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Original Article

Association between plasma homocysteine status and hypothyroidism: a meta-analysis

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Abstract: Purpose: To figure out plasma homocysteine (Hcy) status in patients with subclinical hypothyroidism (SH) and overt hypothyroidism (OH) compared with healthy subjects, and the effect of levothyroxine (L-T4) on plasma homocysteine status in patients with hypothyroidism.Methods: PubMed Web of Science, and The Cochrane Library were used to identify eligible studies. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of selected studies. All analyses were performed using the STATA, version 12 software. Results: Our meta-analysis indicated that plasma Hcy concentrations elevated in OH patients without L-T4 treatment compared with healthy subjects. However, this elevation was not observed in the comparison between patients withSH without L-T4 treatment and healthy subjects. Moreover, plasma Hcy levels were found to be higher in patients with OH without L-T4 treatment than in patients with SH without L-T4 treatment. Finally, plasma Hcy concentrations decreased after L-T4 treatment in patients with SH or OH. Conclusions: Plasma Hcy status is associated with the severity of hypothyroidism and L-T4 treatment is helpful for patients with hypothyroidism to reduce the plasma Hcy levels.

Keywords: Homocysteine, subclinical hypothyroidism, overt hypothyroidism, levothyroxine, meta-analysis

Introduction

Hypothyroidismis divided into two types, subclinical hypothyroidism (SH) and overt hypothyroidism (OH), according to the decrease extent of thyroid function. SH is a condition defined as a persistently raised serum thyroid stimulating hormone (TSH) level in the presence of normal free thyroxine (fT4) [1]. Subclinical thyroid failure is often asymptomatic; 30% patientswith SH may have symptoms indicatingthe deficiency of thyroid hormone [2]. Recently, SH has been reported to be closely associated with atherosclerosis and myocardial infarction in elderly women [3]. OH, defined by high TSH levels with low levels of fT4 and/or free triiodothyronine (fT3), is a risk factor for cardiovascular diseases, especially coronary heart diseases [4].

Increasing attention is paid to the risk of cardiovascular diseases in patients with hypothyroidismrecently. Homocysteine (Hcy), a sulfhydryl-containing amino acid synthesized during the conversion of methionine to cysteine [5], has been identified as an independently risk factor for the progression ofvascular diseases [6]. The association between homocysteineand hypothyroidism has been demonstrated in several studies, however, the conclusion is controversial [7-9]. As the major treatment of hypothyroidism, levothyroxine (L-T4) replacement has been used for a long time. The effect of L-T4 treatment on plasma homocysteine status in patients with hypothyroidism has not yet reached a consensus [10-12].

Considering all those conflicting studies, meta-analysis may be an appropriate way to summarize available data to provide more strong evidences than the individual study. This meta-analysis was to elucidate plasma Hcy levels in patients with hypothyroidism, and to evaluate the effect of L-T4 therapy on plasma Hcy levels in patients with hypothyroidism.

Materials and methods

Search strategy

All the studies that investigated the association between plasma Hcy status and hypothyroid-

Table 1. Characteristics of studies included in this meta-analysis

			Control			Case 1			Case 2			Case 3			Case 4			Quality
Study	Year	Country	N (F/M)	Age (Y)	Hcy (μM)	N (F/M)	Age (Y)	Hcy (μM)	N (F/M)	Age (Y)	Hcy (μM)	N (F/M)	Age (Y)	Hcy (μM)	N (F/M)	Age (Y)	Hcy (μM)	score
Bičíková et al	2001	Czech	No	No	No	No	No	No	No	No	No	14 (12/2)	42± 10	15.6± 3.6	14 (12/2)	42± 10	9.9± 1.6	5
Deicher et al	2002	Austria	No	No	No	37 (31/6)	50± 18	9.9± 2.9	37 (31/6)	50± 18	9.6± 3.5	No	No	No	No	No	No	5
Bičíková et al	2002	Czech	No	No	No	No	No	No	No	No	No	16 (16/0)	35± 8.82	19.2± 3.2	16 (16/0)	35± 8.82	10.6± 2.9	5
Christ-Crain et al	2003	Switzerland	40	54.1± 9.2	11.3± 2.8	63	57.5± 9.8	11.0± 2.7	31	No	11.1± 3.4	61	55.7± 11.7	14.4± 9.1	No	No	No	6
Atabek et al	2003	Turkey	19	15± 1.8	6.6± 1.8	19	14.9± 1.9	6.7± 1.8	No	No	No	No	No	No	No	No	No	5
Luboshitzky et al	2004	Israel	19 (19/0)	51.7± 10.1	9.8± 2.6	44 (44/0)	51.6± 9.7	9.1± 2.4	No	No	No	10 (10/0)	50.1± 8.8	13.0± 7.9	No	No	No	6
Pe'rez et al	2004	Spain	No	No	No	42 (36/6)	51.7± 15	9.5± 2.93	42 (36/6)	51.7± 15	9.4± 3.7	No	No	No	No	No	No	6
Ozcan et al	2005	Turkey	33	41.8± 10.2	9.39± 2.45	84	41.6± 12.4	9.91± 2.30	84	41.6± 12.4	9.34± 2.19	No	No	No	No	No	No	5
Beyhan et al	2006	Turkey	No	No	No	75 (50/25)	42.4± 13.1	10± 2.5	75 (50/25)	42.4± 13.1	9.6± 2.5	No	No	No	No	No	No	6
Cakal et al	2007	Turkey	11	39.9± 12.5	7.9± 0.6	15	41.4± 14.1	9.2± 3.3	15	41.4± 14.1	7.8± 2.1	20	41.3± 11.1	10.3± 3.4	20	41.3± 11.1	7.7± 2.3	6
Turhan et al	2008	Turkey	50 (47/3)	38.2± 10.7	9.6± 3.1	53 (47/6)	40.8± 12.1	10.3± 3.4	No	No	No	No	No	No	No	No	No	6
Erdal et al	2008	Turkey	63 (55/8)	39.43± 13.02	9.71± 6.90	60 (55/5)	42.28± 12.65	9.92± 2.22	60 (55/5)	42.28± 12.65	9.36± 1.90	No	No	No	No	No	No	5
Adrees et al	2009	Ireland	56 (56/0)	47± 8	7.8± 2.1	56 (56/0)	50± 9	10.4± 3.6	52 (52/0)	52± 10	9.1± 2.0	No	No	No	No	No	No	6
Ma et al	2012	China	35 (20/15)	43± 12	10.37± 3.77	No	No	No	No	No	No	35 (25/10)	43± 11	15.78± 6.97	35 (25/10)	43± 11	12.39± 5.67	6
Bamashmoss et al	2013	Yemen	20 (18/2)	29.75± 6.15	11.48± 3.03	No	No	No	No	No	No	30 (27/3)	37.43± 6.92	24.45± 5.50	No	No	No	6
Kutluturk et al	2013	Turkey	No	No	No	No	No	No	No	No	No	54 (47/7)	20-75	9.67± 5.24	54 (47/7)	20-75	8.16± 3.38	6
Anaqnostis et al	2014	Greece	No	No	No	32 (30/2)	52.1± 13.9	11.29± 4.45	32 (30/2)	52.1± 13.9	11.94± 10.28	No	No	No	No	No	No	6

No = undescribed, Control = healthy people, Case 1 = subclinical hypothyroidism without L-T4 treatment, Case 2 = subclinical hypothyroidism after L-T4 treatment, Case 3 = overt hypothyroidism without L-T4 treatment, Case 4 = overt hypothyroidism after L-T4 treatment, Hcy = homocysteine mean ± SD (μM).

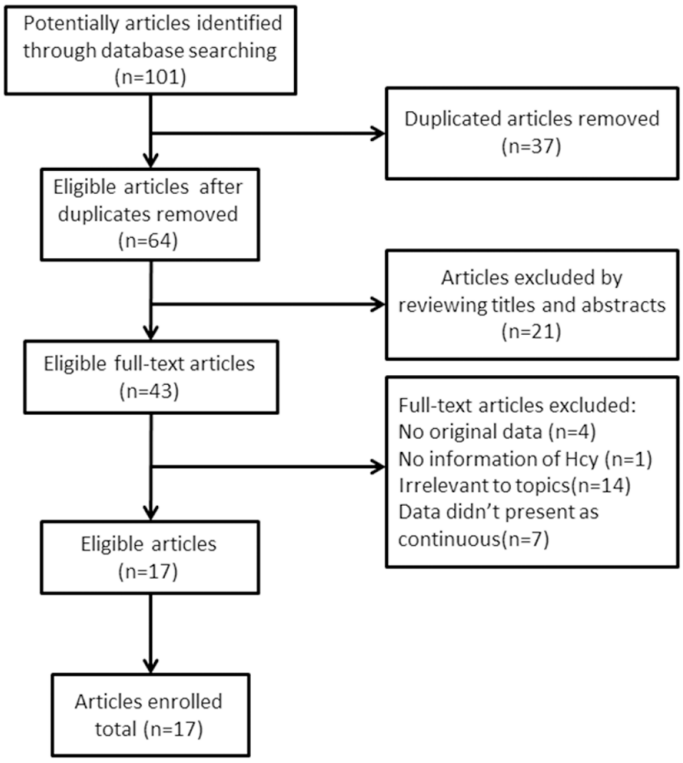

Figure 1. Search strategy for meta-analysis.

ism with/without L-T4 replacement were considered in this meta-analysis. A comprehensive literature search was performed for original articles published up from January 1990 to July, 2014 using PubMed, Web of Science databases and The Cochrane Library. The search was restricted to articles in English.As a search criterion, we used the following terms: "hypothyroidism", "subclinical hypothyroidism", "overt hypothyroidism", "homocysteine", "Hcy", "levothyroxine", "L-Thyroxine", "L-T4" and "thyroid hormone". References of retrieved articles were also reviewed in case of omitting additional published studies not included in PubMed, Web of Science databases and The Cochrane Library.

Study selection

First screening was based on titles and abstracts of retrievedarticles, any article lacking the information regarding plasma Hcystatus in patients with hypothyroidism was rejected. Editorials, abstracts, review articles and *in vitro* studies were also excluded. Next, second screening was based on the full texts of interested articles. Studies were considered eligible if they met the following criteria: 1) cross-sectional, case-control, prospective or cohort study; 2); controlled design studies, plasma Hcy levels in patients with SH or OH compared with healthy subjects; 3) effect of L-T4 treatment on patients with SH or OH; 4) data of interest (plasma Hcy concentration) presented as continuous (mean value± SD); 5) mean duration of L-T4 treatment: at least 2 months.

Quality scale

The Newcastle-Ottawa Quality Assessment Scale was used here toassess the quality of enrolled studies. The quality scores of included studies ranged from 5 to 6 (low quality: 1-3, median quality: 4-6, high quality: 7-9). As showed in **Table 1**.

Data extraction

The data of interest were extracted by two investigators from each article and another senior reviewerchecked all items for completeness and accuracy. Information was recorded as follows: first author's surname, publication year, subjects' country, total number of participant subjects, mean ages of controls and cases, plasma Hcylevels in all groups.

Statistical analyses

Standard mean deviation (SMD) was used as effect measure to assess the differences in plasma Hcyconcentrations among controls and cases. Heterogeneity of SMDs was quantified using I-square (I^2) test. I^2>50% was considered as significant heterogeneity [13]. If there was no heterogeneity, SMDs were calculated using fixed-effects model. If not, random-effects model was applied.Potential publication bias was assessed by Begg's and Egger's test. All analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX, USA).

Results

Literature search

We initially obtained 101 studies from PubMed, Web of Science databases and The Cochrane Library. After 37 duplicated studies removed, 21 studies were then excluded by reviewing titles and abstracts, mainly because they were editorials, reviewsor irrelevant to topics. Then

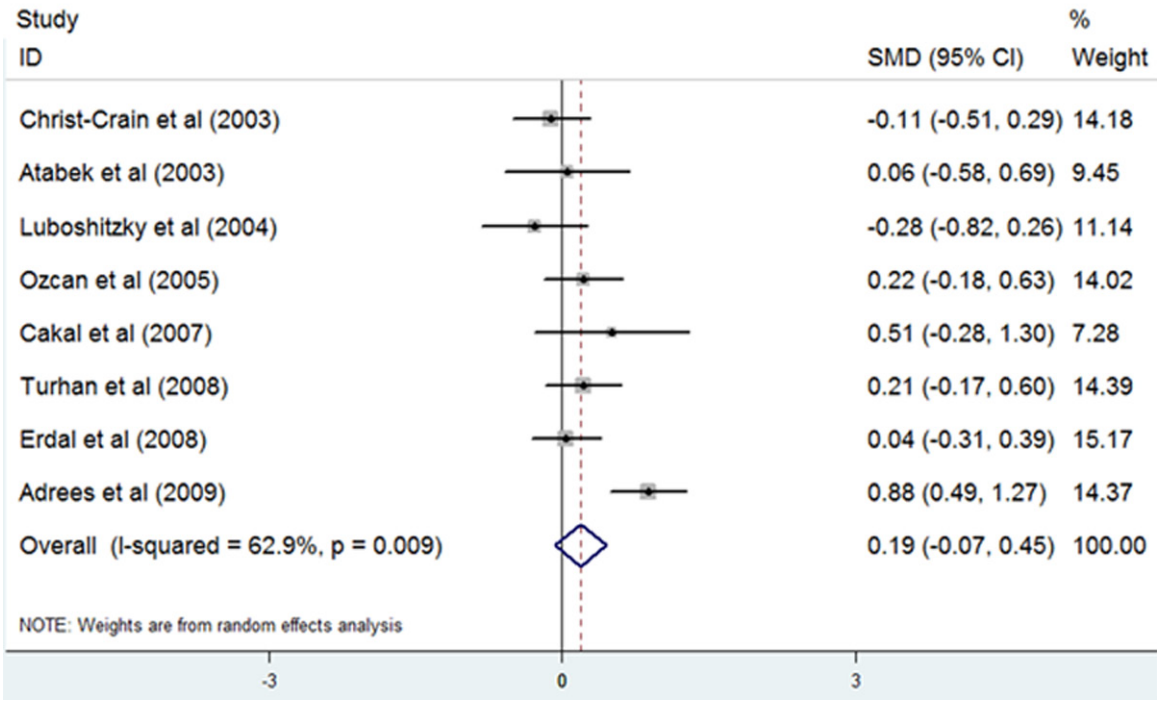

Figure 2. Comparison of plasma homocysteine level between subclinical hypothyroidism patients without levothyroxine treatment and healthy subjects.

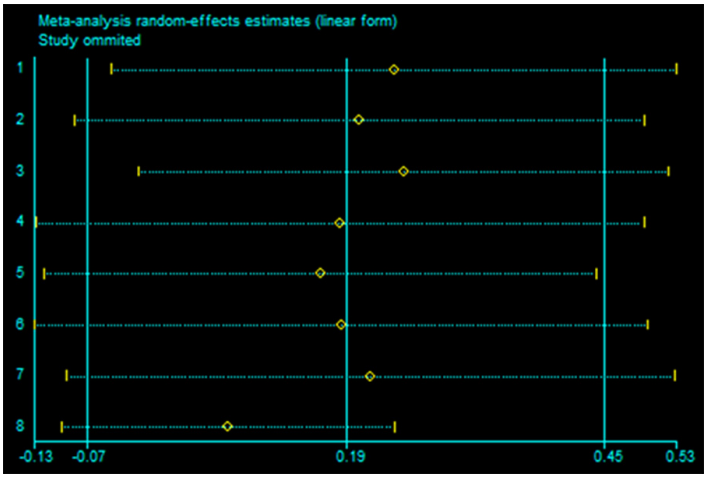

Figure 3. Sensitivity analysis to investigate the influence of a single study on the overall meta-analysis, which compares plasma homocysteine level between subclinical hypothyroidism patients without levothyroxine treatment and healthy subjects.

26 full-text studies were excluded due to some detail reasons showed in **Figure 1**. Finally, 17 studies [4, 7-12, 14-23] were enrolled in our meta-analysis.

Study characteristics

The characteristics of the 17 enrolled studies are shown in **Table 1**. There were 5 case-control studies [4, 8, 9, 18, 21], 12 prospective studies [7, 10-12, 14-17, 19, 20, 22, 23]. The mean age of each group ranged from 14.9 to 57.5 years which were generally matched in healthy controls and other cases. The duration of L-T4 treatment ranged from 2 months to 18 months. The sizes of studies ranged from 14 to 164.

Meta-analysis of plasma Hcy levels

Firstly, we compared plasma Hcy concentrations between patients with SH without L-T4 treatment and healthy subjects, and found that plasma Hcy levels in patients with SH without L-T4 treatment were similar to that in healthy subjects [8 studies, SMD: 0.19, 95% confidence interval (CI): -0.07 to 0.45, p=0.159, as shown in **Figure 2**]. Significant heterogeneity was observed among studies (I^2=62.9%, p=0.009). No evidence of publication bias was noted (Begg, p=0.902; Egger, p=0.858). We then turn to sensitivity analysis, 1 studies [1] was excluded because it was appearing to be outliers with other studies (**Figure 3**). After

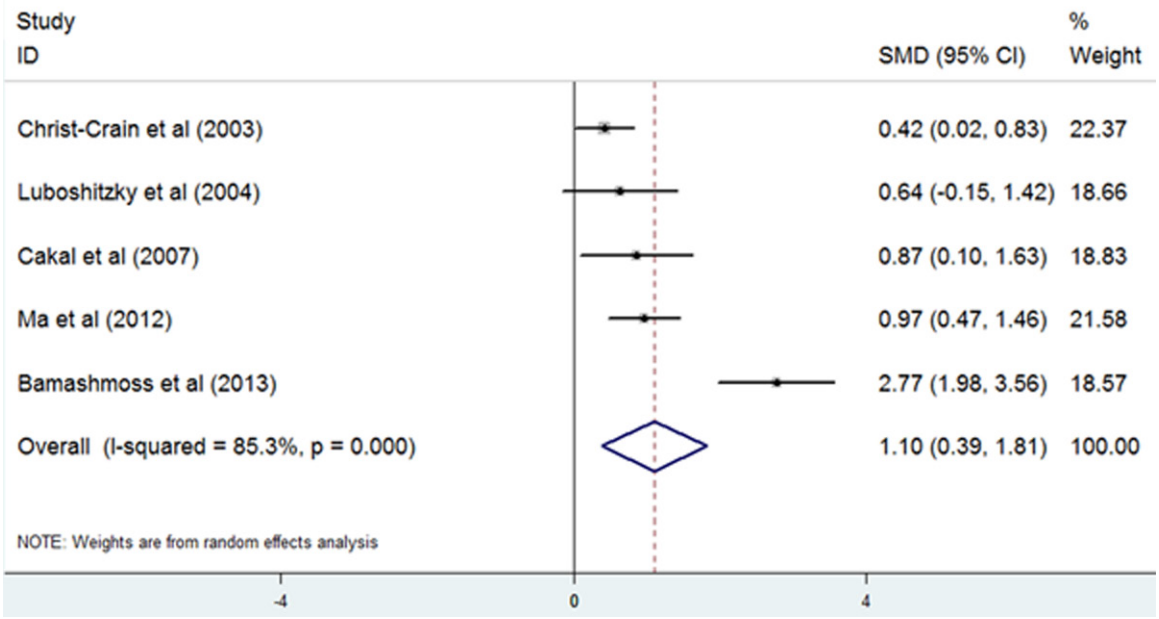

Figure 4. Comparison of plasma homocysteine level between overt hypothyroidism patients without levothyroxine treatment and healthy subjects.

exclusion, a meta-analysis of other 7 studies indicated that the main results remained unchanged, a significant elevation or reduction of plasma Hcy levels was not observed in patients with SH without L-T4 treatment compared with healthy subjects (SMD: 0.07, CI: -0.10 to 0.24, p=0.425). There was no significant heterogeneity among studies (I^2=0.0%, p=0.578). No evidence of publication bias was noted (Begg, p=0.548; Egger, p=0.600).

Next, we compared plasma Hcy concentrations between patients with OH without L-T4 treatment and healthy subjects, and found that plasma Hcy levels were significantly higherin patients with OH without L-T4 treatment than in healthy subjects (5 studies, SMD: 1.10, CI: 0.39 to 1.81, p=0.003, as shown in **Figure 4**). Significant heterogeneity was observed among studies (I^2=85.3%, p=0). No evidence of publication bias was noted (Begg, p=0.462; Egger, p=0.283). We also use sensitivity analysis to exclude those studies that were appearing to be different from others. After excluded 1 study [4], a meta-analysis of other 4 studies indicated that the main results remained unchanged, a significant elevation of plasma Hcy levels was observed in patients with OH without L-T4 treatment compared with healthy subjects (SMD: 0.67, CI: 0.40 to 0.94, p=0). There was no significant heterogeneity among studies (I^2=1.3%, p=0.385). No evidence of publication bias was noted (Begg, p=1; Egger, p=0.562).

Plasma Hcy concentrations were then compared between patients with SH without L-T4 treatment and patients with OH without L-T4 treatment. Results showed that plasma Hcy levels were higher in patients with OH without L-T4 treatment than in patients withSH without L-T4 treatment (3 studies, SMD: 0.56, CI: 0.27 to 0.84, p=0, as shown in **Figure 5**). There was no significant heterogeneity among studies (I^2=0.0%, p=0.383). No evidence of publication bias was noted (Begg, p=1; Egger, p=0.773).

Plasma Hcy levels were lower in patients with SH with L-T4 treatment than patients with SH without L-T4 treatment (9 studies, SMD: -0.18, CI: -0.32 to -0.05, p=0.006, as shown in **Figure 6**). There was no significant heterogeneity among studies (I^2=0.0%, p=0.678). No evidence of publication bias was noted (Begg, p=0.466; Egger, p=0.757).

Finally, we compared plasma Hcy concentrations between patients with OH with L-T4 treatment and patients with OH without L-T4 treatment, and found that plasma Hcy levels were significantly lower in patients with OH with L-T4 treatment than in patients with OH without L-T4 treatment (5 studies, SMD: -1.22, CI: -1.96 to

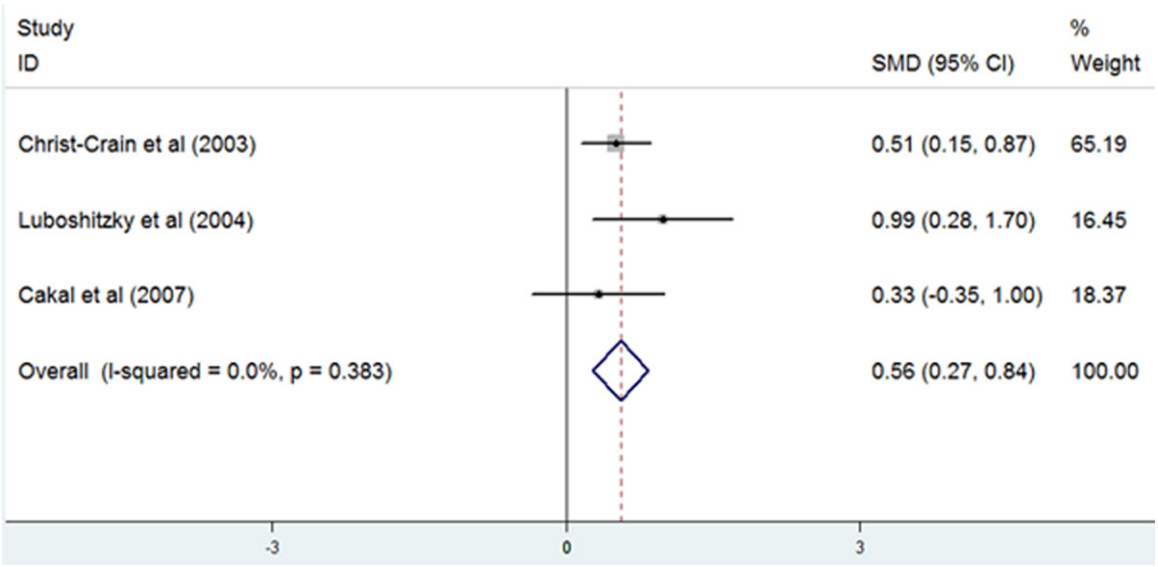

Figure 5. Comparasion of plasma homocysteine level between overt hypothyroidism patients without levothyroxine treatment and subclinical hypothyroidism patients without levothyroxine treatment.

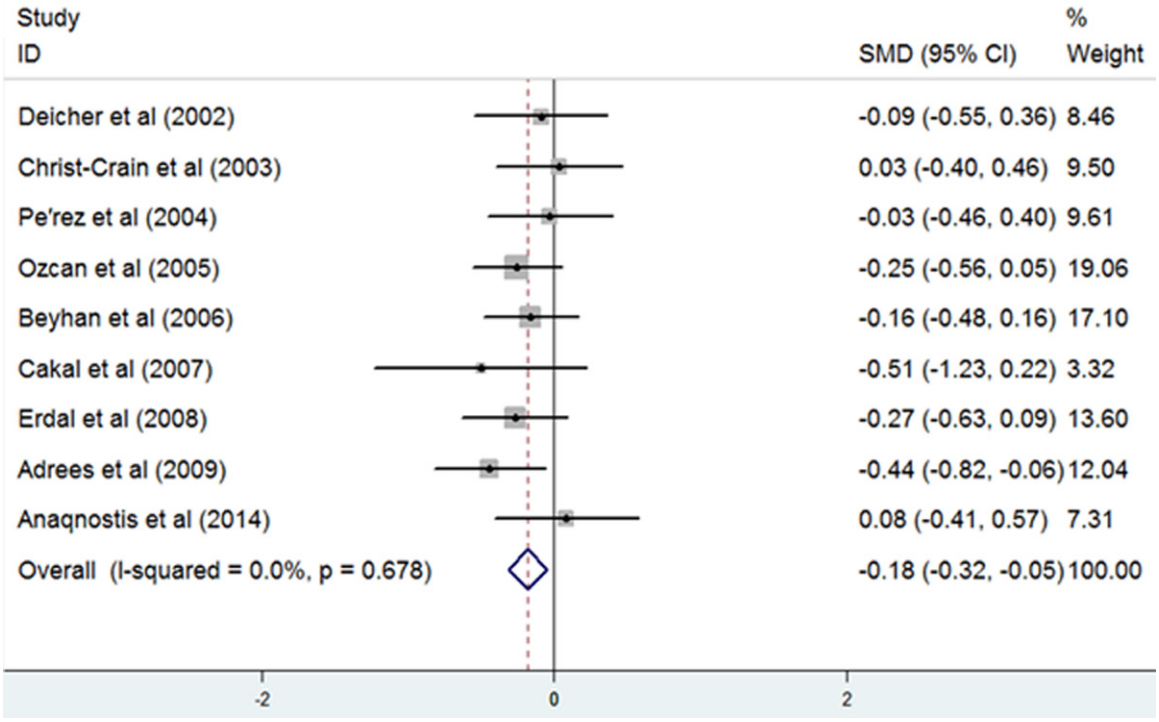

Figure 6. Comparasion of plasma homocysteine level between subclinical hypothyroidism patients with levothyroxine treatment and subclinical hypothyroidism patients without levothyroxine treatment.

-0.47, p=0.001, as shown in **Figure 7**). Significant heterogeneity was observed among studies (I^2=86.4%, p=0). Begg's test (p=0.027) and Egger's test (p=0.007) indicated the existence of publication bias. We then used the trim-and-fill method to adjust for funnel plot asymmetry, however, results showed no trimming performed and data unchanged. After excluded 2 studies [12, 20] by using sensitivity analysis, a meta-analysis of other 3 studies

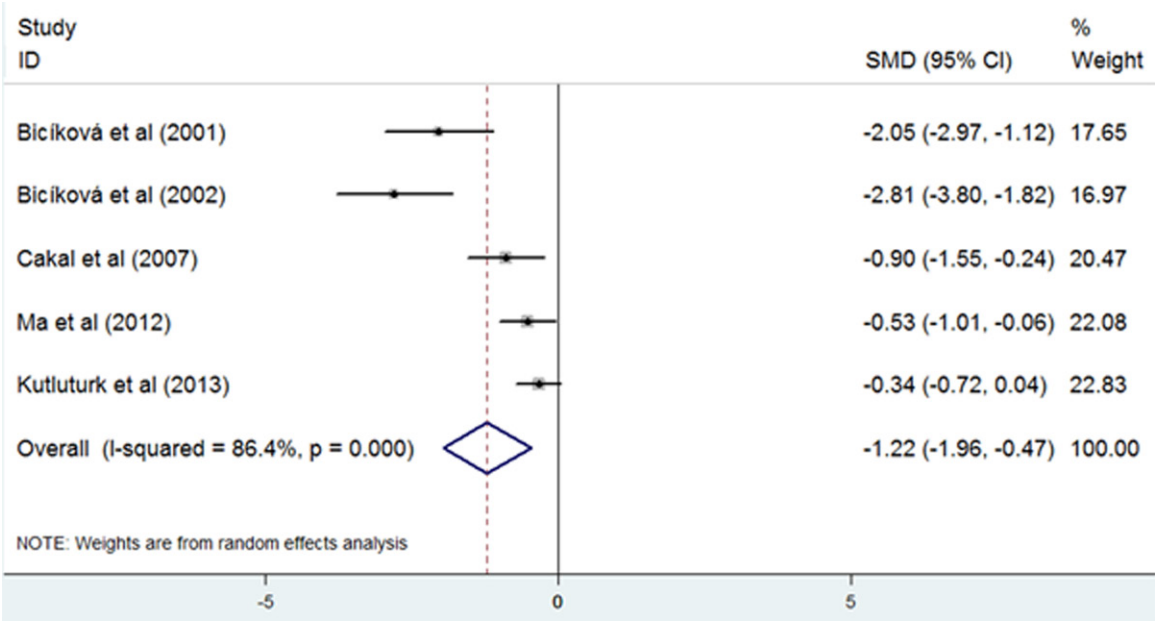

Figure 7. Comparasion of plasma homocysteine level between overt hypothyroidism patients with levothyroxine treatment and overt hypothyroidism patients without levothyroxine treatment.

indicated that the main results remained unchanged, a significant reduction of plasma Hcy levels was observed in patients with OH with L-T4 treatment compared with patients with OH without L-T4 treatment (SMD: -0.50, CI: -0.77 to -0.23, p=0). There was no significant heterogeneity among studies (I^2=4.6%, p= 0.351). Nevertheless, Begg's test (p=0.296) and Egger's test (p=0.010) indicated the existence of publication bias.

Discussion

Plasma Hcy level is affected by several genetic, physiological and life-style factors [24, 25]. The reasons for hyperhomocysteinemia are excess of dietary methionine, deficit of folate and vitamins taking part in Hcy metabolism, and deficit of kidney function [26, 27]. Kidney is a major issue for removal and metabolism of Hcy, which is closely associated with glomerular filtration rate (GFR) and albuminuria [28]. Hyperhomocysteinemia induces endothelial injury, oxidative stress, oxidation of LDL-cholesterol and smooth muscle hypertrophy [29, 30]. Toxic effect of Hcy and its spontaneous oxidation product, homocysteic acid, have the ability to activate N-methyl-D-aspartic acid (NMDA) receptors, then increase intracellular levels of calcium ion and reactive oxygen species [31, 32]. Moreover, platelet aggregation, vasomotor function and plasma anticoagulant function are altered in the presence of elevated plasma Hcy concentrations [33]. Hyperhomocysteinemia is also one of the pathogenic factors for neuropathy, such as brain stroke and Alzheimer's disease [34]. Severe hyperhomocysteinemia can lead to convulsions and dementia [35].

Thyroid hormones strongly affect the heart and the vascular system [36]. Hypothyroidism is a common condition that is related to premature atherosclerosis and its clinical consequences, such as myocardial infarction [37]. Autopsy findingssupportan increase in atherosclerosis events in patients displaying hypothyroidism [38]. Several studies reported that plasma Hcy concentrations elevated in patients with OH compared with those healthy subjects [7, 39]. Consistent with these studies, the results of our meta-analysis indicated a higher plasma Hcy levels in patients with OH than in healthy subjects who have euthyroidism. The elevation of plasma Hcy level can be explained by impaired renal clearance or reduced urinary excretion in hypothyroidism [7]. The haemodynamic effects of hypothyroidism may be the reason of reduced renal blood flow and GFR [40]. Experimental studies have also implied that methylenetetrahydrofolate reductase, a key enzyme in folate metabolism, decreased in patients with hypothyroidism [39, 41]. As the

major determinant of plasma Hcystatus, folate level decreases in patients with hypothyroidism, leading to elevated plasma Hcy status.

Auer J et aldemonstrated that variation of thyroid function within the normal range might affect the presence and severity of coronary atherosclerosis [42]. Taddei and his co-workers also identified a great prevalence of endothelial dysfunction in patients with SH, resulting from a reduction in NO availability [43]. However, the evidences are still judged as insufficient [44, 45]. Our meta-analysis indicated that plasma Hcy concentrations in patients with SH were similar to that in healthy subjects. This phenomenon can beinterpreted as a hypothesis that slight reduction in renal function and methylenetetrahydrofolate reductase may be insufficient to influence plasma Hcy status. We also observed an elevation of plasma Hcy levels in patients with OH compared with patients with SH, which indicated that with the progression of hypothyroidism, the alteration of plasma Hcy concentrations became more and more obvious.

A randomized controlled prospective study, assessing the effect of L-T4 treatment on patients with hypothyroidism, showed a reduction in body weight, although slight, after 3 months [46]. It is also reported that L-T4 replacement decreasedblood pressure and central arterial stiffness and improved endothelium-dependent vasodilatation in patients with SH [15, 47]. Moreover, a significant increase in plasma high-density lipoprotein cholesterollevels was found in patients with SH after 3 months of L-T4 treatment [48]. Another study indicated that L-T4 therapy might cause a reduction inlipoprotein (a) status in patients with OH [49]. However, a conflicting study claimed that L-T4 substitution therapy had no effect on cardiovascular risk profile in patients with hypothyroidism [10]. Besides the dose treatment duration of L-T4, hypothyroidismseverity and duration may also contribute to the elevation of plasma Hcy levels. In our meta-analysis, plasma Hcy concentrations decrease after L-T4 treatment in patients with SH or OH.

Even though our meta-analysis enrolls relatively high-quality articles which shared similar characteristics, there were some limitations existing in this investigation. First, detection methods of plasma Hcy concentration varies among enrolled studies, which mayaffect the accuracy of plasma Hcy concentration. Second, Clinical diversity among the studies enrolled in this meta-analysiswill result in statistical heterogeneity, which mayinfluence the outcomes, although a random effects model is used. Third, calculated Begg's and Egger's tests indicatethe existence of publication bias. We are unable to obtain the original data from corresponding authors.Fourth, we need more high-quality and large-samplestudies included in our meta-analysis.

Taken together, this meta-analysis suggests that the status of plasma Hcy is associated with the severity of hypothyroidism and L-T4 treatment is good for patients with hypothyroidism to reduce the plasma Hcy levels.

Disclosure of conflict of interest

None.

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