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Study the levels of adiponectin, FSH, LH and Sex hormones in Type 2 diabetes (NIDDM)

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Abstract

The hypothalamic/pituitary/gonadal (HPG)axis is central to the mammalian reproductive system . Pulsatile release of GnRH from neurons in the hypothalamus stimulates the secretion of LH and FSH from gonadotropes in the anterior pituitary. It has long been recognized that reproductive function is closely associated with energy balance, and metabolic dysregulation is linked with reproductive abnormalities (Lu *et al*.,2008). Compare the differences in levels of adiponectin, FSH, LH, testosterone and estradiol between the diabetic patients and control group and in diabetic patients according to the durations of disease for both males and females groups .Also study the relationship between adiponectin and hormones for both gender and for both diabetic groups and control also in diabetic patients according to the durations of disease. About five milliliters of venous blood were collected from each subject in the study. The blood was separated by centrifugation at (3000 rpm) for 15 min. The sera were stored frozen at (-20 ºC) until assayed. This study was conducted between November 2010- November 2012 and, it was carried out at the diabetic Centre / Merjan Teaching Hospital in Babel Province, by taking 120 diabetic patients non- insulin dependent diabetes mellitus (NIDDM) (60 male and 60 female)with disease durations(0-5),(>5-10)and (>10)years ,and with age average (35-65 year), most of them were on oral hypoglycemic drugs, and the study included 40 people apparently healthy that included 20 male and 20 female with age average (35-65 year) ,as control matched with disease groups. The statistical analysis of this study showed that patients with Type 2 diabetes of both males and females had significantly lower in adiponectin levels than control group ($P<0.05$),but this level of adiponectin significantly higher in females than males for both diabetic groups and control ($p<0.05$) ,while the levels of FSH and LH had significantly higher in diabetes group than control ($p<0.05$) ,also significantly higher in females than males for both diabetic groups and control ($P< 0.05$). The result of hormonal analysis show there were no significant differences in estradiol and testosterone between diabetic groups and control ($p > 0.05$). According to the durations of disease, the results show significant elevation in adiponectin level in third duration of disease for both males and females groups as compared with first and second duration ($P <0.004$), while the levels of FSH, LH ,estradiol and testosterone show no significant differences among duration($P>0.05$). According to the gender ,levels of adiponectin ,FSH, LH, and estradiol were significantly higher in females than males($P<0.05$) , whereas levels of testosterone was significantly higher in males than females ($P<0.05$) . Correlation analysis showed an inverse correlation between adiponectin and FSH in female diabetic patients. Also an inverse correlation between adiponectin and estradiol was found in females of control group, while the correlation of LH and testosterone with adiponectin appears no significant correlation for both groups and for both males and females . According to the durations of disease, in first duration (0-5year)the study revealed positive correlation between adiponectin and FSH in male diabetic patients . In third duration (>10 year) an inverse correlation between adiponectin and FSH in female diabetic patients. The result also appears no significant correlation among adiponectin and LH,

estradiol and testosterone in both gender among duration . The results of the present study indicate that the patients with Type 2 diabetes of both males and females had significantly lower in adiponectin levels than control group . levels of adiponectin significantly higher in females than males for both diabetic groups and control. Adiponectin levels significantly increased with duration of disease also with age. Levels of FSH and LH had significantly higher in diabetic patients than control also significantly higher in females than males for both groups . Correlation analysis showed inverse correlation between adiponectin and both FSH and estradiol in female diabetic patients also inverse correlation between adiponectin and both FSH and estradiol in third duration of female diabetic patients.

1. Introduction

Adiponectin was first identified in 1995, circulates at relatively high concentration of 2 to 30 µg/ml in blood, accounting for up to 0.01% of total plasma protein in humans (Daimon *et al*.,2003;Shimada *et al*., 2004; Kadowaki *et al*.,2006 ; Heidemann *et al*.,2008). Adiponectin is lower in men than women, possibly as a result of suppression by androgens .Moreover, women have higher proportions of high molecular weight adiponectin than men (Gavrila *et al*.,2003 ; Snijder *et al*.,2006). Adiponectin exists in awide range of multimer complexes in plasma and combines via its collagen domain to create 3 major oligomeric forms: a low–molecular weight (LMW) trimer ,a middle - molecular weight(MMW) hexamer ,and high-molecular weight(HMW) 12-18-mer adiponectin. Several observations support the hypothesis that HMW adiponectin is the more active form of the protein and has a more relevant role in insulin sensitivity and in protecting against diabetes (Shimada *et al*.,2004; Kadowaki, *et al*.,2006 ; Heidemann *et al*.,2008). Testosterone (T) regulates many important physiologic processes, including muscle and fat metabolism, sexual development and function, erythropoiesis, and bone metabolism . Both T replacement therapy for hypogonadism and supraphysiologic administration of T are associated with increases in lean body mass, decreases in fat mass, and increases in muscle strength .T administration reduces overall fat mass and has been reported to decrease central adipose stores. . In mice, castration increased adiponectin levels and insulin sensitivity, effects neutralized by the coadministration of T, whereas ovariectomy had no effect on female mice , implying a role for T in adiponectin regulation in male mice. Together, these studies suggest that T might negatively regulate adiponectin production or serum half-life (Page *et al*.,2005 ; Hugo *et al*.,2008). In study of Tsujimura *et al*.,(2009) refer to inversely relation between adiponectin levels and testosterone in rodents and humans. Insulin is a negative regulator of liver secretion of sex hormone binding globulin(SHBG) . The concept has emerged that SHBG could be an interesting marker of insulin sensitivity in humans , and SHBG level has therefore been included as such among the biochemical markers for the risk of developing type 2 diabetes or cardiovascular diseases(Ducluzeau *et al*., 2003). An inhibitory effect of insulin on SHBG secretion also has been reported by Bonnet *et al*.,(2009), suggesting that increased hyperinsulinemia could decrease SHBG concentration. Arecent study showed that monosaccharide , including glucose or fructose, regulate human SHBG gene expression .The reduction of SHBG secretion in response to increased concentrations of glucose may provide amechanism for the link between low-plasma levels of SHBG and insulin resistance. There is a specific receptor for adiponectin in the liver, suggesting the potential implication of adiponectin in the regulation of the secretion of SHBG.

Materiales and Method

About five milliliters of venous blood were collected from each subject in the study. The blood was separated by centrifugation at (3000 rpm) for 15 min. The sera were stored frozen at (-20 ºC) until assayed.

To determine the serum adiponectin, FSH, LH, estradiol and testosterone the quantitative sandwich enzyme immunoassay technique were used. Moreover, the blood samples were taken in the morning exactly between 08:00 and 10:00 h, minimizing the effect of diurnal variation (Tenhola *et al*.,2010).

Adiponectin / Principle of assay A monoclonal antibody specific for the adiponectin globular domain has been pre-coated onto amicroplate. Standards and sample are pipette into the wells and any adiponectin present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for the adiponectin globular domain is added to the wells. Following awash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of adiponectin bound in the initial step. The color development is stopped and the intensity of the color is measured (R & D systems, Inc., Minneapolis, MN, USA) .

Statistical Analysis:

Analysis were performed using the Statistical Package for Social Sciences (SPSS version 18.0). Hormonal data were analyzed with durations of disease and with age using Factorial experiment with completely randomized design with three factors ,while analyzed between groups using Factorial experiment with completely randomized design with two factors . Data were represented as mean ± SE. Bivaraite correlations were performed using the Pearson correlation coefficient .P value ($P<0.05$) was considered statistically significant .

Results:

The results of present study show there were significant differences in adiponectin level and some hormones levels between the diabetic groups and control.The mean adiponectin concentration differ significantly between two groups. Patients with Type 2 diabetes of both male and female had significantly lower levels of adiponectin concentration than control group ((3.84 ± 0.17) vs. (4.15 ± 0.3) and (5.81 ± 0 .3) vs.(7.3 ± 0.17) (µg/ml)) ($P<0.05$) ,while the levels of FSH and LH had significantly higher in diabetes group than control($p<0.05$). Also the result of hormonal analysis show there were no significant differences in estradiol and testosterone levels between diabetic patients and control ($p > 0.05$) as shown in Table(1). Levels of adiponectin and hormones according to gender had significantly differences in diabetes mellitus .Serum adiponectin concentration was significantly higher in females than males for both control and diabetic groups ((5.81 ± 0.17) vs. (3.84 ± 0.17) (µg/ml)) and (7.3 ± 0.3) vs. (4.15 ± 0.3) (µg/ml)) ($p<0.05$).The levels of FSH, LH and estradiol were significantly higher in females than males for both diabetic groups and control ($P< 0.05$), whereas the testosterone concentration was significantly higher in males than females for both groups ((8.36 ± 0.07) vs. (0.68 ± 0.07) (ng/ml)) and ((7.58 ± 0.06) vs. (1.36 ± 0.06) (ng/ml)) respectively ($P<0.05$) as shown in Table(1).

Discussion

The result of present study show that the patients with Type 2 diabetes of whether male or female had significantly lower in adiponectin concentration than control group and the levels of adiponectin was higher in female than male for both groups (Table 1), this may be due to a number of factors, one of them was the diabetic patients had decreased high molecular weight (HMW) -to- total adiponectin ratio, and HMW adiponectin correlated better with glucose tolerance than total adiponectin also the HMW was acted the active form of this protein . Women have more HMW adiponectin than men, which may partly explain the differences that we have found between men and women (Snijder *et al*.,2006).

Also decreased in adiponectin levels in diabetic patients may due to elevated plasma insulin in diabetic subjects in onset of diabetes and the insulin was down-regulated adiponectin mRNA expression ,and it has been found that the hyperinsulinemia associated with higher levels of adiponectin in Type 1 DM(Hotta *et al*.,2000 ; Huerta,2006; Habeeb *et al*.,2012). Testosterone(T) decrease adiponectin level by sequestering ARA70, acoactivator common to both the androgen receptor (AR) and peroxisome proliferator–activated receptor gamma 1 (PPARg1,2). The AR, and ARA70 are all expressed in human adipocytes, and ARA70 is upregulated during adipocyte differentiation, a PPARg-mediated process. In this model, interaction of the AR with T might compete with PPARg for ARA70, resulting in reduced expression of PPARg-regulated genes such as adiponectin (Page *et al*.,2005). Mankowska *et al*.,(2008) indicate to human plasma adiponectin concentration is associated with sex and is significantly higher in weman than in men. This sexual dimorphism develop during pubertal development in relation to serum androgen. The result of this study agree with the study of Bai *et al*.,(2011) that found the patients with Type 2 diabetes have lower adiponectin serum concentration than healthy individuals. In diabetic patients and according to the duration of disease the results show significant elevation in adiponectin levels in third duration of disease for both males and females groups as compared with first and second duration(Table 2) ,this differences belong to that adiponectin is lowest in the presence of impaired glucose regulation and early diabetes, whereas long diabetes duration is associated with a significant increase in circulating adiponectin, changes in insulin concentration with increasing duration of diabetes could be one mechanism by which serum adiponectin is influenced by diabetes duration (Looker *et al*.,2004 ; Eynatten *et al*.,2009). Also study show the patients with Type 2 diabetes had revealed defect in hypothalamic than pituitary axis .Levels of FSH and LH significantly higher in diabetes group than control ($P<0.05$), while the levels of estradiol and testosterone show no significant differences between groups (Table 4),this is because that insulin is known to facilitate gonadotropin-releasing hormone (GnRH) secretion by hypothalamic neurons(Dhindsa *et al*.,2011). In study by Ermetici *et al*.,(2009) indicated to the insulin-like factor 3 (INSL3), a member of the insulin–relaxin superfamily of peptide hormones, has been used as a specific marker of Leydig cell differentiation and function, since it appears more sensitive than testosterone itself in evaluating function . The global impairment of Leydig cell function in T2DM is confirmed by the finding of reduced circulating levels of INSL3, a novel peptide hormone mainly derived from Leydig cells, which have been indicated as an absolute measure of either quality or number of the Leydig cells, independently from gonadotropin stimulation . The higher LH levels in diabetic patients than in controls might suggest that when few or poor-quality Leydig cells are present, more LH is required to achieve normal circulating testosterone levels. Since the presence of the INSL3 receptor has been demonstrated at pituitary level, a possible negative feedback of INSL3 has also been hypothesized. Also may be because that leydig cells and follicle cells become resistant to gonadotropin hormone as aresult higher levels of FSH and LH with low normal range of estradiol and testosterone in diabetic patients. The result show no significant differences in testosterone concentration between control and diabetic patients whereas the average testosterone concentration was significantly higher in males for both groups than in females and in diabetic pateints among duration(Table 1 and 2),this result agreement with study of Bia *et al*.,(2011) that found there were no significant differences in mean testosterone concentration between the diabetic patients Type 2 and control group , also found that in both patients and control group average testosterone concentration was higher in males than females. These result also show no significant differences between the diabetic patients Type 2 and control group in estradiol concentration which supported by study of AL-Saadi,(2005) that found no significant differences in the levels of estradiol hormone between women with Type 2 diabetes and healthy women in postmenopausal age. According to the gender ,levels of FSH ,LH and estradiol were significant higher in females than males for both control and diabetic

group and in diabetic group among duration of disease(Table 1 and 2) .Bonnet *et al*., (2009) refer that sex hormone-binding globulin levels(SHBG) was higher in females than males for both control and diabetic groups which made the percentage of free estradiol and the negative feedback mechanism in female was highly than in males which may cause the levels of FSH and LH became highly in females than males. In diabetic patients according to the duration of disease, levels of FSH, LH ,estradiol and testosterone show no significant differences among duration (Table 2) .Higher levels of FSH, LH ,estradiol and testosterone in first duration in males and in second duration in females causes lower levels from adiponectin in this duration but this changes not reach to the significant value. Changes in insulin concentration with increasing duration of diabetes and because the insulin is known to facilitate gonadotropin-releasing hormone (GnRH) secretion by hypothalamic neurons (Looker *et al*.,2004 ; Dhindsa *et al*.,2011) . An inverse correlation between adiponectin and FSH in female diabetic patients(Table 3) also in third duration of female diabetic patients(Table 4) ,while the correlation of LH with adiponectin appears no significant correlation for both groups and for both males and females (Table 3) and in diabetic patients among duration(Table 4) ,this is because that adiponectin decreases basal and GnRH-stimulated LH secretion via activation of AMPK. A decrease in cellular ATP activates AMPK that, in turn, inhibits energy-requiring processes and stimulates ATP production by increasing glucose uptake and fatty acid oxidation .Trafficking and fusion of secretory vesicles is ATP dependent, so may be directly inhibited by AMPK. Alternatively, the calcium increases essential for stimulating secretion may be blocked (Lu *et al*., 2008). Adiponectin is present in follicular fluid and induces cyclooxygenase 2,prostaglandin E synthase, vascular endothelial growth factor, and steroidogenic acute regulatory protein mRNAs(Lu *et al*., 2008),this may be result that adiponectin affected in FSH levels more than LH, which may be explain this inverse correlation between adiponectin and FSH also with LH level but in this study not reach to significant levels. An inverse correlation between adiponectin and estradiol was found in females of control group(Table 3), because the estrogen may be involved in adipose tissue disposition and regulation preadipocyte proliferating and differentiation ,thus, could reduce adiponectin (Tworoger *et al*.,2007).

This result supported by result of (Gavrila *et al*., 2003) that found adiponectin has been inversely associated with estrogen levels in healthy women. Despite the negative association between estradiol and adiponectin, it has been reported that women have higher adiponectin levels compared with men , suggesting that in addition to estrogens, other gender-dependent factors, such as body fat distribution or androgen may be of relevance.

Table(1): Differences in levels of adiponectin and some hormones between Type 2diabetic patients and control and between gender.

Groups / Indices	Control (Means± S.E.)		Diabetes groups (Means± S.E.)		P value of gender	P value of group
	Male	Female	Male	Female		
Adiponectin(µg/ml)	4.15 ± 0.3	7.3 ± 0.3	3.84 ± 0.17	5.81 ± 0.17	0.00*	0.04*
FSH(mIU/ml)	8.78 ± 0.3	31.6 ± 0.3	28.01 ± 4.79	38.62 ± 4.79	0.008*	0.03*
LH(mIU /ml)	4.63 ± 0.36	12.53 ± 0.36	6.94 ± 0.36	18.23 ± 0.36	0.00*	0.04*
Estradiol(pg/ml)	21.53 ± 4.95	32.13 ± 4.95	21.07 ± 4.59	35.02 ± 4.59	0.05*	0.85
Testosterone (ng/ml)	8.36 ± 0.07	0.68 ± 0.07	7.58 ± 0.06	1.36 ± 0.06	0.00*	0.27
Testosterone (ng/ml)	8.36 ± 0.07	0.68 ± 0.07	7.58 ± 0.06	1.36 ± 0.06	0.00*	0.27

P value is significant ≤ 0 .05 level. S.E :Standard error

According to the durations of disease, the results show significant elevation in adiponectin level in third duration of disease for both males and females groups (4.28 ±0.31) and (7.6 ± 0.31) as compared with first and second duration (3.35 ± 0.31),(3.89 ± 0.31)and(5.38 ± 0.31) ,(4.44± 0.31) respectively (P <0.004), while the levels of FSH, LH ,estradiol and testosterone show no significant differences among duration(P>0.05). According to the gender ,levels of adiponectin ,FSH, LH, and estradiol were significantly higher in females than males(P<0.05) , whereas levels of testosterone was significantly higher in males than females (P<0.05) as shown in Table (2).

Table(2): Comparison of adiponectin levels and some hormones of Type 2diabetic patients among durations of disease and between gender

Indices	Diabetes groups (Means± S.E.)						P value of gender	P value of duration
	0-5		>5-10		>10			
	Male	Female	Male	Female	Male	Female		
Adiponectin (µg/ml)	3.35 ± 0.31	5.38 ± 0.31	3.89 ± 0.31	4.44 ± 0.31	4.28 ± 0.31	7.6 ± 0.31	0.002*	0.004*
FSH(mIU /ml)	18.16 ± 0.34	36.18 ± 0.34	29.8 ± 0.34	41.31 ± 0.34	36.06 ± 0.34	38.39 ± 0.34	0.008*	0.055
LH(mIU l/ml)	8.52 ± 0.31	15.55 ± 0.31	5.56 ± 0.31	22.95 ± 0.31	6.72 ± 0.31	16.18 ± 0.31	0.00*	0.17
Estradiol (pg/ml)	21.17 ± 4.17	33.98 ± 4.17	20.98 ± 4.17	38.71 ± 4.17	21.07 ± 4.17	32.38 ± 4.17	0.02*	0.97
Testosterone (ng/ml)	8.48 ± 0.09	1.58 ± 0.09	6.00 ± 0.09	1.00 ± 0.09	8.25 ± 0.09	1.51 ± 0.09	0.00*	0.22

P value is significant ≤ 0 .05 level. S.E :Standard error

Correlation analysis showed an inverse correlation between adiponectin and FSH in female diabetic patients (r= -0.35,P= 0.03).Also an inverse correlation between adiponectin and estradiol was found in females of control group, while the correlation of LH and testosterone with adiponectin appears no significant correlation for both groups and for both males and females as shown in Table (3) .

Table(3): Correlation analysis between adiponectin and some hormones of Type 2diabetic patients and control.

Groups / Indices	Adiponectin(µg/ml) Control groups				Adiponectin(µg/ml) Diabetes groups			
	Male		Female		Male		Female	
	r	P value	r	P value	r	P value	r	P value
FSH(mIU /ml)	0.35	0.34	-0.42	0.24	-0.01	0.94	-0.35*	0.03
LH(mIU /ml)	0.25	0.5	-0.41	0.26	0.01	0.92	-0.19	0.34
Estradiol(pg/ml)	-0.67	0.54	-0.25*	0.05	0.06	0.74	-0.14	0.47
Testosterone (ng/ml)	0.59	0.09	0.5	0.16	-0.03	0.88	0.17	0.37

Correlation coefficient (r)

*. Correlation is significant ≤ 0.05 level (2-tailed).

According to the durations of disease, the study revealed in male diabetic patients positive correlation between adiponectin and FSH in first duration was found(r= 0.78,P= 0.01 .In female diabetic patients an inverse correlation between adiponectin and FSH in third duration of female diabetic patients(r= -0.75,P= 0.01) and (r= -0.67,P= 0.04) respectively, The results appears no significant correlation between adiponectin with LH, estradiol and testosterone in both sex among duration as shown in Table (4) .

Table(4): The relationship between adiponectin and hormones of diabetic patients Type 2 according to the durations of disease

Indices	Adiponectin(µg/ml) Diabetes groups											
	0-5				>5-10				>10			
	Male		Female		Male		Female		Male		Female	
	r	P	r	P	r	P	r	P	r	P	r	P
FSH (mIU /ml)	0.78*	0.01	-0.4	0.28	0.15	0.68	-0.11	0.77	-0.26	0.48	-0.67*	0.04
LH(mIU /ml)	0.56	0.11	-0.14	0.7	0.25	0.51	0.02	0.95	0.15	0.68	-0.1	0.79
Estradiol (pg/ml)	-0.15	0.69	-0.25	0.5	-0.07	0.84	-0.23	0.55	0.3	0.42	0.02	0.95
Testosterone (ng/ml)	-0.19	0.6	0.08	0.83	0.64	0.06	-0.28	0.45	-0.35	0.35	0.17	0.65

Correlation coefficient (r) *. Correlation is significant ≤ 0.05 level (2-tailed).

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