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ORIGINAL ARTICLE

An open-label pilot study of the combination therapy of metformin and fluoxetine for weight reduction

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Background: Obesity is a very important risk factor for cardiovascular disease, type 2 diabetes mellitus, hypertension, osteoarthritis, fatty liver, metabolic syndrome and respiratory problems. Many weight-reducing drugs cannot be used in obese patients because of numerous complications. Fluoxetine, an antidepressant, and metformin, an antidiabetic drug, reduce weight as their side effect, but the potency of each drug is not always enough. Here, we studied the effects of combination therapy of them for weight reduction in obese women.
Materials and methods: This study was designed as an open, prospective, controlled clinical trial. Obese and overweight patients referred to obesity clinics were first put under a diet and behavior therapy education program before being invited to this study. The patients who accepted drug therapy were put in the case group. Those who did not accept drug therapy were put in the control group. Fluoxetine, 20 mg daily, and metformin, 500 mg three times daily, were prescribed to the participants. Weight and body mass index (BMI) changes within case and control groups were analyzed by paired *t*-tests and between groups by *t*-testing. Side effects were evaluated by interview and questionnaire.
Subjects: Two hundred and three patients were referred to obesity clinics. Of these, 177 were female with 91 being volunteers for this study. Of this 91, 66 were in the case group and 25 in the control group.
Results: In a 6.68-month period, a 7.89 kg decrease in weight (9.32%) and a 3.43 U decrease in BMI (10.14%) were observed in participants of the case group that was statistically significant ($P<0.0001$). The participants of the control group were followed for a mean period of 8.12 months. In this period, the participants of the control group showed a 0.48 kg decrease in weight (0.52%) and a 0.11 U decrease in BMI (0.42%). This was not significant. No serious side effects of the drugs were observed in the case group.
Conclusion: This open-label pilot study of combination therapy of metformin and fluoxetine gave encouraging weight reduction, and these results suggest the need for a randomized double-blind clinical trial comparing the two components and the combination to placebo.
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Keywords: fluoxetine; metformin; weight reduction

Introduction

Obesity, excess body fat, is a growing health problem in most developed and some developing countries.[1] It is a very important risk factor for cardiovascular disease, and also a risk factor for type 2 diabetes mellitus (DM), hypertension, osteoarthritis, fatty liver, metabolic syndrome and other problems.

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Human obesity is a multifactorial disorder with genetic and environmental causes.[2] The human genome is designed to fight against long-term fasting by conserving energy as fat tissue. Today, excess energy intake as calorie-dense foods and reduced physical activity, given properties of our genetic basis, has resulted in epidemics of obesity in most populations. The problem is that diet therapy is not very effective and tolerable. Most weight-reducing drugs cannot be used in many patients owing to a number of side effects. Orlistat and sibutramine are the only weight-reducing drugs where long-term safety have been demonstrated.[3–5]

Fluoxetine, an antidepressant drug, decreases appetite as its side effect.[6] Metformin, a biguanide, is one of the rare antidiabetic drugs that does not result in weight gain. On the contrary, it causes mild weight loss.[7,8]

Although weight loss observed with each one of these drugs has been statistically significant in some studies, the acceptable clinical weight reduction, defined as 'weight loss more than 10% in a 6-month treatment period'[9] has not yet been achieved. Thus, this makes way for one to question whether or not combination therapy with both drugs results in an added weight loss effect.

This open-label pilot study has been designed to explore the effectiveness, compliance and side effects of combination therapy of fluoxetine and metformin in overweight and obese women.

Subjects and methods

This study was designed as an open, prospective, controlled clinical trial. Obese and overweight patients referred to obesity clinics were first put under a diet and behavior therapy education program before being invited to the study.

Inclusion criteria were females with body mass index (BMI) $>27 kg/m^2$ with other cardiovascular risk factors, or females with BMI $>30 kg/m^2$ with or without such risk factors. Other requirements included subjects must be of age greater than 14 years old and the subject's consent to be included in the study. Exclusion criteria were renal failure (cr >1.4 mg/dl), hepatic failure (based on clinical and laboratory data), pulmonary problems (active asthma and chronic obstructive lung disease), symptomatic heart failure, type 1 DM, uncontrolled type 2 DM (fasting plasma glucose >200 mg/dl) and current metformin or fluoxetine use.

The patients who accepted drug therapy were put in the case group. Those who did not accept drug therapy were put in the control group. Patients, who would not or could not follow regular visits, were excluded from the study. The diet, used in this study was based on National Cholesterol Education Program Adult Treatment Panel III guidelines[10] in a simple educational language for decreasing fat content of foods. The diet was in the form of detailed breakfast (until satiety), regular lunch (before satiety) and brief dinner while omitting intermittent snacks.

All the patients were examined initially and in 6-week intervals until 6 months, and each 3 months thereafter. For all the patients of case group, renal and liver function tests, fasting plasma glucose and lipids, TSH, and urinary free cortisol were evaluated.

Weight measurement for all of the participants was performed by a standard medical scale (Seca, Germany). The scale acuity was 100 g and coefficient of variation less than 1%. All participants were weighted with light clothing and bare feet. Height measurements were performed standing with four parts (heels, buttocks, back and head) touching the stadiometer, heels together and head in Frankfurt plane. All the measurements were performed between 0430–0800 hours by one person using similar methods.

For measurement of BMI, the formula, weight (kg) $\div$ height^2 (m^2) was used.

Drug complications were evaluated at each visit by interview and asking about common complications and then asking if other complications have occurred.

Diet and drug compliance were evaluated by interviews asking about the number of days within a week that a drug or diet had been used as ordered. If this was 5 or more days per week, the patient compliance was defined positive.

In each visit, the results of weight measurement were recorded only if the patient had shown good drug compliance since the previous visit. However, this was omitted in poor compliance patients.

If the patient showed poor drug compliance during the second visit, she was excluded from the study.

Fluoxetine (Lorestan Pharmaceuticals, Lorestan, Iran), in the form of 20 mg capsules was prescribed 20 mg every other day for 1 week and then 20 mg daily.

Metformin (Apo – Metformin APOTEX Inc., Toronto, Canada), in the form of 500 mg tablets, was prescribed 250 mg daily with lunch, increasing 250 mg every 3 days to 250 mg with each main meal (750 mg/day) for the first 6 weeks, followed by 500 mg with each main meal (1500 mg/day) thereafter.

Behavioral therapy was administered by teaching subjects to decrease the frequency of using elevator and remote control systems, and increase physical activity frequency with the goal of exercising 3 h/week, decreasing stress and decreasing restaurant or processed food intake.[11]

Statistical analysis

Weight and BMI, before and after treatment within each group, were compared by paired *t*-tests.

Weight and BMI before and after treatment between groups were compared by *t*-test. For comparison of the demographic characteristics also *t*-test were used. Drug and diet compliance (percent in each group) were compared by χ^2. (The SPSS 11.5 software was used for data analysis.)

Results

Two hundred and three patients were referred to obesity clinic for consultation and treatment. Of these, 177 were female. Ninety-one female patients entered voluntarily to this study by the criteria mentioned above. Sixty-six patients were put in the case and 25 in the control groups. Table 1 presents baseline data of the participants. There was no significant difference between case and control groups in baseline weight, BMI, height and age.

The participants of case group were managed for a mean of 6.68 months (range 1.5–18 months). In this period, a 7.89 ± 4.83 kg decrease in weight (9.32%) and a 3.43 ± 1.95 U decrease in BMI (10.14%) were observed that was statistically significant ($P<0.0001$) (Figure 1).

The participants of the control group were followed for a mean of 8.12 months (range 2–20 months). In this period,

they showed 0.48 kg decrease in weight (0.52%) and 0.11 U decrease in BMI (0.42%) that was not significant (Figure 2).

The case and control groups were compared, and the amount of weight and BMI changes was significantly different ($P<0.0001$).

Thirty-two patients in case group were treated for more than 6 months. This subgroup had 9.43 ± 5.45 kg (11.19%) weight loss and 4.16 ± 1.97 U (12.35%) decrease in BMI. These changes were also significant ($P<0.0001$).

Twelve patients in case group were treated for more than 12 months. This subgroup had 9.83 ± 4.26 kg (11.88%) weight loss and 3.90 ± 1.78 U (11.88%) decrease in BMI. These changes were also significant ($P<0.0001$).

Table 2 presents the results of weight and BMI changes in two groups.

Table 1 Baseline data of participants

Group	*Number*	*Weight*	*Height*	*BMI*	*Age*
Case	66	83.74	158.50	33.61	31.67
Control	25	88.92	158.48	35.54	36.20
P		0.593	0.989	0.153	0.089

Abbreviation: BMI, body mass index.

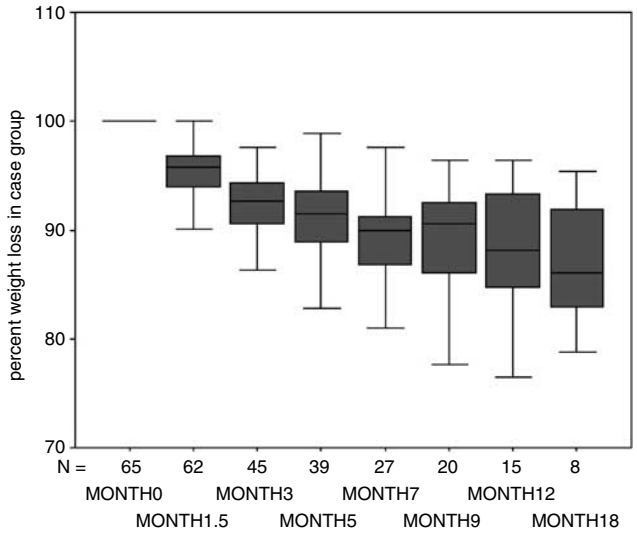

Figure 1 Percent of initial body weight change from baseline (100%) in the case group.

Three patients in case group had controlled hypothyroidism and their levothyroxin dosage was not changed. One patient also had mild subclinical hypothyroidism (TSH 5 mIU/l) without the need for treatment. Seventeen patients in case (25.7%) and eight in control groups (32%) had poor diet compliance. The compliance between two groups was not statistically different ($P=0.214$).

One of the patients displayed some motor problems in her tongue with fluoxetine, necessitating drug discontinuation.

Less than 7% of the patients had mild somnolence, insomnia, anxiety and tiredness. One patient showed decreased libido and interaction with orgasm, necessitating drug discontinuation. Hyperthermia or any serious complications of fluoxetine were not seen.

Twelve percent of the patients had mild gastrointestinal symptoms (nausea, diarrhea and abdominal pain) that abated with time. No case of hypoglycemia was observed.

Discussion

This study reveals a 7.89 ± 4.83 kg weight loss and a 3.43 ± 1.95 U decrease in BMI of the female patients receiving combination therapy of metformin and fluoxetine in a 6.8-month treatment period.

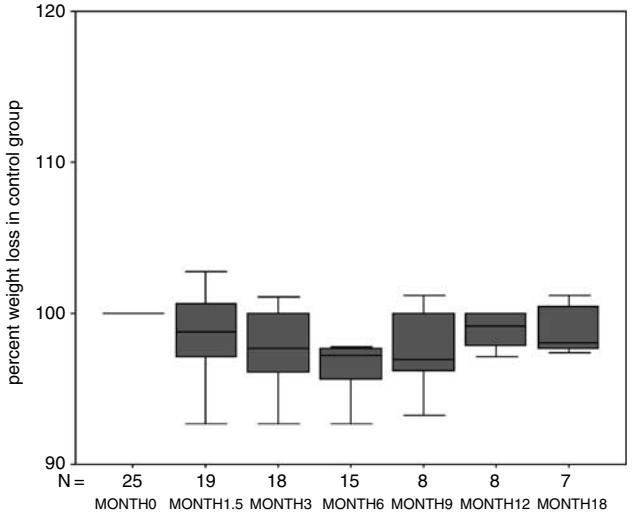

Figure 2 Percent of initial body weight change from baseline (100%) in the control group.

Table 2 Weight and BMI changes in case and control groups

Group	*Primary weight*	*Final weight*	*Primary BMI*	*Final BMI*	*BMI changes (BMI 2-BMI 1)*	*% Change of BMI*	*Duration Mean/range*
All cases	83.74	76.09	33.61	30.26	−3.34	−9.91	6.68/1.5–18
Cases >12 months	83.72	74.28	33.62	29.46	−4.16	−12.35	10.84/6–18
Cases >6 months	83.67	73.83	33.08	28.87	−4.20	−12.79	14.91/12–18
Control	88.92	88.44	35.54	35.26	−0.11	−0.42	8.12/2–20

Abbreviation: BMI, body mass index.

Other studies with fluoxetine show between 0 and 9.1 kg weight losses in 3–12 months time.[12–19] A good recent meta-analysis about pharmacologic treatment of obesity could not present pooled analyses of fluoxetine treatment, because the statistical tests and Forest plot of individual study results revealed too much heterogeneity. However, in six of the seven studies, significant weight loss has been observed as being controlled by placebo.[20] Studies with metformin also show mild decrease in weight and BMI with the decrement range from 1.5 to 3.6 kg in weight and, 0.12 s.d. in BMI.[21,22]

Comparison of the results of this study and other studies with fluoxetine and metformin reveals combination therapy of two drugs has more efficacy than each one combined.

Fluoxetine is a selective serotonin reuptake inhibitor drug used usually in major depression, obsession and bulimia.[15] By blocking the membrane-uptake carrier that transports serotonin from the extracellular space to inside the serotonin nerve terminals, fluoxetine increases extracellular concentrations of serotonin and amplifies signals sent by serotonin neurons. Because serotonin neurons are widespread in the central nervous system, the functional consequences of blocking serotonin uptake are diverse; this includes symptoms such as decreased food intake, altered food selection and endocrine changes.[23,24] In a study where volunteers maintained a dosage of fluoxetine 40 mg or placebo, in a residential laboratory for 16 days, fluoxetine decreased caloric intake by decreasing the number of eating occasions.[25] The resultant weight loss is variable and there appears to be no way of predicting good responders.[26] One problem with fluoxetine is propensity to weight regain, especially after 6 months.[6,20] This is the reason why fluoxetine has not yet been approved as an anti-obesity medication. In this study, similar problem was observed in some of the participants, but as shown in Figure 1, most maintained process of weight reduction albeit with slower speed. Metformin is a biguanide drug mainly used in type 2 DM, but also is increasingly used in metabolic syndrome and associated disorders like polycystic ovary syndrome, hyperlipidemia and cardiovascular problems. The exact mechanism of metformin action is unknown yet, but it seems to act trough AMP-activated protein kinase and increasing glucagon-like peptide-1.[27–29] Great advantages and the low side effect rate have made metformin a progressively used drug in above-mentioned situations. There is only one worrisome adverse reaction of metformin, lactic acidosis, which is very rare and usually present in the setting of renal, hepatic or heart failure. Drug side effects observed in this study were often mild and transient. Other studies have also reported similar side effects and, based on extensive studies with both drugs in their main applications, they are safe medications.

Limitations: The patient selection of the study has not been randomized and the control group has not taken placebo. This can harm the results of the study. Plus, diet compliance of the two groups is different. Although this difference is not significant, it seems the statistical insignificance is due to small number of the participants in control group.

Conclusion

This open-label pilot study shows the combination therapy of fluoxetine and metformin may be an effective and safe drug regimen for weight reduction, but their long-term usefulness for improvement of life quality and decreasing chronic complications of obesity is not approved. These encouraging results suggest the need for a randomized double-blind placebo-controlled trial comparing these two medications and their combination to placebo.

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