

Research Article



Effects of Fluoxetine, Omega 3, or Their Combination on Serum Leptin in Iraqi Obese Subjects

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ABSTRACT

Obesity is an excessive development of fat throughout the body in which a body mass index (BMI) is over 30. According to the world health organization (WHO) reports, obesity is a global epidemic throughout the world. Iraq is in the seventh rank of the prevalence of obesity in the world. The aim is to study the effects of fluoxetine and omega3 drugs alone or their combination on BMI, fasting blood glucose, lipid profile, liver enzymes (ALT, AST), Malondialdehyde (MDA), and leptin. In this research we have forty eight obese subjects and divided into four groups, these subjects were selected from the Al-Kindy Medical College, obesity research and treatment unit where they were visiting for treatment. The first group used placebo drug once daily for two months, and the second group used fluoxetine drug 20 mg once daily for two months. The third group used omega3 2000 mg/day divided for two doses for the same period. The last group used the combination of fluoxetine 20 mg once daily plus omega3 1000 mg twice daily for two months. The finding of the research imply that the comparison between the first treated group and the second treated group showed a non-significant change in this study parameters ($p < 0.05$). However, in comparison between the first group with the third treated group it showed a significant change in cholesterol, TGs, AST, MDA parameters ($p < 0.05$). Comparison the first treated group with the fourth treated group showed significant change in Cholesterol, TGs, HDL, ALT, AST, MDA parameters ($p < 0.05$). It can be concluded that fluoxetine plus omega3 by far is the best choice for obese subjects in this study.

Keywords: obesity, BMI, leptin, fluoxetine, omega3.

INTRODUCTION

Obesity results from an imbalance in energy intake and expenditure. However, researches have shown that modulating these factors alone does not help in weight loss¹. A number of chemical mediators and neurochemical pathways, including negative feedback regulation, are involved in controlling food intake, satiety, energy expenditure and, hence, weight. Two types of adipose tissue can be distinguished, which have essentially antagonistic functions: white adipose tissue stores excess energy as triglycerides and brown adipose tissue is specialized in the dissipation of energy through the production of heat.

Leptin, a protein hormone encoded by the ob gene, is produced and secreted by the white adipose tissue. This hormone reflects fat deposits and its levels are modulated by feeding behaviors.² In the hypothalamus, the two groups of neurons of the arcuate nucleus express insulin and leptin receptors, which respond to food intake and fat stores³. Neuropeptide Y (NPY) and agouti-related protein (AgRP) are co localized as one group and the other group contains the protein prepro-melanocortin (POMC), which releases α -melanocyte-stimulating hormone (α -MSH) to act on melanocortin-4 receptors. Starvation or a fall in energy stores, resulting in reduction in leptin levels, stimulates the first group of neurons to produce NPY and AgRP to increase the food intake and decrease energy expenditure. AgRP, in turn, inhibits the anorexigenic action of α -MSH. An increase in

leptin levels stimulates the second group of neurons to act in an opposite manner; any abnormal functioning in this intricate physiology can disrupt the normal homeostatic processes to result in obesity or under nutrition.³

The leptin receptor is glycoprotein consisting of a single transmembrane-spanning component. The primary structure of leptin receptor belongs to the cytokine-class1 family, the single membrane-spanning receptor, and is highly related to the gp130 signal-transducing component of the interleukin-6 (IL-6) receptor, the granulocyte colony-stimulating factor (G-CSF) receptor, and the leukemia inhibitory factor (LIF) receptor⁴. The leptin receptor is known to have at least six existing isoforms (Ob-Ra, b, c, d, e, and f) from the difference in splicing. These isoforms can be classified into 3 large groups of long form (Ob-Rb), short form (Ob-Ra, c, d, and f) and secretory form (Ob-Re). Three isoforms has common extracellular domains, and only intracellular domains are different.⁵

The general goals for weight management are to reduce body weight (BW), maintain a lower weight over long term and to prevent further weight gain. The general principle of weight loss is to create an energy deficit. A caloric deficit of 500 and 1000 kcal/day could enable a loss of 0.4–0.9 kg/week to achieve a 10% reduction in BW over six months of therapy. A loss of 9–11 kg is usually observed over six months⁶. However, this rate of weight loss declines long term as there are changes in resting



metabolic rates and non-adherence to treatment strategies. Patients should be aware that rapid weight loss is almost always followed by gain of the lost weight.⁶

- Lifestyle modification focusing on improving diet and exercise behavior is the preferred first-line treatment for the management of obesity and associated cardio-metabolic complications.
- Pharmacotherapy can help patients to maintain compliance, ameliorate obesity-related health risks and improve quality of life. It can also help to prevent the development of obesity co-morbidities (e.g. type 2 diabetes mellitus).
 - Fluoxetine selectively inhibits serotonin reuptake *in vitro* and *in vivo* and thus enhances serotonergic action, leading to a decrease in food intake beginning with the first dose and a decrease in body weight or in weight Gain after multiple doses of fluoxetine. Fluoxetine and other drugs that increase serotogenic action decrease food intake with characteristics that make them attractive for use in weight reduction.⁷
 - Omega3 fatty acids, specifically EPA and DHA, have shown promising preliminary results in animal and human studies in the prevention and treatment of obesity. Given their effects on many of the pathways involved in obesity, and specifically in the endocannabinoid and mesocorticolimbic pathways, it have been hypothesize that EPA and DHA supplementation in populations can reduce the reward associated with food, thereby reduce appetite and food intake, and ultimately contribute to the prevention or reduction of obesity.⁸

MATERIALS, SUBJECTS AND METHODS

Forty eight obese subjects (males & females) were participated in this study ($BMI \geq 30 \text{ Kg/m}^2$). Their ages range (18-40 years), and they were randomly allocated into four groups, Each group included 12 obese subjects; Group 1 have been administered placebo capsule once daily and considered as control group; Group 2 were treated orally with 20 mg fluoxetine once daily; Group 3 were treated with omega3 gel capsule twice a day; Group 4 were treated with 20 mg fluoxetine plus omega3 gel capsule. All groups continued treatment for two months; the subjects were selected from the obesity research and treatment center/AI-Kindy medical college. And each of the following parameters were measured (BMI, FBG, Lipid profile, ALT, AST, MDA & Leptin).

RESULTS

In figure 1, treatment with fluoxetine only, or fluoxetine plus omega3 produced non-significant reduction ($P > 0.05$) in BMI (2.97% and 3.7% respectively) after two months compared with pre-treatment value.

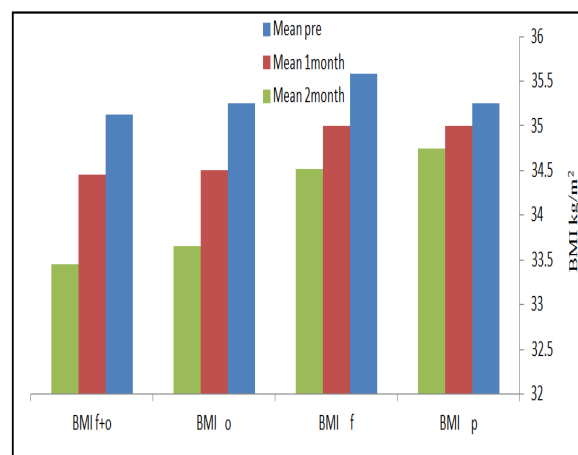


Figure 1: Mean changes in body mass index levels in obese subjects pretreatment, after one, and two months in different treatment groups: BMIP=placebo group, BMIF=fluoxetine group, BMIO=omega3 group, BMIFO=fluoxetine plus omega3 group.

The data presented in figure 2, showed that there are no significant reduction ($p > 0.05$) between fasting blood glucose levels in all groups, when compared with pretreatment values.

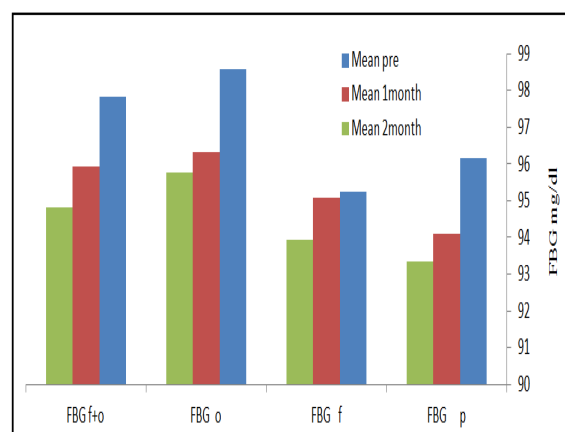


Figure 2: Mean changes in fasting blood glucose levels in obese subjects pretreatment, after one, and two months in different treatment groups: FBGP=placebo group, FBGF=fluoxetine group, FBGO=omega3 group, FBGFO=fluoxetine plus omega3 group.

The effect of fluoxetine, omega3 or their combinations on the serum cholesterol level of obese subjects are demonstrated in table 1. It has been shown that neither fluoxetine nor omega3 or there combination showed a significant reduction for the cholesterol level ($p > 0.05$).

Omega3 and fluoxetine plus omega treated groups produced a significant decrease in total serum triglyceride levels compared with pretreatment values while placebo and fluoxetine treated groups ($P < 0.05$), (table 1).

None of the treated groups in this study showed any significant reduction for serum HDL ($p > 0.05$), Placebo, Fluoxetine, omega3 and fluoxetine plus omega3, all of these treated groups showed anon-significant reduction for serum LDL levels ($p > 0.05$), (table 1).

Table 1: Effect of treatment with placebo, fluoxetine, omega3, fluoxetine plus omega3, on serum cholesterol, triglyceride, HDL and LDL levels.

Lipid Profile Parameter	Tested Groups n=12	Treatment Period		
		Pretreatment	After 1 month	After 2 months
Cholesterol (mg/dl)	Placebo	184.18 ± 11.20	181.92 ± 10.24	180.25 ± 10.01
	Fluoxetine	186.92 ± 17.42	178.67 ± 16.78	171.88 ± 19.97
	Omega 3	182.17 ± 17.47	173.25 ± 17.61	167.15 ± 19.52
	Fluoxetine+ omega 3	183.42 ± 16.87	177.75 ± 11.81	172.17 ± 9.11
TGs (mg/dl)	Placebo	176.25 ± 14.34	174.00 ± 10.04	173.08 ± 14.81
	Fluoxetine	173.33 ± 16.25	167.25 ± 15.63	162.17 ± 13.68
	Omega 3	177.75 ± 8.75	164.25 ± 8.14	151.92 ± 8.74
	Fluoxetine+ omega 3	176.75 ± 13.25	165.42 ± 10.95	149.33 ± 8.80
HDL (mg/dl)	Placebo	39.08 ± 3.58	40.25 ± 2.43	40.83 ± 2.61
	Fluoxetine	40.33 ± 3.23	41.33 ± 3.85	42.50 ± 2.91
	Omega 3	39.92 ± 3.82	41.00 ± 3.20	41.83 ± 2.99
	Fluoxetine+ omega 3	41.75 ± 3.29	42.75 ± 2.08	43.50 ± 1.45
LDL (mg/dl)	Placebo	110.00 ± 11.58	106.67 ± 10.13	105.17 ± 10.77
	Fluoxetine	112.12 ± 19.89	103.67 ± 17.30	96.18 ± 19.65
	Omega 3	107.17 ± 18.60	99.83 ± 16.89	95.08 ± 15.67
	Fluoxetine+ omega 3	106.33 ± 12.25	102.33 ± 16.04	99.33 ± 8.92

*Data were expressed as mean ± SD; n=number of patients; (p<0.05) represents significant difference between groups by using t-test and anova statistics.

Table 2: Effect of treatment with placebo, fluoxetine, omega3, fluoxetine plus omega3 on serum ALT levels.

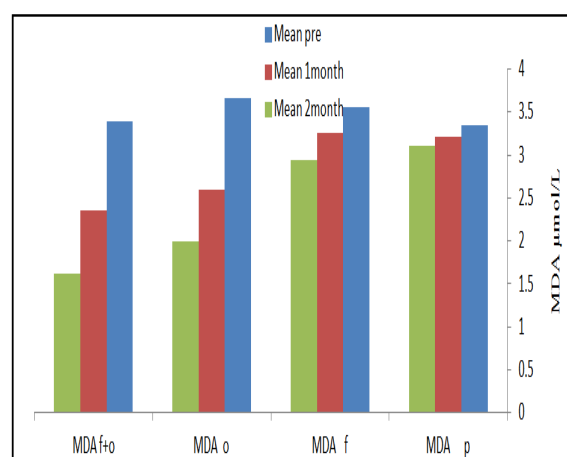
Liver Enzymes Tests	Tested Groups n=12	Treatment Period		
		Pretreatment	After 1 month	After 2 months
ALT (U/L)	Placebo	24.67 ± 2.63	23.75 ± 2.36	23.50 ± 1.90
	Fluoxetine	23.08 ± 1.74	22.83 ± 1.82	22.25 ± 1.34
	Omega 3	24.92 ± 3.48	23.00 ± 2.88	22.33 ± 2.96
	Fluoxetine+ omega 3	22.75 ± 3.11	21.67 ± 2.36	20.58 ± 2.62
AST (U/L)	Placebo	26.08 ± 2.96	25.25 ± 2.76	24.33 ± 1.70
	Fluoxetine	25.50 ± 2.71	25.17 ± 2.60	24.75 ± 1.60
	Omega 3	24.58 ± 2.90	23.27 ± 2.93	22.67 ± 1.68
	Fluoxetine+ omega 3	25.08 ± 3.66	24.16 ± 2.12	22.91 ± 1.08

*Data were expressed as mean ± SD; n=number of patients; (p<0.05) represents significant difference between groups by using t-test and anova statistics.

Placebo, Fluoxetine, omega3 and fluoxetine plus omega3 treated groups showed a non-significant reduction for ALT enzyme after one month and two months of treatment when compared with pretreatment values (p>0.05).

Placebo, fluoxetine, omega3, fluoxetine plus omega3 treated groups showed a non-significant reduction in AST level after two months of treatment (p>0.05), (table 2).

Figure 3 showed that omega3, fluoxetine plus omega3 produced a significant decrease in MDA levels (P<0.05) compared with pre-treatment values after one and two months of treatment, while for placebo and fluoxetine plus omega3 treated group showed a non-significant reduction (p>0.05).

**Figure 3:** Mean changes in serum MDA levels in obese subjects pretreatment, after one, and two months in different treatment groups: MDAP=placebo group,

MDAF=fluoxetine group, MDAO= omega3 group, MDAFO=fluoxetine plus omega3 group.

Figure 4 show the placebo, fluoxetine, omega3, fluoxetine plus omega3 treated groups showed a non-significant reduction in leptin level after one month and two months of treatment ($p>0.05$).

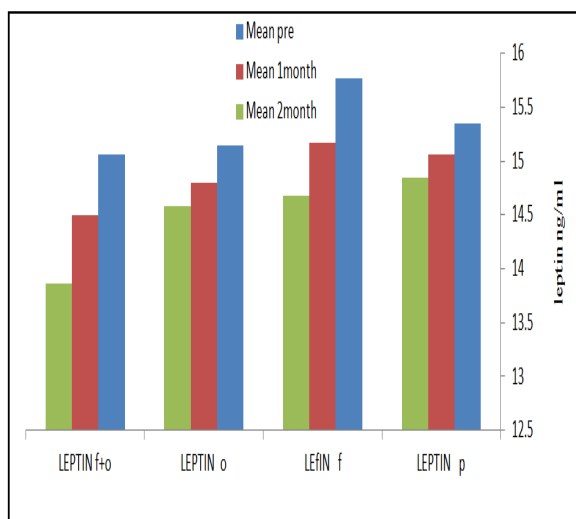


Figure 4: Mean changes in serum leptin levels in obese subjects pretreatment, after one, and two months in different treatment groups: leptinP=placebo group, leptinF=fluoxetine group, leptin O= omega3 group, leptin FO=fluoxetine plus omega3 group.

DISCUSSION

In present study, the participants were not depressed patients, but they are obese subjects, the analysis demonstrated that fluoxetine which was given 20 mg per day produced clinically meaningful changes but they were not significant ones in body weight ($P>0.05$), this confirmed that the metabolic benefit of fluoxetine was independent of its anti-depressive effect⁹.

Fluoxetine exhibited modest and non-significant weight loss effect ($p>0.05$) after one month and two months of treatment. Even moderate weight loss can lead to considerable blood pressure and glucose improvement in obese patients with non-diabetic populations, but the weight can be easily regained after the medication is discontinued¹⁰.

Compared with placebo, omega3, fluoxetine plus omega3 treated groups, fluoxetine group showed a non-significant effect ($p>0.05$), because the patients weight loss depend mostly on diet and exercise more than the effect of the drug.

Omega3 promotes BMI loss because it reduces insulin levels. High insulin levels contribute to fat being stored in the body instead of being burned, which is a major factor in weight gain. Consuming omega3 as part of a balanced diet is a proactive way to support weight loss and improve the overall health and wellbeing¹¹.

Previous studies that addressed the role of omega3 fatty acids in weight reduction have shown variable results and applied different study designs, delivery modalities, and outcome goals. The most common anthropometric study finding was a decrease in body fat mass in the supplemented group; however, the participants in those studies tended to have more baseline metabolic abnormalities, such as diabetes, hypertension, hyperlipidemia, or severe obesity^{11,12}.

Significant reduction ($p<0.05$) in FBG were showed with fluoxetine and fluoxetine plus omega3 treated groups after one month and two months of treatment. Previous studies were agreed with the data presented¹³.

Omega3 treated group showed a non-significant decrease in FBG after one and two months of treatment ($p>0.05$), Which agrees with other study that the high mean value of fasting blood glucose in obese subjects tended to decrease again by omega3 administrations in treated group. In agreement, it was indicated that omega3 polyunsaturated fatty acids may have a tissue-specific impact in restoring insulin sensitivity¹⁴. But disagree with other studies that reported omega3 fatty acids have often a transient increase in glucose level¹⁵.

Fluoxetine plus omega3 treated group has a non-significant effect on FBG after one month and after two months of treatment ($p>0.05$) since neither fluoxetine nor omega3 has hypoglycemic effect. Fluoxetine treated group showed a non-significant effect in all lipid profile parameters that have been measured in this study after one month and two months of treatment ($p>0.05$), fluoxetine treated group showed a non-significant difference ($p>0.05$) in compared with other treated groups.

On the other hand for triglyceride parameter, fluoxetine treated group showed a significant difference in compared with the other treatment groups ($p<0.05$) except with placebo treated group ($p>0.05$). Previous studies agreed with these findings¹⁶, other studies disagreed¹².

In the present study, omega3 treated group have a non-significant effect on serum cholesterol, HDL, and LDL after one month and two months of treatment ($p>0.05$), omega3 treated group for serum cholesterol in compared with placebo showed a significant difference ($p<0.05$), studies agreed with our findings¹⁷, while other studies disagreed; suggesting that lipid profile might be increased by consuming omega3 depending on the dose that the subject consumes¹⁸. Omega3 treated group showed a significant reduction in serum triglyceride level ($p<0.05$).

Fluoxetine plus omega3 treated group showed a non-significant effect in serum cholesterol, HDL and LDL levels ($p>0.05$) after one month and two months of treatment. For serum cholesterol and HDL parameters and in comparison with other treated groups, it showed a significant difference with placebo ($p<0.05$), serum triglyceride showed a significant reduction in fluoxetine

plus omega3 treated group after one month and two months of treatment and in compared with other treated groups, it showed a significant difference with placebo, fluoxetine treated group ($p < 0.05$).

Fluoxetine treated group showed a non-significant reduction for both ALT and AST liver enzymes after one month and two months of treatment when compared with pretreatment values ($p > 0.05$). Omega3 treated group had a non-significant effect on ALT, AST serum enzymes ($p > 0.05$), and these findings are agreed with previous studies¹⁹.

Fluoxetine plus omega3 treated group, found only significant with placebo treated group ($p < 0.05$) after two months of treatment. Meanwhile for serum AST enzyme in comparison with other groups, it showed a significant difference with placebo, fluoxetine ($p < 0.05$).

Fluoxetine drug with 20 mg dose daily has minor antioxidant effect which result in no significant reduction on MDA levels ($p > 0.05$), the potentially favorable antioxidant effect of the fluoxetine could be mediated by inhibiting lipid peroxidation, eliminate free radicals and chelate iron ions, which are important elements of free radical reactions. It has been noted that fluoxetine restores not only normal metabolism of monoamines but also their physiological levels in synaptic clefts²⁰.

Omega3 treated group showed a significant reduction on serum MDA levels ($p < 0.05$), similar results have been reported by others, other studies disagreed with these results and revealed no marked changes were observed in serum MDA after taking omega3²¹.

Fluoxetine plus omega3 treated group showed a significant reduction in serum MDA levels after first month and second months of treatment ($p < 0.05$).

On the 60th day of fluoxetine treatment, the group showed a low effect on the serum leptin ($p > 0.05$), which consistent with other studies²². Omega3 treated group showed a non-significant reduction on leptin level in the obese subjects ($p > 0.05$), our findings were in accordance with results of previous studies which proposed that supplementation with omega3 fatty acids will improve the level of serum leptin but non-significantly²³.

In comparison with other treated groups fluoxetine plus omega3 treated group showed no significant effect on serum leptin ($p > 0.05$).

CONCLUSION

The results of this study clearly demonstrated that fluoxetine plus omega3 combination has the potent effect on most of the measuring parameters in the present study cholesterol, triglyceride, and MDA.

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