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ORIGINAL ARTICLE

Fasting leptin and glucose in normal weight, over weight and obese men and women diabetes patients with and without clinical depression

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Abstract A large number of diabetes patients suffer from major depression and are at high risk of mortality. In view of a role of leptin in diabetes, depression and energy homeostasis, the present study concerns circulating levels of leptin in different BMI groups of un-depressed and depressed diabetes patients. Six hundred thirty male and female patients with a primary diagnosis of diabetes were grouped according to BMI and with or without clinical symptoms of depression. Age matched healthy, normal weight male and female volunteers without clinical symptoms of depression or diabetes were taken as controls. Blood samples were obtained after an overnight fast of 12 h. Serum was stored for the determination of leptin and glucose. We found that there were more female than male diabetes patients with comorbid depression. Fasting leptin was higher in normal weight non-diabetes women than men; but comparable in normal weight men and women diabetes patients. Fasting glucose levels were higher in diabetes than non diabetes groups; values were comparable in men and women. Depression was associated with a decrease and increase in leptin respectively in normal-overweight and obese men and women diabetes patients. Glucose levels were also higher in obese depressed than un-depressed diabetes patients. The results suggested that the female gender is at greater risk to comorbid diabetes with depression. Adipo-insular axis plays an important role in diabetes, associated depression and in the greater risk of the female gender to comorbid diabetes with depression.

Keywords Leptin · Diabetes · Depression · Obesity · Gender difference · Adipo-insular axis

Introduction

The increasing prevalence of depression in diabetes patients is becoming a matter of global health concern. About 18% of type 2 diabetes patients suffer from clinical depression (Ali et al. 2006) and are at an increased risk of mortality (Bot et al. 2012; Katon et al. 2008; Lin et al. 2009; Siddiqui 2014). The association between diabetes and depression seems bidirectional; because depression can impair diabetes self care and management to lead to poor glycemic control (Lustman and Clouse 2005) while psychological distress in diabetes (Fiore et al. 2015) can predispose to depression. In addition, evidence suggests that excessive weight gain and obesity can also predispose to type 2 diabetes (Eckel et al. 2011) as well as depression (Luppino et al. 2010; Haleem 2016).

Leptin a peptide hormone is secreted from adipocytes and acts centrally to elicit negative feedback control over energy homeostasis (Haleem 2014, 2016). Although normal or smaller circulating levels of leptin also sometimes occur in obesity (Ioffe et al. 1998) but mostly human obesity is associated with higher levels of circulating leptin (Monti et al. 2006). Leptin receptors are also expressed in beta pancreatic cells and leptin inhibits insulin secretion by binding to these receptors (Fehmann et al. 1997; Seufert et al. 1999; Kieffer and Habener 2000) suggesting a role of leptin in the regulation

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of insulin secretion and in the etiology of type 2 diabetes. In addition, circulating levels of leptin also depend on factors such as age, gender and food intake (Haleem 2014).

A role of leptin in the treatment of depression and other stress related disorders is also gaining attention (Haleem 2014, 2016). Leptin receptors are widely distributed in brain areas involved in emotional control and injected leptin has been shown to produce anxiolytic and antidepressant like effects in experimental animals (Lu et al. 2006; Liu et al. 2010; Haque et al. 2013). Stress effects on food intake, hypothalamo-pituitary-adrenocortical (HPA) axis, anxiety and depression like behavior are also reversed by exogenous leptin (Haque et al. 2013). On the other hand, clinical investigations linking human depression with circulating leptin are not consistent. Lower plasma leptin levels observed in normal weight depressed patients (Kraus et al. 2001; Jow et al. 2006) and suicide attempters (Atmaca et al. 2002; Westling et al. 2004), suggests that leptin deficiency is involved in human depression. But lower plasma leptin is also associated with bipolar depression and mania (Atmaca et al. 2002), while higher leptin levels have been observed in women with clinical depression (Esel et al. 2005).

In view of a role of leptin in diabetes, depression and energy homeostasis, the present study concerns circulating levels of leptin in different BMI groups of un-depressed and depressed diabetes patients. We hypothesize that leptin resistance which blunts its central action, not only produces obesity, but is also involved in the precipitation of depression. A key question addressed in the present study is whether the inhibitory effects of leptin on insulin secretion and therefore on fasting glucose levels are also dysregulated in diabetes associated depression. In view of gender differences in circulating levels of leptin, samples from men and women patients are placed in separate groups. Serum glucose is monitored to determine relationships with circulating leptin.

Method

Setting and subjects

The participants (diabetes patients) were recruited from the outpatient department of the Baqai institute of Diabetology and endocrinology. Informed consent was taken from the patients. Approval to conduct the study was taken from the ethics committee of the institute. Six hundred thirty patients with a primary diagnosis of diabetes presenting to the outpatient Clinic from Jan. 2013 to December 2013 were included in this study. The subjects (male =252, female =378) were of 35–65 years of age and met the American Diabetes association criteria for type 2 diabetes. Patients having history or presence of clinically significant hepatic, renal, gastrointestinal or respiratory diseases were not included in the study. Clinical depression was diagnosed by a psychiatrist using DSM-IV criteria. BMI was calculated as the ratios of weight (kg) to the square of height in meters and values from 18.5 to 24.9 were considered normal weight; from 25 to 29.9 overweight and 30 or above considered obese. Thirty healthy volunteers of both genders (Male =15, Female =15) of normal weight, BMI (18.5 to 24.9) and age ranging 35–65 years were also included in the study for comparison of biochemical parameters. Consent was also taken from the volunteers before starting any procedure.

Specimen collection and analyses

No medications were taken on the morning of the study day. Because number of patients in depressed normal weight men (n = 3), depressed over weight men (n = 9) and depressed normal weight women (n = 8) groups were less than 15; blood samples from all of these patients were included for biochemical analysis. Only 15 samples from each of the other groups were selected randomly for biochemical analysis. Blood samples were obtained via venipuncture at 8:00–10:00 a. m after an overnight fast of 12 h for the determination of serum leptin and glucose.

Fasting blood glucose was estimated by enzymatic colorimetric method [auto analyzer, Selectra Jr. Merck, Korea]; leptin levels were determined using enzyme –linked immunosorbent assay (ELISA) method for which Kit was purchased from the DIA-Source; Leptin-EASIA (Belgium).

Statistical analyses

Results are presented as means ± S.D. Data on serum levels of leptin and glucose in different BMI groups of male and female diabetes patients with and without clinical depression were analyzed by three way ANOVA. Data on serum levels of leptin and glucose in normal weight male and female diabetes and non-diabetes patients were analyzed by two way ANOVA. Post-hoc analysis was performed by Tukeys's test and p values less than 0.05 were taken as significant. Bivariate Pearson correlation was used to determine relationship of circulating glucose and leptin.

Results

Figure 1 shows that of the 630 diabetes patients, 84 (40%) were men and 126 (60%) women, suggesting that female than the male gender in Pakistani population is at a greater risk of diabetes. Categorization based upon the diagnosis of depression shows that 34.3% of women and 32.9% of men do not have clinical depression while 25.7% of women and only 7.1% men are diagnosed with depression, suggesting that comorbid diabetes and depression is greater in women than men. Further division based upon BMI shows that greater

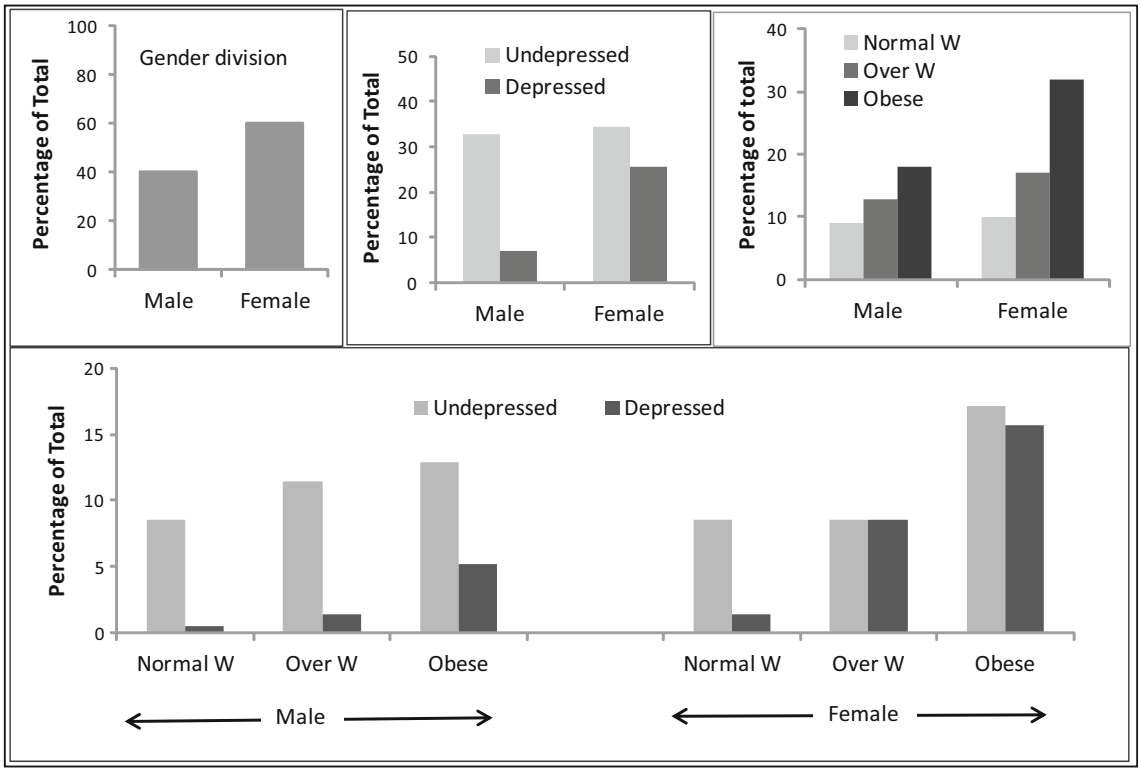

Fig. 1 Number of underweight, overweight and obese, un-depressed and depressed, male and female diabetes patients recruited from the outpatient department of the Baqai institute of Diabetology and endocrinology. Values are a percentage of total (630) patients

occurrence of comorbid diabetes-depression in women is largely due to their greater body weight (overweight or obese).

Figure 2 shows serum leptin levels in male and female diabetes patients of different BMI groups with or without depression. Three way ANOVA shows a significant effect of BMI (F = 262 df2,143 $p < 0.01$) and depression (F = 7.9 df1,143 $p < 0.01$). Gender effects (F = 1.5 df1,143 $p > 0.05$) are not significant. Interaction between gender and BMI (F = 3.05 df2,143 $p = 0.05$), depression and BMI (F = 36.42 df2,143 $p < 0.01$) are significant. Interaction between gender and depression (F = 2.9 df1,143 $p > 0.05$) and for gender x depression x BMI (F = 36.42 df2,143 $p > 0.05$) are not significant. Post hoc comparison shows that overweight and obesity are associated with a weight dependent increase in serum leptin in un-depressed as well as depressed diabetes patients. Leptin levels are significantly smaller in normal weight men and women patients of depressed group than the respective un-depressed group. The decrease in over weight depressed group compared to respective un-depressed group is not significant. Leptin levels are higher in obese men with depression than the respective un-depressed group, but these decreases in women are not significant.

Figure 3 shows serum glucose levels in male and female diabetes patients of different BMI groups with or without depression. Three way ANOVA shows a significant effect of BMI (F = 30.2 df2,143 $p < 0.01$) and depression (F = 66.9 df1,143 $p < 0.01$). Gender effects (F = 3.86 df1,143 $p > 0.05$) are not significant. Interaction between gender and depression (F = 2.58 df1,143 $p > 0.05$), gender and BMI (F = 0.60 df2,143 $p > 0.05$) and for gender x depression x BMI (F = 0.189 df2,143 $p > 0.05$) are also not significant. Interaction between depression and BMI is significant (F = 13.2 df1,143 $p < 0.01$). Post hoc comparison shows that depression in overweight and obese diabetes men is associated with an increase in serum glucose compared to respective un-depressed group. Depressed than un-depressed diabetes women also have higher glucose levels, but these increases in overweight women depressed than un-depressed women are not significant.

Figure 4 shows serum leptin (a) and glucose (b) levels in normal weight non diabetes subjects and diabetes patients. Data on serum leptin analyzed by two way ANOVA shows significant gender (F = 12.05 df1,56 $p < 0.01$) and diabetes (F = 38.8 df1,56 $p < 0.01$) effects and a significant (F = 8.0 df1,56 $p < 0.01$) interaction between gender and diabetes. For glucose levels, diabetes effects are significant (F = 183.7 df1,56 $p < 0.01$) but gender effects (F = 0.10 df1,56 $P > 0.05$) and interaction between gender and diabetes (F = 0.004 df1,56 $p > 0.05$) not significant. Post hoc test shows that leptin, but not glucose levels are higher in non diabetes women than men. Serum glucose levels are higher in diabetes than non diabetes men as well as women. Diabetes men, but not women have higher circulating leptin compared to the respective non diabetes group. There is a significant positive correlation between serum leptin and glucose (Fig. 3c) and R2 value is much higher in men than women.

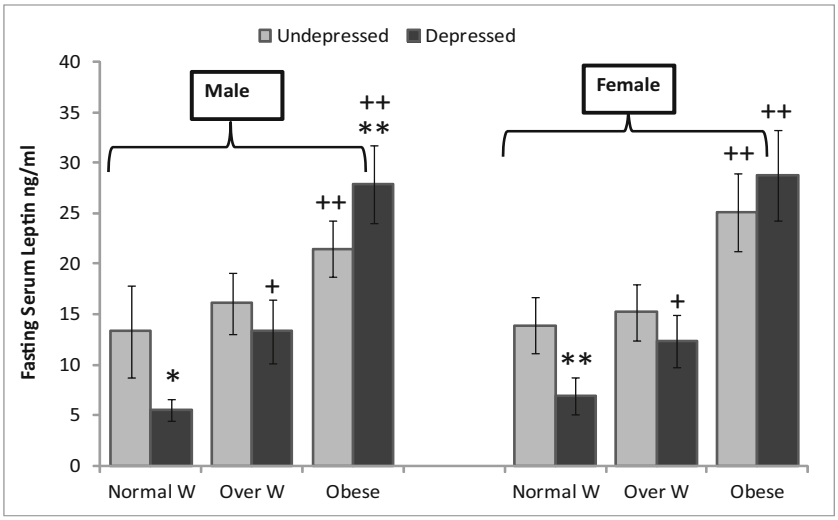

Fig. 2 Serum Leptin levels in normal weight, overweight and obese diabetes patients of un-depressed and depressed groups. Values are means ± SD. Significant differences: *$p < 0.05$; **$p < 0.01$ from respective un-depressed group; +$p < 0.05$, ++$p < 0.01$ from respective normal weight group following three way ANOVA

Relationship of serum leptin and glucose with BMI in men and women diabetes patients is shown in Fig. 5. There is a positive correlation between serum leptin and BMI as well as serum glucose and BMI. Regression analysis shows that R2 values for leptin and BMI as well as glucose and BMI association are much higher for depressed than un-depressed groups.

Figure 6 shows correlation between fasting glucose and leptin in different BMI groups of un-depressed and depressed diabetes patients. There is a significant positive correlation between the two variables. The R2 value is much higher for depressed than un-depressed patients, but R2 value based on gender is only slightly greater in women than men.

Discussion

The present study was conducted to evaluate a role of leptin in depression associated with diabetes. We hypothesized that diabetes patients with depression have higher levels of leptin in circulation and insensitivity to excessively produced leptin i.e. leptin resistance precipitates depression in diabetes. The finding that circulating leptin is higher in both men and women depressed than un-depressed, obese diabetes patients supports our hypothesis (Fig. 2). On the other hand, smaller levels of circulating leptin in particularly normal weight depressed than un-depressed diabetes patients is indicative of leptin deficiency and not insensitivity to leptin associated with depression in diabetes. The decreases of leptin associated with depression in overweight diabetes patients are not significant.

Leptin is produced and released primarily by adipocytes, its levels in circulation are therefore proportional to body fat and BMI (Considine et al. 1996; Klok et al. 2007; Hopkins and Blundell 2016). It can cross blood brain barriers to act via its receptors in the hypothalamus, resulting in an inhibition of orexigenic and facilitation of anorexigenic signals (Haleem 2016). Administration of exogenous leptin has been also shown to decrease food intake and body weight gain in experimental animals (Haque et al. 2013; Haleem et al. 2015). On the other

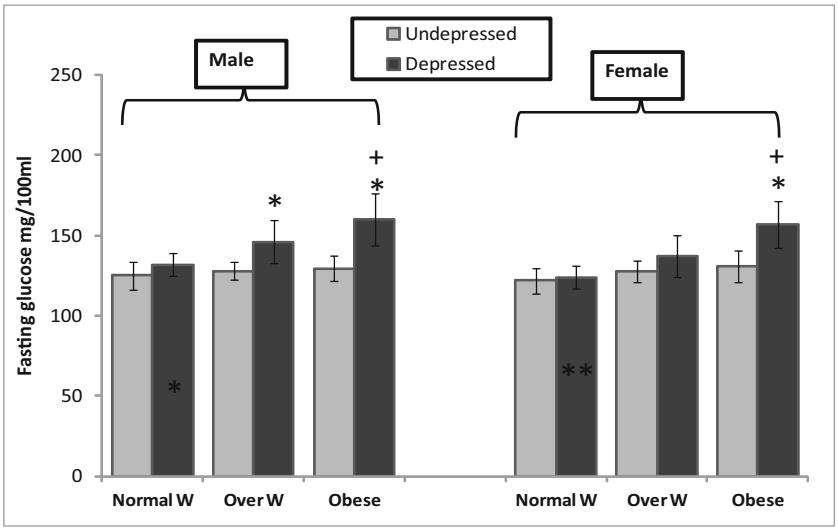

Fig. 3 Serum glucose levels in normal weight, overweight and obese diabetes patients of un-depressed and depressed groups. Values are means ± SD. Significant differences: *$p < 0.01$ from respective un-depressed group; +$p < 0.01$ from respective normal weight group following three way ANOVA

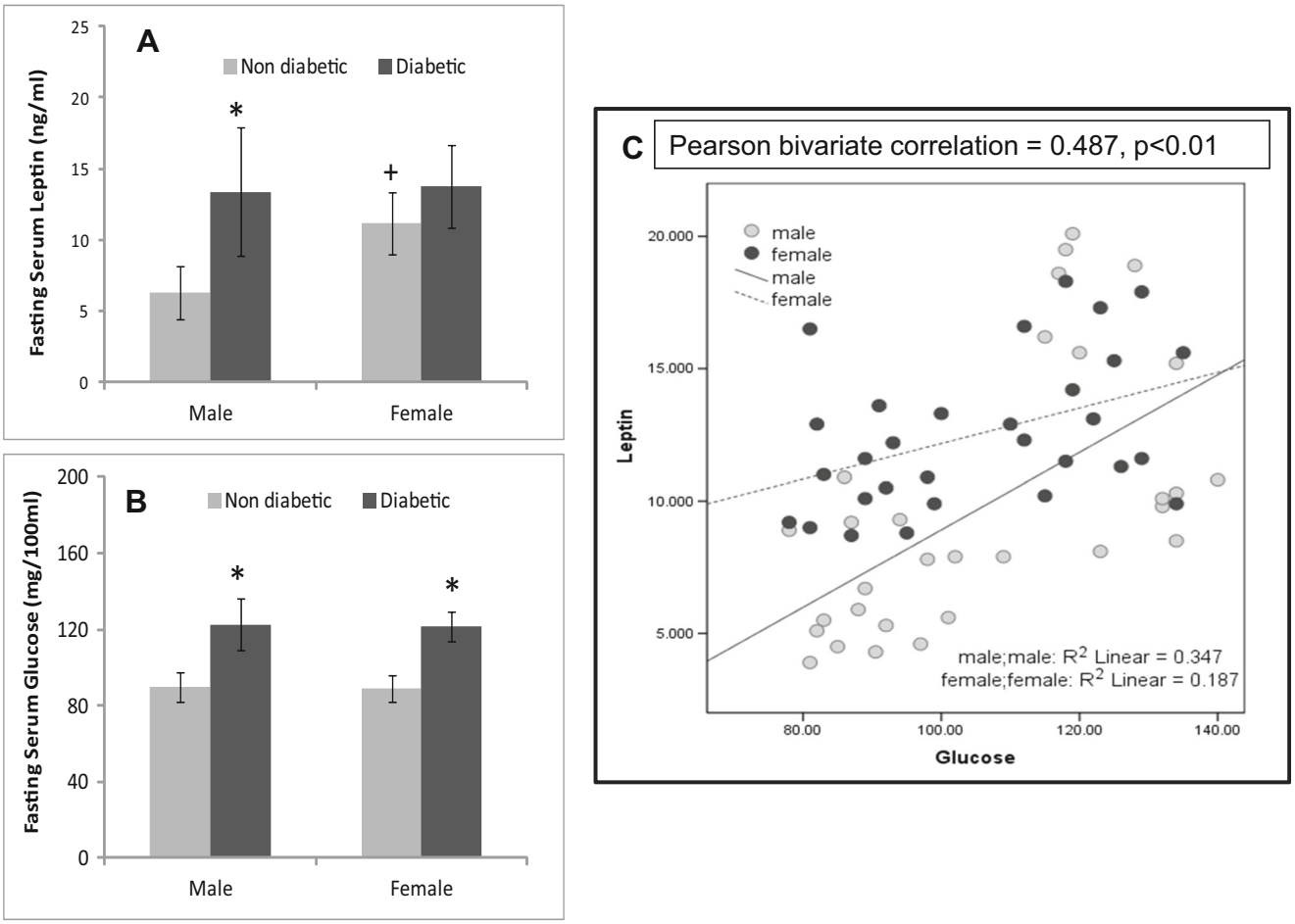

Fig. 4 Fasting leptin (**a**) and glucose (**b**) levels; in normal weight men and women, non diabetes subjects and diabetes patients. Values are means ± SD (n = 15). Significant differences: *$p < 0.01$ from respective non diabetes controls, +$p < 0.01$ from a similar group of male gender following two way ANOVA. Correlation and regression line between serum leptin and glucose is shown in (**c**)

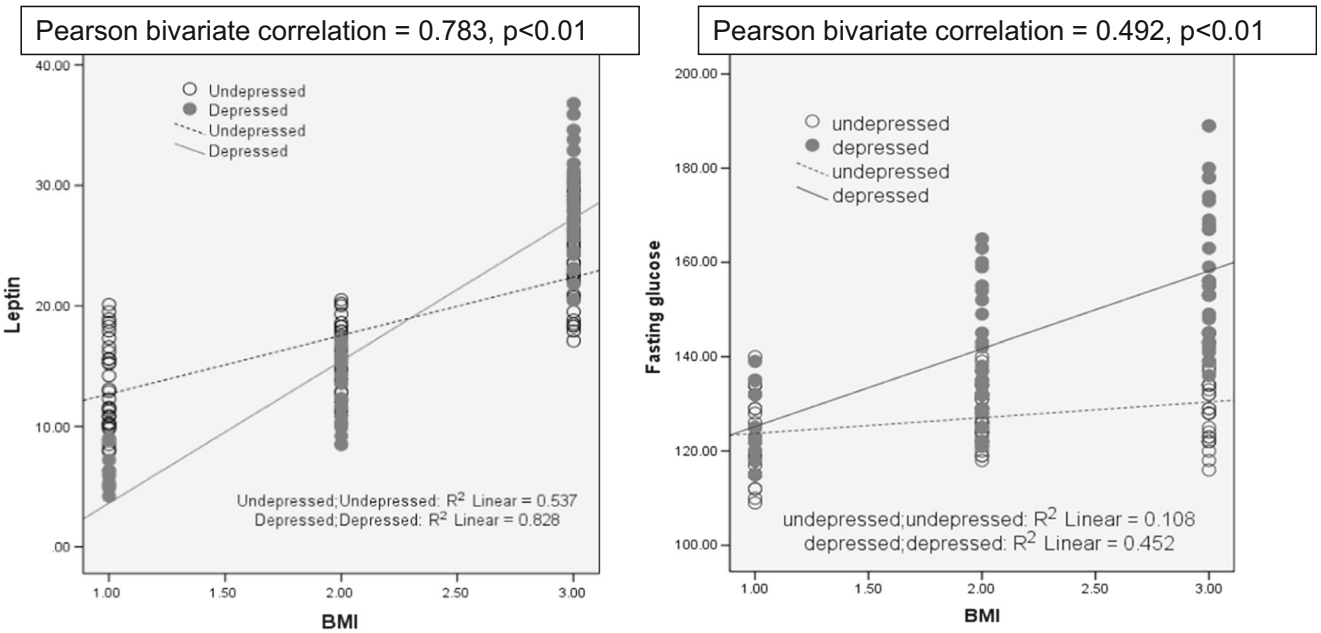

Fig. 5 Relationship of BMI with serum leptin and glucose levels in un-depressed and depressed groups of diabetes patients

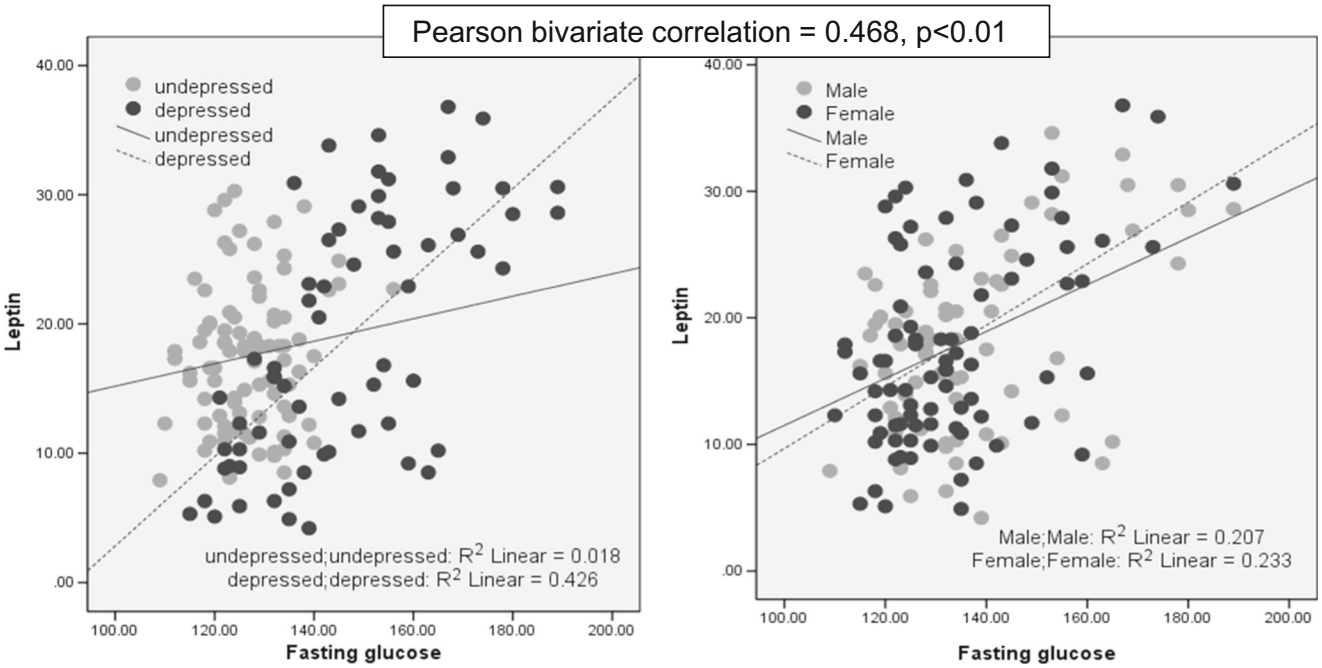

Fig. 6 Correlation between serum leptin and glucose levels in normal weight, over weight and obese diabetes male and female patients with and without depression. Regression lines between the two variables are drawn to compare depression and gender influence

hand, human obesity is largely associated with excessive production of leptin. The coexistence of elevated leptin levels with obesity is widely interpreted as evidence of "leptin resistance" (Haleem 2016; Meyer et al., 2010). We also find an increase in circulating leptin associated with an increase in BMI in both male and female diabetes patients (Fig. 2). A significant positive correlation between circulating leptin and BMI together with much higher R2 value for depressed than un-depressed patients (Fig. 5) suggests that greater leptin resistance is a contributing factor of depression in obese diabetes patients while leptin deficiency may produce depression in normal weight diabetes patients.

Leptin inhibits insulin secretion by binding to the functional leptin receptors expressed in pancreatic β-cells (Fehmann et al. 1997; Seufert et al. 1999; Kieffer and Habener 2000; Könner and Brüning 2012; Borer 2014). These studies raise the possibility that leptin is involved in the aetiology of type 2 diabetes through its effect on the regulation of insulin secretion. On the other hand, reports on circulating levels of leptin in diabetes patients are not very consistent. An increase (Fischer et al. 2002), no association other than BMI (Bandaru and Shankar 2011) and even a decrease (Sayeed et al. 2003) are reported to occur in diabetes patients. We therefore determined circulating leptin and glucose in normal weight non-diabetes subjects to compare it with values observed in normal weight diabetes patients (Fig. 4). Higher circulating leptin in normal weight non-diabetes women than men, as observed in the present study, is also reported by other authors (Hickey et al. 1996; Haffner et al. 1996; Geer and Shen 2009). Gender differences in fat size and distribution, testosterone and estrogens (Van Harmelen et al. 1998; Montague et al. 1997; Sudi et al. 2000; Fuente-Martín et al. 2013) are thought to play a role in the gender differences of circulating leptin in healthy normal weight subjects. In addition, we show that gender differences of circulating leptin do not occur in normal weight diabetes patients (Fig. 4).

Although fasting leptin levels are higher in women than men non-diabetes healthy subjects; gender differences do not occur in glucose levels; and fasting glucose levels are comparable in men and women non diabetes subjects (Fig. 4). These are also comparable in normal weight men and women diabetes patients. A positive correlation between serum leptin and glucose in normal weight men and women diabetes and non diabetes subjects, as observed in the present study, is consistent with the view that an inhibitory effect of leptin on insulin secretion is involved in the aetiology of type 2 diabetes (Seufert 2004); while a higher R2 value for men than women is due to greater increase of circulating leptin in men than women normal weight diabetes patients.

Leptin-induced inhibition of insulin release is only one part of bidirectional feedback loop between adipose tissue and pancreas. The adipogenic effects of insulin have been also demonstrated (Laferrère et al. 2002; Moreno-Aliaga et al. 2001; Smith and Kahn 2016). The inhibitory effects of leptin on insulin secretion together with stimulatory effects of insulin on leptin biosynthesis and release represent physiologically adapted set points within the adipo-insular axis of energy homeostasis. The present findings (Fig. 4) are relevant that due to the gender differences of circulating leptin, the physiologically adapted set points within the adipo-insular axis are different in men and women.

Insulin resistance associated with type 2 diabetes increases fasting glucose levels. It may be speculated that the

stimulatory effects of insulin on leptin release are also diminished in type 2 diabetes. Higher circulating leptin in normal weight diabetes than non diabetes men (Fig. 4) is therefore not explainable in terms of insulin resistance. It would suggest that greater circulating leptin inhibits insulin release from the pancreatic cells to lead to type 2 diabetes. Women seem to be more sensitive to this inhibitory effect of leptin and only marginal increases in leptin are associated with the increases in glucose comparable to male diabetes patients.

An important finding of the present study is smaller circulating leptin in normal-over weight depressed compared to the respective weight un-depressed diabetes patients. The results support leptin deficiency hypothesis of depression (Haleem 2014; Lu et al. 2006; Liu et al. 2010; Haque et al. 2013). On the other hand, higher circulating leptin in the depressed than un-depressed group of obese diabetes patients is relevant that resistance to the central effects of leptin (Haleem 2016) is involved in depression observed in the obese group of diabetes patients.

It is important to note that despite smaller circulating levels of leptin, glucose levels are no smaller in normal-over weight depressed compared to the respective weight un-depressed diabetes patients (Figs. 2 and 3). The results cannot be explained in terms of smaller inhibition of insulin release from the pancreas. It is however possible that greater insulin resistance in depressed than un-depressed normal-overweight diabetes patients decreases circulating leptin to precipitate depression. On the other hand, higher circulating leptin as well as glucose associated with depression in obese group of diabetes patients is indicative of a greater inhibitory effect of circulating leptin on insulin release in depression associated with obesity in diabetes patients.

Despite gender differences observed in circulating levels of leptin in normal weight non diabetes subjects, it is important to note that gender differences in circulating leptin do not occur in diabetes patients (Figs. 1 and 4). Both men and women diabetes patients exhibit a weight dependent increase in leptin. Fasting glucose levels are also higher in depressed than un-depressed diabetes patients, particularly in the obese group. The correlation between serum glucose and leptin is therefore determined to monitor the responsiveness of pancreatic beta cells to circulating leptin. A positive correlation with higher R2 value for depressed than un-depressed diabetes patients (Fig. 6) but comparable R2 values in men and women patients representing greater inhibition of leptin-induced insulin release in depression suggests an important role of adipo-insular axis in comorbid diabetes with depression.

That prevalence of diabetes is greater in women than men, is reported in other studies (McCollum et al. 2005; Juutilainen et al. 2004; Siddiqui et al. 2013). The present study shows that the occurrence of comorbid depression and diabetes is greater in women than men (Fig. 1). A number of preclinical and clinical studies show that the female sex is at a greater risk for depression because of gender differences in responses to stress (Gobinath et al. 2015; Haleem 2011; Ter Horst et al. 2012). Exogenous leptin inhibits stress-induced increase in HPA axis activity to produce anxiolytic and antidepressant like effects (Haleem 2014; Haque et al. 2013). Sex related studies on stress reducing effects of leptin may well explain greater occurrence of depression in women than men diabetes patients.

In conclusion, the present study shows that female gender is at greater risk to comorbid diabetes with depression. Adipo-insular axis seems to have an important role not only in diabetes, but also in depression observed in diabetes patients and in the greater risk of the female gender to comorbid diabetes with depression. Resistance to the stimulatory effects of insulin on leptin release seems to have a role in depression observed in normal-overweight diabetes patients, while greater leptin resistance may produce depression in obese group of diabetes patients. Gender differences in the physiologically adapted set points within the adipo-insular axis can increase depression risk in women than men diabetes patients. The findings may help to improve understanding of leptin resistance and therapeutics in diabetes, obesity and depression.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

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