A randomized, triple masked, placebo-controlled clinical trial for controlling childhood obesity

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Background: **The efficacy of pharmacological treatment in controlling childhood obesity is controversial. We aimed to compare the effects of three types of drug regimens and placebo on generalized and abdominal obesity among obese children and adolescents who did not succeed to lose weight 3 months after lifestyle modification (diet and exercise).**

Methods: **This triple-masked randomized clinical trial was conducted among 180 participants aged 10-16 years. They were assigned randomly to 4 groups of equal number to receive metformin, fluoxetine, a combination of the two drugs or placebo. The trial lasted for 12 weeks and participants were followed up for an additional 12-week period.**

Results: **Overall, 91.1% (*n*=164) of the enrolled participants completed the trial. After the 12-week trial, the body mass index decreased significantly in all groups receiving medications [approximately -1.2 (0.2) kg/m^2, *P*<0.05]. This decrease was not significant in the placebo group. Waist circumference decreased significantly in the groups receiving metformin [-2.1 (0.4) cm, *P*=0.03)] as well as in the group receiving a combination therapy of metformin and fluoxetine [-2.5 (0.4) cm, *P*=0.01)]. In the 24-week follow-up study, these anthropometric indexes remained lower than the baseline in the group that had received a combination therapy of metformin and fluoxetine. No serious drug side-effect was reported.**

Conclusions: **A limited period of such treatment may help weight control, and might be used to encourage those children who have been refractory to weight loss for continuing the non-pharmacological programs. Our findings should be confirmed in future studies with longer follow-up period.**

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treatment

Introduction

During the past two decades, the prevalence of childhood obesity has shown a dramatic rise worldwide,[1] and is no longer limited to industrially developed countries.[2] Similar to many developing countries, Iran is facing a double burden of weight disorders among children and adolescents.[3] Because of its short- and long-term complications,[4] it is important to control childhood obesity. Similar to adults, however, changing lifestyle of children is difficult and adding pharmacologic treatment to lifestyle modification may help weight control and would encourage children and their families for continuing the weight loss programs. The efficacy of pharmacologic treatment in controlling childhood obesity is still controversial.[5-7]

One of the drugs used in this regard is metformin; it may be effective by inhibiting hepatic glucose production, increasing the sensitivity of peripheral tissues to insulin as well as inhibiting the increase of gluconeogenesis in the liver and kidney.[8-11] Moreover, metformin has additional health benefits independent of its effects on glucose and insulin levels; these include antioxidant activity, weight reduction, improvement of lipid profile and high blood pressure.[12,13] The mechanisms of its effects on weight loss are not limited to improving insulin resistance, but also by reduction in gastrointestinal absorption of carbohydrates,[12,14] induction of an anorectic and lipolytic effect,[15] and decreasing leptin levels.[13,16]

Furthermore, some neuropharmacologic aspects have been considered for weight control; the integration

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of numerous signals in energy regulatory centers within the central nervous system is necessary for regulation of the appetite. These centers provide the pharmacological potential to modify human appetite. Selective serotonergic reuptake inhibitors such as fluoxetine have been used to normalize unusual eating behavior and to modify the expression of human appetite, thus reducing caloric intake by modifying appetite.[17,18] The effects of fluoxetine in reducing caloric intake by modifying appetite are documented in both lean and obese humans. Specifically, it may reduce appetite before and after the consumption of fixed caloric loads, and reduce pre-meal appetite and caloric intake at ad libitum meals.[19,20] A combination of metformin and fluoxetine has been successful for weight loss of obese adults.[21]

In this randomized clinical trial, we compared the effects of three types of drug regimens and placebo on measures of generalized and abdominal obesity among obese children and adolescents who did not succeed to lose weight 3 months after non-pharmacologic treatment (diet and exercise).

Methods

Study participants

This triple-masked randomized clinical trial was conducted among 180 children and adolescents, aged 10-16 years. The participants were consecutively recruited from obese children who were referred to the Pediatric Obesity and Metabolic Syndrome Research Clinic of the Pediatric Preventive Cardiology Department, Isfahan Cardiovascular Research Center (ICRC). By considering alpha=0.05 and a power level of 0.8, the sample size was calculated as 160, and by considering the attrition during the follow-up, we increased it to 180. The study was approved by the Ethics Committee of ICRC (NIH Code: FWA 0000t8578). After providing detailed oral information to children and their parents, we obtained written informed consent from the parents and oral assent from all eligible study participants.

Eligibility criteria for participation included age between 10 and 18 years, failure in weight loss after 3 months of non-pharmacologic treatment (by lifestyle modification advised in our clinic) and body mass index (BMI) equal to or greater than the age- and sex-specific 95th percentile according to the revised Centers for Disease Control and Prevention (CDC) growth charts.[22] Individuals with syndromal obesity, endocrine disorders, any physical disability, history of chronic medication use, using Mono Amine Oxidase Inhibitor drugs, history of mood disorder in parents and first degree relatives (depression or bipolar), history of any chronic diseases, e.g., kidney disorders, lung diseases and/or hepatitis were excluded from the study. As there was no previous experience in dealing with the possible side effects of the combination of medications used in this trial in the pediatric age group, we designed a short-term trial, hence if it would have successful outcomes, without marked side-effects, a trial of longer duration would be conducted. We conducted a trial of 12-week because previous studies showed favorable changes after lifestyle modification of shorter period.[23,24] The participants were randomly assigned into four groups (n=45 for each group) by a computer-generated random numbers table using the children's records numbers in our clinic.

Measurements

The age calculated from birth until the date of interview was recorded. Weight (Wt) and height (Ht) were measured by calibrated scale and stadiometer (Seca, Japan) with subjects lightly clothed and barefoot to the nearest 0.1 cm and 0.1 kg, respectively. BMI was computed as Wt (kg) divided by Ht (m) squared. As our national survey[25] revealed a strong agreement between BMI percentiles of Iranian children with those of CDC, we calculated the BMI and BMI SD score (SDS) on the basis of the revised CDC growth charts.[22] Waist circumference (WC) was measured at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration. Waist-to-height ratio (WHtR) was computed by dividing the WC by Ht. WHtR>0.5 was considered as abdominal obesity.[26] All measurements were made by the same trained general physician and under the supervision of the same pediatrician.

Intervention

All participants were advised to increase their physical activity and to follow healthy eating behaviors. In order to increase physical activity, we asked them to reduce their sedentary time, e.g., watching television and playing computer video games to less than two hours a day. In addition, we asked them to have at least 30 minutes of enjoyable, moderate-intensity physical activities every day, which could be provided in one session or divided into at least two 15-minute periods or three 10-minute periods.[27] To be understandable for families, we gave simple explanation about the intensity of physical activity as provided by the US Centers for Disease Prevention and Control: "As a rule of thumb, on a scale of 0 to 10, where sitting is a 0 and the highest level of activity is a 10, moderate-intensity activity is a 5 or 6. When your child does moderate-intensity activity, his heart will beat faster than normal

and he will breathe harder than normal. Vigorous intensity activity is a level 7 or 8. When your child does vigorous intensity activity, his heart will beat much faster than normal and he will breathe much harder than normal."[28]

A registered dietitian conducted the nutrition education session. The recommended diet was based on a diet containing 30% fat, 15% proteins and 55% carbohydrates with an energy content based on the calorie requirement for height.[29]

The participants were asked to use unrefined carbohydrate, dietary fiber primarily in the form of high-fiber whole grains (5 servings per day), vegetables (3 servings per day), fruits (2 servings per day), protein-based foods (2-3 servings per day) and low-fat dairy (2-3 servings per day). The families of the participants were advised not to use hydrogenated fat, which is commonly used fat in our community. Necessary information about limiting the use of saturated and trans fatty acids was provided, and increased in consumption of fruits and vegetables was encouraged.

The 12-week pharmacological part of the trial was conducted in a triple-masked randomized method, i.e., the physician who prescribed the drug, the nurse of the aforementioned childhood obesity research clinic who gave the drug, and the participants were not aware of the type of the drug used. The drugs and placebo had the same size and color, and were prepared in the Pharmaceutics' Department of the Faculty of Pharmacy, Isfahan University of Medical Sciences. Metformin (Arya Pharmaceuticals, Tehran, Iran, and Fluoxetine (Lorestan Pharmaceuticals, Lorestan, Iran) were used. The placebo content consisted of two commonly used filler in manufacturing of tablet and capsule: lactose and calcium phosphate.

One group received metformin, with its dosage increased weekly from 500 mg/day to 1500 mg/day. The other group received fluoxetine, with the initial dosage of 10 mg and was increased to 20 mg/day after 3 weeks. The third group received a combination of the aforementioned drugs that was prepared in the form of a single drug, and the fourth group received placebo. All the participants and their accompanying parents were trained to know the signs and symptoms of hypoglycemia and necessary actions taken to control them. Although hypoglycemia was possible only for those individuals receiving metformin, similar education was provided for all groups considering the blindness of the study. To prevent hypoglycemia, the participants were asked to take drugs during meal eating. A card including clinic's phone numbers and a 24-hour cell phone number was given to the parents to call us in the case of any question, and to inform us about any possible side-effects. The trial was free of charge for the participants.

To increase the compliance of the participants during the trial, all participants and their parents were followed up by telephone call monthly. The baseline measurements were repeated after the 12-week trial and 12 weeks after the end of the trial, i.e., 24 weeks after the baseline survey.

Statistical analysis

SPSS for Windows (SPSS Inc., Chicago, IL) was used for data analysis. The normality of the distribution of variables with a Kolmogorov-Smirnov test was verified and no significant deviation from normality. Data were analyzed by the method of intention to treat. Analyses were initially stratified by gender, but as the differences were not significant, results are presented for both girls and boys. The results were presented as mean ± standard deviation (SD). Analysis of variance (ANOVA) and the Chi-square test were used to determine the significance of any baseline differences between different groups. We compared data at baseline, and each follow-up study separately for each group by using repeated measurement ANOVA and Bonferroni post hoc test. Linear regression analysis was used to assess mean changes in anthropometric parameters. The significance level was set at $P<0.05$.

Results

The baseline characteristics of the four groups were not significantly different (Table 1). The study flow diagram

Table 1. Baseline characteristics of the participants

	Groups			
	Metformin (n=45)	Fluoxetine (n=45)	Metformin+Fluoxetine (n=45)	Placebo (n=45)
Age (y)	13.1 (1.4)	13.5 (1.2)	13.7 (1.1)	13.4 (1.4)
Body mass index (kg/m^2)	26.4 (0.5)	26.5 (0.7)	26.6 (0.8)	26.2 (0.6)
Body mass index-SDS	2.4 (0.01)	2.3 (0.04)	2.4 (0.01)	2.4 (0.02)
Waist circumference (cm)	81.5 (2.7)	82.7 (3.1)	80.5 (1.2)	82.6 (3.4)
Waist-to-height ratio	0.61 (0.02)	0.64 (0.01)	0.65 (0.03)	0.62 (0.02)

Data are expressed in mean (SD). None of the differences was significant between the groups.

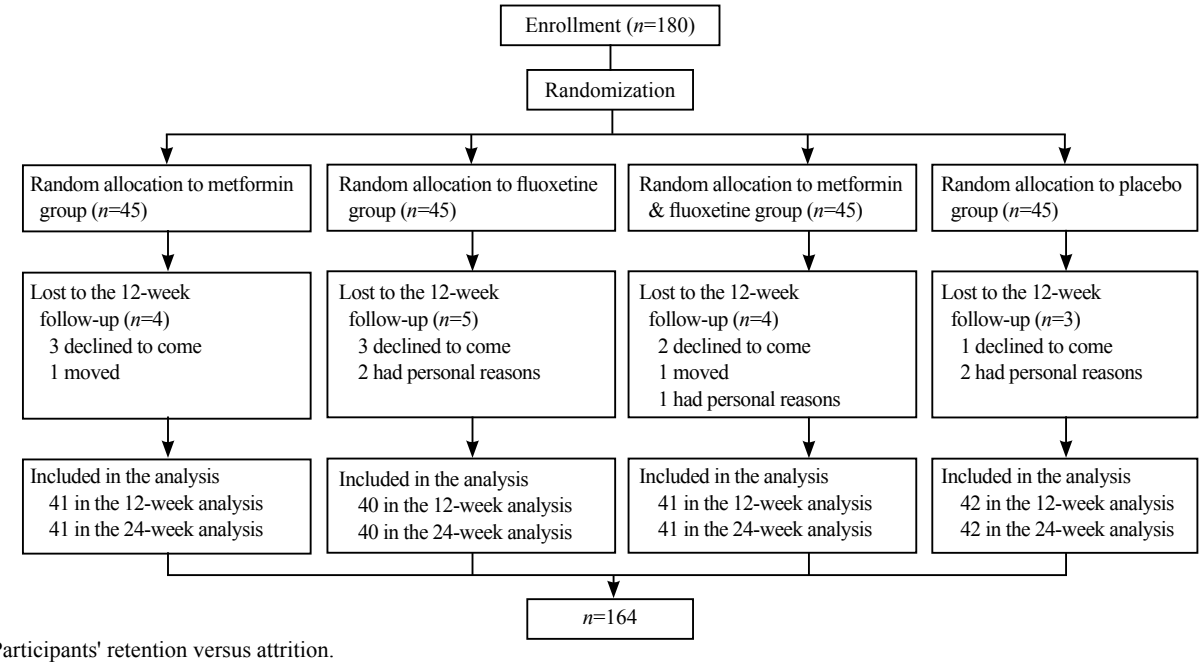

Fig. Participants' retention versus attrition.

Table 2. Mean (SD) of changes (Δ) in anthropometric indexes among the groups studied from baseline to 12 and 24 weeks

	12 weeks	24 weeks
Δ Body mass index (kg/m^2)		
Metformin group	-1.1 (0.2)*‡	0.9 (0.1)
Fluoxetine group	-1.2 (0.3)*‡	-0.6 (0.1)
Metformin+Fluoxetine group	-1.2 (0.2)*‡	-0.9 (0.02)†§
Placebo group	-0.5 (0.05)	0.2 (0.04)
Δ Waist circumference (cm)		
Metformin group	-2.1 (0.4)*‡	-0.4 (0.03)
Fluoxetine group	-1.3 (0.5)	-0.4 (0.02)
Metformin+Fluoxetine group	-2.5 (0.4)*‡	-1.1 (0.2)†§
Placebo group	-0.4 (0.05)	-0.2 (0.04)

*: P<0.05 for within group difference of the baseline *vs.*12 weeks after the beginning of the intervention; †: P<0.05 for within group difference of the 12-weeks *vs.* 24 weeks after the beginning of the intervention; ‡: P<0.05 for between group difference of the baseline *vs.*12 weeks after the beginning of the intervention; §: P<0.05 for between group difference of the baseline *vs.* 24 weeks after the beginning of the intervention.

is demonstrated in the Fig. Overall, 164 (91.1%) of the enrolled children and adolescents completed the trial.

The mean (SD) of changes (Δ) in anthropometric indexes assessed among the four groups is presented in Table 2. After the 12-week trial, BMI decreased significantly in all groups receiving drugs. This decrease was not significant in the placebo group. In addition, WC decreased significantly in the groups receiving metformin as well as in the group receiving a combination therapy of metformin and fluoxetine. In the 24-week follow-up study, the values of BMI and WC in the group receiving a combination therapy of metformin and fluoxetine were lower than the baseline values. We received 7 phone calls about the side effects of metformin (2 cases of headache, 2 cases of abdominal pain and 3 cases of loose stool) and 5 calls about the side effects of fluoxetine (3 cases of dry mouth and 2 cases of loose stool); all these side effects were minor and tolerable. The participants continued their medications and were followed up. All of the reported side effects were transient.

Discussion

We found that the combination therapy of fluoxetine and metformin may be effective for weight reduction in children and adolescents. This effect might be due to the different weight loss mechanisms of the medications such as control of insulin resistance and lowering of the appetite,[16] reduction of gastrointestinal absorption of carbohydrates,[13,15] and decrease of leptin levels[13,17] by metformin as well as reducing caloric intake by modifying appetite and normalizing unusual eating behavior by fluoxetine.[17-20] The decrease of waist circumference in the groups receiving metformin not in the group receiving only fluoxetine suggests the effect of metformin is through controlling insulin resistance.

Data on the use of pharmacological therapy for pediatric overweight are inconclusive. It is documented that metformin treatment is effective in reducing insulin resistance and also ameliorating metabolic complications induced by insulin resistance in obese adolescents with hyperinsulinemia.[30] Previous trials have been conducted in adults notably in women with polycystic ovarian syndrome (PCOS), e.g., a study in

PCOS women with abdominal obesity found that long-term treatment with metformin added to hypocaloric diet induced a greater reduction of body weight and abdominal fat, particularly the visceral depots, and a more consistent decrease of serum insulin than placebo did.[31] Similar positive effects of metformin have been documented in adolescents with PCOS.[32] A study among adolescents with simple obesity revealed that metformin can be useful in weight reduction only when accompanied with modest lifestyle changes.[9]

Selective serotonergic reuptake inhibitors such as fluoxetine have all been used to normalize eating behavior by modifying appetite in normal weight and overweight individuals,[18-20] and also have been effective in weight reduction of adult patients with eating disorders.[33] A study found that fluoxetine resulted in a greater mean reduction in anthropometric and metabolic parameters when compared to metformin.[34] Some studies have used a combination therapy of metformin and fluoxetine. In an open-label pilot study, the combination therapy with these two drugs was effective for weight reduction.[21]

Overweight and obesity are supported by and a reflection of lifestyle. In the case of children, the lifestyle is usually set up and controlled by the parents. As a result, parents must closely evaluate the family lifestyle. The goal is to maintain lifetime healthy behaviors; however lifestyle change is not easy in many cases.

Although the treatment of obesity among children seems to give better results than treating adults, there is no evidence on drug or surgical treatment of pediatric obesity and no drug is licensed currently for the treatment of simple obesity in children. Pharmacological treatment has to be taken into consideration for adolescents with severe obesity.[35]

Our study should be considered with its limitations and strengths. The main limitation is that we did not assess the insulin resistance of the participants and their exact changes in dietary and physical activity habits. We should also acknowledge that we did not assess the pubertal stage because of difficulties in physical examinations in determining the Tanner stage. However the mean age of the participants was not significantly different between the groups, and there was an appropriate distribution of age groups (and consequently pubertal stage) in all groups under study. Moreover, the amount of weight loss was not strong in none of the groups possibly because the participants were not severely obese. The strength of our study is its triple-masked random placebo-controlled design and its novelty in the pediatric age group.

Our findings might be useful for future trials with longer duration to assess the effects of pharmacologic treatment as well as the sustainability of changes among children and adolescents who did not succeed to lose weight with non-pharmacologic treatment. A limited period of such pharmacological treatment may help on weight control, and would encourage the children and adolescents who have been refractory to weight loss by lifestyle change for continuing the non-pharmacological weight loss programs. However we should acknowledge that prevention of obesity should have a high priority and should be started as early possible especially in obesogenic families, and lifestyle modification has a pivotal role in controlling childhood obesity even among those who are under pharmacologic treatment.

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