Serum Ghrelin is Related to Beta-Cell Function, not to Insulin Resistance in Type 2 Diabetic

Running Head:
Ghrelin and Beta-cell function in diabetic

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ABSTRACT

Background and Objective: Ghrelin, an acylated 28 amino-acid play an important role in glucose metabolism and energy homeostasis. In the present study, we investigated the relationship between ghrelin with beta cell function and insulin resistance in type 2 diabetic patients. Methods: For this purpose, Forty three adult males with type 2 diabetes (BMI≥30) were enrolled to participate in this study by easy sampling. Blood samples were obtained from each participant in order to measure serum levels of ghrelin, insulin and glucose. Pearson correlations were used to establish the relationship between serum ghrelin levels and fasting glucose (p≤0.001). There were no correlations between serum ghrelin and insulin resistance in this patients. Conclusion: Our findings supports the role of ghrelin in the glucose blood levels in type 2 diabetic patients and this is due to the ghrelin effect on beta cells function rather than its impact on insulin resistance.

Keywords: Ghrelin, Insulin, Glucose, Beta-cell function, Diabetic.

INTRODUCTION

Type 2 diabetic is the most common endocrine abnormality in the worldwide [1]. Initial treatment of this disease is by glucose restoration and normalization of lipid levels through diet [2]. Increase of adipose tissue plays an important role in this phenomenon, although the molecular relationship between increase of adipose tissue and insulin resistance are not fully understood [3, 4]. Several findings support obesity or increase of body fat levels, especially abdominal obesity, as a major cause of Type 2 diabetes in past youth age [5]. Increase of blood glucose and insulin resistance syndrome are of the initial signs of type 2 diabetes pathogenesis and multiple mechanisms involve in this phenomenon [6]. Hyperglycemia in these patients is occurred on the one hand because of insulin resistance in body tissues such as skeletal muscle, liver and adipose tissue and on the other hand, due to the inability of pancreatic beta cells to compensate this resistance [7]. Recently, some study focused on the role of hormones secreted by adipose tissue and some peptide hormones named cytokines as regulators of skeletal muscle metabolism, insulin resistance and ultimately type 2 diabetic. Recent studies suggest that ghrelin plays an important role in glucose homeostasis, particularly in diabetic patients [8, 9]. Studies on Animal [10] and human [11] have shown that approximately 75 to 80 percent of this 28 amino acid peptide hormone is derived from the stomach and the rest is mostly secreted by the small intestine and some other tissues such as pancreatic.

Some recent studies have stated that the use of ghrelin in healthy human leads to increasing blood glucose and have mentioned a positive correlation between these two variables [12]. Some studies also suggest that the changes in ghrelin levels are effective on insulin resistance [13]. These studies have indicated that, low insulin resistance in accompanied with decrease in ghrelin concentration in diabetic patients [14]. On the other hand, some other studies have reported an inverse relation between ghrelin and insulin levels [12, 15]. Although the effect of ghrelin on insulin secretion and changes in blood glucose concentration in humans is not fully understood yet, clinical studies support the role of these peptide hormones in regulating glucose metabolism and energy balance [16]. In addition, some studies also state that ghrelin secreted from the pancreas Epsilon cells [17] and ghrelin receptors in beta cells regulate insulin secretion by these cells [18]. Ghrelin injection has lead to inhibiting insulin secretion from pancreatic beta cells [16]. In this field, Broglie et al. based on their findings has concluded that despite appetite stimulation and growth hormone stimulation, ghrelin also is effective in controlling insulin secretion and glucose and fat metabolism [19]. These studies point out that ghrelin has an inhibitory effect on insulin secretion from pancreatic beta cells [20, 21]. Both ghrelin and GH secretagoues receptor (GHSR) are expressed in human / rat pancreatic islets on both alpha and beta-cells [22, 23, 24, 25]. Ghrelin inhibition or taking its antagonists increases insulin release from the pancreas in order to reduce blood glucose levels in obese subjects [22, 26]. Most studies have noted that serum ghrelin levels have a positive relation with blood glucose concentration. Also increase of blood glucose levels in diabetic patients compared to healthy subjects and its direct correlation with insulin resistance and its effect on blood glucose levels have also been observed in some studies [8, 27, 28]. But despite these observations, the question is which one of the factors including insulin resistance and Beta Cells function, both of which play significant roles in regulating blood glucose, blood Ghrelin level in diabetic patients affects most.

This study, therefore, aims to look into the correlation of serum ghrelin level with glucose, insulin resistance and beta cell function on the one hand and whether the possible increase ghrelin induced glucose in these patients is more rooted in the correlation between ghrelin and Beta Cells dysfunction or the correlation between ghrelin and insulin resistance on the other

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hand. In other words, which one of the two factors (insulin resistance and beta cells dysfunction) has closely relation with serum ghrelin levels?

METHODS

The present study was conducted on a group of adult men with at least five years experience of type 2 diabetes. The studied population included 43 obese men with type 2 diabetes with age range of 38 to 54 years and average weight of 83 to 110 kg who participated in the study through easy sampling method. Inclusion criteria for study group were determined as existing type 2 diabetic for at least five months, having a BMI of 30 or above. Cerebrovascular disease, kidney and liver disease, growth hormone deficiency and anemia were of exclusion criteria of the study. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. Those who were unable to avoid taking hypoglycemic drugs or insulin sensitivity-altering drugs for 12 hours before blood sampling were also barred from participating in the study. All patients were asked to avoid from any heavy physical activity for 48 hours before blood sampling. Initial information was collected regarding diabetes and diabetes treatment drug use clinical history.

Body composition monitor (BF508-Omron made in Finland) with a precision error of less than 100 g was used to measure weight and body fat percentage of the subjects. Subjects’ height was carefully measured while standing along the wall without shoes while their shoulders were in normal conditions. Body mass index (BMI) was calculated using weight divided by squared height. Those with BMI lower than 30 (kg/m2) were excluded. After anthropometric measurements, blood samples were taken between 7:00 and 8:00 a.m. after 10 to 12 hours overnight fast to measure fasting glucose, insulin and serum ghrelin. Serum glucose was determined by enzymatic (GOD-PAP, glucose oxidase-amino antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran), the Intra-assay and interassay coefficient of variation was 1.74% and 1.19% and sensitivity of the method was 5 mg/dL. The blood was centrifuged immediately at 4 °C and stored at −80 °C. Samples were centrifuged immediately for 10 minutes with 3500 rpm in +4 °C in order to measure serum ghrelin levels. The intra-assay and inter-assay coefficient of variation of ghrelin (Biovendor, Austria) were 8.10% and 8.3% respectively. Plasma insulin was determined by ELISA method (Demeditec, Germany) and the intra- assay and inter-assay coefficient of variation of the method were 2.6% and 2.88 respectively.

Depending of the values of insulin and glucose Beta cell function (%B) and insulin resistance index (HOMA2) was calculated using the HOMA Calculator computer program v2.2.2 [29]. It is also important to note that lack of a control group (healthy group) is one of the limitations of this study.

Statistical analysis: Statistical analysis was performed with the SPSS software version 16.0 using a Pearson correlation method to determine the relationship between ghrelin with glucose, insulin, insulin resistance and beta cells function. A p-value < 0.05 was considered to be statistically significant.

RESULTS

In present study, the pattern of relationship between serum ghrelin levels with determinative markers of diabetes was performed in 43 male obese adults with type 2 diabetes. Anthropometric indexes measurements showed that all patients were in obese diabetic category. The ghrelin level of ghrelin was significantly positive associated with glucose concentration (p≤0.001, figure 1). In other words, the increase in serum ghrelin levels was associated with increase in fasting glucose concentration.

Ghrelin was found to be negatively associated with serum insulin (p≤0.001, figure 2). So that, the significant negative correlation between ghrelin and serum insulin showed that increase of blood ghrelin concentration is accompanied reduction in insulin levels. In other hand, findings presented a strongly inverse correlation between the serum ghrelin concentration and beta cells function index (p≤0.001, figure 3). Although increased serum ghrelin was accompanied with increased insulin resistance in the studied population, but this relation in these two variables was non significant (p = 0.083).

Figure 1: Correlation between serum ghrelin and glucose concentration in patients.
DISCUSSION

Findings of the present study support a significant positive relationship between serum ghrelin and glucose concentration. This findings suggest that in diabetic patients, increase in either ghrelin or glucose is associated with increase of other circulation levels. These findings indicate that ghrelin has an important role in systematic glucose homeostasis [16].

But, whether ghrelin affects directly glucose levels or indirectly through insulin-dependent system in diabetic patients. In this context, some studies suggest that there is a significant relationship between serum ghrelin and insulin resistance which is of the major determinants of increase of blood glucose in type 2 diabetic patients [14]. But in our study, despite a strong correlation between ghrelin and glucose concentration, but serum levels of this peptide hormone was not correlated with insulin
resistance in these patients. In fact, although serum ghrelin tended to be positively correlated with insulin resistance, this did not reach statistical significance. On the other hand, our findings showed that there is a strongly inverse relation between serum ghrelin levels and insulin and also beta cells function. Citing these findings, it can be concluded that increase in ghrelin reduces pancreatic beta cells function and leads to reduction of insulin secretion by these cells. Hence, ghrelin indirectly increase blood glucose levels through beta cell dysfunction. In this area, a recent study of Tang et al. showed that ghrelin reduces beta cells function [30]. Regarding the effect of ghrelin on beta cells, recent studies on humans and animal models have shown that the ghrelin changes beta cells function by affecting some neural mediators such as epinephrine, which regulates pancreatic function [31, 32]. To support these findings, intravenous injection of ghrelin to a group of healthy young men (0.3 nmol/kg or 1.0 μg/kg) significantly increased fasting plasma glucose levels followed by a reduction in serum insulin levels beginning at 15 and 30 min after ghrelin administration, respectively, suggesting inhibition of insulin secretion [33].

Significant inverse relationship of serum ghrelin levels with beta cells function index and insulin in the present study shows that ghrelin increase in diabetic patients has a deteriorating effect on beta cells function. These findings have also been observed in some other studies [22, 34]. Changes in blood glucose response to glucose tolerance test concomitant with taking antagonists of ghrelin receptors in pancreas is associated with increase of insulin secretion [30]. Ghrelin gene deletion was shown to prevent glucose intolerance induced by a high-fat diet, an environmentally-induced model of hyperglycemia [21]. The effect of ghrelin on glucose [35] or insulin sensitivity [36] cannot be ignored either. These findings support the physiological effect of ghrelin with endogenous origin in plasma insulin reduction and thereby blood glucose concentration [30]. On the other hand, some studies have revealed that ghrelin could have a direct effect on beta cells or act indirectly by stimulating the secretion of counter-regulatory hormones that affect insulin secretion, or activating neural pathways that regulate islet function such as cortisol or by activating neural pathways that regulate pancreatic function [37, 38]. In this regard, a recent study shows that effect ghrelin on insulin secretion from beta cells is associated with direct relationship between cortisol and ghrelin [16]. An another study showed that deletion or inhibition of genes responsible for producing ghrelin, improves glucose tolerance and increases insulin secretion which refers to the physiological role of ghrelin in pancreatic function [23]. Our observations are in keeping with several in vitro studies that have provided evidence that ghrelin have an inhibitory effect on insulin secretion of pancreatic β-cells [20, 21, 22, 25, 34]. At the end, it is also important to note that regardless the lack of a control group (healthy group), the significant correlation observed between glucose and Ghrelin as well as other variables in diabetic subjects shows that Ghrelin plays an important role in the pathophysiology of this disease which is noteworthy from a clinical perspective.

Conclusion

Altogether, the findings of the current study in support for some other studies suggest that increase of serum ghrelin is accompanied to increasing fasting glucose level and the damage in insulin secretion from beta cells is of the main causes of increase of glucose levels caused by ghrelin. This study showed that increase of blood glucose level is more rooted in the impact of ghrelin on insulin secretion or pancreatic beta cells dysfunction rather than the relationship between ghrelin and insulin resistance. These studies provide a clear explanation for pharmacologically role of ghrelin in glycemic control in diabetic patients.

Acknowledgement: We appreciate of all participant patients, diabetes support association of Islamic Azad University and Danesh hematology laboratory in Saveh city who helped the executors and authors of this study to conduct this project.

REFERENCES


