

Subclinical hyperthyroidism: the cardiovascular point of view

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Abstract. – OBJECTIVE: Subclinical hyperthyroidism (SHyper), defined as reduced thyrotropin with free hormones within the reference range, is a common medical finding, in particular in elderly people. In the last years has gained attention due to its health-related conditions, in particular at the cardiovascular level.

MATERIALS AND METHODS: We searched electronic database (PubMed) and search engines (Google Scholar) of articles and reviews using the terms “subclinical hyperthyroidism”, “Atrial fibrillation”, “Ischemic stroke”, “Hypertension”, “Heart failure”, and “Mortality”.

RESULTS: Subclinical hyperthyroidism was clearly associated with the onset of atrial fibrillation and, consequently, with ischemic stroke. However, the latter association is less clear. The effect on hypertension is doubtful and fair. Subclinical hyperthyroidism could increase the risk of acute heart failure, possibly by increasing heart rhythm. Data on mortality are scanty but seem to suggest a possible association, probably linked to the detrimental effect on the cardiovascular system.

CONCLUSIONS: Current findings mainly described possible associations with rhythm alterations, heart failure, and stroke but the effective beneficial effects of the treatment of subclinical hyperthyroidism are still lacking.

Key Words:

Subclinical hyperthyroidism, Atrial fibrillation, Heart failure, Ischemic stroke, Mortality.

roxine (FT4) below the lower limit of the reference range. Subclinical hypothyroidism (SHypo), is a milder form of hypothyroidism with increased TSH level and normal FT4. Similarly, hyperthyroidism is divided in overt disorder, with suppressed TSH and increased free hormones, and subclinical hyperthyroidism (SHyper), which is characterized by reduced TSH and FT4 within the reference range.

Thyroid disorders are associated with many cardiovascular risk factors, some of which are included in the definition of metabolic syndrome^{3,4}. Excess of thyroid hormone has been linked to alteration in the cardiovascular hemodynamic⁵, modifications of heart rhythm⁶, and arterial wall structure⁷. While the effects of thyroid hormone excess on the cardiovascular risk factors are clear for some of them, for others are still debatable⁸. On the other hand, hypothyroidism has been associated with a worse lipid profile^{9,10}, and the use of thyroid analogs has been proposed as a treatment for dyslipidemia in subjects with normal thyroid function¹¹. However, due to side effects, their use is still not recommended.

Guidelines do not offer a clear indication for the treatment of SHyper due to the lack of univocal scientific evidence. For this reason, the treatment is based on clinical judgment. In this review, we described and summarized the main cardiovascular complications that can be related to the presence of SHyper.

Introduction

Thyroid hormones regulate different processes in the body homeostasis. Due to their ubiquitous effects, variations of hormones are associated with different diseases^{1,2}. Thyroid disorders are commonly classified in two groups (hypothyroidism and hyperthyroidism), each of which is further divided in additional 2 subgroups (overt and subclinical). Overt hypothyroidism is diagnosed with increased thyrotropin (TSH) levels and free thy-

Materials and Methods

PubMed and Google Scholar were searched using the following keywords: “Subclinical hyperthyroidism”, “Atrial fibrillation”, “Ischemic stroke”, “Hypertension”, “Heart failure”, and “Mortality”. Search returned 585 articles. We first removed duplicates (n = 168), then we manually inspected all articles of particular interest, and 20 articles were finally selected to review (Figure 1).

Epidemiology

SHyper is frequently found in the general population, but its prevalence changes across States. These differences can be related to age, gender, race, genetic predisposition, iodine status, and the definition of SHyper, which may vary in the different studies. In Spain, Lucas et al¹² reported an overall prevalence of thyroid dysfunction of 8.9%, with a greater predominance of females (71.2%), while the frequency of SHyper was 1.3%. In Jutland, the prevalence of low-TSH was 10%, again with clear female predominance¹³. In Italy, the prevalence of undiagnosed SHyper was 2.4%¹⁴. The frequency of SHyper is higher in older people and can be as high as 15.4% in patients aged at least 75 years¹⁵. In the United States, the prevalence of SHyper is 2-5% of the general population¹⁶.

Progression to Overt Hyperthyroidism

The evolution of SHyper is variable. While some patients may progress to overt hyperthyroidism, other can remains stable over the years or revert to euthyroidism. The etiology of SHyper can help to understand the possible evolution. SHyper may be transient in case of autoimmune origin and normalizes in 25-50% of the patients¹⁷. Indeed, SHyper in patients with multinodular goiter is relatively stable over the years in an area with iodine deficiency. On the other hand, the same subjects living in an area with adequate iodine intake have a risk of 10% to progress to overt hyperthyroidism (e.g., toxic multinodular goiter) after 5 years of follow-up¹⁸. In longitudinal studies, basal TSH levels were a strong predictor of progression. Indeed, Vadiveloo et al¹⁹ analyzed and followed a sample of 2024 patients with SHyper for 7 years after the diagnosis. They found that 0.7% of the sample developed overt hyperthyroidism at the end of the follow-up, but the majority remained as SHyper (63%). Interestingly, 35.6% of the sample reverted to euthyroidism, and this was more common in those who had baseline TSH between 0.1-0.4 mUI/l. Similar data have been obtained in another study, which included 102 women aged 60 or older. Rosario²⁰ reported that the risk to progress to overt hyperthyroidism was low (1% per year), and the only predictor of progression of SHyper was baseline TSH value < 0.2 mUI/L. Das et al²¹ included 323 SHyper patients, followed for a mean duration of 32 months. They found that subjects with TSH < 0.1 have a higher risk of progression to overt hyperthyroidism than those with baseline TSH between 0.1-0.4 mUI/l.

The risk of progression in SHyper patients is largely unpredictable and mainly related to baseline TSH level. The risk seems higher in those with TSH < 0.1 mUI/l and can precipitate in case of iodine overload, which can occur in case of contrast agent during computed tomography or drugs (e.g., amiodarone) used to treat cardiac arrhythmias.

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, which often occurs during aging. Excess of thyroid hormone is associated with the onset of atrial fibrillation, in particular in case of overt hyperthyroidism, and the European Society of Cardiology suggests to check thyroid function in all patients with new onset AF. However, it should be noted that SHyper is infrequently found in subjects with AF. In addition, subjects with hyperthyroidism have an increased risk of late ventricular potentials²², which disappeared after propranolol therapy²³. The first study that found an association between AF and SHyper was published in 1994 by Sawin et al²⁴. They analyzed 2007 subjects aged at least 60 without a previous diagnosis of AF, with low TSH values (≤ 0.1 UI/l) or slightly low values (0.1-0.4 mUI/l). During the 10-year follow-up period, the relative risk of AF in those with low serum TSH was 3.1, as compared to euthyroid subjects. Interestingly, the incidence of AF in patients with slightly low TSH values was comparable to the control group. Following studies confirmed these results. For example, analysis by Auer et al²⁵ reported an increased frequency of AF in both overt and subclinical hyperthyroidism in comparison to control group (13%, 14%, and 2%, respectively). Albeit the study was strengthened by the wide sample (over 23,000 subjects aged 45 or older), its cross-sectional design precludes causal inferences. Other than SHyper, authors also reported an independent association between AF and FT4 -treated as continuous variable-, both in euthyroid and in SHyper. The possible association between thyroid hormone and AF even in subjects with normal thyroid function was reported by Heeringa et al²⁶. This study included 1426 subjects aged at least 65 years with TSH within the reference range and followed for 8 years. Interestingly, participants with the lowest quartile of TSH had a 2-fold increase risk of AF, as compared to those in the highest quartile. Due to the well-known inverse association between TSH and FT4, authors were also able to find a graded association

Table I. TSummary of studies and cardiovascular outcomes.

Atrial fibrillation	n	Age	TSH	Result
Vadiveloo et al ¹⁹	1491	66.1 (16.0)	0.40-0.10	Increased risk of atrial fibrillation
	414	67.7 (15.6)	< 0.10	Increased risk of atrial fibrillation
Sawin et al ²⁴	187	> 60	0.40-0.10	Increased risk of atrial fibrillation
	61	> 60	< 0.10	Increased risk of atrial fibrillation
Auer et al ²⁵	613	67.9 (9.2)	< 0.40	Increased risk of atrial fibrillation
Rosario et al ²⁷	90	74 (65-82)	0.23 (0.11-0.38)	No association
Ischemic stroke	n	Age	TSH	Result
Bengtsson et al ³²	31	NA	Subclinical and overt hyperthyroidism	Increased frequency of stroke
Schultz et al ³³	24	74 (10)	0.26 (0.12-0.34)	Increased frequency of stroke
Selmer et al ³⁴	852	60.4 (19.1)	0.22-0.10	No association
	3623	60.9 (19.8)	< 0.10	No association
Collet et al ³⁵	2188	71 (64-100)	< 0.45	No association
Hypertension	n	Age	TSH	Result
Walsh et al ⁴⁰	36	50.7 (15.1)	< 0.40	Increased frequency of hypertension
Kaminski et al ⁴¹	44	45.9 (11.0)	0.16 (0.10)	Increased frequency of elevate nocturnal hypertension
Volzke et al ⁴²	163	61 (49-69)	< 0.25	No association
Volzke et al ⁴³	203	59 (48-66)	< 0.25	No association
Heart failure	n	Age	TSH	Result
Rodondi et al ⁴⁵	44	73.8 (6.9)	0.24 (0.13)	No association
Nanchen et al ⁴⁶	71	75.2 (3.1)	0.18 (0.13)	Increased risk of heart failure
Gencer et al ⁴⁷	494	NA	0.44-0.10	No association
	16	NA	< 0.10	Increased risk of heart failure
Mortality	n	Age	TSH	Result
Parle et al ⁴⁸	71	> 60	< 0.50	Increased risk of mortality from all cause and cardiovascular cause
Pearce et al ⁴⁹	19	85.5 (0.4)	< 0.40	No increased mortality
Ochs et al ⁵¹	NA	NA	NA	Increased risk of mortality
Haentjens et al ⁵⁰	NA	NA	NA	Increased risk of mortality
Singh et al ⁵²	NA	NA	NA	No increased mortality

between FT4 and AF, whose frequency increased from the second to the fourth quartile of FT4.

A part of some sporadic negative reports²⁷, data agree that SHyper increased the risk of AF in particular in those with low/suppressed TSH^{19,25}, independently of its etiology²⁸. However, the role of exogenous SHyper is less studied, with a reported association with premature atrial beats²⁹. While the treatment of SHyper led to conversion to sinus rhythm in 19%, in particular in patients without an underlying heart disease²⁵, no prospective and randomized studies are available to understand whether the treatment of SHyper reduces the risk of AF.

In conclusion, available data suggest a strong association between AF and SHyper, in particular in predisposed subjects (e.g., older patients)³⁰. Indeed, these patients have an intrinsic higher risk of AF, which may further increase by the presence of long lasting SHyper (Table I). However, it is not known whether SHyper triggers AF in genetically predisposed subjects or directly acts on the duration of the repolarization phase of the action potential, increasing the risk of arrhythmias³¹. Another possibility is an indirect effect of SHyper, which might act on others independent risk factors for AF (heart failure, hypertension, angina), in particular in those who have an underlying cardiac disease.

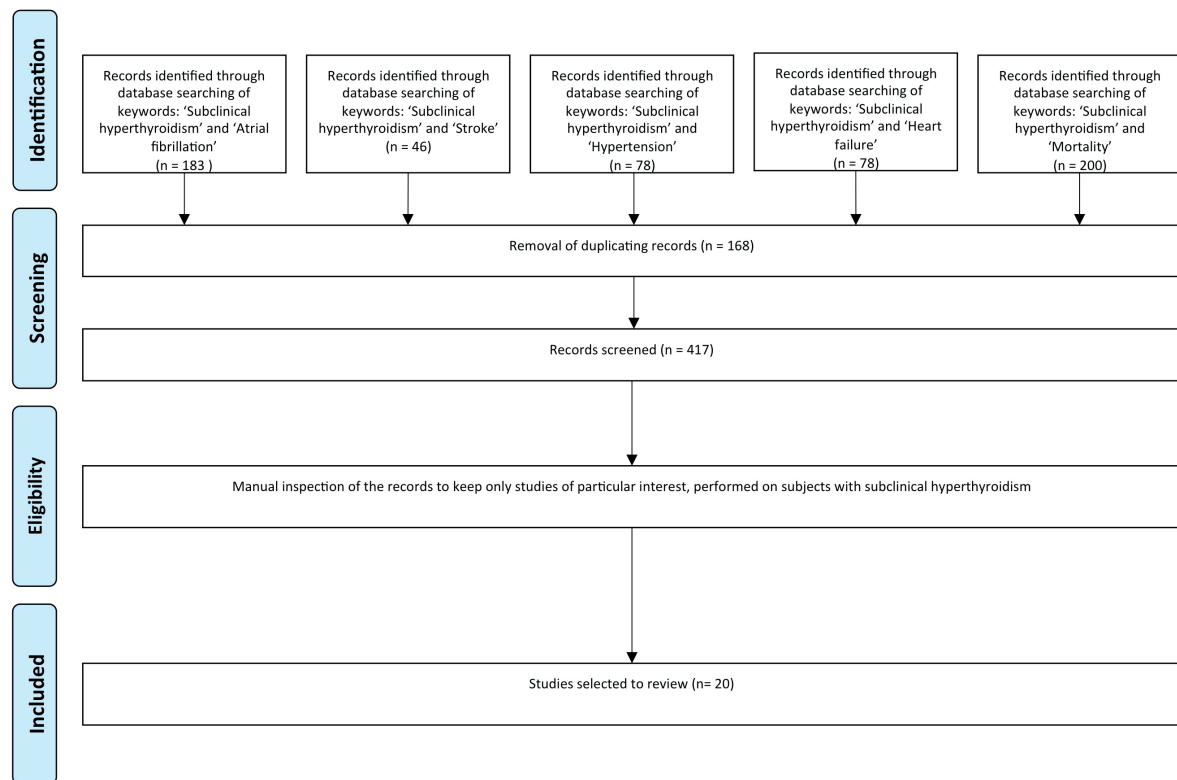


Figure 1. Articles selected to review.

Ischemic Stroke

The risk of stroke in patients with SHyper has been postulated for its association with AF, a common cause of embolic stroke. Bengtsson et al³² reported the frequency of previously unknown overt and SHyper in 153 Swedish patients with acute ischemic stroke. Authors categorized patients accordingly to the possible etiology (embolic and non-embolic) and found a prevalence of thyroid disorders in 12% of the sample. SHyper was more common in those with AF compared to non-AF group (13% vs. 3%, $p = 0.048$). Similarly, Schultz et al³³ analyzed a cohort of 609 patients aged 50 or older (4.1% with SHyper) with normal left ventricular function and reported major cardiovascular events. After a median 5-year of follow-up, 28 patients had a stroke, and its incidence was increased among subjects with SHyper, with an HR of 3.39, after adjusting for age, sex, and AF. Albeit the association between SHyper and stroke seems possible, due to the co-occurrence of AF, other studies reported different results. For example, Salmer et al³⁴ from Denmark analyzed over 47,000 patients who consulted their general practitioner and showed that SHyper was not

associated with stroke as a single outcome. But the combined endpoint of major cardiovascular events (cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction) was increased in patients with SHyper. A recent pooled analysis reported the results 52,674 participants from 10 cohort³⁵ and found that in age adjusted analysis, stroke frequency was not increased. SHyper might have a role not only for the acute ischemic stroke but also as function outcome in patients with cerebrovascular events. Indeed, Wollenweber et al³⁶ analyzed a cohort of 165 consecutive patients with acute ischemic stroke, divided in three different groups: SHyper, SHypo, and euthyroidism, according to the level of TSH. Patients were followed for 3 months after the stroke, and analyses were adjusted for possible confounders, such as AF, total cholesterol, and body mass index. They found that 11.5% of the sample had SHyper, which had a substantially increased risk of functional disability 3 months after stroke, compared to euthyroid. Similar results have been obtained from Lee et al³⁷, which analyzed patients with acute ischemic stroke treated with reperfusion therapy. The authors included 156 consecutively

patients and divided in euthyroid and SHyper. The primary outcome was functional disability at three months, and the secondary outcome was successful reperfusion. Patients with SHyper had an increased risk of poor functional outcome at three months (OR 2.5) and decreased the rate of successful reperfusion after therapy.

In conclusion, the relation between ischemic stroke and SHyper is not univocal and might be associated with the co-occurrence of AF, whose frequency is higher in patients with SHyper.

Hypertension

Hypertension is the most common cardiovascular disease affecting 30-45% of the population, with a progressive increase during aging³⁸ and a clear gender difference³⁹. The effect of SHyper on blood pressure is not clear. First reports on their possible association have been reported in the Busselton Study⁴⁰. Here, the authors included 35 subjects with SHyper and reported an increased frequency of hypertension. However, results were limited by the small sample, as acknowledged by the Authors. Kaminski et al⁴¹ reported the results of 24-hours ambulatory blood pressure monitoring in 44 subjects with SHyper and found a higher nocturnal mean systolic and diastolic blood pressure and higher mean blood pressure compared to euthyroid. On the contrary, findings from Study in Pomerania⁴² reported no association between SHyper and hypertension. Results were confirmed in 2009 when the same group reported no changes in blood pressure, pulse pressure, and incident hypertension in patients with SHyper⁴³. The analyses were of particular interest because while the 5-year hypertension incidence in SHyper compared to euthyroid was higher in the univariate analysis (31% vs. 19%), the multivariate logistic analysis, adjusted for age and other cardiovascular risk factors, revealed that both groups had a comparable risk of hypertension.

In conclusion, the effect of SHyper on hypertension is not clear. Whether possible, it has been defined as statistically significant but clinically insignificant⁴¹.

Heart Failure

Heart failure (HF) is a chronic and progressive disease that affects the pumping power of the heart. It is the only cardiovascular disease with increasing incidence and prevalence due to the aging of the population⁴⁴. The importance of thyroid hormones in the pathophysiology of HF is underlined by the fact that European guidelines

of the European Society of Cardiology suggest to check thyroid hormones in all patients with acute HF. But the exact role of SHyper in HF is not clear. Rodondi et al⁴⁵ analyzed 3,044 patients aged 65 or older who were initially free of HF in the Cardiovascular Health Study. Over the course of 12 years, patients with SHyper had a comparable risk to develop acute HF compared to euthyroid. On the other hand, the incidence rate of HF hospitalization was increased in 71 patients with SHyper compared to patients with euthyroidism (HR=3.27) in the PROSPER study⁴⁶. A recent pool analysis⁴⁷ of 6 cohort studies, including over 25,000 participants, clearly demonstrated that the risk of HF was increased in subjects with SHyper. The authors also demonstrated that the HR increased accordingly to TSH level, from 1.3 in those with TSH > 0.1 to 1.9 in those with TSH < 0.1. Findings reported by Nanchen et al⁴⁶ also demonstrated that SHyper increased the rate of admission for HF.

In conclusion, available data suggest that SHyper could increase the risk of acute HF. A possibility is that SHyper can increase the risk of atrial arrhythmias, such as AF, or tachycardia in general, which in turn cause acute decompensated HF. No prospective studies for the treatment of SHyper are available to test whether the reduction of heart rate will prevent HF in these patients.

Mortality

The first report that showed an increased mortality in patients with SHyper has been done by Parle et al⁴⁸ in 2001. This study reported the analyses from a cohort of 1191 individuals free from thyroid medications, aged 60 or older, and followed for 10 years. 509 out of 1191 people died during the follow-up, and the Authors were able to demonstrate that SHyper increased the mortality from all causes in year 2-5, and in particular mortality to circulatory and cardiovascular disease. Conversely, Pearce et al⁴⁹ on 643 subjects aged over 84 years found that SHyper was not related to a worse survival over 9 years than euthyroid individuals. Even meta-analysis gave conflicting results. Indeed, Haentjens et al⁵⁰ analyzed results of 7 cohorts including 290 patients and found that SHyper increased by 41% the relative mortality from all cause compared to euthyroid, in particular in males aged 60 or older. Similar results have been reported by Ochs et al⁵¹ in an investigation including 10 surveys and 14,449 participants. These authors found that SHyper was associated with a modest rise in mortality as well

as an increase for coronary artery disease. On the other hand, Singh et al⁵² reported no association between SHyper and mortality from cardiovascular causes.

In conclusion, the association between SHyper and mortality can be explained by the unfavorable effect of SHyper on the cardiovascular system. Indeed, cardiac function, blood pressure, heart rate, and arterial stiffness⁵³ are impaired in case of excess of thyroid hormone, even if mild. Increased arterial stiffness may be a dynamic adaptation to the hypermetabolic state, or it may be a consequence of peripheral vasodilation and cardiac reflex, which in turn increase stroke volume and heart rate. However, the effect of SHyper on mortality seems modest and although SHyper is quite common in elderly, guidelines suggest against its screening.

Conclusions

The decision to treat patients with SHyper is mainly based on clinical judgment and on physician experience, after a careful evaluation of comorbidities. A clinical approach could first be to confirm the presence of SHyper with a second test and, once confirmed, to suggest treatment to older patients, in particular to those with increased risk of atrial fibrillation. Data for younger patients are insufficient to draw firm conclusions and expert panel suggest against the routine treatment of SHyper in young and asymptomatic patients.

Here, we highlighted the importance of SHyper on the cardiovascular diseases, both of which are becoming more prevalent due to an increase of elderly subjects. Unfortunately, prospective studies on its treatment are rather scanty, without a control arm, and we cannot draw firm conclusions when treating SHyper. In addition, no specific studies addressed specific outcomes of its treatment.

Author Contributions

Gianpaolo Vidili: Manuscript Preparation and Literature Search; Alessandro Delitala: Manuscript Preparation and Literature Search; Roberto Manetti: Manuscript Preparation and Literature Search.

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