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The Relationship of Ghrelin with Diabetes Mellitus and/or Obesity

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Abstract: **Ghrelin is well known endogenous peptide. Its role in managing obesity and/or diabetes was not well defined.**

Objective: **To define the relationship of ghrelin with diabetes mellitus and/or obesity.**

Methods: A comparison of four group of subjects had taken place. A control group composed of normal healthy subjects. The second, third and fourth group are diabetic non-obese subjects, obese non-diabetic subjects, and diabetic obese subjects.

All the patients are recruited from King Abdulaziz University Hospital. Blood samples had been taken from fasting patients measuring serum ghrelin, fasting blood glucose, insulin level, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglyceride and haemoglobin A1C.

Results: **The diabetes obese group was the most abundant with statistically significant correlations and most of the varibles were negatively correlated with serum ghrelin The values are successively -0.640, -0.322, 0.201, 0.068, 0.151, -0.694, -0.555, -0.529 for BMI, LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol, Triglyceride, Fasting Blood Glucose, Hb A1C, andum Insulin.**

Conclusion: **A negative relationship is concluded between serum ghrelin and BMI, FBG and serum insulin levels. This suggests suggest a suppressive controlling mechanism of ghrelin secretion in obese and diabetics.**

No relationship can be established between ghrelin level and serum lipids.

Keywords: **Ghrelin, diabetes, patients, BMI, LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol, Triglyceride, Fasting Blood Glucose, Hb A1C, andum Insulin.**

1. INTRODUCTION

Ghrelin first discovered in gastric extract. It was defined as growth hormone release peptide, food intake modulator and some other physiological features. The molecular mechanism of ghrelin biosynthesis is a result of alternative splicing of the ghrelin gene or extensive post-translational modifications. Ghrelin gene is localized on chromosome 3p25-26[1].

Ghrelin is an endogenous hormone. Although the fact that, in vivo it powerfully stimulates the Growth Hormone GH release, however most of the physiological studies could not pinpoint the exact role of ghrelin in GH regulation[2]

Appetite studies showed that ghrelin-containing neurons are found in the ARC of the hypothalamus, a region involved in appetite regulation[3]. This localization suggests a role of ghrelin in controlling food intake. Based on electrophysiologic recording, ghrelin stimulates the activity of accurate NPY neurones in the paraventricular nucleus PVN of hypothalamus. They proposed that at these sites, release of ghrelin may stimulate the release of orexigenic peptide and neurotransmitters, thus representing a novel regulatory circuit controlling energy homeostasis. [4]

Animal studies for appetite had shown that ghrelin is causing rats to increase their food intake after the injection of ghrelin icv, iv or sc[5]

Several trials succeeded to figure out the relationship of ghrelin and vagus nerve in regulating appetite. [6-8] Ghrelin receptors are synthesized in the vagal afferent neurones. Vagotomy inhibits the ability of ghrelin to stimulate the food intake as well as abolishing the ghrelin induced gastric acid secretion.

It has been found that ghrelin levels increase immediately before each meal and fall to the minimum levels within 1 hour after eating.[9] This rise in ghrelin levels had been studied on humans where subject hunger score had been positively correlated with level of plasma ghrelin.[10]

Human being trials failed to confirm the relationship of ghrelin and insulin levels. In general type II diabetes mellitus or insulin resistance have low ghrelin levels.[11]. It can be presumed that both insulin and ghrelin levels are dependant on plasma glucose level. Insulin secretion increases by higher level of plasma glucose while ghrelin secretion suppresses with higher glucose levels.

Ghrelin is negatively correlated with weight[12] and higher ghrelin levels were found in patients on low calorie diet in patients suffering from cancer, cardiac disease, or anorexia nervosa. [13]. Diet and exercise leading to weight loss increases the level of the circulating ghrelin.

Objective:

To define the relationship of ghrelin level with weight in diabetic patients

Subject:

The total number of subjects is 120. Table 1 illustrates the distribution of subjects over the groups. All the 120 subjects had been recruited from King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Table 1: Subjects Distribution per study group

Group of Subjects	Participating Subjects
Group 1 – Control (Healthy Non-Obese Subjects)	30
Group 2 - Obese Non-Diabetic Subject	30
Group 3 - Type II DM Obese Patients	30
Group 4 - Type II DM Non-Obese Patients	30

DM= Diabetes Mellitus

The Diabetets Mellitus diagnosis is based on differential diagnosis for type I and type II according to WHO criteria. Obesity was determined by body mass index BMI according to WHO 1998 criteria. The subject is considered obese once the BMI is higher than 30.

2. METHODS

Laboratory:

To measure the active ghrelin, the Active Gshrelin ELISA kit 96-well plate has been used for non-radioactive qualification of active ghrelin in EDTA plasma.

Insulin measurement has utilized the electrochemiluminescence immunoassay "ELICA" methods supplied from Roch Diagnostics GmbH, Germany based on MODULAR ANALYTICS E170 (Elecsys Insulin Module) immunoassay analyzer

Automated FLEX® reagent cartridges had been used for the determination of LDL Cholesterol, HDL Cholesterol and Triglyceride

Statistical Methodology:

Descriptive statistics are used for continuous demographic variables. T-test has been used for difference in two means for testing the investigational against the control arms.

Linear regression has been used to figure out the correlation between 2 continuous variables to model an equation for the phenomena if found.

3. RESULTS

The following table is summarizing the laboratory findings of each group

Table 2: Population demographics and other study findings

	Control group	Diabetic group	Obese group	Diabetic-Obese group
Gender F/M	17/13	14/16	14/16	17/13
Age (mean±SD)	42.57±2.66	43.40±2.34	42.47±2.46	42.33±2.0
BMI (mean±SD)	21.74±0.45	22.27±0.40	36.82±0.99*	5.25±0.99*
LDL-Cholesterol (mean±SD mmol/l)	2.01±0.14	2.87±0.23*	3.64±0.22*	3.27±0.21*
HDL-Cholesterol (mean±SD mmol/l)	1.32±0.06	1.26±0.07	1.18±0.03*	1.07±0.04*
Total Cholesterol (mean±SD mmol/l)	2.78±0.17	5.10±0.16*	5.15±0.20*	5.58±0.19*
Serum Triglycerides (mean±SD mmol/l)	1.10±0.07	2.75±0.24*	1.58±0.12*	2.66±0.16*
FBG (mean±SD mmol/l)	5.16±0.07	13.09±0.81*	5.44±0.07*	14.39±0.76*
Hb A1C	6.02±0.07	11.87±0.42*	6.34±0.10*	18.29±0.98
Serum Insulin U/I	8.17±0.61	22.41±1.86*	12.83±0.88*	6.60±3.70*
Serum Ghrelin pmol/l	110.35±4.11	89.52±3.68*	54.52±2.59*	45.60±2.18*
Duration of Diabetes Years (mean±SD)	NA	12.20±1.10	NA	8.27±0.67

F: Female, M:Male, SD: Standard Deviation, *: P value <0.05,

The onset of disease was not much severe between the diabetic and diabetic-obese group.

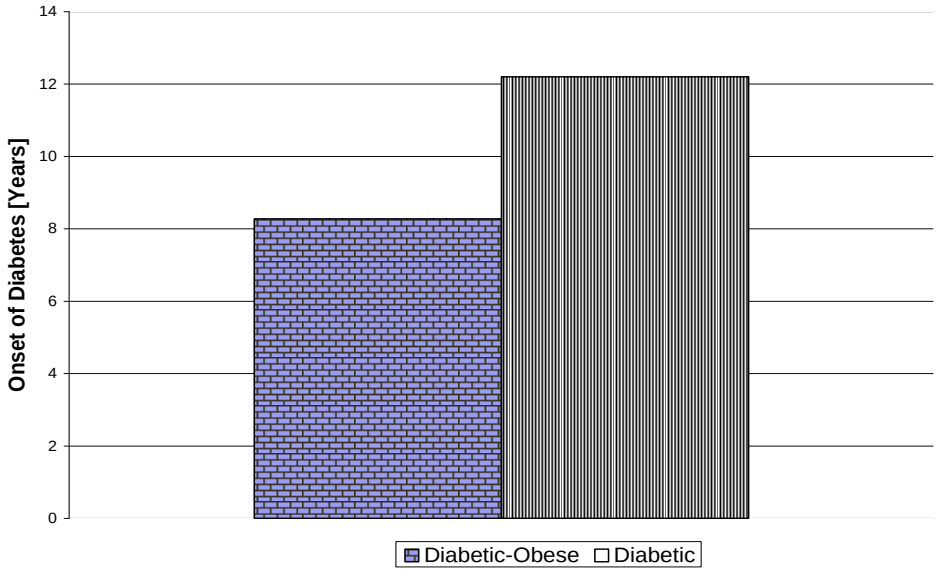

Figure 1: On Set of Diabetes in Diabetic Patients vs Diabetic Obese Patients

Based on the statistical plan the Pearson correlation had been calculated in each group per each variable against the ghrelin serum level. It has been interesting that no variable had shown any statistically significant correlation in the control group.

The body mass index was the most likely to have a strong responsive correlation in the three arms: Diabetes, Obese, Diabetes-Obese arms. It looks like that BMI is always negatively correlated with serum ghrelin levels.

The results of diabetic-obese group is the only group having strong negative correlation of serum ghrelin with fasting blood glucose FBG, haemoglobin A1C HbA1c and serum insulin.

Total cholesterol and total triglyceride are having negative correlation serum ghrelin in diabetic group. This observation is worthy because diabetes group is the only group having this phenomenon.

Table 3: Bivariate Pearson's correlation coefficient of Serum Ghrelin

	Control group	Diabetes group	Obese group	Diabetic-Obese group
Age	0.12	0.111	0.292	-0.166
BMI	-0.247	-0.362*	-0.465*	-0.640*
LDL-Cholesterol	0.182	0.015	-0.291	-0.322
HDL-Cholesterol	-0.006	0.031	-0.059	0.201
Total Cholesterol	0.218	-0.114	0.042	0.068
Triglyceride	0.215	-0.111	0.086	0.151
FBG	-0.178	-0.115	-0.283	-0.694*
Hb A1C	-0.208	-0.023	0.273	-0.555*
Serum Insulin	-0.216	-0.072	-0.171	-0.529*

* Correlation co-efficient is statistically significant based on P <0.05 and 2-sided distribution

4. DISCUSSION

BMI findings show a very strong correlation of ghrelin level with BMI. BMI mean values of both obese and diabetic-obese arms are statistically significant versus control arms and the bivariate analyses of them shows a negative correlation of ghrelin level with BMI. In the same arms the haemoglobin A1C levels were significantly higher than the control arm. This observation might partially confirm that the presence of higher levels of plasma glucose levels suppress the release of ghrelin.

The relationship of ghrelin with LDL-cholesterol levels can not be identified based on the study findings. The LDL-cholesterol is higher in obese and diabetic-obese arms versus control arm. Although bivariate correlation is negative and statistically significant in both arms, but diabetes arm has positive correlation and much lower level of LDL-cholesterol. It can not be precisely judged which one of obesity or diabetes is affecting relationship of LDL-Cholesterol with ghrelin level.

Upon testing the mean ghrelin levels obtained in each group with LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol and Total triglycerides only a straight forward relation can be established between serum ghrelin and HDL-cholesterol. The linear regression has established a statistical significant correlation between HDL-cholesterol and serum ghrelin regardless the study group.

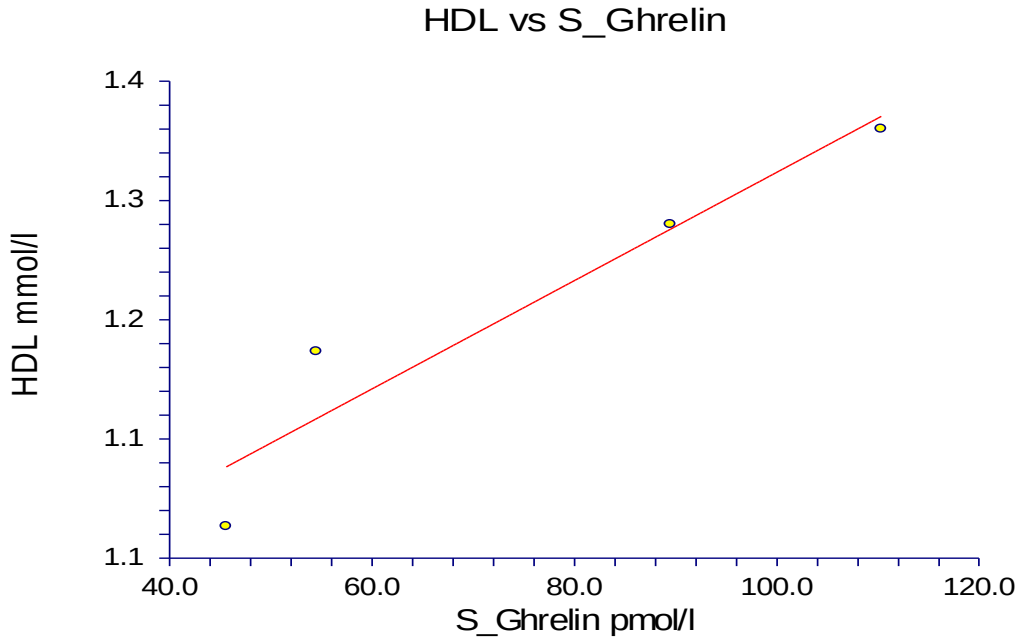

Figure 2: Relationship of HDL-Cholesterol levels and Serum Ghrelin Levels

The general overview is that serum ghrelin is decreasing with obesity and/or diabetes. These lower levels can be related to prolonged higher levels of plasma glucose levels leading less expression of ghrelin. This finding is complying with Capiello et al 2002

5. CONCLUSION

A negative relationship is concluded between serum ghrelin and BMI, FBG and serum insulin levels. This suggests suggest a suppressive controlling mechanism of ghrelin secretion in obese and diabetics.

No relationship can be established between ghrelin level and serum lipids

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