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Article

Oxytocin and Interleukin-14: New suggested indicators for prediction of type 2 diabetes-induced nephropathy

Rasha Hasan Jasim[1,], and Mohammed Abbas Khulaibus[1]*
[1] Department of Chemistry, Faculty of Education for Girls, University of Kufa, Iraq
** Correspondence: Email: rasha.alfahham@uokufa.edu.iq*
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ABSTRACT

Diabetes is one of the major risk factors for chronic renal failure (CRF). The present work involved studying the effect of lifestyle factors such as (age, gender, smoking and area of residence) which can affect chronic renal diseases. Also, the study estimated Oxytocin (Oxt) and Interleukin-14 (IL-14) using the sandwich ELISA technique in the serum of type 2 diabetic patients with CRF who presented to hemodialysis and a control group. Blood samples of (50) diagnosed type 2 diabetic patients with CRF from both sexes were compared with (40) samples from healthy individuals as a control group. The results demonstrated significant elevation ($p<0.05$) in Oxt and IL-14 concentrations for patients with CRF compared to the control group. As for the subgroups, the statistical test showed a significant difference ($p < 0.05$) when comparing Oxt levels between the same sex in the two groups. While no significant difference was observed when comparing IL-14 in the same or the two groups. The parameters Oxt and IL-14 are necessary tools for predicting renal failure.

Keywords: Oxytocin, Interleukin-14, Type 2 Diabetes Mellitus, Hemodialysis

INTRODUCTION

When the thickness of the kidneys increases and the elasticity of the internal structures of the kidneys, especially the glomeruli, decreases due to diabetes, this leads to damage and disorder of the kidneys, known as diabetic nephropathy. It is characterized by proteinuria and a gradual decrease in kidney function. Common names for this disorder are Kimmelstiel-Wilson disease, diabetic glomerulosclerosis, and diabetic kidney disease [1]. The complications of diabetes in the kidneys worsen; the number of hardened or destroyed glomeruli increases until the kidneys' ability to filter is impaired and protein leaks into the urine. With the passage of time and the development of complications caused by diabetes, we reach the stage of acute kidney failure, which, after several years, becomes chronic kidney failure [2]. The ability of beta cells to compensate for the lack of insulin decreases, which leads to the occurrence of T2D, and with the presence of insulin resistance, the formation of sugar increases, and the blood sugar level rises. It is not only obesity and insulin resistance that influence the risk of developing complications of type 2 diabetes [3]. The accumulation of tissue toxins,

as well as sorbitol (the reduced sugar product when it accumulates), leads to diabetic nephropathy and a genetic predisposition [4].

The Oxytocin (Oxt) molecules (the first peptide hormone to be biochemically described and synthesized) are components of a "natural medicine" capable of both preventing and treating various disorders and influencing a broad range of diseases. There is abundant evidence for diverse functions and health benefits of the molecule known as Oxt [5].

Oxt has been tested in treating conditions as apparently diverse as autism spectrum disorders, schizophrenia, postpartum depression, anxiety, cardiovascular diseases, and cancer [6]. Oxt's capacity of particular importance to promoting health and influence behavior is the growing evidence for the actions of Oxt throughout the immune system and its major role as an anti-inflammatory and antioxidant [7]. Effects on immunity and inflammation suggest another source of apparently "non-specific" effects of Oxt. Components of the immune system also control protein production, which regulates the capacity of Oxt to cross membranes [8].

Interleukin-14 (IL-14) is one of the subfamilies of a major family of inflammation-related proteins known as "cytokines" [9,10]. ILs have diverse and complex roles and are categorized according to their homology sequence, main functions, and receptors [11]. Through IL control of the immune system, it is associated with autoimmune dysfunction [12]. IL-14 is a member of a group of molecules called human B-cell growth factors (BCGFs). It can cause activated B-cell proliferation, which is a B-cell growth factor. Estimating the concentration of ILs is a good diagnostic tool for many human diseases, including cancers, heart diseases, neurological disorders, and kidney diseases [13]. This study highlighted the biological role of IL-14 and its involvement in the development of renal disorders.

MATERIALS AND METHODS

From the beginning of February to the end of July 2021, sera samples were collected from 90 individuals (50 diagnosed type 2 diabetic patients presented to hemodialysis and 40 healthy controls); their ages ranged between 40 and 70 years. Patient samples were collected from the dialysis center/teaching hospital in Al-Diwaniyah Governorate-Iraq before performing the dialysis process. Early diagnosis of this group was made clinically by specialists. Healthy individuals were selected as a control group based on several criteria. The two study groups were divided according to their gender and age. Table 1 summarizes the total information about the participants in the study.

The Sandwich ELISA technique was applied to quantify Oxt and IL-14 levels in the sera samples of study groups, using a Human Oxt ELISA Kit and a human IL-14 ELISA Kit prepared by Sun Long Biotech Company, LTD Laboratory, China. Statistical analysis of the results in the current study was done using version 24 of SPSS. The results were expressed in terms of mean ± SD. An independent student's t-test, where the statistical comparison was made between the two main study groups, while the ANOVA test was used to compare the results of the study subgroups. The results were statistically significant at a probability value less than 5%.

RESULTS

The current study included 90 individuals distributed in two main groups. The First is the type Π diabetic patients with renal failure undergoing dialysis. The Second group included the healthy individuals. The socio-demographic

characteristics of the present study groups are shown as observational data in Table 1.

Parameters	Type Π Diabetic Patients 50	Healthy Controls 40	*p-value*
Weigh (kg)	65.536±12.327	66.536±10.327	**0.091**
Height (m)	1.622±0.302	1.635±0.341	**0.082**
BMI (kg/m^2)	25.524±4.794	26.675±3.328	**0.095**
Age of Onset (years)	52.960±6.718	48.300±5.734	**0.130**
Familiar History (Yes/No)	37/13	6/34	-
Sex (Female/Male)	22/28	17/23	-
Treated/Untreated	41/9	-	-
Smoking (Yes/No)	31/19	3/21	-
Rural/Urban	**38/12**	**25/15**	-

Table 1. Detailed information about the participants in the study groups. The mean difference is significant at 0.05 level.

A significant variation (p=0.008) in Oxt concentration and (p=0.009) in IL-14 concentration was recorded when the patients and control groups were compared using an independent student's t-test, as shown in Table 2.

The Studied Parameter	Subjects(n)		*p-value*
	Patients (50)	Controls (40)	
	Mean ± S.D. Min-Max Range	Mean ± S.D. Min-Max Range	
Oxt (pg/mL)	121.714±67.726 56.200–397.500 341.300	59.867±17.171 31.200–116.300 85.100	0.008
IL-14 (ng/L)	23.230±22.493 6.100–122.800 116.700	16.850±5.311 5.300–28.200 22.900	0.009

Table 2. Oxt (pg/ml) and il-14(ng/l) in the study individuals. The mean difference is significant at 0.05 level.

The comparison among the sub-study groups was carried out using the analysis of variants (ANOVA) test. The elevation in the Oxt levels in the female patients compared to their peers in the control subgroup was observed (p=0.003). The same results were recorded when the two male subgroups were compared (p=0.000). Also, a significant difference was recorded when the two genders in the patient group were compared together (p=0.030). At the same time, the results of IL-14 were dissimilar to those in the Oxt measurement, as shown in Table 3.

The Studied Parameter	Subjects (n)			
	Patients (50)		Controls (40)	
	Female (22)	Male (28)	Female (17)	Male (23)
	Mean ± S.D. Min-Max Range	Mean ± S.D. Min-Max Range	Mean ± S.D. Min-Max Range	Mean ± S.D. Min-Max Range
	p-value			
Oxt (pg/mL)	103.023±24.863 56.200–161.200 105.000	135.248±84.461 61.700–397.500 335.800	52.700±13.155 31.200–78.000 46.800	**65.165±18.104** **36.200–116.300** **80.100**
	1vs2 **0.030**	**2vs4** **0.000**	**1vs3** **0.003**	**3vs4** **0.445**
IL-14 (ng/L)	20.414±24.175 6.100–122.800 116.700	25.269±21.394 8.900–103.800 94.900	15.058±5.352 8 .900–28.200 19 .300	18.173±4.986 5.300–25.800 20.500
	1 vs 2 **0.328**	**2 vs 4** **0.144**	**1 vs 3** **0.343**	**3 vs 4** **0.573**

Table 3. Oxt (pg/ml) with il-14 (ng/l) levels in the study subgroups. 1: Diabetic female patients with renal failure, 2: Diabetic male patients with renal failure, 3: Healthy female control, and 4: Healthy male control. The mean difference is significant at 0.05 level.

Patients with Diabetic nephropathy have a predominance of increased plasmatic and urinary levels of inflammatory mediators. The extent of renal damage caused by immune cell-derived cytokines and chemokines and the importance of such inflammatory mechanisms on the development and progression of Diabetic nephropathy requires further investigation. Renal biopsies are considered the gold standard for the diagnosis of glomerulopathies.

The present study recorded a clear increase in Oxt levels in patients undergoing dialysis compared to the control group and a slight increase in the levels of IL-14 (male patients in particular) compared to healthy individuals. This increase may be reversing for inflammatory states induced by renal failure. Thus, it can be described as a predictive function of renal failure based on the increased levels in the results in patients.

In addition to increasing the correlation between Oxt expression and interstitial inflammation in diabetic nephropathy patients, the results of the present work showed a significant positive correlation between Oxt and IL-14 with (r=0.770) for patients group, (r=0.391) for the health controls group, as shown in **Table 4**.

Subjects (n)	The Studied Parameter		*p-value*
	Oxt (pg/mL)	**IL-14 (ng/L)**	
	Pearson Correlation		
Patients (50)	0.770**		**0.000**
Controls (40)	**0.391***		**0.013**

Table 4. the relationship of correlations(r) for oxt (pg/ml) with il-14 (ng/l) in patients and healthy controls groups of the study individuals

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a common endocrine disease characterized by hyperglycemia and insulin resistance. Excess glucose and nutrient intake lead to oxidative stress, which induces elevated levels of pro-inflammatory cytokines. These increased cytokines result in impaired insulin action on peripheral glucose metabolism. However, cytokines are involved in the development of insulin resistance [14]. Moreover, further studies using this type of sample to investigate mechanisms associated with the expression of inflammatory mediators involved in Diabetic nephropathy pathogenesis are required [15].

CONCLUSIONS

Oxt and IL-14 may be good prognostic parameters of nephropathy induced by DM complications.

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