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Full Length Research Paper

Evaluation of serum cortisol, growth and thyroid hormones and its relation with lipolysis in non-diabetic obese and diabetic obese subjects attending Sohag Governorate, Egypt

Ali Taha A. Hassan[1], Hossam El-Din M. Omar[2], Nagwa M. Elsawi[3]* and Amira M. Ahmed[3]

[1]Department of Internal Medicine, Faculty of Medicine, Sohag University, Sohag 82524, Egypt
[2]Zoology Department, Faculty of Science, Assiut University, Assiut 71516, Egypt
[3]Department of Chemistry, Faculty of Sience, Sohage University, Sohage 82524, Egypt

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The study aim to estimate the level of some hormones and free fatty acids which have a role in metabolic processes and its relation to obesity and diabetes 2 type. Cortisol, growth and thyroid hormones were determined by ELISA in serum of 85 subjectes including 30 controls, 31 non-diabetic obese and 24 obese diabetic. Obesity is described according to BMI. Blood pressure and glucose level were measured for all participants. Free fatty acids (FFAs) analysis was performed by gas chromatography technique. Hormonal assays were performed by ELISA methods Results: Blood levels of cortisol in non-diabetic obese subjects was non-significantly decreased compared to control group, while in obese diabetic group increased significantly compared to non-diabetic obese subjects. Growth hormone in both non-diabetic obese and obese diabetic groups was decreased compared to controls. Thyroid hormones T_3 and T_4 showed a non-significant decrease in non-diabetic obese subjects compared to control group, however, increased significantly in obese diabetic group compared to non-diabetic obese group. Blood FFAs showed various changes in unsaturated and saturated among the three groups. In conclusion, the present study found that changes in the levels of cortisol, growth hormone and thyroid hormones were correlated with BMI and the level of FFAs in serum.

Keywords: obesity, diabetes type 2, cortisol, growth hormone, thyroid hormones and FFAs.

INTRODUCTION

Obesity is a fast growing epidemic problem in worldwide (James et al., 2004). Obesity is associated with several metabolic disorders which lead to increase the risk factor of several diseases such as diabetes and vascular diseases (Fagot-Campagna et al., 1998; Lakka et al., 2001; Kenneth et al., 2006). There are several hormones having a role in regulation of metabolism such as corticosteroids and thyroid hormones. Cortisol is one of the important corticosteroid hormones which secreted as a result of stress (Sapolsky et al., 2000). Cortisol contributes in regulation of carbohydrate and protein metabolism and involved in regulation of mineral ocorticoid and blood pressure (Johnson et al., 2006). Cortisol is an antagonist of insulin because it

*Corresponding Author E-mail: elsawinagwa@yahoo.com

reduces the ability of tissue to uptake glucose leads to hyperglycemia and increase the lipolysis (Bjorntorp et al., 1999). So, dysregulation of cortisol level results in insulin resistance, prediabetes, and type 2 diabetes (Bjorntorp, 1997).

Thyroid gland is the source of two types of iodothyronine hormones, triiodothyronine (T_3) and thyroxine (T_4) (Godman and Gilman, 2006). Thyriod hormones are important for normal growth and development (Gereben et al., 2008), they stimulate metabolism of cholesterol and hypercholesterolemia is a characteristic feature of hypothyroid states. Thyroid hormones increase the specific binding of low-density lipoprotein (LDL) by liver cells (Salter et al., 1988). In addition, thyroid hormones play a major role in thermogenesis in adipose tissue by increasing basal metabolic rate (Cannon et al., 2004), and appetite regulation (López et al., 2010; Ishii et al., 2003; Luis et al., 2012). Leptin, one of important adipokines, has an important role in thyroid hormones regulation (Iacobellis et al., 2005).

Pituitary gland produces and releases growth hormone which has several physiological processes such as differentiation of preadipocytes into adipocytes and stimulate β-oxidation of fatty acids in adipose tissue and enhance gluconeogenesis in the liver (Campbell et al., 1988). Also, it inhibits the cellular uptake of glucose and enhances endogenous production of glucose leads to hyperglycemia (Yong et al., 2012).

NEFAs are released by lipolysis of triacylglycerols (TAG) stored in the adipocytes as a source of energy during fasting and stress. Through its capacity to store NEFAs, the adipose tissue controls the daily lipid flux in the body (Frayn, 2002). An imbalance between NEFA storage and release, as observed in obese subjects, has major metabolic consequences and increases cardiovascular risk (Frayn et al., 2004). The adipose tissue of obese persons releases more NEFAs into the circulation, and subjects with type 2 Diabetes have high NEFA concentrations (Fraze et al., 1985; Paolisso et al., 1996). A high plasma NEFA concentration is a risk factor for decline of glucose tolerance independent of the other insulin resistance or insulin secretion markers that characterize subjects at risk for type 2 diabetes (Charles et al., 1997; Saloranta et al., 1996). Chronically elevated plasma NEFA concentrations stimulate gluconeogenesis, cause hepatic/muscle insulin resistance (Boden, 1996; Bergman et al., 2000; Reaven et al,. 2004).

Subjects

The study had the full approval of the Sohag University Hospital Ethics Committee. Three groups of subjects were studied, each comprising six males. Group A represent control group had BMI values less than 25 kg/m^2, group B represent obese group had BMI values from ≥30 kg/m^2, and group C which is obese diabetic patients had BMI values ≥ 30 kg/m^2.

MATERIAL AND METHODS

Blood samples were collected in the morning from the subjects after an overnight fasting. A syringe and needle was used to collect 5ml of blood sample from the subjects for analysis. Blood pressure was measured for all subjects**,** also fasting and postprandial 2 hours was performed. The biochemical parameters that were measured in this study included, serum cortisol, human growth hormone (hGH), triiodothyroxine (T_3) and thyroxine (T_4) were measured by enzyme immunoassay method. Serum cortisol and human growth hormone were determined by kits were obtained from DBC Diadnostic biochem Canada Inc, Canada according to (Brock et al., 1978) and (Beck et al., 1965) methods. Serum T_3 and T_4 were determined by kits were obtained from Pishaz tep diagnostics, Irane according to (Barjer et al., 1948) method. Serum FFAs was extracted by Folch reagents (Folch et al., 1967) and quantized by separated by GC-MS at Analytical Unit, Department of Chemistry, Faculty of Science, Assiut University.

Statistics

Statistics was performed using the statistical graph pad prism 5. One way analysis of variables (ANOVA) was used posted by Newman-keuls test. All results are expressed as mean ± SE and the level of significance between groups were*$p<0.05$, ** $p<0.01$, *** $p<0.0001$.

RESULTS

The total number of study subjects was 85 subjects, 30 (35.2%) individuals with BMI 20.11 were control, 31(36.4%) subjects with BMI 31.99 were obese and 24 (28.2%) subjects with BMI 30.62 were obese diabetic type 2. Table 1 showed the demographic data of the participants in which control showed waist circumference with mean 82.10 cm, but waist circumference for obese non-diabetic group was raised to 118.2 and for obese diabetic group was 119.9. Both blood glucose level and blood pressure showed a significant increase in obese non-diabetic and diabetic obese groups compared to control subjects.

Table 2 showed that the level of cortisol in non-diabetic obese group decreased non-significantly compared to control, however, it non-significantly increased in obese diabetic group compared to control and in obese diabetic group compared to non-diabetic obese subjects. The level of growth hormone was decreased significantly in non-diabetic obese and diabetic obese groups compared

Table 1. Demographic data of the study participants

Parameters	***Control n=30***	***Non-diabetic obese n=31***	***Diabetic obese n=24***
BMI (kg/m^2)	20.11±0.3217	31.99±0.4219^{***a}	30.62±0.2871^{*b}
Waist circumference (cm)	82.10 ±0.8608	118.2 ±1.545 ^{***a}	119.9 ±1.505
Systolic blood pressure (mmHg)	116.0 ±2.724	124.6 ±2.665 ^{*a}	145.3±3.961 ^{***b}
Diastolic blood pressure (mmHg)	84.93±2.820	92.17±2.454^{*a}	103.5±2.245^{**b}
Fasting blood glucose level	84.30 ±1.247	95.90 ±2.175 ^{*a}	126.7±5.938 ^{***b}
Postprandial 2 hours blood glucose level	108.8±3.252	118.0±2.811	257.3±11.78^{***b}

Data are expressed as mean ± SE, where the number of asterisk (*) indicates the levels of significant at p<0.05, 0.01, 0.0001.
Letter^{a} referred to the significant difference between non-diabetic obese and control.
Letter^{b} referred to the significant difference between diabetic obese and control.
Letter^{c}referred to the significant difference between non-diabetic obese and diabetic obese

Table 2. Serum levels of cortisol, thyroid hormones (T_3 and T_4), growth hormone in control, non diabetic obese and diabetic obese subjects.

Parameters	***Control (n=30)***	***Non-diabetic obese (n=31)***	***Diabetic obese (n=24)***
Cortisol (µg/dl)	17.91 ±1.057	15.98 ±0.944	21.22±1.972^{*c}
GH (ng/ml)	0.7019 ±0.182	0.344 ±0.066^{*a}	0.169 ±0.04^{**b}
T3 (ng/ml)	2.188±0.088	1.984 ±0.035	2.839 ±0.244$^{**b\&***c}$
T4 (µg/dl)	8.415 ±0.293	8.104 ±0.209	10.05 ±0.505$^{**b\&***c}$

Data are expressed as mean ± SE, where the number of asterisk (*) indicates the levels of significant at p<0.05, 0.01, 0.0001.
Letter^{a} referred to the significant difference between non-diabetic obese and control.
Letter^{b} referred to the significant difference between diabetic obese and control.
Letter^{c}referred to the significant difference between non-diabetic obese and diabetic obese

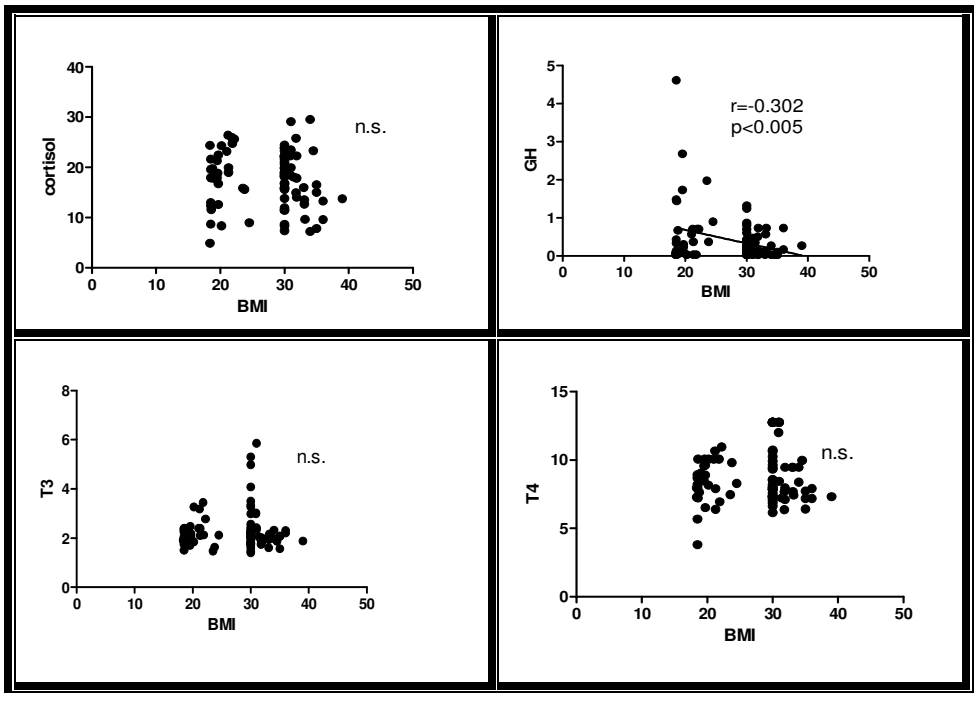

Figure 3. Correlation between BMI and the serum levels of cortisol, GH, T_3 and T_4

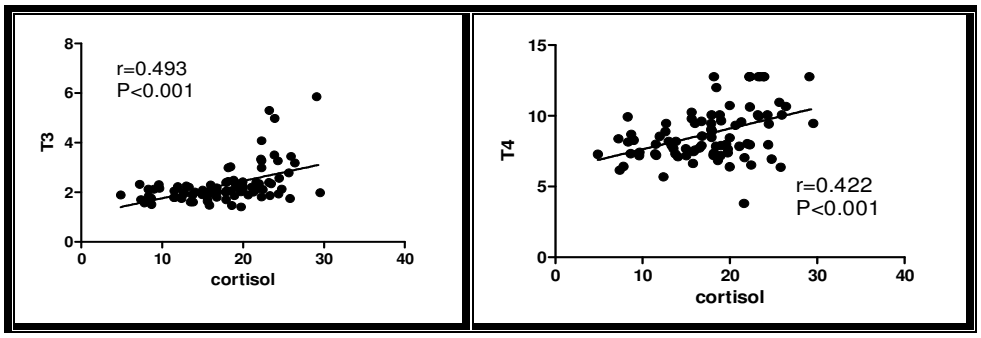

Figure 4. Correlation between serum levels of cortisol and thyroid hormones

Table 3. Mean relative percentage values of FFAs in serum of different subjects groups.

Fatty acids		Control	Obese	Obese diabetic
Saturated fatty acids	**C10**	0.992	0.754	1.385
	C14:0	N.D	N.D	0.462
	C16:0	10.331	11.35	16.37
	C18:0	3.889	2.019	4.033
	C20:0	0.856	N.D	N.D
	Total SFA	**16.068**	**14.123**	**22.25**
Monounsaturated Fatty acids	**C14:1**	N.D	N.D	0.663
	C16:1	0.691	N.D	1.032
	C18:1	4.11	5.083	7.08
	Total MUFA	**4.801**	**5.083**	**8.775**
Poly unsaturated fatty acids	**C18:2**	4.011	1.173	1.804
	C20:3	2.089	2.331	N.D
	C20:4	2.484	N.D	0.429
	C22:4	1.237	N.D	0.598
	Total PUFA	**9.821**	**3.504**	**2.831**

to controls, however, it non-significantly decreased in obese diabetic group compared to non-diabetic obese individuals (table 2). The concentration of T_3 in non-diabetic obese group was non-significantly decreased compared to control, but it significantly increased in obese diabetic group compared to control group and increased significantly in diabetic obese compared with non-diabetic obese subjects. The level of T_4 non-significantly decreased in obese group compared to controls, but it was significantly increased in obese diabetic group compared to controls and non-diabetic obese subjects.

Relationship between hormones and BMI

As shown in figure 3, no significant differences was noted between serum level of cortisol and BMI of controls and obese diabetic or obese non-diabetic groups, however, the level of serum GH showed a negative correlation with BMI (r= -0.302) with significant value (p<0.005). There is no correlation between thyroid hormones levels in serum and the BMI of controls and obese diabetic or non-diabetic obese.

Relationship between cortisol and thyroid hormones

Figure 4 showed a significant positive correlation serum level of T_3 with cortisol (r=0.493, P<0.001), and T_4 with cortisol (r=0.422, P<0.001) of controls, non-diabetic obese and diabetic diabetic groups.

Serum FFAs

Analysis of FFAs in serum by gas chromatography found that capric acid (C10:0) was increased in obese diabetic group compared to control and non-diabetic obese subjects. Myristic acid (C14:0) was not detected in control and non-diabetic obese groups, but detected in diabetic obese group. Palmitic acid (C16:0) was increased in diabetic obese group in comparison with control and non-diabetic obese groups. Stearic acid (C18:0) was decreased in non-diabetic obese compared to control and

increased in obese diabetic group compared to both control and non-diabetic obese. Arachidic acid (C20:0) and myristoleic acid (C14:1) were only detected in control group. Palmitoleic acid (C16:1) was higher in diabetic obese than control groups and not detected in non-diabetic obese subjects. Oleic acid (C18:1) was higher in diabetic obese than control and non-diabetic obese groups. Linoleic acid (C18:2) was decreased in non-diabetic obese and obese diabetic groups than controls. Dihomo-*c*-linolenic acid (C20:3) was not detected in diabetic obese group. Arachidonic acid (C20:4) and adrenic acid (C22:4) were not detected in non-diabetic obese group and detected by small % in diabetic obese group in comparison with controls.

DISCUSSION

The present study showed that non-diabetic obese subjects had non-significant lower level of serum cortisol compared to control group, but diabetic obese group showed higher significant level ($p<0.001$) than control and non-diabetic obese. This result indicates a non correlation between obesity and cortisol (Odeniyi et al., 2015). Another study found that level of cortisol was significantly higher in subjects with insulin resistance characterized by impaired fasting glucose than subjects with normal glucose tolerant (Mamza et al., 2013). However, other studies reported that the level of cortisol was increased with obesity due to enhancement of hypothalamic pituitary adrenal axis (Pasquali et al., 1993).

In the present study, the serum level of GH showed a decrease in non-diabetic obese group in comparison with controls, and in obese diabetic group compared with non-diabetic obese group, this result indicate a negative correlation between GH and BMI. The decrease in GH secretion in obesity may be due to hyperinsulinemia, decrease level of adiponectin, and leptin resistance, which results in increased fat accumulation (Makimura et al., 2008).

The level of thyroid hormones T_3 and T_4 showed a non-significant decrease in non-diabetic obese subjects compared to controls, but they significantly increased in diabetic obese group compared to controls. These results mean a negative correlation between the thyroid hormones levels in serum and BMI. In fact, hypothyroidism in non-diabetic obese group may be has a role in the development of obesity (Pearce et al., 2012) because thyroid hormones effect in thermogenesis. Moreover, it's known that T_3 is antagonist to insulin action. So, increased T_3 level lead to increase in the absorption of splanchnic glucose, increase hepatic glucose output, enhanced lipolysis and increase of plasma FFAs. Accordingly, thyroid dysfunction is a good participant in insulin resistance (Kemp et al., 1997).

The composition of serum FFAs in fasting state is a good model for reflecting fatty acid metabolism (Conquer et al., 1998). Serum FFAs supply is an important energy source and they also act as signaling molecules in various cellular processes relating to hypertension (Keigo et al., 2003). Fasting serum FFAs composition not only reflects the dietary fat intake, but also the endogenous fatty acid synthesis. Obesity is one of the greatest public health problems in industrialized countries (Olshansky et al., 2005). Obese subjects have increased insulin resistance and FFAs (Boden et al., 2001). These FFAs from adipose tissue are primarily an important energy substrate for a number of organs and involved in the regulation of a number of metabolic processes in the body. The associations between serum FFAs and carbohydrate and insulin metabolism have been known for a long time (Sandro et al., 2006; Randle, 1998). Increased serum level of FFA caused a change in the action of insulin and considered an independent predictive factor for progression to type 2 diabetes mellitus (T2DM) (Charles et al., 1997; Knowler et al., 1990). In the present study, FFAs analysis showed that palmitic acid (C16) has the highest relative value in all FFAs detected sera of all subjects groups. The level of stearic acid was higher in control group compared to non-diabetic obese subjects. The higher levels of saturated fatty acids detected in diabetic obese have high level compared to both control and non-diabetic obese group and it may be have a role in inflammation as cited by Stryjecki et al. (2012) who found that an inverse relationship between circulating stearic acid levels and the markers of inflammation in young lean adults (Stryjecki et al. 2012). In the present results, increased monounsaturated fatty acids in diabetic obese subjects were previously recorded by different studies. For example, myristoleic acid (C14:1), palmitoleic (C16:1), and oleic acid (C18:1), were elevated in diabetic obese groups leading to increased the risk for metabolic syndrome (Kim et al., 2013; Gil-Campos et al., 2008).

Omega-6 and omega-3 fatty acids are essential because humans like all mammals, cannot make them and must obtain them in their diet. Omega-6 fatty acids are represented by linoleic acid (18:2) and omega-3 fatty acids by a-linolenic acid (18:3). Both acids are metabolized to longer-chain fatty acids of 20 and 22 carbon atoms. Leptin is adipocyte hormone and has an important role in regulation of body weight homeostasis and energy balance (Lonnqvist et al., 1995; Halaas et al., 1995; Nagwa et al., 2015). Administration of lenoleic acid in diet decrease body fat mass and body weight (Jae-Young et al., 2001) and decrease the level of serum leptin (Delany et al., 1999), this reveal that the low level of serum lenoleic acid, in our analysis, has a role in increase body weight. Moreover, there is a positive association between BMI and dihomo-c-linolenic acid (20:3) (Savvas et al., 2004). Both of arachidonic acid

(C20:4) and adrenic acid (22:4) represented by low percentage in diabetic obese group compared to controls and not detected in non-diabetic obese subjects. In summary, development of insulin resistance syndrome is associated with altered composition of circulating fatty acids characterized by higher saturated fatty acids, higher palmitoleic acid and dihomo- c-linolenic acid and lower levels of linoleic acid (Warensjo et al., 2005). In conclusion, the present study found that changes in the levels of cortisol, growth hormone and thyroid hormones were correlated with BMI and the level of FFAs in serum.

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