Ghrelin Level in Male PatientsWith Hypothyroidism

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Abstract:-

Background:-Circulating ghrelin concentration is inversely associated with the body mass index; thus, obese individuals have lower levels than lean individuals.Abnormalities of lipid metabolism associated with hypothyroidisms patients,many of them are obese. Many diseases such as hypothyroidism can effect ofghrelin level.

Objective:-To study the relation between Ghr and insulin resistance (IR), β-cell function (B%), insulin sensitivity (S%), atherogenic index(AI), in patients with hypothyroidism.

Subjects and methods:-Sixty males were enrolled in this study which were divided into two groups as follows: control subject group consisted of 30apparentlyhealthy individuals, (30) males with hypothyroidism, blood was collected from patients attended the National Diabetes Centre from October 2012 to June 2013.Serum of ghrelin, insulin and lipid profile levels were evaluated in patients andcontrol groups.

Results:-The results in this study revealed that mean of serum ghrelin levels wereshowed significant decrease differences in patients with hypothyroidismcompared with control group and a significant negative correlation between ghrelin and TSH, and a significant positive correlation between ghrelin and insulin resistance.

Conclusion:-We conclude that serum ghrelin, T3, T4, HDL, S% and B% levels were decrease in males with hypothyroidism andC-peptide,FSG,insulin,IR,TC,AI, VLDL, TC/HDL, LDL/HDLlevels were increase in them. Serum ghrelincorrelate with altering lipid profile insulin resistance and TSH, our suggestion that possible follow up serum TSH and ghrelin and insulin resistance to prevent developing other diseases.

Keywords: Ghrelin, lipid profile, hypothyroidism disease, Insulin resistance

Introduction

Ghrelin (Ghr) is a 28-amino-acid peptide produced primarily in the stomach and so called for its property of stimulating growth hormone (GH) secretion in human, increases food intake, and produces weight gain [1,2]. Fatty acid modification of Ghr is essential for Ghr-induced GH release from the pituitary and appetite stimulation [3]. Blood concentrations of Ghr are lowest shortly after consumption of a meal, then rise during the fast just prior to the next meal [4]. Ghr has been shown to activate the endothelial isoform of nitric oxide synthase in a pathway that depends on various kinesis[5, 8]. There is also strong evidence that Ghr has a peripheral appetite modulatory effect on satiety by affecting the mechano-sensitivity of gastric vagal afferents, making them less sensitive to distension resulting in over eating [6]. Obese individuals have lower Ghr levels than those who are thin [7]. Obesity is one of the major risk factors for development of many diseases such as hypothyroidism, which is caused either by inadequate function of the gland itself (primary hypothyroidism) or by not enough stimulation by thyroid-stimulating hormone (TSH), centralhypothyroidism [9, 10]. In overt primary hypothyroidism TSH levels are high; T4 and T3 levels are low. TSH usually rises after T4 and T3 levels drop. Hypothyroid patients have increased levels of total cholesterol (TC) and low density lipoprotein (LDL). Indeed, hypothyroidism is a common cause of secondary dyslipidemia [11]. Decreased thyroid function not only increases the number of LDL particles, but also promotes LDL oxidability[12]. Most patients with hypothyroidism are obese, and obesity itself causes some degree of insulin resistance [13].

The aim of this study is to study the relation between Ghr and insulin resistance (IR), β-cell function (B %), insulin sensitivity (S %),atherogenic index (AI), in patients with hypothyroidism.

Subjects and methods:-

Sixty male (age 30-45) years were enrolled in this study. Blood was collectedand the sera were separated from (30) males with hypothyroidism who were attended the National Diabetes Centre from October 2012 to June 2013and 30 healthy males as a control group.

All males patients were diagnosed to have hypothyroidism by physicians and other chronic diseases were excluded such as cardiovascular disease, diabetes mellitus, and renal failure,hypertension. The range of body mass index (BMI) (mass kg/height^{2}m^2) for the patients and control was (30-35) Kg/m2 and the range of body fat percentagewas (28-36) [BFP% = (1.2 x BMI) + (0.23x age)-5.4-(10.8 x gender], female =0 and male =1).Serum of patients and control groups were determined the following parameters:

- Ghrelin, TSH, T_3, T_4 and C-peptide levels were measured by enzyme-linked immune sorbet assay (ELISA) method [14, 15].

- Total cholesterol (TC) was determined using enzyme-catalyzed colorimetric method [16].
- Total triglyceride (TG) was determined using enzyme-catalyzed colorimetric method [17].
- Serum HDL was measured using Burstein separation method using HDL-C kit [18].
- By using the Friedwald equation, low density lipoprotein (LDL) = TC-[TG/5 + HDL] ,very low density lipoprotein (VLDL)=TG/5, atherogenic index (AI)= Log(TG/HDL) [19] .
- Fasting serum glucose (FSG) was determined using enzymatic colorimetric method (Glucose oxidase-peroxidase) [20].
- Mathematical formulas were used to measure: IR, B% and S% by use an updated HOMA model(HOMA2),insulin; Fasting glucose (mg/dL)×fasting Insulin(μU/mL)/405 = IR, which used in HOMA-IR[21].

Statistical Analysis: Data are presented as mean ±SD using SPSS program. The differences between two groups were analyzed by t-test. P-value less than 0.05 considered significant .Pearson's correlation coefficient was used to examine between (Ghr) and other parameters in patients and control groups.

Results :-

Mean ± SD of T_3,T_4 and TSH for hypothyroidism patients and control were shown in table (1) which was revealed thatT3 and T4 were significantly differences lower than in the control group, while TSH was significantly differences higher.Mean ± SD of TC, AI, VLDL, TC/HDL, LDL/HDL were revealed that significantly differences higher in patients when compared with control group, so TG, LDL levels were non significantly higher than the control group, while HDL was significantly differences lower, shown in table (2) .

Table(1):Mean ± SD and P-value of T3,T4 and TSH for the control and hypothyroidism patients.

Groups / parameter	Mean±SD		P-Value
	Control	hypothyrodisim	C-HT
T3(ng/mL)	1.4±0.3	0.4±0.13	0.0012
T4 (ng/dL)	1.9±0.8	0.62±0.21	0.0004
TSH (mU/L)	2.1±0.83	20.12±8.3	0.02

Table(2):Mean ± SD and P-value of Ghr, ,IR,TG,TC,HDL,AI and other parameters for the control and hypothyroidism patient

Groups / Parameters	Mean ± SD		P-Value
	Control	hypothyroidism	C-HT
TG (mg/dL)	129.6±32.8	136±53.5	0.08
TC(mg/dL)	166.0±27.3	232.8±57.2	0.04
HDL(mg/dL)	44.1±9.2	30.3±12.3	0.13
LDL(mg/dL)	101.0±15.9	128.6±45.7	0.32
VLDL(mg/dL)	25.2±6.5	37.1±11.4	0.038
TC/HDL	4.01±0.92	5.20±1.88	0.03
LDL/HDL	2.40±0.71	3.13±1.39	0.042
AI (mg/dL)	0.34±0.1	0.8±0.14	0.005

Mean±SD of Ghr, C-peptide, FSG, insulin,IR, S%, B% and glucose/insulin, for hypothyroidism patients and control were shown in table (3) which was revealed that Ghr, S% and B% levels were significantly differences lower and the others were higher than in the control groups

Table(4) showed the correlation between Ghr and T_3, T_4, TSH, TG, TC, HDL, AI, LDL, VLDL, TC/HDL,LDL/HDL,C-peptide, FSG, insulin, IR, S%, B% and glucose/insulin, for hypothyroidism patients and control which were revealed that.

Table(3):Mean±SD and P-value of FSG,C-peptide, insulin, IR ,S%, B%, Glucose/Insulin and Ghr for the control and hypothyroidism patients

Groups / Parameters	Mean ± SD		P-Value
	Control	hypothyroidism	C-HT
FSG(mg/dL)	96.2±9.6	102±23.5	0.9
C-peptide (ng/mL)	0.19±0.04	0.21±0.06	1.2
Insulin(µU/mL)	2.21±1.94	2.34±1.03	0.09
IR	0.51±0.43	1.32±0.66	0.044
S%	173.5±49.4	152±62.2	0.039
B%	20.7±4.4	12.6±9.7	0.8
Glucose/Insulin	67.9±34.6	73.8±30.6	1.02
Ghr (ng/mL)	0.81±0.06	0.52±0.18	0.0062

Table (4): Correlation coefficients andP values between Ghrelin hormone levels and other parameters for control and hypothyroidism groups

Groups / Ghrelin	**Control**		**Hypothyroidism**	
	r	**p-value**	**r**	**p-value**
T3(ng/mL)	0.32	0.08	0.01	0.75
T4(ng/dL)	0.11	0.65	0.12	0.76
TSH(mU/L)	0.32	0.054	-0.42	0.02
T C (mg/dL)	0.212	0.12	-0.045	0.91
TG (mg/dl)	0.31	0.055	0.012	0.21
LDL (mg/dL)	0.127	0.87	-0.26	0.08
VLDL (mg/dL)	0.11	0.23	0.31	0.069
HDL (mg/dl)	-0.102	0.07	-0.09	0.058
TC/HDL	0.03	0.3	-0.03	0.07
LDL/HDL	0.19	0.43	-0.10	0.08
AI	0.023	0.078	0.08	0.058
FSG (mg/dl)	-0.102	0.125	-0.015	0.099
C-peptide (ng/ml)	0.11	0.211	0.25	0.067
Insulin (µU/ml)	-0.231	0.08	0.04	0.052
IR	0.09	0.22	0. 51	0.01
S%	-0.191	0.085	-0.08	0.096
B%	0.026	0.062	0.041	0.075
Glucose/Insulin	-0.29	0.5	-0.41	0.08

- There is + rewith significant correlation between ghrelin and IR in patients, but failed to show state significant in the control group.
- There is +re correlation but failed to show significant with T_3, T_4, TG , AI, VLDL, C-peptide, insulin and B% in patients group.
- There is -re correlation with significant between ghrelin and TSH in patients' hypothyroidism, but failed to show state significant in control group.
- There are –re-correlation between ghrelin and LDL, HDL, TC/HDL, LDL/HDL, S% and glucose/insulin in patients group and failed to show state significant.
- There are +re correlation but failed to show significant with T_3, T_4, TG, TC, AI, LDL, VLDL, TC/HDL,LDL/HDL,C-peptide, FSG and B% in control group.
- There are -re correlation between Ghr and HDL, FSG, insulin, IR and glucose/insulin but failed to show significant in control group.

Discussion:

In this study we observed a decrease level of ghrelin in males with hypothyroidism when compare with control group, and we found a negative correlation between ghrelin and TSH but positive correlation with insulin resistance. We observed an increase level of atherogenic index in males with hypothyroidism and a positive correlation with ghrelin.

A reciprocal relationship between thyroid hormones and ghrelin levels has been demonstrated in some studies[22].Some studies have shown that ghrelin levels are reduced in overt hyperthyroidism, but not in subclinical hyperthyroidism, more conflicting data are reported in hypothyroid patients with studies showing higher, normal, and even lower serum ghrelin levels.Hypothyroidisms are also both associated with insulin resistance and altering HDL-c and other lipid profile [23] .

The presence of hypertriglyceridemia, low HDL-C concentrations, and high TG/HDL-C ratio almost never occurred as isolated disorders, and were nearly always associated with insulin resistance because insulin affects TG and HDL-C metabolism.Previous studies have shown that several lipid ratios have been proposed as clinically simple and useful indicators of hyperinsulinemia or insulin resistance. The TG/HDL-C ratio has shown similar potential for insulin resistance, though the generalizability of this association has been not entirely consistent[24].

Greater basal abdominal VLDL-TG storage may help explain the accumulation of upper-body fat in insulin-resistant individuals [25].An elevated TC/HDL-C ratio in men is observed among overweight, hyperinsulinemic, and hyper-triglyceridemic individuals[26].HDL protects beta-cells from cholesterol-induced beta-cell dysfunction [27].

Ghrelin may serve a compensatory physiological role in hypothyroidism[28].Ghr also controls glucose metabolism[29].It has been shown that Ghr concentrations are reduced in different pathophysiological conditions with metabolic disturbances[30].Previous studies have shown that Ghr may play an important role in adipogenesis and storage of energy in adipose tissue[31,32].

Low Ghr concentrations have been associated with metabolic disturbances, such as insulin resistance and metabolic syndrome. Ghr levels are elevated only in advanced status of atherosclerotic disease. In humans, Ghr levels in obese subjects are lowtherefore, a negative association between Ghr and atherogenic ratios may be expected[33]. Studies have shown a positive association between Ghr concentrations and HDL levels[34]. Unacylated ghrelin is positively associated with HDL-c level, and may contribute to the highly prevalent low HDL-c level seen in obesity[35].

Ghr inhibits glucose-induced insulin release via a paracrine mechanism, Ghr levels correlated negatively with fasting insulin levels and c-peptide , positively with the insulin sensitivity[36].Study has shown that insulin and HOMA-IR are associated negatively with Ghr[37]. Ghr may be associated with the B% and first-phase insulin secretion defects [36] .

Conclusion of this study that,when serum TSH in hypothyroidism patients was high,then IR was high and Ghr level become low, thereforeGhrserve a compensatory physiological role in hypothyroidism patients to prevent increase glucose level in blood and increase insulin level and IR.So Ghr level can be usedas indicator for hypothyroidism patients and possible follow up serum Ghr for patients with hypothyroidism.

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