Original Article

Effect of leptin level in non insulin dependant (type 2) obese diabetic subjects

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Summary:

Background: Determine how do obesity and type2 diabetes intertwined? and what it takes to turn an obese person into a person with diabetes. That link may help to understand why some obese people never develop diabetes while many others do.

Serum sugar level was used as indicator of insulin level; leptin level was used as indicator of leptin resistance.

A total of 50 obese subjects were involved in this study, 25 obese subject (BMI >30) had diabetes mellitus type 2(no insulin dependant), selected from Baghdad teaching Hospital in Baghdad /Iraq. The remaining 25 obese (BMI >30) were normal healthy individuals.

Patients and Methods: ELSA technique was used for the measurement of serum leptin. Blood sugar was determined by using colorimetric method. Data were expressed as mean ± SD results and were evaluated using the student t-test for paired data. Conventional methods were used for the correlation and regression analyses.

Results: Obtained results showed that the level of serum leptin in healthy obese subjects were significantly lower than that of obese diabetes subjects. , serum sugar in non diabetic obese subjects was significantly lower than obese diabetes type2 subjects.

Serum leptin correlated negatively with level of serum sugar at the same time had a positive correlation with BMI in non diabetic obese group whereas level of serum leptin correlated positively with each of BMI and serum sugar in diabetic type2 group. All results are thoroughly discussed in the text.

Conclusion: The present study indicates the possibility of future development of a new class of anti diabetic agents that act centrally and independent of insulin action.

Keywords: leptin, diabetes mellitus, obesity & BMI

Introduction:

The maintenance of appropriate body weight is very important for the survival of higher organisms. In order to have a constant weight .there must be an energy balance. Despite short term mismatches in energy balance, energy intake can generally be matched to energy expenditure with great precision due to the existence of several types of signaling biomolecules such as leptin(1,2,3). Obesity is associated with significant morbidity and mortality and poses an immense and increasing public health burden (4). It can be attributed to increased risk of a number of medical conditions including type 2 diabetes mellitus, hypertension and coronary heart disease, which are most common cause of premature mortality in the obese population (5) Leptin is an adiposity-derived hormone that decreases food intake and body weight via its receptor in the hypothalamus. It also modulates glucose by increasing insulin sensitivity (6). Level of insulin is largely determined By glucose (and amino acid from protein) levels. In many people with diabetes, insulin levels are also determined by how much insulin they are taking many have told that what they eat does not matter as long as they take enough insulin to cover it (7). As critical as insulin is to our health, leptin may even more so. New research is revealing that glucose and therefore insulin levels may be largely determined by leptin (8).

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Subject and Method:

A total of 50 subjects were included in this study: 25 of obese diabetic type2 subjects (BMI > 30 Kg /m²) and the remaining 25 subject were obese (BMI > 30 Kg / m²) non diabetic individuals. Age range of the patients was between 35 and 50 years with a mean of 45±8.4 and a mean of (BMI 37.6 ± 2.2 Kg / m²). The remaining 25 non diabetic obese subjects had age range matching to patient's age with mean of 38± 10.2 and a mean of (BMI 36.1 ± 2.4 Kg / m²).

Enzyme linked immune assay (ELSA) was used for the measurement of serum leptin level (9). Colorimetric method was used in the determination of glucose level.

The weight and standing height were obtained to calculate the body mass index (BMI). Data expressed

as mean ± SD results, were evaluated using the student t-test for paired data .Conventional (Rank correlation) methods were used for the correlation and regression analyses.

Results:

The characteristics of non diabetes and diabetic type2 obese subjects are shown in table1.

Table 1: basal characteristics of non diabetic and diabetic type 2 obese subjects

Parameters	Non diabetic obese subjects	Diabetic type2 obese subjects
No. investigated	25	25
BMI Kg/m	36.1 ± 2.4	37.6 ± 2.2
Serum leptin ng /ml	12.9 ± 3.7	29.2 ± 5.5**
Serum sugar mg/dl	134.2 ± 21	253.8 ± 36.1**

Values are expressed as a mean ± SD, BMI, p*< 0.01

This table shows that the level of serum leptin in non diabetic obese subjects is significantly lower than diabetic type2 obese subjects, whereas blood glucose level in diabetic type2 obese subjects is significantly higher than non diabetic obese subjects. The two studied groups have no significant difference in BMI (body mass index). By simple linear regression analysis it was found that level of serum leptin to be negatively associated with serum glucose(fig1) and positively associated with BMI in non diabetic obese group whereas level of serum leptin correlated positively with each of BMI and serum glucose (fig2) in the diabetic type2 group (table 2).

Table 2: the relationship of serum leptin to serum sugar and BMI in both studied subjects (diabetic & non diabetic) obese subjects.

Parameters	Leptin level in non diabetics obese subjects	Leptin level in diabetics type2 obese subjects
BMI	0.9**	1.0**
glucose level	-0.8**	+ 0.7**

P* < 0.0

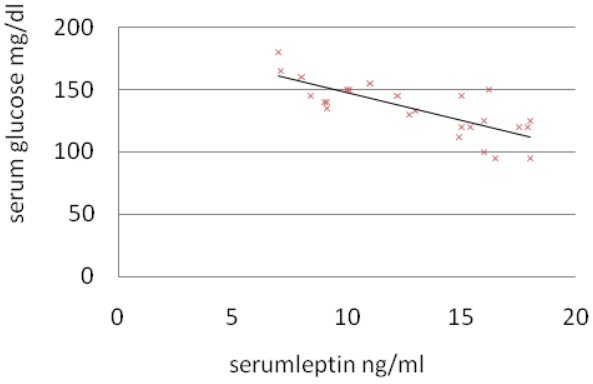

FIG1:correlation between leptin level and glucose level in non diabetic obese group with r= - 0.8,p<0.01)

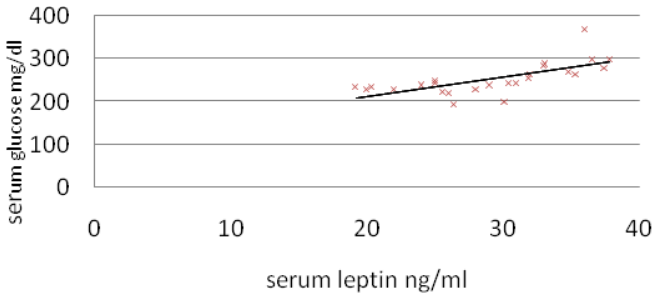

FIG2:correlation between leptin level and glucose level in diabetic type2 group with r=0.7,p<0.01)

Discussion:

The present research tries to shed some light on two epidemics: obesity and diabetes type 2, like two peas in a pod, but how these two epidemics are intertwined? Popular belief is that if one eats too much sugar, he will get fat and develop diabetes, and if he doesn't get diabetes it's merely because his body is producing enough insulin to keep up with sugar (10).The balance between sugar release from the liver, and sugar intake from the diet, is crucial to diabetes type 2 and its precursor conditions, improved glucose tolerance and insulin resistance (11). People with full-blown diabetes have lost the fight between insulin and sugar, and their insulin supply falls woefully short as stressed beta islet cells begin to die (12). Researchers have discovered evidence that there's more to obesity –diabetes connection than this classic way of thinking: the missing link? Leptin(13,14,15) Normally leptin is secreted acutely in response to a meal or chronically in response to increase fat stores. In leptin -sensitive individual, leptin will reduce hunger, increase fat burring, and reduce fat storage (16). leptin's function is to reduce appetite and induce fat burning (among many other function). That is what high leptin

signaling in a brain does. Low leptin in the brain is an indication to eat more fat (that is, to successfully reproduce, and to live long enough to do so) (17). Research on mice has suggested that leptin regulates blood sugar through two different brain –body passageways: (one: responsible for controlling appetite and fat storage, two: responsible for telling the liver what to do with its stored glucose (18). That brain – liver leptin signal pathway is involved in glucose homeostasis , or the circulation of blood sugar by blood sugar feed back loops(19,20) .If there is a lot of sugar in the blood ,homeostatic processes would keep the liver from releasing glucose by tapping into its stored-up supply glucagon ,or long-chain sugar . But if blood sugar gets low the liver might get a signal to release some of its sugar (21). Hormones that control eating such as, leptin and insulin circulate in the blood at concentrations proportional to body-fat mass. They decrease appetite by inhibiting neurons that produce the molecules neuropeptide Y (NPY) & agouti-related protein (AGRP) (stimulate eating), while stimulating melanocortin -producing neurons (inhibit eating) in the arcuate-nucleus region of the hypothalamus, near the third ventricle of the brain (22). It had been previously believed that insulin sensitivity of muscle and fat tissues were the most important factor in determining whether one would become diabetic or not . Elegant new studies are showing that the brain and liver are most important in regulating a person's blood sugar levels especially in type 2 or insulin-resistant diabetes (23).These studies also illustrates the complexity of hormonal orchestration .Especially with very important hormones like insulin and leptin with far ranging effects, a particular cell can be resistant to one effect while the other stays intact. For instance, it had been shown previously that cells may become resistant to the effects of insulin on glucose influx (which may be protective in limiting the amount of glucose entering cells and thus intracellular glycation), while that same cell may not become resistant to the effects of insulin on cellular proliferation that tell cells to multiply, as these are mediated by two separate pathways (24, 25). Present study's results demonstrated that fasting blood serum level of leptin and sugar is elevated in obese diabetic type 2 group, they are likely have leptin-resistant, but how do they become leptin resistant? It was believed that people become leptin resistant by same general mechanism that diabetic type2 become insulin resistant (26); by overexposure to high levels of the hormone. High blood glucose levels causes repeated surges in insulin, and this causes cells to become "insulin-resistant," which leads to further high levels of insulin and diabetes. It is much the same as being in a smelly room for a period of time .soon, you stop being able to smell it because the signal no longer gets through (27). It was believed that the same happens with leptin. It has been shown that as sugar gets metabolized in fat cells, fat release surge of leptin. Those surge result in leptin- -resistance, just as insulin over –exposure results in insulin resistance. Insulin resistance leads to high glucose which contributes to high leptin and leptin resistance, and they both conspire to make people fat and accelerate incidence of diabetes (28). In other words: on one hand, overproduction of adipocyte-dervied hormones: leptin, visfatin, adiponectin, Retinol-Binding Protein-4(RBP4) and resistin are associated with hyperinsulinemia or insulin resistance, high circulating RBP4 levels enables to impair insulin sensitivity and modulate glucose homeostasis (29), high level of sugar and high level of insulin in blood lead to further increase in leptin level, on the other, obesity increaseTumor necrosis factor-alpha(TNF-α) which decrease the insulin sensitivity (30). It was found that Rosiglitazone, a drug used to treat diabetes, lowers circulating RBP4 levels and normalize insulin sensitivity(31).studies was found ,deleting the RBP4 gen in mice increase insulin sensitivity (32).non diabetes obese group may impair the expression of RBP4 gen, genetic studies may be more useful in answering this question. Leptin not only determines how much fat we have, but also where that fat is deposited. When one is leptin resistant, he puts that fat mostly in his belly (his viscera), causing the so-called "apple shape" that is linked to disease. some of that fat permeates the liver, impeding the livers ability to listen to insulin and further hastening diabetes(33).this point can perhaps affect the level of sugar and leptin in non diabetic obese group ?calculation of fat percentage gives more accuracy than measurement of total body mass to clarify this side of discussion. The result of the study is in agreement with the new research (34, 35) which is based on mice that the researchers genetically modified to disable the leptin- STATE 3 cell – signaling passageway that leads from the brain to the body. The mice, called the s/s strain, could still produce both leptin and the receptor it binds to when sending STATE 3 signals to the body. The s/s mice ate too much and become obese, but they did not develop diabetes even after six months, a long time for a mouse. More while, other strains of mice that made no leptin, or have no leptin receptor, all became obese and died of diabetes (36). The present study is also supported by other studies (37, 38): that have shown the brain and liver to be of paramount importance in regulating blood sugar levels especially in type 2 or insulin resistant diabetes. It had been previously.In turn regulates much of our "autonomic" functions; those functions that don't necessarily think about but which determines much of our life (and health). Metabolism can thoroughly be defined as the Chemistry that turns food in to life. Insulin and

Leptin. Therefore, are critical to health and disease..Insulin and liptin work together to control the quality ofmetabolism (and, to a significant extent, the rate of metabolism (39). Present finding suggest that , there is more to the obesity –diabetes link than if you eat too much sugar , you will get fat and get diabetes –and that if you don't get diabetes ,its only because you are making more insulin to keep up with sugar, there is something else contributing.

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