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Original Article

Effect of Vitamin E and Metformin on Fatty Liver Disease in Obese Children- Randomized Clinical Trial

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Abstract

Background: We evaluated the effect of vitamin E and metformin on fatty liver disease in obese children.

Methods: This interventional study has been done on 119 children with Non-alcoholic fatty liver disease (based on sonography results). Patients were divided into four treatment groups; they received metformin 1gr daily (age< 12 years), metformin 1.5 gr daily (age> 12 years), vitamin E 800 U daily and vitamin E 400 U daily. Liver sonography was performed for patients for two periods of two months. This trial was registered in Iranian Registry of Clinical Trials (IRCT), No.IRCT2013021012421N1

Results: The study group comprised 119 individuals (62 females, 57 males). The mean age was 10± 3.19 yr**.** There was no significant difference in terms of sex and BMI between the groups. Overall liver sonography showed normal liver in 66 patients (55.46%), 66.63% after two months and 33.37% after four months. After two months, the most therapeutic response observed in the group which received vitamin E 800 u daily (48.1%) and the least therapeutic response was in the group which received vitamin E 400 u daily (14.3%). After four months, the greater response was seen in vitamin E 400 u daily group (45.8%) and the least response in the metformin 1 gram daily group (19%).

Conclusion: In comparison with metformin, vitamin E is more influential in remission; however both are efficient in treatment of fatty liver. Vitamin E 400 u daily responses better in four-month treatment.

Keywords: Fatty liver disease, Obesity, Children, Metformin, Vitamin E

Introduction

Non-alcoholic fatty liver disease (NAFLD) is now the most prevalent chronic liver disease among children that mostly emerges after the age of 10 (1, 2). This disease happens in some clinical disorders like diabetes, obesity and malnutrition and exacerbates the danger of affliction with heart disease and liver cirrhosis (3, 4). At present, treatment has focused on the control of medical problems and disorders causing fatty liver; including diet, and its modification, exercise and weight loss (3, 5-7). Some new medicines like metformin and vitamin E have been introduced for fatty liver treatment (8-11).

Resistance to insulin is prevalent in fatty liver and medications like metformin, which reduce insulin resistance, improve liver enzymes (10). According to various studies, metformin therapy in patients suffering from NAFLD causes weight loss, reduction of liver transaminases, better histology of liver (reduction of liver steatosis and inflammatory

necrosis), improvement of insulin sensitivity and reduction of liver fibrosis (12-14). Thiazolidinediones affect glucose and lipid metabolism in insulin-sensitive tissues, which reduces the lipid content of the liver but they have limited effect regarding biochemical and histology, and not studied in children (13, 15, 16).

One of the features of fatty liver disease is high level of serum aminotransferases, which indicates liver cells damage (17, 18). Antioxidants, reduce the effect of oxidant chemicals which are produced in liver cells during the disease process. It is suggested that vitamin E, a powerful and cheap antioxidant, has therapeutic effects on fatty liver in children and adults (2, 8, 19).

The results of the researches about the effects of metformin and vitamin E in fatty liver disease are controversial. In a research have been showed that vitamin E is superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes (19). On the other hand, in another study no significant therapeutic effect was observed between the vitamin E, metformin and placebo on fatty liver disease in obese children (8). These authors also previously have been reported efficacy of oral vitamin E administration to decrease serum aminotransferase and alkaline phosphatase levels in obese children with NASH, but their study had not placebo group (2).

According to the little data and controversies about therapeutic effects of vitamin E and metformin and potential complications of fatty liver disease for children, we decided to evaluate the therapeutic effects of these two drugs for obese children suffering from fatty liver disease referring to Pediatric Clinic of Kashan University of Medical Sciences in 2012-13, in hope to find an efficient and inexpensive treatment for this disease.

Material and Methods

In this interventional study, liver sonography was performed on 376 obese children of 4-18 years old (BMI over 95th percentile) who referred to Pediatric Clinic of Kashan University of Medical Sciences due to obesity. Overall, 234 persons (61%) had fatty liver disease and 128 persons entered the study after rule out of other causes of fatty liver disease. With a test power of 80%, confidence level of 95% and maximum negligible error of 20% the least needed population was counted 26 persons in each group. Obese children under the age of 4 yr or over the age of 18, children with history of alcohol consumption, hereditary syndromes associated with obesity, such as prader willi syndrome, pathological obesity (like as cushing syndrome, hypothyroidism and psudohypoparathyroidism) and obese children suffering from chronic diseases (related to liver, kidney,…) were excluded from the study.

Laboratory tests included fasting blood sugar, lipid profile, insulin and liver enzymes after 12 hour fasting were performed. BMI of the patients was calculated before treatment and after every two-month period. Having written consent, patients were randomly divided into four groups. The first group was given vitamin E 400 U daily, the second group, vitamin E 800 U daily, the third one (children under 12 years old) metformin500mg twice daily and the forth group (children over 12 years) metformin 500 mg three times per day. After two months, liver sonography was done for the patients. If no response was there, medicinal treatment would be continued for two more months and again sonography would be done by the same radiologist. All the patients were advised the same, in terms of diet, weight loss program, and exercise during the treatment.

Having collected the data, all the information was entered SPSS software and the results before and after the treatment were compared through paired *t* test and wilcoxon signed-rank test. Moreover, changes in the degree of fatty liver, concerning the type of the medicine was analyzed by using chi-square test. This trial was registered in Iranian Registry of Clinical Trials (IRCT), No.IRCT20130-21012421N1.

Results

From 128 patients who had fatty liver disease, nine patients under treatment with metformin were excluded because they could not tolerate gas-

trointestinal side effects of the drug and 119 patients remained until the end of the study. Among them 62 children (52.1%) were female and 57 children (47.8%) were male. The mean age was 10± 3.19years**.** The least age was 4 year and the maximum was 15.5. The distribution of patients within therapeutic groups showed in the Table1.
Neither groups has not BMI standard deviation score (BMI SDS) changes after two (*P*=0.989) and four (*P*=0.492) months of treatment. Table 2 shows frequency distribution of fatty liver grade in all groups before and during treatment and details of therapeutic response. At the end of study, liver sonography showed normal liver in 66 patients (55.46%); 66.63% after two months and 33.37% after four months.

Table1: Statistical indices of age and sex in the groups

Age	TOTAL	AGE MEAN ±SD	*P* value	MALE n (%)	FEMALE n (%)	*P* value
Metformin 1g daily	36	8.24±2.17	<0.001	15(41.7)	21(58.3)	0.38
Metformin 1.5g daily	28	13.53±1.27		18(64.3)	10(35.7)	
Vitamin E 400 U daily	28	9.05±3.12		14(50)	14(50)	
Vitamin E 800 U daily	27	9.86±3.06		10(37)	17(63)	

Table 2: Frequency distribution of sonographic grade of fatty liver disease before and during treatment

Groups	Evaluation	Without fatty liver	FLD G1 n (%)	FLD G2 n (%)	*P* value
Metformin 1g daily	Before treatment	-	34(94)	2(5.9)	-
	2 months later	14(38.9)	22(61.1)	-	<0.001
	4 months later	4(19)	17(81)	-	0.031
Metformin 1.5g daily	Before treatment	-	24(88.9)	3(11.1)	-
	2 months later	11(39.3)	17(60.7)	-	<0.001
	4 months later	5(29.4)	11(64.7)	1(5.9)	0.188
Vitamin E 400 U daily	Before treatment	-	24(85.7)	4(14.3)	-
	2 months later	4(14.3)	23(82.1)	1(3.6)	0.07
	4 months later	11(45.8)	13(54.2)	-	<0.001
Vitamin E 800 u daily	Before treatment	-	24(92.3)	2(7.7)	-
	2 months later	13(48.1)	14(51.9)	1(8%)	<0.001
	4 months later	4(28.6)	10(71.4)	1(1.3%)	0.063

Seven patients had changed from grade 2 or 3 to grade 1 and overall 73(61.34%) patients had remission or cure from fatty liver disease. After two months, the most therapeutic response observed in the group which received vitamin E 800 u daily (48.1%) and the least therapeutic response was in the group which received vitamin E 400 u daily (14.3%). After four months, the most therapeutic response was seen in the group which received vitamin E 400 u daily (45.8%) and the least response was in the group which received metformin 1 gr daily (19%). In the first two-month period of treatment, there was a significant relation among the groups in terms of remission (*P*=0.043). There was a significant relation between fatty liver grade and remission in the group

which received metformin 1gr daily in each period of treatment (*P*= 0.031%). Also there was a significant relation in the group which received metformin 1.5 gr in the first two-month period ,but after the second two-month period there was no significant relation (*P*= 0.188%).

In the group which received vitamin E 400 u daily, there was no significant relation in the first two-month period (*P*= 0.07), but after continuance of treatment there appeared a significant relation (*P*<0.001). In the group which received vitamin E 800 u daily, there was a significant relation in the first two-month period (*P*<0.001), but in the second two-month period there was not such a significant relation (*P*=0.063).Summary of therapeutic response to 4 regimens have been showed in Table 3.

Table3: Summary of remission rate, two and four months after onset of treatment

Groups	Remission n (%) 2 months later	Remission n (%)4 months later	Total
Metformin 1 g daily	14(38.9)	4(11.1)	18(50)
Metformin 1.5 g daily	11(39.3)	5(17.8)	16(57.1)
Vitamin E 400 U daily	4(14.3)	11(39.2)	15(53.5)
Vitamin E 800 U daily	13(48.1)	4(14.8)	17(62.3)
P value	0.043	0.275	

Discussion

The present study evaluated the effects of vitamin E and metformin for fatty liver disease in obese children. There are evidences of histological improvement with metformin and vitamin E but studies that are more conclusive are needed (20). In this study overall remission rate with metformin was 50%. We have not control or placebo group. Other limitation of our study was the absent of histological data of patients. There is little data about effects of vitamin E and metformin for fatty liver disease in obese children. On the other hand, the significance of sonographic evidence of fatty liver disease in the absence of high level of serum aminotransferases is not well known. Most similar to our study performed by Nadeau, et al. (2009), they used metformin 850 mg twice daily for fifty obese, insulin-resistant adolescents (mean age 15.1 yr, mean BMI 39.8 kg/m2) for six months, the diagnosis of fatty liver disease and follow up performed by ultrasonography. Fatty liver prevalence, severity, and fasting insulin improved significantly with metformin compared to placebo (10). Nar, et al. reported 16% decrease in the prevalence of sonographic evidence of fatty liver disease with metformin therapy in obese patients with newly diagnosed type 2 diabetes mellitus and 20% in patients with lifestyle changes only, both interventions equally affected the plasma leptin levels and BMI (14).Lower remission rate in this study may be due to type 2 diabetes mellitus. Nobili, et al. studied 57 obese children for 24 months to evaluate the effect of metformin (1.5g daily) along with change of life style on fatty liver disease. The patients achieved improvement in serum ALT and liver inflammation and reduction in insulin resistance but the changes was not greater than patients that treated with lifestyle change (12). In a study, on 173 children with fatty liver disease, there was no significant difference between therapeutic effect of vitamin E, metformin and placebo (8). In some recent studies, in comparison to placebo or life style, there was no benefit in treatment with metformin through evaluation of liver histology or CT and aminotransferase levels (8, 21, 22). In a study 66 obese children of 7-18 years old were divided into two groups; one programmed for diet/exercise and other for diet/exercise and metformin for 6 months, metformin therapy improved weight loss and reduced abdominal adiposity, but did not enhance the beneficial effect of diet and exercise on markers related to inflammation or hepatic fat (23).

Schwimmer, et al. used metformin 500 mg twice daily for 24 weeks in ten obese children with biopsy-proven non-alcoholic steatohepatitis. ALT normalized in 40% and AST normalized in 50% of subjects. Children demonstrated significant improvements in liver enzymes, liver fat (measured by MRI), insulin sensitivity and quality of life (24). After 6 months of treatment with metformin, remission in the mean of serum level of aminotransferases and insulin resistance was reported, although there was no change in liver histology after one year (25).

Other effect of metformin that make it attractive for obese children is reduction of weight and BMI (23, 26). In this study there was no significant difference in BMI and BMI standard deviation score (BMI SDS) before and after the treatment. Perhaps if we extend duration of treatment with metformin, more than four months, treatment will reduce BMI, like other studies. Other drug that used in our research was vitamin E with two different dosages: 400 and 800 U daily. The effect of vitamin E on BMI in the present study is the same as the other studies and patients had not change of BMI after treatment. The remission rate with vitamin E 400 U daily for four months was 53.5% that is similar to metformin 500 mg twice daily. There are little data about therapeutic effect of vitamin E for fatty liver disease in obese children. Vajro, et al. (prescribed vitamin E 400 U daily for two months and then 100 U daily for three months but they not found decrease in prevalence of fatty liver disease by sonographycal evaluation (27). Also in our study the response to vitamin E 400 U daily for two months was low (14.3%). A recent meta-analysis did not found significant effect of vitamin E over placebo in normalizing serum ALT in obese children with fatty liver disease. They analyzed five randomized trials with a total of 270 participants and concluded that the data on the long-term effect of vitamin E on histological improvements in NAFLD children are still lacking and larger, well-controlled trials are still needed to answer this question (28). In the present study the most therapeutic response (reduction of fatty liver degree or its eradication) in the first two-month period is observed in the group which received vitamin E 800 U daily(48.1%), this dose is relatively high and its effect was similar to 400 U for four months. In a study 173 obese children with fatty liver disease in three groups received vitamin E 800 unit, metformin 1000 mg and placebo for 96 weeks, no significant therapeutic effect was observed between the vitamin E, metformin and placebo (8). They also previously studied 11 children under the age of 16 years with chronically elevated serum aminotransferases (ALT and AST) levels for greater than 3 months. Vitamin E 400 to 1200 U daily was given to patients for three months. Body mass index did not differ in this study, treatment with vitamin E for 2-4 months result to normalization of ALT; but in any case treatment continuance was needed for permanent effect (2). In a clinical trial 800 U daily Alpha-Tocopherol was prescribed to 84 subjects with nonalcoholic steatohepatitis for 96 weeks. In this study, greater decline of aminotransferases was observed in patients receiving vitamin E in comparison to placebo, (43% vs. 19%) (19).

Conclusion

Both metformin and vitamin E are effective in treatment of fatty liver disease in obese children based on sonographycal findings, and the effect of metformin, especially dose of 1.5g daily, in comparison with 1 g daily is remarkable and comparable with the effect of vitamin E. It can be also concluded that vitamin E 400 u daily needs more than two months of treatment and treatment for four months would response better. Since changes of BMI SDS were not observed in the present study before and after the treatment, it could be said that cause of the remission is the medicine itself or it could be the natural process of the disease.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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