ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 6, 2015

ISSN - 0974-2441

Review Article

SCOPE OF INFLAMMATORY MARKERS IN SUBCLINICAL HYPOTHYROIDISM

GAURAV GUPTA[1], PREETI SHARMA[1]*, PRADEEP KUMAR[1], RACHNA SHARMA[2]

[1]Department of Biochemistry, Santosh Medical College & Hospital (Santosh University), Ghaziabad, Uttar Pradesh, India. [2]Department of Biochemistry, TSM Hospital & Medical College, Lucknow, Uttar Pradesh, India. Email: prcdri2003@yahoo.co.in

Received: 22 July 2015, Revised and Accepted: 07 September 2015

ABSTRACT

Subclinical hypothyroidism (SCH) and inflammatory diseases are now a day's one of the most popular topics of research. Previous studies have shown that the patients with SCH have increased levels of triglycerides and signs of low-grade inflammation (raised C-reactive protein levels). Disorder might be a risk factor for the development of cardiovascular and other inflammatory diseases. However, there is still some controversy concerning the inflammatory impact of SCH. Treating patients with thyroid stimulating hormone values of <10 mIU/L is not compelling, except in pregnant women. Fortifying the association between SCH and inflammation and a better understanding of research data may provide a more compelling argument for future treatment.

Keywords: Thyroid stimulating hormone, C reactive protein, interleukin-6, inflammation

INTRODUCTION

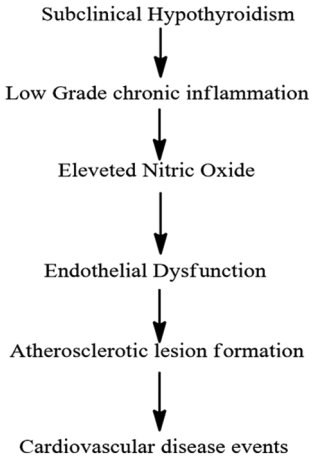
Subclinical hypothyroidism (SCH) is a common endocrine disorder, which affects worldwide population [1]. Around 3-8% prevalence of general population is affected by this disorder [2,3]. The Colorado study has observed that 9% of the US population were presented with SH having elevated thyroid stimulating hormone (TSH) level [4]. In India, not an exception, its prevalence varies from 9% to 12% approximately [5]. Although it is not gender specific disease; however, it is quite common in female compared to male population and grows with age [6,7]. 13.5% female population from North India is affected by SCH during the first trimester of pregnancy [8]. SCH is an oscillated state between euthyroidism to overt hypothyroidism without previous history of thyroid disorder. It is an asymptomatic disorder or present few to various well-defined symptoms of overt hypothyroidism [9,10]. The biochemical presentation of thyroid profile confirms the presence of SCH with mildly elevated TSH above the upper limit of normal concentration while free thyroxine (FT_4) and tri iodothyronine (T_3) within the reference range [11]. Thyroid hormones are quite known to affect the various metabolic process of the body which can create various diseases in future [12]. The irregular concentration of thyroid hormones produces adverse effects on different metabolic systems, which can give rise to various inflammatory diseases, e.g. myocardial infarction [13], rheumatoid arthritis [14], atherosclerosis [15], or ischemic heart disease, etc., as disease progress. Inflammatory disease is initiated by inflammation, a biological complex protective response in which leukocytes migrate from the vasculature into damaged tissues to destroy the agents that potentially can cause tissue injury [16]. It mediates tissue effects including vasodilation, edema, and cell proliferation through complex immunologic pathways [17]. Weight gain, a characteristic feature of hypothyroidism, can leads to the obesity [18], one of the factors for low-grade chronic inflammation by increasing the expression of some cytokines [19]. Various other signs or symptoms of hypothyroidism might be responsible for the development of inflammatory disorder [20,21] due to which, investigating the role of inflammatory markers could be useful to predict the risk of disease. SCH presents mimic reactions to overt hypothyroidism which might suggest a possibility of inflammatory disorder in coming future [22]. The reason behind presenting this review was not to revisit what has already been done or has been investigated. Instead of that the purpose is to give the researchers to considerate their focus to investigating the role of inflammatory markers in SCH, which is not clearly defined and the physiology or mechanism behind this is still unclear.

ASSOCIATION BETWEEN INFLAMMATORY MARKERS AND SCH

SCH is associated with increased prevalence of atherosclerosis, a disease of lipid accumulation, may be initiated or promoted by chronic inflammation by adverse effects on vascular endothelium and may be one of the reasons for increased endothelium dysfunction which leads to cardiovascular risk [23-27]. A variety of inflammatory markers are found to be increased in SCH which could play a crucial role in insulin resistance disorder [28], supporting the mechanism that TSH is responsible to induce tumor necrosis factor-α (TNF-α) in bone marrow cells [29]. TNF-α, mediating the downstream anti-resorptive effects of TSH on the skeleton [30] can impair nitric oxide (NO) activity in endothelial cells by promoting endothelial dysfunction. Yang *et al*. concluded that TNF-α and interleukin 6 (IL-6) expression in serum were increased in SCH rats [31]. TNF-α related apoptosis inducing ligand (TRAIL) is associated with atherosclerosis. The circulating TRAIL level was decreased in SCH and positively associated with endothelial function [32]. In a clinical study, Taddei *et al*. concluded that low-grade chronic inflammation causes not only lipid alteration but can also triggers a endothelial dysfunction in patient with SHT by observing elevated C-reactive protein (CRP) and IL-6 levels and suggested that endothelial dysfunction, being an independent promoter of cardiovascular events, dependent vasodilation could be one of the early mechanism promoting atherosclerosis and cardiovascular disease [33]. Likewise Türemen *et al*. proposed that inflammatory markers including IL-6, CRP, and TNF-α were elevated in SCH patients along with the positive correlation of flow-mediated dilatation (FMD) with inflammation markers promoting that low-grade chronic inflammation could be one of the factors to leads endothelial dysfunction in SCH patients [34]. Thyroid peroxidase Abs, positively correlated with TSH, may promote the release the variety of cytokines, e.g. IL-6, TNF-α, and interferon γ [35,36].

Elshenawy *et al.* concluded that SCH is characterized by elevated concentration of IL-6; a pro-inflammatory cytokine [37], over produced in obesity [38], found to be detrimental to endothelium, and atherosclerosis [39] is also induced by TSH in adipocytes [40]. Furthermore, CRP an acute phase reactant produced by liver under inflammatory response later discovered as one of the important markers for cardiovascular risk is observed to be increased in SCH [41,42] CRP, indirectly promoted by IL-6, plays an important role in the progression of atherosclerosis [43]. Elevated concentration of CRP, observed in SCH [44,45] was associated with vascular alteration, characterized by increased carotid arterial stiffness values [46] positively correlated

with TSH [47,48] and in Taiwanese population [49]. CRP stimulates the production of IL-6 and endothelin 1 (ET-1) and quenches an unidentified inhibitory factor, such as NO, known to decrease IL-6 and ET-1 secretion [50]. Feutin A, an indicator of inflammation which induces low-grade chronic inflammation and represses adiponectin production in humans [51] positively correlated with high-sensitivity [52] found to be low as a negative acute phase reactant in patients with SCH [53]. Reduced level of Feutin A was considered to make worsening the cardiovascular events via vascular calcification and inflammatory process in atherosclerosis [54]. In recent years level of homocystein, considered as marker of inflammation which is found to associated with cardiovascular risk [55] was increased with patients with SCH [56] inflammation increases the synthesis of NO which is responsible to increases the level of homocystein through the binding to B12 by inhibiting enzymatic activity of methionine synthase in the remethylation reaction [57].



It has been discovered TSH is able to produce various effects binding through different receptors. TSH is able to bind hepatocyte TSH receptors to promote cholesterol synthesis [58] bind adipocyte TSH receptor (TSHR) to induce IL-6 synthesis and bind bone marrow cell TSHR to increase TNF-α secretion [59]. These actions are promising to associate with endothelial dysfunction, and this underlying mechanism promotes the correlation of SCH and endothelial function [60].

L-thyroxine treatment in SCH

Achievement of euthyroidism in SCH patients by treating the levothyroxine seems to be beneficial in various studies. Proper amount of L-thyroxine (LT4) aids to the increase in serum FT4 and FT3 which lowers the concentration of TSH by negative feedback mechanism on the pituitary [61,62]. There are insufficient evidences to support the hypothesis that increased inflammation can be reduced by the addition of LT4 in SCH patients. In the study carried out by Bilgir *et al*. concluded that LT4 therapy exerts anti-inflammatory and anti-apoptotic effects in the 3 months follow-up of levothyroxine treatment [63]. Similar to this in another study Sengül *et al*. observed there was a remarkable significant reduction in homocystein concentration in SCH after the treatment with L-thyroxine LT4 [64]. Similarly in 12 weeks, double blind, randomized crossover study concluded that all the cardiovascular events, e.g. total cholesterol, low-density lipoprotein cholesterol, waist-to-hip ratio were improved in SCH patients by the treatment of LT4 [65]. All these studies support that LT4 treatment could be beneficial in the achievement of euthyroidism as well as reduce the cardiovascular risk in SCH patients.

However, contradictory result was also observed in SCH patients when treated with LT4 [66]. A replacement study showed that the improvement of 12 months L-T4 treatment on FMD and mean carotid intima-media thickness were significantly different between SCH and control group [67]. In another study, where 6 months treatment with LT4 in SCH does not effective as thyroid substitution therapy does not affect lipidemic profile and systemic inflammation in patients with SCH [68]. Similar to this Aksoy *et al*. did not find any improvement in any parameters after the treatment with LT4 in SCH patients [69].

CONCLUSION

SCH was found to be associated with endothelial dysfunction due to increased level of inflammatory markers through various mechanisms. As the earliest sign of atherosclerosis, endothelial dysfunction is most frequently observed in SCH patients. These studies support the future occurrence of cardiovascular risk in SCH patients. LT4 therapy found to be beneficial in most of the studies, specially (TSH >10 μIU/ml), in the achievement of euthyroidism and improvement in the early stage of endothelial dysfunction, prevent from future risk of cardiovascular diseases. A controversial opinion exists due to LT4 therapy may increase the risk of osteopenia and arterial fibrillation in elderly. More studies with large sample size should be conducted to establishing the fact.

REFERENCES

1. Hennessey JV, Espaillat R. Subclinical hypothyroidism: A historical view and shifting prevalence. Int J Clin Pract 2015;69(7):771-82.
2. Staub JJ, Noelpp B, Grani R, Gemsenjager E, Hauenstein M, Girard J. The relationship of serum thyrotropin (TSH) to the thyroid hormones after oral TSH-releasing hormone in patients with preclinical hypothyroidism. J Clin Endocrinol Metab 1983;56:449-53.
3. Karmisholt J, Andersen S, Laurberg P. Variation in thyroid function tests in patients with stable untreated subclinical hypothyroidism. Thyroid 2008;18(3):303-8.
4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160(4):526-34.
5. Deshmukh V, Behl A, Iyer V, Joshi H, Dholye JP, Varthakavi PK. Prevalence, clinical and biochemical profile of subclinical hypothyroidism in normal population in Mumbai. Indian J Endocrinol Metab 2013;17(3):454-9.
6. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National health and nutrition examination survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489-99.
7. Papi G, Uberti ED, Betterle C, Carani C, Pearce EN, Braverman LE, *et al.* Subclinical hypothyroidism. Curr Opin Endocrinol Diabetes Obes 2007;14(3):197-208.
8. Dhanwal DK, Prasad S, Agarwal AK, Dixit V, Banerjee AK. High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India. Indian J Endocrinol Metab 2013;17(2):281-4.
9. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: Who to treat and how. Drugs 2012;72(1):17-33.
10. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, *et al.* Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA 2004;291(2):228-38.
11. Rugge B, Balshem H, Sehgal R, Relevo R, Gorman P, Helfand M. Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism. Rockville, MD: Agency for Healthcare Research and Quality (US); 2011. (Comparative Effectiveness Reviews, No. 24.) Introduction. Available from: http://www.ncbi.nlm.nih.gov/books/NBK83492/.
12. Hulbert AJ. Thyroid hormones and their effects: A new perspective. Biol Rev Camb Philos Soc 2000;75(4):519-631.
13. Satar S, Seydaoglu G, Avci A, Sebe A, Karcioglu O, Topal M. Prognostic value of thyroid hormone levels in acute myocardial infarction: Just an epiphenomenon? Am Heart Hosp J 2005;3(4):227-33.
14. Staykova ND. Rheumatoid arthritis and thyroid abnormalities. Folia Med (Plovdiv) 2007;49(3-4):5-12.
15. Ichiki T. Thyroid hormone and atherosclerosis. Vascul Pharmacol 2010;52(3-4):151-6.
16. Doherty DE, Downey GP, Worthen GS, Haslett C, Henson PM. Monocyte retention and migration in pulmonary inflammation. Requirement for neutrophils. Lab Invest 1988;59(2):200-13.
17. Boots CE, Jungheim ES. Inflammation and human ovarian follicular dynamics. Semin Reprod Med 2015;33(4):270-5.
18. Zulewski H, Müller B, Exer P, Miserez AR, Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: Evaluation of patients with various grades of hypothyroidism and controls. J Clin Endocrinol Metab 1997;82(3):771-6.

19. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89(6):2548-56.
20. Longo DL, Fauci AS, Kasper DL, Hausar SL, Jameson JL, Lozcalzo J. Disorders of thyroid gland. In: Harrison's Principles of Internal Medicine. 18th ed., Vol. 1. New York: McGraw Hill Publication; 2012. p. 2919.
21. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, *et al.* So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 2013;11:200.
22. Gao CX, Yang B, Guo Q, Wei LH, Tian LM. High thyroid-stimulating hormone level is associated with the risk of developing atherosclerosis in subclinical hypothyroidism. Horm Metab Res 2015;47(3):220-4.
23. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam study. Ann Intern Med 2000;132(4):270-8.
24. Valentina VN, Marijan B, Chedo D, Branka K. Subclinical hypothyroidism and risk to carotid atherosclerosis. Arq Bras Endocrinol Metabol 2011;55(7):475-80.
25. Hamdy N, Adly N, Bakr Y, Salem A, Aty SA. Association between subclinical hypothyroidism and metabolic syndrome. Int J Adv Res 2014;2(6):213-26.
26. Taddei S, Salvetti A. Endothelial dysfunction in essential hypertension: Clinical implications. J Hypertens 2002;20(9):1671-4.
27. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation 2001;104(22):2673-8.
28. Guzel S, Seven A, Guzel EC, Buyuk B, Celebi A, Aydemir B. Visfatin, leptin, and TNF- α: Interrelated adipokines in insulin-resistant clinical and subclinical hypothyroidism. Endocr Res 2013.
29. Wang HC, Dragoo J, Zhou Q, Klein JR. An intrinsic thyrotropin-mediated pathway of TNF-alpha production by bone marrow cells. Blood 2003;101(1):119-23.
30. Hase H, Ando T, Eldeiry L, Brebene A, Peng Y, Liu L, *et al.* TNFalpha mediates the skeletal effects of thyroid-stimulating hormone. Proc Natl Acad Sci U S A 2006;103(34):12849-54.
31. Yang SS, Tang L, Li RG, Ge GH, Qu XK, Ma JW, *et al.* The effects of subclinical hypothyroidism on serum lipid level and TLR4 expression of monocyte in peripheral blood of rats. Neuro Endocrinol Lett 2014;35(1):80-6.
32. Xiang G, Yue L, Zhang J, Xiang L, Dong J. The relationship between circulating TRAIL and endothelial dysfunction in subclinical hypothyroidism. Endocrine 2015;49(1):184-90.
33. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, *et al.* Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. J Clin Endocrinol Metab 2006;91(12):5076-82.
34. Türemen EE, Çetinarslan B, Sahin T, Cantürk Z, Tarkun I. Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. Endocr J 2011;58(5):349-54.
35. Sieminska L, Wojciechowska C, Kos-Kudla B, Marek B, Kajdaniuk D, Nowak M, *et al.* Serum concentrations of leptin, adiponectin, and interleukin-6 in postmenopausal women with Hashimoto's thyroiditis. Endokrynol Pol 2010;61(1):112-6.
36. Nielsen CH, Brix TH, Leslie RG, Hegedüs L. A role for autoantibodies in enhancement of pro-inflammatory cytokine responses to a self-antigen, thyroid peroxidase. Clin Immunol 2009;133(2):218-27.
37. Elshenawy SZ, Hemi MH, Attia H. Serum levels of pro-inflammatory cytokines (interleukin 6 and interleukin 15) and adiponectin in hashimoto's thyroiditis with different thyroid function States. J Am Sci 2011;7(6):1156-62.
38. Olszanecka-Glinianowicz M, Zahorska-Markiewicz B, Janowska J. Increased concentration of interleukin-6 (IL-6) is related to obesity but not to insulin resistance. Pol J Endocrinol 2004;4:437-41.
39. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101(15):1767-72.
40. Antunes TT, Gagnon A, Bell A, Sorisky A. Thyroid-stimulating hormone stimulates interleukin-6 release from 3T3-L1 adipocytes through a cAMP-protein kinase A pathway. Obes Res 2005;13:2066-71.
41. La Vignera S, Condorelli R, Vicari E, Calogero AE. Endothelial dysfunction and subclinical hypothyroidism: A brief review. J Endocrinol Invest 2012;35(1):96-103.
42. Roy S, Banerjee U, Dasgupta A. Effect of sub clinical hypothyroidism on C-reactive protein and ischemia modified albumin. Mymensingh Med J 2015;24(2):379-84.
43. Libby P. Inflammation in atherosclerosis. Nature 2002;420(6917): 868-74.
44. Karoli R, Fatima J, Shukla V, Chandra A, Khanduri S, Rawat A. Hospital based study of carotid intima media thickness and high sensitivity C-reactive protein in young hypothyroid patients. J Indian Acad Clin Med 2014;15(2):116-9.
45. Mahto M, Chakraborthy B, Gowda SH, Kaur H, Vishnoi G, Lali P. Are hsCRP levels and LDL/HDL ratio better and early markers to unmask onset of dyslipidemia and inflammation in asymptomatic subclinical hypothyroidism? Indian J Clin Biochem 2012;27(3):284-9.
46. Tian L, Gao C, Liu J, Zhang X. Increased carotid arterial stiffness in subclinical hypothyroidism. Eur J Intern Med 2010;21(6):560-3.
47. Tuzcu A, Bahceci M, Gokalp D, Tuzun Y, Gunes K. Subclinical hypothyroidism may be associated with elevated high-sensitive C-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J 2005;52(1):89-94.
48. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. Clin Lab 2011;57(9-10):719-24.
49. Yu YT, Ho CT, Hsu HS, Li CI, Davidson LE, Liu CS, *et al.* Subclinical hypothyroidism is associated with elevated high-sensitive C-reactive protein among adult Taiwanese. Endocrine 2013;44(3):716-22.
50. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, *et al.* Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation 2002;105(16):1890-6.
51. Hennige AM, Staiger H, Wicke C, Machicao F, Fritsche A, Häring HU, *et al.* Fetuin-A induces cytokine expression and suppresses adiponectin production. PLoS One 2008;3(3):e1765.
52. Ix JH, Shlipak MG, Brandenburg VM, Ali S, Ketteler M, Whooley MA. Association between human fetuin-A and the metabolic syndrome: Data from the Heart and Soul Study. Circulation 2006;113(14):1760-7.
53. Muratli S, Uzunlulu M, Gonenli G, Oguz A, Isbilen B. Fetuin A as a new marker of inflammation in Hashimoto thyroiditis. Minerva Endocrinol 2015;40(1):9-14.
54. Bakiner O, Bozkirli E, Ertugrul D, Sezgin N, Ertorer E. Plasma fetuin-A levels are reduced in patients with hypothyroidism. Eur J Endocrinol 2014;170(3):411-8.
55. Wu JT. Circulating homocysteine is an inflammatory marker and a risk factor of life threatening inflammatory diseases. J Biomed Lab Sci 2007;19(4):107-12.
56. Andrees M, Boran G, Clarke G, Connor GO. Homocysteine in subclinical hypothyroidism, a risk factor for atherosclerosis? Endocr Abstr 2003;5:280.
57. Mariotto S, Suzuki Y, Persichini T, Colasanti M, Suzuki H, Cantoni O. Cross-talk between NO and arachidonic acid in inflammation. Curr Med Chem 2007;14(18):1940-4.
58. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, *et al.* A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology 2010;52(4):1401-9.
59. Lu M, Yang CB, Gao L, Zhao JJ. Mechanism of subclinical hypothyroidism accelerating endothelial dysfunction (Review). Exp Ther Med 2015;9(1):3-10.
60. Dardano A, Monzani F. Recombinant human TSH acutely impairs endothelium-dependent vasodilation. Eur J Endocrinol 2007;157(3):367.
61. Haynes R. Thyroid and antithyroid drugs. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. New York: McGraw Hill, Inc.; 1993. p. 1361-83.
62. Colucci P, Yue CS, Ducharme M, Benvenga S. A review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. Eur Endocrinol 2013;9(1):40-7.
63. Bilgir O, Bilgir F, Calan M, Calan OG, Yuksel A. Comparison of pre- and post-levothyroxine high-sensitivity c-reactive protein and fetuin-a levels in subclinical hypothyroidism. Clinics (Sao Paulo) 2015;70(2):97-101.
64. Sengül E, Cetinarslan B, Tarkun I, Cantürk Z, Türemen E. Homocysteine concentrations in subclinical hypothyroidism. Endocr Res 2004;30(3):351-9.
65. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: Randomized, crossover trial. J Clin Endocrinol Metab 2007;92:1715-23.

66. Monzani F, Dardano A, Caraccio N. Does treating subclinical hypothyroidism improve markers of cardiovascular risk? Treat Endocrinol 2006;5(2):65-81.
67. Cabral MD, Teixeira P, Soares D, Leite S, Salles E, Waisman M. Effects of thyroxine replacement on endothelial function and carotid artery intima-media thickness in female patients with mild subclinical hypothyroidism. Clinics (Sao Paulo) 2011;66:1321-8.
68. Anagnostis P, Efstathiadou ZA, Slavakis A, Selalmatzidou D, Poulasouchidou M, Katergari S, *et al.* The effect of L-thyroxine substitution on lipid profile, glucose homeostasis, inflammation and coagulation in patients with subclinical hypothyroidism. Int J Clin Pract 2014;68(7):857-63.
69. Aksoy DY, Cinar N, Harmanci A, Karakaya J, Yildiz BO, Usman A, *et al.* Serum resistin and high sensitive CRP levels in patients with subclinical hypothyroidism before and after L-thyroxine therapy. Med Sci Monit 2013;19:210-5.