

Commentary

Known effects of levothyroxine and folic acid on serum homocysteine level

This refers to Dr. Ziaee et al.'s manuscript published in your valuable journal about serum homocysteine level entitled "Effects of folic acid plus levothyroxine on serum homocysteine level in hypothyroidism". In this clinical trial study the efficacy of concomitant administration of folic acid and levothyroxine versus single levothyroxine prescription on serum homocysteine level was compared with hypothyroid patients. The authors concluded that "levothyroxine can decrease serum homocysteine level partly; still its combination with folic acid empowers the effect. Combination therapy declines serum homocysteine level more successfully (1)."

Thyroid hormone deficiency is associated with increased cardiovascular events, which cannot be fully explained by the atherogenic changes in lipid profile observed in these patients. Increased homocysteine serum level can help to explain this increased risk in hypothyroidism patients because homocysteine serum level is an important and independent risk factor for cardiovascular disease. Homocysteine is an amino acid which is derived from methionin during its metabolism. Disturbance of methionin metabolism in hypothyroidism has been suggested as the reason of serum homocysteine level rising. Increasing the rate of homocysteine catabolism and diminution of its renal excretion was also reported in patients with hypothyroidism (1, 2).

The association between serum homocysteine level and ischemic heart disease was shown in a cohort study (3). Decrease in serum homocysteine level is expected to decrease the mortality rate of ischemic heart disease about 15% (3, 4).

Hypothyroidism decreases the hepatic levels of enzymes involved in the re-methylation pathway of homocysteine; Therefore, an increased serum homocysteine level is observed in hypothyroid patients even though serum homocysteine is known as a considerable risk factor for cardiovascular system, It is seen that hypothyroidism treatment by levothyroxin will control the cardiovascular risks (2).

A dosage of 1 mg/d has been shown in a meta-analysis to produce the maximum homocysteine reduction. There is a dose-response relationship between serum homocysteine level and prescribed folic acid dose with no further reduction with a higher dosage (5mg/day) (4). This maximum reduction is about 25% (about 3 $\mu\text{mol/L}$) (4, 5). The patients with higher initial serum homocysteine level are more sensitive in response to prescribed daily folic acid (4, 5).

It seems that using folic acid in conjunction with levothyroxine can decrease the potential harmful effects of homocysteine on cardiovascular system (1, 6). Based on our clinical experience, there is a clear effect of prescription of folic acid 1 mg/day accompanied with levothyroxine on serum homocysteine reduction.

We fully support the valuable advice of the author, but it should also be noted that high homocysteine serum level in hypothyroid patient is secondary to their underlying pathology (2-4). Therefore, prescription of folic acid after the normalization of thyroid hormones and confirmation of high homocysteine serum level will be a logical advice. We suggest in the hypothyroid patients with high serum homocysteine level a prescription of 1 mg daily folic acid postponed up to 6 weeks after the patients become euthyroid.

Ali Jabbari (MD, MPH)^{*1, 2}

Jila Masrou Roudsari (MD)³

Shabnam Tabasi (MD)⁴

1. Department of Anesthesiology and intensive care, Golestan University of Medical Sciences, Gorgan, Iran.
2. Department of Anesthesiology and intensive care, Babol University of Medical Sciences, Babol, Iran.
3. Infectious Diseases and Tropical Medicine Research Center, Babol University of Medical Sciences, Babol, Iran.
4. Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Correspondences: Ali Jabbari, Department of Anesthesiology and Intensive care, Babol University of Medical Sciences, Babol, Iran.

Email: Amir_a_78@yahoo.com

Tel and Fax: 0111 2238296

Received: 11 April 2012

Revised: 20 April 2012

Accepted: 5 May 2012

References

1. Ziaee A, Tehrani NH, Hosseinkhani Z, et al. Effects of folic acid plus levothyroxine on serum homocysteine level in hypothyroidism. *Caspian J Intern Med* 2012; 3: 417-20.
2. Hussein WI, Green R, Jacobsen DW, Faiman C. Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism. *Ann Intern Med* 1999; 131: 348-51.
3. Wald NJ, Watt HC, Law MR, et al. Homocysteine and ischemic heart disease: results of a prospective study with implications regarding prevention. *Arch Intern Med* 1998; 158: 862-7.
4. Wald DS, Bishop L, Wald NJ, et al. Randomized Trial of Folic Acid Supplementation and Serum Homocysteine Levels. *Arch Intern Med* 2001; 161: 695-700.
5. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998; 316: 894-8.
6. Rezvanian H, Hajigholami A, Kachuei A, et al .The effect of folic acid and levothyroxine combination therapy on serum homocysteine levels of hypothyroid patients. *Iran J Endocrinol Metabol* 2006; 7: 315-9. [In Persian]