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Original Research Article

The relationship of serum leptin, serum TNF-α, plasma lipids and obesity parameters in patients treated with weight neutral antidepressants

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ABSTRACT

Background: Leptin and tumor necrosis factor (TNF-α) are involved in weight regulation1. Elevated lipids are frequently encountered in obese people which are helpful in the formation of atherosclerotic plaques in the coronary arteries. This study helps us to know whether weight neutral antidepressant therapy can be therapeutic option in those with obesity associated with depression.
Methods: It is a Longitudinal study of sample size 72 where Patients with obesity attending to JSS hospital who are found to be depressive in both inpatients and out patients fulfilling the inclusion and exclusion criteria.
Results: Our study showed mean difference value of weight, BMI and waist circumference, S. leptin, S.TNF-α, S. total cholesterol, S. LDL-C, S. VLDL-C, triglycerides of obese patients treated with lifestyle modifications, psychotherapy and weight neutral antidepressants at baseline and 3rd month was significantly decreased when compared to obese patients treated with lifestyle modifications, psychotherapy alone at baseline and 3rd month is 3.5kgs, 1.2kg/m^2, 0.89cm, 9.53pg/ml, 10.86pg/ml, 22.34mg/dl, 17.94mg/dl, 4.42mg/dl, 21.78mg/dl and 1.2kgs, 0.32kg/m^2, 0.02cm, 5.22pg/ml, 7.86pg/ml, 11.72mg/dl, 15.37mg/dl, 1.98mg/dl, 9.54mg/dl respectively (p=0.0001).
Conclusions: Our study demonstrated a significant weight loss, and significant decrease in S. Leptin, S. TNF- α, TC, LDL-C, VLDL-C, triglycerides, when obese patients treated with lifestyle modifications, psychotherapy and weight neutral antidepressant (Desvenlafaxine).

Keywords: Antidepressants, Depression, Lipid profile, Obesity, Serum leptin, Serum TNF-α

INTRODUCTION

Leptin and tumor necrosis factor (TNF- α) are involved in weight regulation.[1] To assess whether weight neutral antidepressant therapy is useful in reducing the weight as depression is commonly associated with obesity.

Leptin, which is synthesized by adipocytes, regulates appetite and body weight by activating leptin receptors in the satiety center of the hypothalamus.[2-3] Administration of leptin reduces nutrient intake and body weight. Plasma leptin levels have prominent effects on body mass index (BMI) and body fat ratio. Leptin with its class-I cytokine receptor modulates the cellular immune response, and inflammatory cytokines such as TNF- α liberate leptin from adipocytes.[3]

Circulating levels of TNF- α and its soluble receptors are increased in obese subjects compared to lean controls and decrease with weight loss.[4,5] In vitro and some in vivo data suggest that the TN system and leptin are linked together.[6]

Hypercholesterolemia, high triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels and low high-density lipoprotein cholesterol (HDL-C) levels are frequently encountered in obese people which are helpful in the formation of atherosclerotic plaques in the coronary arteries.[7,8]

This study helps us to know whether weight neutral antidepressant therapy can be therapeutic option in those with obesity assosciated with depression.

Objectives of the study was to compare the effect of weight neutral antidepressant therapy in primary obesity and to compare the relationship of serum leptin, serum TNF- α, serum lipids and clinical obesity parameters in obese patients treated with lifestyle modifications, psychotherapy, weight neutal antidepressants and lifestyle modications, psychotherapy alone.

METHODS

Source of data

It is a Longitudinal study of sample size 72 where Patients with obesity attending to JSS Hospital who are found to be depressive in both inpatients and out patients during the study period from October 2015 to September 2017, fulfilling the inclusion and exclusion criteria.

Inclusion criteria

- Age: >20yrs
- Patients who are obese according to south asian BMI
- Mild and moderate depression according to HAM-D rating scale

Exclusion criteria

- Bipolar disorder patients
- Schizophrenia
- Acute or chronic inflammation and infection or auto immunological, endocrinological or hematological disease or cardiovascular diseases
- Those with oedema irrespective causes

Selection of cases

After meticulous screening, those patients who satisfied inclusion criteria were enrolled for this study and consent taken.

Sampling procedure

72 patients with obesity with mild or moderate depressive disorder will be selected and divided into 2 groups, one group with 36 patients selected and treated with lifestyle modifications and psychiatric counselling and another group of 36 patients treated with weight neutral antidepressants (Tab Desvenlafaxine) along with lifestyle modifications and psychiatric counselling for 3months. Before starting the treatment physical parameters and relevant investigations would be conducted. Patients who satisfy inclusion and exclusion criteria will be followed up with physical parameters and relevant investigations at baseline and 3rd month.

Clinical charts were reviewed, severity of depression through HAM-D scale, previous usage of antidepressants. Detailed physical examination of the patients done including the Height, weight, BMI, waist circumference and detailed systemic examination was done. Laboratory data like complete blood count, RFT, LFT, Thyroid profile were measured at baseline. serum leptin, serum TNF-α and Lipid profile were measured at baseline and 3rd month.

Description of tests

Serum Leptin and serum TNF-α was measured using the R&D System the Quantikine human TNF-alpha immunoassay and Quantikine human leptin immunoassay is a 3.5 or 4.5hour solid phase ELISA designed to measure human TNF-alpha and human leptin in cell culture supernates, serum, and plasma. The inter-assay coefficients of variation were 7.4% for TNF-α and 5.4% for Leptin. We measured serum TNF-a and serum leptin in 72 blood samples at baseline and 3rd month.

Statistical analysis

Data collected will be entered in MS-excel 2010 and analysed using SPSS version-22. Descriptive statistical measures like percentage, mean and standard deviation will be applied. Inferential statistical tests like chi-square test and repeated measures ANOVA will be applied.

RESULTS

Gender distribution of all subjects taken in the study

Total subjects taken in the study was 72, Among females occupying the percentage 59.7 % (43) more among males occupying the percentage 40.3% (29) as shown in Figure 1.

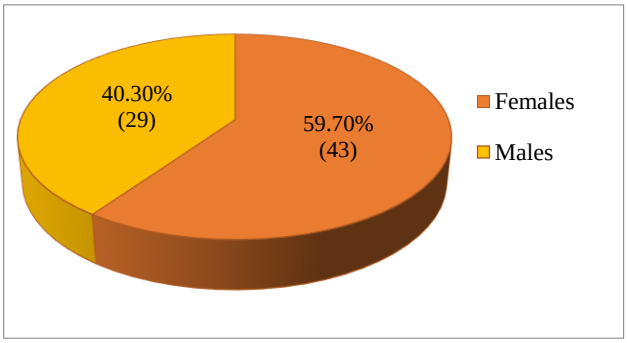

Figure 1: Gender distribution.

HAM-D scale of subjects in correlation to weight neutral antidepressants

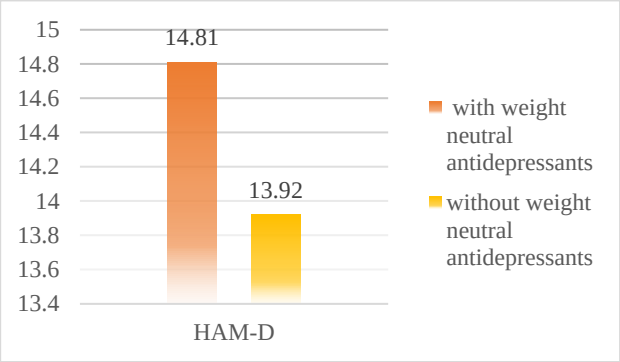

Figure 2: HAM-D scale.

In this study the mean HAM-D scale among individuals treated with weight neutral antidepressant is 14.81 with a standard deviation of 1.99 which is higher when compared to the mean of individuals treated without weight neutral antidepressants as shown in Figure 2.

Our study showed mean difference value of weight, BMI and waist circumference of obese patients treated with lifestyle modifications, Psychotherapy and weight neutral antidepressants at baseline and 3rd month was significantly decreased when compared to obese patients treated with lifestyle modifications, psychotherapy alone at baseline and 3rd month is 3.5kgs, 1.2kg/m^2, 0.89cm and 1.2kgs, 0.32kg/m^2, 0.02cm respectively.

In this study, our study showed Mean difference value of serum leptin and serum TNF- α of obese patients treated with lifestyle modifications, psychotherapy weight neutral antidepressants at baseline and 3rd month was significantly decreased when compared to obese patients treated with lifestyle modifications, Psychotherapy alone at baseline and 3rd month is 9.53pg/ml, 10.86pg/ml and 5.22pg/ml, 7.86pg/ml respectively (p=0.0001) (Table 1.)

Table 1: Obesity parameters of subjects in correlation to weight neutral antidepressants.

	With antidepressants					Without antidepressants				
	Baseline	**SD**	**3rd month**	**SD**	**P value**	**Baseline**	**SD**	**3rd month**	**SD**	**P value**
Weight (kgs)	90.13	13.3	86.63	12.8	0.0001	85.53	10.7	84.303	9.4	0.314
Height (cms)	164.03	6.5	163.7	5.7	0.552	161.4	7.7	161.1	7.5	0.536
BMI (kg/m^2)	33.38	3.47	32.18	3.41	0.001	32.79	3.25	32.47	3.15	0.370
Waist CIR (cms)	115.14	5.38	114.25	5.15	0.0001	115.69	5.72	115.67	6.01	0.937

Table 2: Serum leptin and serum TNF-α of subjects in correlation to weight neutral antidepressants.

	With weight neutral antidepressants					Without weight neutral antidepressants				
	Baseline	**SD**	**3rd month**	**SD**	**P value**	**Baseline**	**SD**	**3rd month**	**SD**	**P value**
Mean s. leptin (pg/ml)	58.06	8.09	48.53	8.18	0.0001	56.78	7.89	51.56	7.370	0.0001
Mean S.TNF-α (pg/ml)	79.47	9.72	68.61	9.01	0.0001	79.69	9.25	71.83	9.25	0.0001

Table 3: Lipid profile of subjects in correlation to weight neutral antidepressants.

Mean	With weight neutal antidepressants					Without weight neutral antidepressants				
	Baseline	**SD**	**3rd month**	**SD**	**P value**	**Baseline**	**SD**	**3rd month**	**SD**	**P value**
Total cholesterol	214.17	31.7	191.83	24.1	0.0001	212.06	30.30	200.28	23.5	0.0001
HDL	39.69	5.00	45.47	4.18	0.0001	42.97	6.07	46.69	5.12	0.0001
LDL	173.47	26.49	155.53	20.2	0.0001	134.67	26.2	119.3	20.6	0.0001
VLDL	34.83	5.51	30.42	5.24	0.0001	35.78	6.37	33.8	5.76	0.001
Triglyceride	174	27.8	152.2	26.4	0.0001	179.25	31.86	169.61	28.6	0.001

Among lipid profile, our study showed Mean difference value of Serum Total cholesterol, serum LDL, serum VLDL, serum Triglycerides of obese patients treated with weight neutral antidepressants at baseline and 3rd month was significantly decreased when compared to obese patients treated without weight neutral antidepressants at baseline and 3rd month is 22.34mg/dl, 17.94mg/dl, 4.42mg/dl, 21.78mg/dl and 11.72mg/dl, 15.37mg/dl, 1.98mg/dl, 9.54mg/dl respectively (p=0.0001) as shown in Table 2.

Mean Serum High density lipids (HDL) of the obese patients treated with weight neutral antidepressants has significant increase in 5.78mg/dl at 3rd month (BL-39.69, SD-5.00 and 3rd month-45.47, SD-4.18) when compared to the obese patients treated without weight neutral antidepressants with significant increase 3.72mg/dl at 3rd month (BL-42.97, SD-6.07 and 3rd month-46.69, SD-5.12 (p=0.0001) (Table 3.)

DISCUSSION

During treatment of various diseases, increased body weight is regarded as a sign of improvement. However, drug induced alterations of the mechanisms regulating appetite may result in excessive weight gain and thus endanger compliance with the medical treatment. Various drugs can alter body weight as a negative outcome of their therapeutic effects. These drugs include psychotropic drugs such as antipsychotics, antidepressants and mood stabilizers. Weight gain is thought to be partially caused by both reduced physical activity caused by the sedative effects of the drugs and excessive consumption of high-calorie diet. Excessive fat deposition in adipose tissue and abdominal distribution of this fat negatively influence health in humans.

Abdominal obesity is strongly related to disorders involving glucose, insulin and lipid metabolism. In addition to its role in energy storage, adipose tissue also secretes various biologically active adipokines. Among these, leptin and tumor necrosis factor (TNF-α) are involved in weight regulation.

Altered lipid and lipoprotein metabolism in obese individuals have been demonstrated in several studies. Hypercholesterolemia, high triglyceride and LDL-C levels, and low HDL-C levels are frequently encountered in obese people. The altered lipoprotein levels and composition are possibly associated with a higher obesity-related risk of cardiovascular diseases.

A considerable amount of data shows that diets rich in saturated fatty acids are associated with increases in overall adiposity and bias fat accumulation in abdominal stores. As compared to individuals on a Mediterranean diet, those consuming a diet high in saturated fat have increased weight gain, a greater volume of visceral adipose tissue, larger waist circumference and more cardiovascular disease mortality.[9-11] Evidence suggests that diets high in saturated fat and relatively low in polyunsaturated and monounsaturated fatty acids contribute to the pathogenesis of both mood and metabolic disorders during obesity. A successful reducing diet is one that an individual can adhere to for several months to lose 5% to 10% of initial weight. Greater weight loss is desirable because it is associated, in a linear manner, with greater improvements in CVD risk factors, including HbA1c, blood pressure, triglycerides, and high-density lipoprotein cholesterol.[12]

Physical activity also offers several other benefits (mental and physical) than weight loss. It is well documented that it increases self-confidence, improves mood, decreases cardio-vascular disease (independent of weight loss) and the risk of drug use. But physical activity alone without diet Changes has a smaller effect on weight loss than that obtained with both interventions.[13,14]

Recent studies from NAMI, there will be good evidence that mild to moderate depressive episodes respond well to psychological treatments. The present study was designed longitudionally to investigate the effect of lifestyle modifications, psychotherapy and weight neutral antidepressant (Desvenlafaxine) on clinical obesity paramaters (weight, BMI, waist circumference), serum leptin, serum TNF-α and lipid profile.

Age and gender distribution

The study included total of 72 subjects and 43 of them were females and 29 of them were Males and majority among them with age group 20-40years. Out of 36 subjects treated with weight neutral antidepressants, 21 of them were females and 15 of them were males and majority among them with age group 20-40years. According to the National Family Health Survey (NFHS), the percentage of ever-married women aged 15-49yrs who are overweight, and obesity are more than three times higher in urban areas. This may be due to lesser physical activity in the urban areas.

WHO states that the burden of depression is 50% higher for females than males and Indians are reported to be among the world's most depressed. The prevalence of depression is 9%, of which major depressive episode is 36%, and the average age of onset of depression is 31.9years, in India. The prevalence rates of depression from India range from 1.5/1000 to 37.74/1000.[15] Women have the greatest risk for developing depressive disorders during their child-bearing years. Psychosocial events such as role stress, victimization, sex-specific socialization, internalization, coping style, disadvantaged social status, and perceived stigma of mental illness, more in females have all been considered to contribute to the increased vulnerability of women to depression.

Obesity parameters in correlation to weight neutral antidepressants

Our study showed mean difference value of weight, BMI and waist circumference of obese patients treated with lifestyle modifications, Psychotherapy and weight neutral antidepressants at baseline and 3rd month was significantly decreased when compared to obese patients treated with lifestyle modifications, psychotherapy alone at baseline and 3rd month is 3.5kgs, 1.2kg/m^2, 0.89cm and 1.2kgs, 0.32kg/m^2, 0.02cm respectively.

Obesity markedly increases the odds of developing depression. Mood disorders are now well recognized as significant risks of obesity and related metabolic illnesses. A meta-analysis of longitudinal data figures obesity (BMI $\geq$ 30) to increase the overall risk of onset of depression by 55% in Americans while overweight (BMI 25-29.9) to heighten the incidence of depression by 27%.[16]

Abdominal adiposity and poor diet quality have been implicated in the development of depressed mood. There is also a bidirectional association between obesity and depression such that depressed individuals are more likely to gain excessive weight due to poor food choices and reduced physical activity. External or psychological stressors can have divergent effects on feeding behavior such that some individuals increase food intake in response to a stressful experience while others eat less.

Drug induced weight gain is a common side effect of many antidepressants. weight gain compromises the patient's treatment compliance and increases the risk of endocrine and vascular diseases. Among antidepressants TCAs (Tricyclic antidepressants), MAOIs (Monoamine oxidase inhibitors), and mirtazapine are known to have more problems related to weight gain. Antidepressants are interacting with various chemical receptors in the brain which are especially assosciated with a proclivity towards weight gain with antagonist effect of a receptor. Muscarinic acetylcholine receptors and histamine receptors are blocked by the antidepressants has more weight gain when compared to others which didn't block them. Antidepressants such as TCAs blocked these receptors and reliably made people weight gain. SSRIs have more anticholinergic activity and cause more weight gain.

In our study, desvenlafaxine has significant weight loss 3.5kgs in asssosciated with lifestyle modification and psychotheraphy. Studies suggest that the SNRI venlafaxine extended release (ER) is no more likely than SSRIs to cause weight gain in the short term and that significant weight changes are no more common with maintenance treatment with venlafaxine ER (up to 2years) than with placebo.[16-18] Desvenlafaxine was not associated with clinically significant weight change during short- or longer-term treatment.[19,20]

Serum leptin and TNF-α in correlation to weight neutral antidepressants

In our study, serum leptin and serum TNF-α are related to the weight regulation and these adipokines significantly decreased along with weight when obese patients treated with Desvenlafaxine, lifestyle modifications and psychotherapy.

Serum leptin levels are higher in females than males, partly as a result of inhibition by androgens, stimulation by estrogen and depot-related differences in leptin expression. Leptin synthesis is greater in subcutaneous than in visceral adipose tissue, and the higher circulating concentration of leptin in females is likely to be due, in part, to a higher proportion of subcutaneous fat and smokers have low leptin levels. Kraus and Haack studies suggest that the fat cell derived hormone leptin and the tumor necrosis factor alpha (TNF alpha) cytokine system are pathophysiologically involved. The activation of the TNF-alpha cytokine system is an early, sensitive, and specific marker of weight gain induced by antidepressants. In contrast, the effects of such drugs on leptin production seem to be less sensitive with respect to weight gain and more variable.[21]

Studies from max plank conclude that weight gain induced by anti-depressants may occur without increased circulating levels of leptin. However, activation of the TNF- α system might be an early and sensitive marker of ensuing weight.[22]

Lipid profile in correlation to weight neutral antidepressants

In our study, serum Total cholesterol, VLDL-C, LDL-C, Triglycerides are significantly decreased incorresponace to significant weight loss, significant decrease in serum leptin and TNF-α in obese patients treated with lifestyle modifications, psychotheraphy and desvenlafaxine.

Treatment of obesity-associated dyslipidemia should be focused on lifestyle changes including weight loss, physical exercise and a healthy diet. Physical exercise has been shown to increase Lipoprotein Lipase (LPL) and hepatic lipase activity, which stimulates TG lipolysis.[23,24] Obesity is a pro-inflammatory state due to macrophages that infiltrate adipose tissue.

The cytokines produced by macrophages and the adipokines that are produced by fat cells also alter lipid metabolism 25. The pro-inflammatory cytokines, TNF and IL-1, stimulate lipolysis in adipocytes increasing circulating free fatty acid levels, which will provide substrate for hepatic triglyceride synthesis. Obesity increases serum leptin levels and leptin stimulates lipolysis in adipocytes, which will increase serum free fatty acid levels.

Beyazyuz et al total cholesterol and triglyceride levels were elevated by paroxetine but were reduced by fluoxetine.[26] Yosmaoglu et al found that there was an increase in total cholesterol level and a borderline elevation in HDL levels in their study, in which several antidepressants were used.[27] Archer and David et al suggests that no evidence for an increased risk of cardiovascular, cerebrovascular, or hepatic events associated with desvenlafaxine 100mg/day compared with placebo for the treatment of menopausal vasomotor symptoms.[28]

Limitations of the study was found to be our study is limited by its small sample size and there is lack of uniformity among the individuals in the given cohort because they were on different lifestyles for the disease processes related to our study and which can alter the serum leptin, TNF-α and lipid profile which are the variables of interest. The distribution of sex is not even in the given cohort with female population predominate than the male population. Also, our study restricted to the population of south Indian ethnicity.

CONCLUSION

In summary our study demonstrated a significant weight loss, and significant decrease in S. leptin, TNF-α, TC, LDL-C, VLDL-C, triglycerides, when obese patients treated with lifestyle modifications, psychotherapy and weight neutral antidepressant (Desvenlafaxine) compared to the obese patients treated with lifestyle modifications, psychotherapy alone. HDL-C are significantly increased in the obese patients treated with lifestyle modifications, psychotherapy and weight neutral antidepressant (Desvanlafaxine) compared to the obese patients treated with lifestyle modifications, psychotherapy alone. Further studies about the mechanisms of these immunoendocrine effects are likely to enhance our understanding of weight neutral antidepressants and might ultimately lead to novel strategies for prevention and treatment of obesity, dyslipidemia, and coronary artery diseases.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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