Subclinical Hypothyroidism – What is Responsible for its Association with Cardiovascular Disease?

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Subclinical hypothyroidism (SH) is a common condition, with prevalence estimates ranging from 4–20%, depending on the population demographics. Although epidemiological analysis associates it with an increased risk of cardiovascular disease, clinical practice guidelines express uncertainty about whether to monitor or to treat. As we await large-scale, well-designed randomised clinical trials regarding treatment of SH, a review of pathophysiological considerations may be informative to better understand this disorder.

Keywords

Subclinical hypothyroidism, cardiovascular disease, thyroid-stimulating hormone, inflammation, cholesterol, adipocytes, endothelial cells, vascular smooth muscle cells

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Subclinical hypothyroidism (SH), sometimes referred to as mild hypothyroidism, is a cumbersome term used to describe the compensatory increase in thyroid-stimulating hormone (TSH) levels to preserve normal thyroid hormone levels before they fall below normal, thus averting thyroid gland failure. An unresolved issue is whether SH merits treatment when diagnosed, or whether observation is acceptable to monitor for progression to overt hypothyroidism, as there is a lack of evidence from well-designed randomised clinical trials measuring clinical outcomes.[1] The objective of this review is to provide an overview of studies that have investigated the association of SH with an elevated cardiovascular disease (CVD) risk.

Is there a link between subclinical hypothyroidism and cardiovascular disease risk?

A series of longitudinal population studies have found that SH is associated with a higher risk of CVD, and this was confirmed in a large meta-analysis published in 2010.[2] The extent of the CVD risk was proportional to the degree of the TSH elevation. The effect was not related to traditional risk factors such as obesity, hypertension or dyslipidemia, and it was not related to the underlying autoimmune dysfunction that underlies the most common cause of SH, Hashimoto's thyroiditis.[3] No effect of age was noted in this meta-analysis,[2] although an earlier population study suggested that the elderly may have reduced CVD risk with SH.[4] A higher risk of stroke, another major vascular disease, with SH was observed in subjects younger than 65 and those with higher TSH concentrations.[5]

What mediates the higher cardiovascular disease risk of subclinical hypothyroidism?

SH is a pro-inflammatory and pro-coagulant state. Elevations in interleukin (IL)-6 and C-reactive protein (CRP) have been detected in SH patients.[6,7] Metabolic effects include higher levels of free fatty acids (FFA), which can also lead to inflammatory cellular actions.[8] SH patients also display platelet hyper-reactivity.[9] Endothelium-dependent relaxation is also impaired in these patients,[6,7] and an altered pattern of endothelial-derived microparticles is associated with SH in patients with heart failure.[10] A recent meta-analysis addressed the controversy about whether lipid profiles are altered in SH, and found evidence of higher serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides.[11] In a small intervention study, thyroxine treatment of subjects with SH reduced the elevated levels of serum total cholesterol and LDL-C.[12]

Are these alterations mediated by extra-thyroidal thyroid-stimulating hormone action?

To explore whether TSH is capable of inducing such responses, investigators have studied thyroid cancer survivors who have been treated with thyroidectomy and radioiodine ablation of any remnant tissue, and who are on treatment with levothyroxine. Some of these patients undergo exogenous TSH administration to screen for early evidence of thyroid cancer recurrence by determining if stimulated thyroglobulin blood levels are high or not. For these few days, TSH levels

rise acutely and are quite elevated, whereas thyroid hormone levels remain unchanged. This setting provides researchers with an interesting model to study the extra-thyroidal effects of acute TSH elevations *in vivo* (i.e., no thyroid gland). It turns out that acute TSH stimulation leads to many of the same responses seen in SH. These include impaired endothelium-dependent vasodilation, higher platelet reactivity, elevations in FFA, CRP, and IL-6.[13–16] Other acute responses include rises in tumour necrosis factor (TNF) α, leptin, lipoperoxide and microparticles.[13,17,18]

Which extra-thyroidal sites are targeted by thyroid-stimulating hormone to cause the subclinical hyperthyroidism-associated alterations?

The compensatory elevated level of TSH is beneficial in overcoming partial thyroid failure to preserve thyroid function in SH. However, the same TSH elevation may disrupt the functions of TSH receptor (TSHR)-expressing non-thyrocyte cells. We have an incomplete understanding of this evolving research area. It is increasingly recognised that TSHR expression is not restricted to thyrocytes.[19–22] This might explain the abnormalities seen in SH.

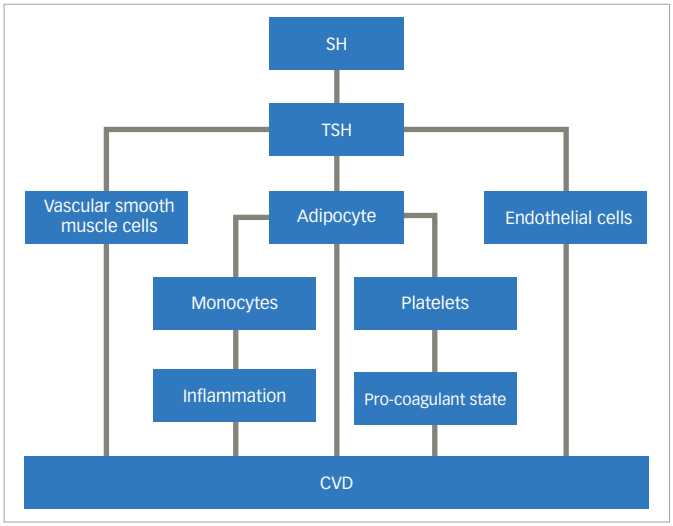
The most studied cell type in this regard is the adipocyte, with studies going back several decades showing that TSH was one of several ligands capable of stimulating G proteins in rodent adipocytes.[23] An adipose-selective conditional deletion of the TSHR in mice caused adipocyte hypertrophy, higher basal lipolysis and a reduced lipolytic response to exogenous TSH.[24] TSHR expression has been documented in human adipocytes,[25,26] with higher expression in the neonatal/paediatric age range.[27] TSH-stimulated human adipocytes undergo lipolysis, increase production and release of IL-6 and MCP-1 *in vitro*, and are more resistant to insulin.[15,16,28–31] These responses are consistent with the pattern seen in SH and in the acute TSH stimulation setting of thyroid cancer patients. The factors they release could also indirectly contribute to the abnormalities in endothelial and platelet function in these conditions.

Recently, it was suggested TSH may have an anti-lipolytic/pro-lipogenic effect. TSH decreased adipose triglyceride lipase (ATGL) expression,[32] and increased TG accumulation due to induction of glycerol 3-phosphate acyltransferase (GPAT) 3, the rate-limiting step for TG synthesis.[33] These results are at odds with findings of several other groups, including lipolytic effects of TSH on human adipocytes in culture,[15,28] elevated FFA levels that occur in patients with subclinical hypothyroidism[8] and following rhTSH administration *in vivo*,[15] that expression of TSHR in adipocytes in mice induces lipolysis *in vivo*,[34] and TSH inhibiting expression of the lipogenic enzyme fatty acid synthase (FAS).[35]

TSHR expression has also been observed in human aortic endothelial cells, which increased NO production is response to TSH.[36] Using human microvascular endothelial cells, TSH was shown to stimulate angiogenesis and proliferation.[37] Upregulation in intercellular adhesion molecules, and down-regulation of prostacyclin and eNOS was induced by TSH in human umbilical vein endothelial cells.[38] Therefore, it is possible that direct action of high TSH levels on the endothelium could be responsible for the endothelial dysfunction in SH.

Another vascular target could be vascular smooth muscle cells. They have been reported to express TSHR at the mRNA level,[39] but others failed to confirm this expression, perhaps due to low abundance of the receptor.[40] TSH stimulation of human coronary artery smooth muscle cells does lead to cAMP elevations, and human umbilical artery smooth muscle cells are induced to proliferate upon TSH treatment *in vitro*.[41,42]

Figure 1: Subclinical hypothyroidism and cardiovascular disease



CVD = cardiovascular disease; SH = subclinical hypothyroidism; TSH = thyroid-simulating hormone. Depiction of potential pathways through which the extra-thyroidal effects of elevated thyroid-stimulating hormone (TSH) levels might lead to cardiovascular disease (CVD). TSH-induced dysfunction of adipocytes may lead to release of adipokines that directly act on the vasculature, or indirectly act through activation of monocytes and/or platelets. TSH-stimulated disruption of vascular smooth muscle cells and endothelial cells may also promote CVD. Please refer to the text for details, as well as for discussion of other atherogenic processes associated with subclinical hypothyroidism, such as dyslipidemia.

Hepatocytes have been identified as expressing TSHR.[43] TSH increases 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase expression and activity, suggesting a link to cholesterol hepatic synthesis.[44] TSH also decreases an 5' AMP-activated protein kinase-mediated inhibitory phosphorylation of HMG CoA reductase, further promoting higher HMG CoA reductase activity.[45] In addition, TSH increases sterol regulatory element-binding protein 1 (SREBP-1) action, promoting hepatic lipogenesis,[46] and inhibits bile acid formation.[47]

Other extra-thyroidal sites of TSHR expression include the retro-orbital tissue and bone. However, it is not likely that TSH action at those sites would induce responses that would predispose to cardiovascular risk.

Concluding statement

Cardiovascular disease is a major cause of morbidity and mortality. Many modifiable risk factors have been identified for CVD, and targeting these risk factors can prevent CVD.[48] SH, a lesser-known predisposing condition, deserves more attention in the strategy to reduce CVD.[49] It is heartening to know that a randomised controlled trial called the Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism a randomised placebo-controlled Trial among older adults (NCT01660126) is finally underway. It is hoped that within the next few years we will know much more regarding the best approach to SH and the prevention of CVD. ❑

1. Rugge JB, Bougatsos C, Chou R, Screening for and Treatment of Thyroid Dysfunction: An Evidence Review for the U.S. Preventive Services Task Force, *Ann Intern Med*, 2015;162:35-45.
2. Rodondi N, den Elzen WP, Bauer DC, et al., Subclinical hypothyroidism and the risk of coronary heart disease and mortality, *JAMA*, 2010;304:1365–74.
3. Collet TH, Bauer DC, Cappola AR, et al., Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis, *J Clin Endocrinol Metab*, 2014;99:3353–62.
4. Gussekloo J, van Exel E, de Craen AJM, Thyroid status, disability and cognitive function, and survival in old age, *JAMA*, 2004;292:2591–9.
5. Chaker L, Baumgartner C, den Elzen WP, et al., Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis, *J Clin Endocrinol Metab*, 2015;100:2181–91.
6. Taddei S, Caraccio N, Virdis A, et al., Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy, *J Clin Endocrinol Metab*, 2003;88:3731–7.
7. Taddei S, Caraccio N, Virdis A, et al., Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis, *J Clin Endocrinol Metab*, 2006;91:5076–82.
8. Caraccio N, Natali A, Sironi A, et al., Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine, *J Clin Endocrinol Metab*, 2005;90:4057–62.
9. Lupoli R, Di Minno MN, Tortora A, et al., Primary and secondary hemostasis in patients with subclinical hypothyroidism: effect of levothyroxine treatment, *J Clin Endocrinol Metab*, 2015;100:2659–65.
10. Berezin AE, Kremzer AA, Martovitskaya YV, et al., Pattern of circulating endothelial-derived microparticles among chronic heart failure patients with dysmetabolic comorbidities: the impact of subclinical hypothyroidism, *Diabetes Metab Syndr*, 2016;10:29–36.
11. Liu XL, He S, Zhang SF, et al., Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis, *Med Sci Monit*, 2014;20:1432–41.
12. Iqbal A, Jorde R, Figenschau Y, Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromso Study, *J Intern Med*, 2006;260:53–61.
13. Dardano A, Ghiadoni L, Plantinga Y, et al., Recombinant human TSH reduces endothelium-dependent vasodilation in patients monitored for differentiated thyroid carcinoma, *J Clin Endocrinol Metab*, 2006;91:4175–8.
14. Desideri G, Bocale R, Milardi D, et al., Enhanced proatherogenic inflammation after recombinant human TSH administration in patients monitored for thyroid cancer remnant, *Clin Endocrinol*, 2009;71:429–33.
15. Gagnon A, Antunes TT, Ly T, et al., TSH-stimulates lipolysis in adipocytes in culture and raises serum free fatty acid levels in vivo, *Metabolism*, 2010;59:547–53.
16. Antunes TT, Gagnon A, Chen B, et al., Interleukin-6 release from human abdominal adipose cells is regulated by thyroid-stimulating hormone: effect of adipocyte differentiation and anatomic depot, *Am J Physiol Endocrinol Metab*, 2006;290:E1140–E4.
17. Santini F, Galli G, Maffei M, et al., Acute exogenous TSH administration stimulates leptin secretion in vivo, *Eur J Endocrinol*, 2010;163:63–7.
18. Burger D, Gagnon A, Lochnan HA, et al., Thyroid-stimulating hormone acutely increases levels of circulating pro-coagulant microparticles, *Clin Endocrinol*, 2015;83:285–7.
19. Davies TF, Marians R, Latif R, The TSH receptor reveals itself, *J Clin Invest*, 2002;110:161–4.
20. Sorisky A, Antunes TT, Gagnon A, The Adipocyte as a novel TSH target, *Mini Rev Med Chem*, 2008;8:91–6.
21. Williams GR, Extrathyroidal expression of TSH receptor, *Ann Endocrinol*, 2011;72:68–73.
22. Sorisky A, Gagnon A, Freedom of expression beyond the thyroid: the thyroid-stimulating hormone receptor in the adipocyte, *OA Biochemistry*, 2014;2014;2:2.
23. Rodbell M, Novel Lecture - Signal transduction: evolution of an idea, *Biosci Rep*, 1995;15:117–33.
24. Elgadi A, Zemack H, Marcus C, Norgren S, Tissue-specific knockout of TSHr in white adipose tissue increases adipocyte size and decreases TSH-induced lipolysis, *Biochem Biophys Res Commun*, 2010;393:526–30.
25. Bell A, Gagnon A, Grunder L, et al., Functional TSHR receptor in human abdominal preadipocytes and orbital fibroblasts, *Am J Physiol: Cell Physiol*, 2000;279:C335–C40.
26. Nannipieri M, Cecchetti F, Anselmino M, et al. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: effects of weight loss, *Int J Obes*, 2009;33:1001–6.
27. Janson A, Rawet H, Perbeck L, Marcus C, Presence of thyrotropin receptor in infant adipocytes, *Pediatr Res*, 1998;43:555–8.
28. Marcus C, Ehrén H, Bolme P, Arner P, Regulation of lipolysis during the neonatal period. Importance of thyrotropin, *J Clin Invest*, 1988;82:1793–7.
29. Hellmer J, Marcus C, Sonnenfeld T, Arner P, Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells, *J Clin Endocrinol Metab*, 1992;75:15–20.
30. Gagnon A, Langille ML, Chaker S, et al., TSH signaling pathways that regulate MCP-1 in human differentiated adipocytes, *Metabolism*, 2014;63:812–21.
31. Felske D, Gagnon A, Sorisky A, Interacting effects of TSH and insulin on human differentiated adipocytes, *Horm Metab Res*, 2015;47:681–5.
32. Jiang D, Ma S, Jing F, et al., Thyroid-stimulating hormone inhibits adipose triglyceride lipase in 3T3-L1 adipocytes through the PKA pathway, *PLoS One*, 2015;10(1):e0116439.
33. Ma S, Jing F, Xu C, et al., Thyrotropin and obesity: increased adipose triglyceride content through glycerol-3-phosphate acyltransferase 3, *Sci Reports*, 2015;5:7633.
34. Endo T, Kobayashi T, Expression of functional TSH receptor in white adipose tissues of hyt/hyt mice induces lipolysis in vivo, *Am J Physiol Endocrinol Metab*, 2012;302:E1569–75.
35. Chen J, Ren J, Jing Q, et al., TSH/TSHR signaling suppresses fatty acid synthase (FASN) expression in adipocytes, *J Cell Physiol*, 2015;230:2233–9.
36. Donnini D, Ambesi-Impiombato FS, Curcio F. Thyrotropin stimulates production of procoagulant and vasodilatative factors in human aortic endothelial cells, *Thyroid*, 2003;13:517–21.
37. Balzan S, Del Carratore R, Nicolini G, et al., Proangiogenic effect of TSH in human microvascular endothelial cells through its membrane receptor, *J Clin Endocrinol Metab*, 2012;97:1763–70.
38. Tian L, Zhang L, Liu J, et al., Effects of TSH on the function of human umbilical vein endothelial cells, *J Mol Endocrinol*, 2014;52:215–22.
39. Sellitti DF, Hill R, Doi SQ, et al., Differential expression of thyrotropin receptor mRNA in the porcine heart, *Thyroid*, 1997;7:641–6.
40. Busuttil BE, Frauman AG, Extrathyroidal manifestations of Graves' disease: the thyrotropin receptor is expressed in extraocular, but not cardiac, muscle tissues, *J Clin Endocrinol Metab*, 2001;86:2315–9.
41. Sellitti DF, Dennison D, Akamizu T, et al., Thyrotropin regulation of cyclic adenosine monophosphate production in human coronary artery smooth muscle cells, Thyroid, 2000;10:219–25.
42. Tian L, Ni J, Guo T, et al., TSH stimulates the proliferation of vascular smooth muscle cells, *Endocrine*, 2014;46:651–8.
43. Zhang W, Tian L, Han Y, et al., Presence of thyrotropin receptor in hepatocytes: not a case of illegitimate transcription, *J Cell Mol Med*, 2009;13:4636–42.
44. Tian L, Song Y, Xing M, 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;52:1401–9
45. Zhang X, Song Y, Feng M, et al., Thyroid-stimulating hormone decreases HMG-CoA reductase phosphorylation via AMP-activated protein kinase in the liver, *J Lipid Res*, 2015;56:963–71.
46. Yan F, Wang Q, Lu M, et al., Thyrotropin increases hepatic triglyceride content through upregulation of SREBP-1c activity, *J Hepatology*, 2014;61:1358–64.
47. Song Y, Xu C, Shao S, et al., Thyroid-stimulating hormone regulates hepatic bile acid homeostasis via SREBP-2/HNF-4alpha/CYP7A1 axis, *J Hepatology*, 2015;62:1171–9.
48. Schwalm JD, McKee M, Huffman MD, Yusuf S, Resource effective strategies to prevent and treat cardiovascular disease, *Circulation*, 2016;133:742–55.
49. Gencer B, Rodondi N, Should we screen for hypothyroidism in patients with cardiovascular disease?, *Eur Heart J*, 2016 Jan 12. [ePub ahead of Print].