicts of interests regarding this paper.

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