ORIGINAL ARTICLE

Effect of folic acid and metformin on insulin resistance and inflammatory factors of obese children and adolescents

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Background: Considering the increasing trend of obesity, especially in developing countries such as Iran, and the role of inflammatory factors and insulin resistance (IR) in the occurrence of obesity-related complications as well as the safety of some agents such as folic acid and metformin, this clinical trial was designed to investigate the effect of metformin and folic acid on inflammatory factors and IR among obese children. **Materials and Methods:** In this randomized, double-blind, controlled clinical trial study, sixty obese children aged 6–12 years were enrolled. Selected obese children were randomly allocated in two interventional (1 mg/daily folic acid or 1000 mg metformin for 8 weeks) groups. Biochemical measurements including homeostasis model assessment of IR (HOMA-IR), homocysteine (Hcy), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) were measured between and within the groups before and after trial. **Results:** In each group, thirty obese children were studied. The groups were age- and sex-matched. After folic acid and metformin administration, mean of Hcy, HOMA-IR, TNF-α, and IL-8 decreased significantly ($P < 0.05$). IL-6 decreased significantly after folic acid use ($P < 0.05$). **Conclusion:** The findings of this trial indicated that both metformin and folic acid could decrease IR and level of Hcy in obese children and adolescents. The effectiveness of metformin on IR was more significant than folic acid. Regarding the effectiveness of the two studied agents on inflammatory factors, it is suggested that the role of folic acid was superior to metformin. It is suggested that metformin is a proper agent for obese children with IR and folic acid is an appropriate supplement for obese children with increased inflammatory factors.

Key words: Children, folic acid, homocysteine, inflammation, insulin resistance, metformin, obese

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INTRODUCTION

Childhood obesity has been considered an emerging health problem during the recent century.[1] The prevalence of obesity among children and adolescents has increased dramatically during the last decades.[1] It is associated with serious consequences and related comorbid disease at an early age. Moreover, most of the noncommunicable diseases in adulthood including cardiovascular disease (CVD) are originated from early life.[2,3] Hence, prevention and management of obesity, as a major risk factor for mentioned complications, is crucial.

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Several studies indicate that body fat and visceral adipose tissue in obese children and adolescents are predictive of obesity-related comorbidities including CVD and insulin resistance (IR).[4,5] Furthermore, IR is the most important denominator for most of the obesity-related metabolic and cardiovascular complications. Its most important consequence is type 2 diabetes mellitus, a disease which has been considered a serious public health problem affecting children as young as 6-year-old, mostly obese ones.[6,7]

Evidences indicated that in obese patients, inflammation, oxidative damage, and IR are the suggested main factors which increase the risk of CVD and diabetes.[8] In addition,

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there are many clinical and experimental evidences which indicate that reducing oxidative stress and inflammation in obese patients could have a significant effect on limiting the burden of obesity-related complications including diabetes and CVD.[9,10]

It seems that using pharmacological approach for targeting the inflammatory pathway or reducing IR would be a novel strategy of controlling and reducing obesity-related complications among pediatric population and consequently in adulthood.[11,12]

Although there are limited pharmacotherapy options for the treatment of pediatric obesity, some evidences mostly from clinical trials among adult population show that some pharmacological agents such as metformin and folic acid could have improving effect on the inflammatory status and IR of obese patients.[13-15] There are few studies among pediatric populations in this regards and also, there are no conclusive reports regarding the appropriate duration of medical therapy with the above-mentioned agents.[16,17]

Considering the increasing trend of obesity, especially in developing countries such as Iran,[18] and the role of inflammatory factors and IR in the occurrence of obesity-related complications as well as the safety of the above-mentioned agents, this clinical trial was designed to investigate the effect of metformin and folic acid on inflammatory factors and IR among obese children.

MATERIALS AND METHODS

In this randomized, double-blind, controlled clinical trial study, sixty obese children, aged 6–12 years, attended the endocrinology clinic, affiliated to Shahrekord University of Medical Sciences, were enrolled.

Children with body mass index (BMI) >95th percentile were included in the study. Those with secondary obesity (due to endocrine disorder or genetic syndromes), renal and hepatic dysfunction, history of using anticonvulsant agents, estrogen, thiazides, metformin, cholestyramine, methotrexate, fibrates, nicotinic acid, and vitamin supplement (1 month before study) were excluded. In addition, those who were underweight, lost diet, or had not appropriate cooperation and regular follow-up were also excluded.

The protocol of the study was approved by the Pediatrics Review Board and Regional Bioethics Committee of Shahrekord University of Medical Sciences. The study was registered in the Iranian Registry of Clinical Trials (IRCT), IRCT registration number (2014020116435N1). Written informed consent was obtained from all the selected patients or their parents after explanation of the methods and goal of the study.

Selected obese children were randomly allocated into two interventional (folic acid 1 mg/daily or metformin 1000 mg/daily) groups [Figure 1].

- Folic acid (1 mg) supplied by Rouz Darou Pharmaceutical Company, Tehran, Iran
- Metformin (500 mg) supplied by Chemidarou industrial Company, Tehran, Iran.

All patients were examined clinically and their demographic and anthropometrics (BMI) information was recorded by a trained nurse using a questionnaire. The level of homocysteine (Hcy), IR, interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) were measured in all participants before and after trial.

The levels of biochemical measurements before and after trial between and within the groups were compared.

Laboratory measurements

Venous blood samples were obtained from each participant after overnight fasting.

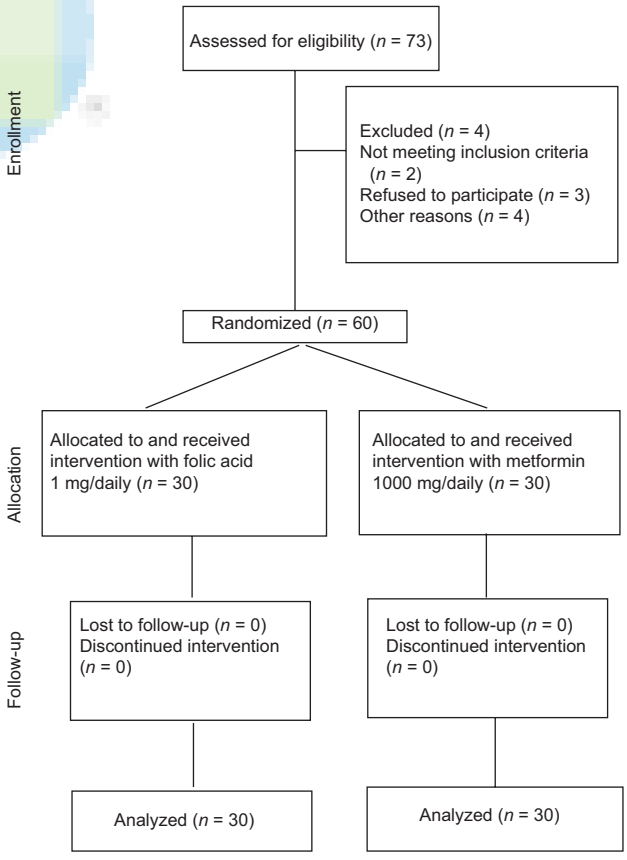

Figure 1: Consort diagram of the study

Hcy was measured by immunoassay method using Axis-Shield Diagnostics (Dundee, UK) kit.

TNF-α, IL-6, and IL-8 were measured enzymatically with standard auto-analyzer kits (Pars Azmoon, Tehran, Iran).

IR was measured using homeostasis model assessment of IR (HOMA-IR) formula (HOMA-IR = fasting insulin [μU/mL] × fasting glucose [mg/dL]/405).

Statistical analysis

Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was evaluated with Kolmogorov–Smirnov test. Mean of the studied variables before and after the study and between the groups was compared using paired *t*-test and independent samples *t*-test. The differences were considered as significant at $P < 0.05$.

RESULTS

In this trial, sixty obese children were allocated in two interventional groups (thirty obese children in each group). Demographic characteristics of the studied populations in the two groups are shown in Table 1. The two groups were age- and sex-matched, and the mean of BMI was not significantly different ($P > 0.05$).

Mean ± standard deviation (SD) of biochemical measurements including Hcy, HOMA-IR, IL-6, IL-8, and TNF-α in the studied groups before and after the trial is shown in Table 2. Mean ± SD differences (before and after) of the studied biochemical variables in the two interventional groups are shown in Table 3.

Table 1: Demographic characteristics of obese and overweight children in two studied groups (folic acid 1 mg/daily and metformin 1000 mg/daily)

Variables	Folic acid 1 mg/daily (*n*=30)	Metformin 1000 mg/daily (*n*=30)	*P*
Sex (female/male)	13/17	12/18	0.08
Age (years)	9.5±2.1	10.1±2.2	0.57
BMI (percentile)	94±3.7	95±2.5	0.87

BMI = Body mass index

There was not any significant relation between IR and Hcy and studied inflammatory factors ($P > 0.05$).

DISCUSSION

In this study, the effectiveness of folic acid and metformin on reducing inflammation and IR of obese children and adolescences was investigated. The results of the current study indicated that both metformin and folic acid could have an improving effect on IR and some inflammatory factors such as TNF-α, IL-8, and Hcy. Folic acid could significantly reduce the level of IL-6 whereas metformin did not. Metformin have a superior effect on reducing IR and acid folic on reducing IL-6.

Evidences indicated that the level of Hcy and inflammatory factors is higher in obese children and the increased level of both mentioned factors is associated with a higher risk of CVD in this group of population.[19,20] Hence, we hypothesize that if administration of the two studied agents, i.e., folic acid and metformin could decrease the level of Hcy and inflammatory factors, using these agents with lower side effects could have protective effect on the occurrence of CVD in this group of children.

Literature review in this regard indicated that there were few studies in this field among pediatrics population and there were no similar studies which compare the effectiveness of the two relatively safe pharmacological agents in this field.

Several studies have indicated the proper effect of metformin in the management of obese children, but regarding its anti-inflammatory effects, there were few studies.[21,22] Results of different clinical trials on the effectiveness of metformin in childhood obesity were controversial in various fields of obesity management. Regarding the role of metformin in inflammation among obese children, the findings of different studies are also controversial.[23]

Gómez-Díaz *et al*. have indicated that using 850 mg metformin for 12 weeks in 4–17-year-old children with glucose intolerance could have improving effect

Table 2: Mean±standard deviation of biochemical measurements including homeostasis model assessment of insulin resistance, homocysteine, tumor necrosis factor-alpha, interleukin-6, and interleukin-8 in the two studied groups before and after trial

Variables	Folic acid 1 mg/daily			Metformin 1000 mg/daily		
	Before	After	*P*	Before	After	*P*
HOMA-IR	4.43±0.23	2.70±0.7	<0.001	5.12±3.81	2.32±0.8	<0.001
Hcy (μmol/L)	9.87±1.13	7.10±1.83	<0.001	10.72±2.7	7.19±2.41	<0.001
TNF-α (pg/ml)	90.18±15.3	60.64±11.56	<0.001	93.66±20.43	67.56±12.91	0.002
IL-8 (pg/ml)	111.30±22.81	90.78±14.18	0.001	110.18±23.16	86.68±11.42	0.002
IL-6 (pg/ml)	338.39±25.12	294.21±23.76	0.001	326.17±24.75	328.76±31.16	0.89

HOMA-IR = Model assessment of insulin resistance; Hcy = Homocysteine; TNF-α = Tumor necrosis factor-alpha; IL = Interleukin

Table 3: Mean±standard deviation differences (before and after) of studied biochemical variables including homeostasis model assessment of insulin resistance, homocysteine, tumor necrosis factor-alpha, interleukin-6, and interleukin-8 in the two interventional groups

Variables	Folic acid 1 mg/daily	Metformin 1000 mg/daily	*P*
HOMA-IR	−2.13±0.99	−3.87±1.71	<0.001
Hcy (μmol/L)	−2.71±3.01	−3.53±4.12	0.38
TNF-α (pg/ml)	−29.53±68.44	−31.38±51.63	0.90
IL-8 (pg/ml)	−20.51±30.39	−23.49±38.80	0.74
IL-6 (pg/ml)	44.18±48.75	2.59±101.19	0.002

HOMA-IR = Model assessment of insulin resistance; Hcy = Homocysteine; TNF-α = Tumor necrosis factor-alpha; IL=Interleukin

on HOMA-IR and HbA1c, but no significant effect on inflammatory factors including TNF-α, IL-6, IL-1α, and C-reactive protein (CRP).[24]

Evia-Viscarra *et al*. evaluated the effect of administration of 1000 mg metformin for 3 months on inflammatory factors such as IL-6, TNF-α, and CRP among obese adolescents with IR. According to their results, metformin could significantly reduce IR and the level of TNF-α.[25]

The effect of metformin use on Hcy level of obese children was not studied previously, and the results of adult studies in this field were different.[26,27]

In this study, metformin had a lowering effect on Hcy, IR and IL-8, and TNF-α, but it had no significant effect on IL-6. In one study among adult diabetic patients, metformin had no significant effect on the level of IL-6.

There are some studies which investigated the effect of folic acid on Hcy level and IR of obese population.[28,29] Studies among children population were scarce.

Solini *et al*. in Italy have investigated the effect of 12-week folic acid treatment on insulin sensitivity and some biochemical parameters such as Hcy and some inflammatory factors. After that period, Hcy decreased and insulin sensitivity increased significantly among obese adults.[30] They showed that folic acid use could reduce the circulating level of some inflammatory mediators independently of weight change. They concluded that folic acid could have a protective role for atherogenesis and CVDs in obese subjects.[30]

Peña *et al*. in Austria have indicated that administration of folic acid in obese children decreased the Hcy level.[31]

In a study in Greece, Papandreou *et al*. showed that oral folic acid could efficiently reduce the serum Hcy levels.[32]

Although evidences indicated that there is a link between inflammation and obesity and metabolic biomarkers such as HOMA-IR in adult population, recent studies showed that the association was not similar for children and adolescents.[33]

In our trial, folic acid has a decreasing effect on all studied variables, especially on inflammatory factors.

Galcheva *et al*. have shown that though the level of HOMA-IR was higher in obese prepubertal children, they did not find any association between TNF-α and IL-6 and adiposity.[34] In another study, Zabaleta *et al*. have not indicated a significant association between HOMA-IR and TNF-α and IL-8.[33] Some studies also did not report any association between IL-6 and IR among children and adolescents. Roth *et al*. found a correlation between IL-6 and HOMA-IR score changes over 1 year in an intervention study on obese children.[35] Bugge *et al*. also did not demonstrate any cross-sectional association between IL-6 and HOMA-IR, but they indicated that IL-6 level at age 9 correlates with HOMA-IR at age 13 years, especially among girls.[36]

Similar to the previous studies, we did not find any association between HOMA-IR and IL-6, IL-8, and TNF-α in our studied obese children.

The limitation of the current study was shorter duration of the study. As this study was the first study in this field, we tried to design the trial for short duration and then plan future studies for longer duration and also in combination with lifestyle modification. In addition, it seems that the effect of studied agents in obese children with and without IR would be more helpful for proper management of childhood obesity.

The strength of this trial was its novelty, which compared the efficacy of the two relatively safe pharmacological agents for the treatment of pediatric obese population.

CONCLUSION

The findings of this trial indicated that both metformin and folic acid could decrease IR and level of Hcy in obese children and adolescents. The effectiveness of metformin on IR was more significant than folic acid. Regarding the effectiveness of the two studied agents on inflammatory factors, it is suggested that the role of folic acid was superior to metformin. These results could help us for proper management of obese children regarding their condition. It is suggested that metformin is a proper agent for obese children with IR, and folic acid is an appropriate supplement for obese children with increased inflammatory factors. Further studies with larger sample size and longer duration are recommended.

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Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTION

All authors contributed in all stages of the work including, design, concept, and all stages of the trial. All authors read and confirmed the draft of the manuscript before submission.

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