Original Article

Effects of folic acid plus levothyroxine on serum homocysteine level in hypothyroidism

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Abstract

Background: Rise in serum homocysteine level may be associated with higher prevalence of cardiovascular diseases in hypothyroidism. Levothyroxine can partly diminish serum homocysteine level. Folic acid participates in homocysteine metabolic cycle in the human body. The effect of concomitant administration of folic acid and levothyroxine on serum homocysteine level was evaluated in the present study.

Methods: Sixty patients with hypothyroidism participated in this double-blinded clinical trial study. They were divided into two equal groups; Group A received oral levothyroxine 50-100 µg daily. Group B took oral folic acid 1 mg on a daily basis in addition to levothyroxine with similar schedule to group A. The patients were followed up for two months. The serum homocysteine levels of these two groups were measured before and after the study. This study was registered in Iranian Registry of clinical trial (IRCT number: 201112077723N1).

Results: Mean serum homocysteine level fell from 11.5±4.2 to 9.9±3.5 µmol/lit and from 11.2±3.1 to 6.9±1.9 µmol/lit in group A and B, respectively ($p<0.001$). The mean reduction in serum homocysteine levels were 1.6±1.2 µmol/lit and 4.3±1.4 µmol/lit in group A and B, respectively ($p<0.001$).

Conclusion: Levothyroxine can decrease serum homocysteine level partly; still its combination with folic acid empowers the effect. Combination therapy declines serum homocysteine level more successfully.

Keywords: Hypothyroidism, Homocysteine, Folic acid, Levothyroxine

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Atherosclerosis is a main cause of mortality and morbidity in developed countries. As many studies have shown, atherosclerosis and cardiovascular diseases will stand on top of the list of prevalent diseases in the world until 2020. Prevention of cardiovascular diseases have warranted so many studies to identify their risk factors in different levels (1). The risk of cardiovascular diseases is high in hypothyroidism, too (2). Hypertension and high serum low density lipoprotein (LDL) levels may contribute to this, but they are not seen in all the patients with hypothyroidism (3-5). Moreover, the rise of serum homocysteine level is suggested as an independent risk factor for cardiovascular diseases (6, 7). Homocysteine is an amino acid which is derived from methionin during its metabolism. Folic acid deficiency, administration of folate antagonists such as methotrexate and carbamazepine and disturbance of methionin metabolism after hypothyroidism have been suggested as the reasons of rise in serum homocysteine level (1). Decrease in rate of homocysteine metabolism and diminution of its renal excretion was reported in patients with hypothyroidism (8. 9). It has been reported that treatment with levothyroxine reduces serum homocysteine level (10, 11). With regard to the role of folic acid in homocysteine metabolic cycle as well as low serum folic acid level in patients with hypothyroidism, it seems that the addition of folic acid to levothyroxine may decrease serum homocysteine level more efficiently (11).

Many studies have demonstrated that levothyroxine diminishes serum homocysteine level (7, 9, 12-14). However, in many studies, combination therapy with levothyroxine and folic acid has shown better results (7, 9, 12, 15). Serum homocysteine levels in patients with hypothyroidism after treatment with levothyroxine alone and in combination with folic acid have been compared in the current study.

Methods

In this double blinded clinical trial study, 60 patients with hypothyroidism were selected from the patients referred to the Endocrinology Center, Outdoor Patient Department, Booali-Sina Hospital in Qazvin City, a large town in the central part of Iran from March 2009 to March 2010. They were divided into two equal groups randomly. The inclusion criteria included clinical findings concordant with hypothyroidism, TSH>10 mIU/L, normal renal function, no use of phenobarbital, phenytoin, tamoxifen, methotrexate, and theophyline, anemia, diabetes mellitus, or other systemic diseases, negative history of pregnancy and negative history of cigarette smoking. Any patient who had anemia in requested cell blood count (CBC) was excluded from the study, too. Informed consent for contribution in the study was obtained from all the patients. After inclusive history taking and physical examination and confirmation of the diagnosis, serum homocysteine and thyroid stimulating hormone (TSH) levels for each patient were determined.

The patients in group A received oral levothyroxine 50-100 µg plus placebo daily for two months. The patients in group B took oral folic acid 1mg/kg daily as well as levothyroxine like group A. Neither the patients nor their responsible physicians know which group they have been assigned to. The patients visited two months later when they became euthyroid i.e. they had optimal level of TSH. Then, their serum homocysteine level was rechecked. Serum homocysteine level was measured through EIA method with kits from AXIS- SHIELD Company. Its normal limit was 5-15 µmol/l. Serum folic acid level was measured through RIA method with kits from De medi tec Company. Its normal range was 3.1-17.5 ng/ml. Serum TSH level was measured through ICMA (CIA) with kits from Monobind. Its normal limit was 0.39-6.16 mIU/L. The study was registered in Iranian registry of Clinical Trials (IRCT number: 201112077723N1).

Statistical analysis: The results were reported as mean ± standard deviation. All gathered data were statistically analyzed by the means of SPSS (version16). Paired t-test and independent t-test were used for statistical analysis on account of normal distribution of the variables. A difference in a p value less than 0.05 was considered significant.

Results

The patients in the two studied groups were comparable in sex and age distribution. There were 29 females and 1 male in each group. The mean age of the patients in group A and B were 33.6±4.6 and 33.7±4.7 years, respectively. Serum levels of homocysteine, folic acid, and TSH in both groups before and after intervention were demonstrated in table 1.

Table 1. serum levels of homocysteine, folic acid and TSH in study and control groups before and after intervention

variables	Study group Mean±SD	Control group Mean±SD	pvalue
Homocysteine (µmol/l)			
before	11.2±3.1	11.5±4.2	0.734
after	6.9±1.9*	9.9±3.5*	0.000
differences between before and after	4.3±1.4	1.6±1.2	0.000
Folic acid (ng/ml)			
before	7.7±4.6	5.8±2.6	0.060
after	11.3±3.1*	7.3±2.6*	0.000
differences between before and after	-3.7±2.1	-1.4±1.1	0.000
TSH (mIU/L)			
before	32.9±8.8	30.4±7.4	0.244
after	2.3±0.9*	2±1*	0.305
differences between before and after	30.6±8.7	28.4±7.3	0.290

*p<0.001 paired t-test vs. b efore t-test

Also, the differences of each variable before and after intervention in study and control groups were not significant. The groups did not have differences in serum homocysteine and folic acid levels before intervention, but later on the differences were statistically significant ($p<0.001$). Serum TSH levels of the groups showed no differences before and after the intervention.

Discussion

Cardiovascular diseases result in lots of mortality and morbidity in the entire world. Various metabolic diseases include hypothyroidism that put up with the risk, too (2). The risks of cardiovascular diseases can be moderated by some safe, economical, yet effective means. The role of increase in serum homocysteine level as an independent risk factor for cardiovascular diseases bring special attention nowadays. Some studies have suggested that reduction in serum homocysteine level can cut the chance of cardiovascular diseases 10-25% (7,16-18).

Orzechowska et al. showed that treatment with levothyroxine can decline serum homocysteine level significantly in patients with hypothyroidism (12). Diekman et al. have demonstrated that treatment with levothyroxine until its achievement, euthyroid state diminishes serum homocysteine level from 17.6±10.2 to 13±4.7 ($p<0.005$) (13). Many studies have affirmed that levothyroxine therapy can decrease serum homocysteine level in hypothyroidism (7, 9, 14). Catargi et al. have confirmed that the effect is not satisfactory and should be supplemented with folic acid (15). The effect of folic acid in reduction of serum homocysteine level has been displayed in many studies (19, 20).

In the current study, the mean serum homocysteine level diminished more drastically (3±1.6 µmol/l). In the study group compared to the control group; in spite of many studies, it had been shown that serum homocysteine level would elevate appreciably in hypothyroidism (2, 7, 9, 14, 15). The elevated serum homocysteine level may damage vascular endothelium induces vascular smooth muscles proliferation, gives rise to hypercoagulability, and finally increases the risk of cardiovascular diseases (21).

A similar study conducted in Iran had confirmed that serum homocysteine level declined more markedly in treatment with levothyroxine plus folic acid as compared to levothyroxine alone, the reduction was from 15.27 to 10.8 in the group that had taken levothyroxine plus folic acid and from 15.69 to 13.9 in the group that had taken levothyroxine alone (22). The results of the present study suggest that combination therapy with levothyroxine plus folic acid will diminish serum homocysteine level more effectively; so this treatment regimen is preferable to levothyroxine alone in hypothyroidism. Folic acid is an easy available, safe, and low-cost drug.

Its administration along with levothyroxine can lessen the risk of cardiovascular disease by decreasing serum homocysteine level in hypothyroidism.

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Conflict of Interest: None declared.

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