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Study the relationship between adiponectin with thyroid hormones and cortisol in Type 2 diabetic patients (NIDDM)

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ABSTRACT

Thyroid hormones has profound effects of lipid metabolism and carbohydrate homeostasis . Abnormalities in serum lipids and lipoproteins are frequent findings in thyroid dysfunction, mainly in hypothyroidism. Impaired glucose tolerance and insulin resistance have been documented in patients with thyroid dysfunction. In addition, thyroid hormones are remarkable regulators of energy metabolism, being the adipose tissue the largest fuel storage compartment. Furthermore, thyroid hormones share some physiological actions with adiponectin, such as reduction of body fat by increasing thermogenesis and lipid oxidation .However, a few number of studies have found low adiponectin levels in hypothyroid subjects (Díez and Iglesias, 2009). Cortisol excess in man is characterized by abdominal obesity, hypertension, glucose intolerance or diabetes and dyslipidemia. All these features share a state of insulin resistance, and contribute to high cardiovascular risk typical of this condition. Glucocorticoids negatively regulate adiponectin mRNA in human visceral adipose tissue. Cortisol counteracts the action of insulin at multiple sites, and increases hepatic gluconeogenetic efficiency (Fallo *et al*.,2004). Study the relationship between adiponectin with thyroid hormones and cortisol for both gender and for both control and diabetic groups also in diabetic patients according to duration of disease. 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(Type II DM) (60 male and 60 female) with disease duration (0-5),(>5-10)and (>10)years ,with age average (30-65 year)and most of them were on oral hypoglycemic drugs. While the study included 40 people apparently healthy that included 20 male and 20 female with age average (30-65 year).

Introduction

The classical perception of adipose tissue as a storage place of fatty acids has been replaced over the last years by the notion that adipocytes and adipose tissue produce a wide range of hormones and cytokines involved in glucose metabolism (e.g. adiponectin, resistin), lipid metabolism (e.g. cholesteryl ester transfer protein, CETP), inflammation (e.g. TNF-a, IL-6), coagulation (PAI-1),blood pressure (e.g. angiotensinogen , angiotensin II), and feeding behaviour (leptin) ,thus affecting metabolism and function of many organs and tissues including muscle, liver, vasculature, and brain. Plasma adipocytokine levels rise with an increase in adipose tissue and adipocyte volume, except for plasma adiponectin which is lower in obesity. These adipocyte products acting in autocrine, paracrine and endocrine ways, are capable of influencing not only local adipocyte physiology, but also the function of different organ systems (Hajer *et al*.,2008 ; Díez and Iglesias, 2009).

Adiponectin encoded by gene APM1which has been mapped to chromosome 3 q 27 ,consist from 244 amino acid, abundantly synthesized and secreted by the adipose tissue ,and has structural homology to complement factor C1q and collagen VIII and X (Nedvidkova *et al*.,2005). Murine studies show the half-life of circulating adiponectin to be 75 minutes with clearance mediated by the liver (Robinson *et al*., 2011). 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).

Thyroid hormones influence many aspects of reproduction, growth, differentiation, and metabolism. Many of these actions occur cooperatively with other hormones, and the thyroid hormones enhance their effectiveness. This cooperative role for thyroid hormones is referred to as apermissive action whereby thyroid hormones produce changes in target tissues that “allow” these tissues to be more responsive to another hormone. The importance of thyroid hormones is reflected in the observation that the incidence of thyroid disease in humans is exceeded only by the incidence of diabetes mellitus .Under normal conditions, circulating T4 levels are much greater than T3 levels (Norris,2007).

Thyroid hormone excess is associated with weight loss, reduction in fat mass, depletion in lipid storage and reduction of some serum lipids. Glucose intolerance and insulin resistance are also frequent findings in patients with thyrotoxicosis. In rats, adiponectin concentrations correlated positively with serum T4

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and T3 and negatively with TSH. A positive correlation between adiponectin and free T4 in patients with hyperthyroidism before and after treatment has also been reported.It has also been suggested that elevated levels of adiponectin in hyperthyroid patients might be the result of stimulating action of thyroid hormones on transcriptional induction of adiponectin through PPARγ pathway, and it could be a crosstalk between PPAR and thyroid hormone signalling pathways (Fernandez-Real *et al*., 2003).

One postulated mechanism for anti-inflammatory of glucocorticoid is the glucocorticoid-induced inhibition of the kallikreins, enzymes which catalyze formation of kinins from a plasma precursor protein. Kinins induce inflammation by causing release of histamine normally observed following the combination of antigen and antibody. Another suggestion for glucocorticoid anti-inflammatory activity stems from observations of their effects on lysosomes. Glucocorticoids causes stabilize lysosomal membranes, thereby reducing release of hydrolytic enzymes following cell injury and hence reducing the spread of the inflammatory reaction. Inhibition by glucocorticoids of the cyclooxygenase enzyme necessary for prostaglandin synthesis reduces prostaglandin induction of inflammation. Glucocorticoids also inhibit the synthesis of cytokine agents (e.g., interleukins) that mediate inflammation and cell-mediated immune responses (Norris,2007).

In study of Venkatesh *et al*.,(2009) on healthy volunteers refer to asignificant positive relation between plasma cortisol and adiponectin, particularly in males.

Sundbom *et al*.,(2008) indicate that patients with type 2 diabetes have high intracellular levels of glucocorticoids . Glucocorticoids have been shown to decrease the levels of adiponectin in animal models and in humans.

In study by Lehrke *et al*.,(2008) indicated that increased in cortisol levels causes diabetes because the cortisol increased glucose availability by augmentation of hepatic glucose production via transcriptional and post-transcriptional activation of gluconeogenic enzymes including glucose-6-phosphatase and phosphoenolpyruvate. In addition, cortisol inhibits glucose uptake and utilisation by peripheral tissues and cortisol excess impairs glucose tolerance and causes diabetes.

Materials 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 used for measurement of lipid profile while the remaining stored frozen at (-20 ºC) until assayed.

To determine the serum adiponectin, cortisol, TSH, T3 and T4 the quantitative sandwich enzyme immunoassay technique were used.

Statistical Analysis

Analysis were performed using the Statistical Package for Social Sciences (SPSS version 18.0). Data were represented as mean ± SE. Bivaraite correlations were performed using the Pearson correlation coefficient .P value (P<0.05) was considered statistically significant.

Result:

Correlation analysis showed an inverse correlation between adiponectin and cortisol in female diabetic patients(r= -0.36,P= 0.05) ,while in male diabetic patients there was positive correlation between adiponectin and T4 was found(r= 0.46,P= 0.01) . The correlation of TSH and T3 with adiponectin appears no significant correlation for both groups and for both males and females as shown in Table (1) ,Figure (1) and Figure(2).

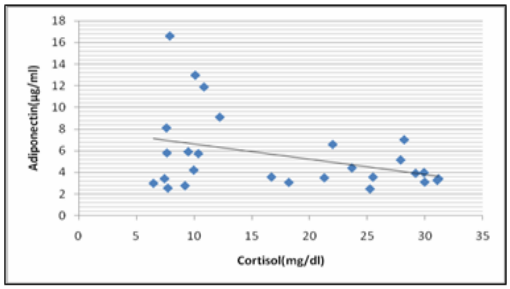
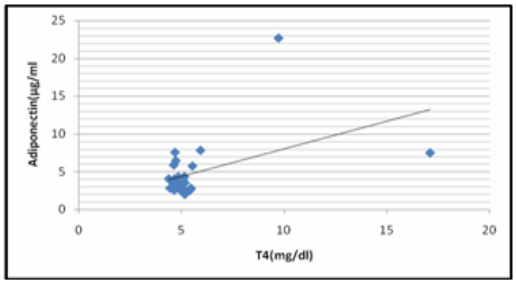
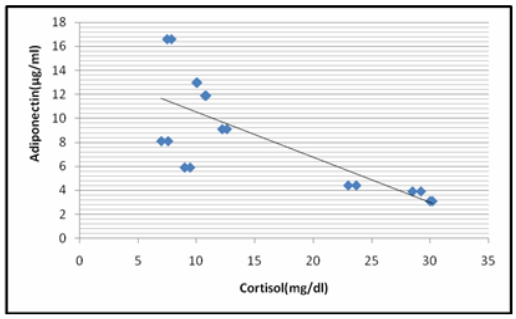


Figure (1): The relationship between cortisol(mg/dl) and adiponectin (µg/ml) in females of diabetes group

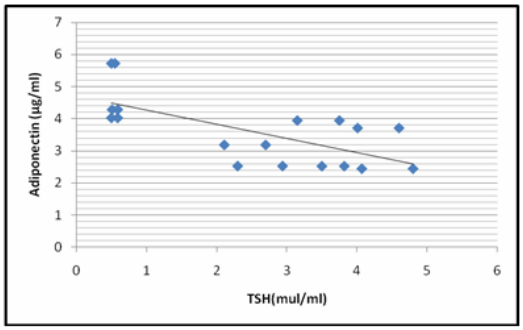


Figure(2): The relationship between T4(mg/dl) and adiponectin (µg/ml) in males of diabetes group.

The study revealed positive correlation between adiponectin and T4 in second and third duration in male diabetic patients (r= 0.91, P= 0.001) and (r= 0.92, P= 0.00) respectively, while an inverse correlation between adiponectin and TSH in male diabetic patients in first duration (r= -0.68,P= 0.04) .In female diabetic patients an inverse correlation between adiponectin and T3 in second duration(r= -0.68,P= 0.04) ,also found between adiponectin with cortisol in third duration of female diabetic patients(r= -0.75,P= 0.01) as shown in Table (2), Figure (3), Figure (4) , Figure (5) , Figure (6) and Figure(7).



Figure(3): The relationship between cortisol (mg/dl) and adiponectin (µg/ml) in females of diabetic third group (>10 year) duration



Figure(4): The relationship between TSH (mIU /ml)and Adiponectin (µg/ml) in males of diabetic first group(0-5 year) duration

Table(1): Correlation analysis between adiponectin and hormones of control and diabetic patients Type 2.

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
Cortisol(mg/dl)	0.1	0.78	0.39	0.28	-0.13	0.5	-0.36*	0.05
TSH(mIU /ml)	-0.31	0.4	-0.24	0.53	0.12	0.54	-0.14	0.47
T3(ng/ml)	0.38	0.3	-0.21	0.58	0.06	0.76	0.17	0.37
T4(mg/dl)	0.2	0.6	0.3	0.42	0.46*	0.01	0.22	0.26

Correlation coefficient (r)

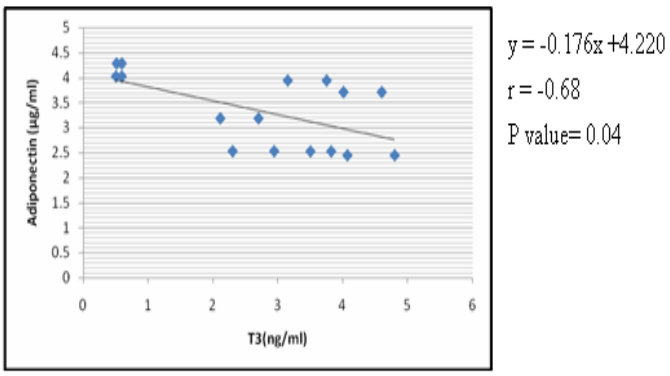
*. Correlation is significant ≤ 0.05 level (2-tailed).

Table(2): The relationship between adiponectin and hormones of diabetic patients Type2 according to the durations of disease

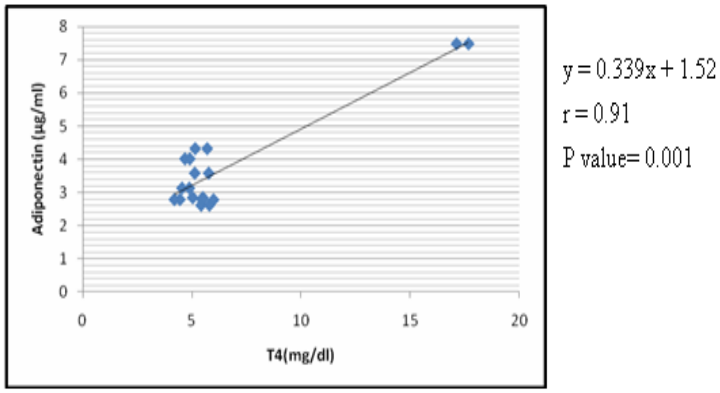
Indices	Adiponectin(µg/ml) Diabetes groups											
	0-5				>5-10				>10			
	Male		Female		Male		Female		Male		Female	
	r	P	r	P	r	P	r	P	r	P	r	P
Cortisol (mg/dl)	0.58	0.09	0.22	0.55	0.55	0.12	-0.1	0.79	-0.37	0.31	-0.75*	0.01
TSH(mIU /ml)	-0.68*	0.04	0.04	0.9	0.12	0.75	-0.25	0.51	0.51	0.15	-0.46	0.21
T3 (ng/ml)	0.02	0.95	0.2	0.6	0.1	0.78	-0.68*	0.04	-0.39	0.28	-0.06	0.86
T4 (mg/dl)	0.18	0.62	0.28	0.45	0.91*	0.001	0.52	0.14	0.92*	0.00	-0.15	0.68

Correlation coefficient (r)

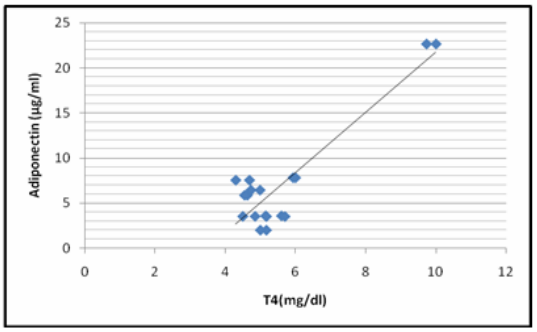
*. Correlation is significant ≤ 0.05 level (2-tailed).



Figure(5): The relationship between T3(ng/ml) and Adiponectin (µg/ml) in females of diabetic second group(>5-10 year) duration



Figure(6): The relationship between T4(mg/dl)and Adiponectin (µg/ml) in males of diabetic second group(>5-10 year) duration



Figure(7): The relationship between T4(mg/dl) and Adiponectin (µg/ml) in males of diabetic third group(>10 year) duration

Discussion

In males diabetic patients there was positive correlation between adiponectin and T4 and also was the correlation in second and third duration of disease while the correlation of TSH and T3 with adiponectin appears no significant correlation for both groups and for both males and females (Table 1),this result supported by study of Díez and Iglesias, (2009) that indicate healthy subjects with high adiponectin levels had higher serum T4 levels , and T4 was found to be a predictive variable for adiponectin concentrations in humans.

Thyroid hormone increases transcriptional induction of adiponectin through PPARγ or SREBP stimulation. It has been reported that thyroid hormone can induce the expression of PPARγ in hepatocytes , and PPARγ stimulation increases serum adiponectin by transcriptional induction in adipose tissue ,also thyroid hormone stimulates an increase in the mature sterol regulatory element-binding protein-1 (SREBP-1), a protein that binds the promoter regions of several lipogenic genes , controls adiponectin gene expression in differentiated adipocytes (Díez and Iglesias, 2009).

Fernandez-Real *et al*.,(2003) point to the carboxy terminal globular structure of adiponectin, through its use of gC1q receptor found in the mitochondria of the thyroid, could be a regulator of thyroid hormone production .Additional evidence for a role of thyroid hormones in the regulation of adiponectin expression comes from a recent study showing increased adiponectin levels in mice exposed to cold.

In males diabetic patients an inverse correlation between adiponectin and TSH in first duration (Table 2), this result supported by study of Iacobellis *et al*., (2005)that found the TSH was inversely related with adiponectin concentrations in obese women.

Also the result show an inverse correlation between adiponectin and T3 in female diabetic patients in second duration (Table 2), ,this result supported by study of Malyszko *et al*., (2006) that reported for the first time a negative correlation between adiponectin and T3 in healthy volunteers.

Correlation analysis showed an inverse correlation between adiponectin and cortisol in female diabetic patients (Table 1), also in third duration in female diabetic patients(Table 2), this due to that cortisol negatively regulate adiponectin mRNA in human visceral adipose tissue (Fallo *et al*., 2004).

Sundbom *et al*.,(2008) indicated that glucocorticoids have been shown to decrease the levels of adiponectin in animal models and in humans . Also Tenhalo *et al*.,(2010) refer that glucocorticoids have negative effect on adiponectin and cause inhibited adiponectin release from human adipocytes.

This study agreement with study of Ferrandez-Real *et al*.,(2005) that found free cortisol correlated negatively with adiponectin only in women but not in men.

While other study found significant positive relation between plasma cortisol and adiponectin has been shown in healthy volunteers, particularly in males. A possible mechanism for the positive relation could be that the promoter region for the adiponectin gene contain consensus sequences for glucocorticoid receptor binding (Venkatesh *et al* ., 2009).

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