

The current state of knowledge regarding thyroid-stimulating hormone lowering/suppressive therapy and its cardiovascular risks in differentiated thyroid carcinoma: A review

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REVIEW

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ABSTRACT

Background

Thyroid-stimulating hormone acts as a growth factor for thyroid follicular cells, so some patients with differentiated thyroid carcinoma (DTC) are placed on thyroid hormone suppressive therapy. However, (TSH) suppression is not without risks.

Aims

We thought to assess the potential benefits and cardiovascular risks among patients on TSH suppressive therapy following thyroid surgery for DTC.

Methods

A systematic electronic search was conducted in PubMed, MEDLINE, and Google Scholar for relevant articles. All human and cell lines studies published during the period 2009-October 2019 were eligible. The keywords TSH suppression, differentiated thyroid carcinoma, TSH level,

cardiovascular risk, cardiovascular morbidity, cardiovascular mortality, atrial fibrillation, and left ventricular volume were used. One hundred and eighty-five articles were retrieved and only eighteen met the inclusion and exclusion criteria.

Results

Out of 185 articles, eighteen studies were included, more than half (55.6 per cent) were published in Europe, 22.2 per cent were from Asia, 11.1 per cent from Latin America and one study was from the USA, the majority (72.2 per cent were observational studies). Patients on TSH suppression were at a high risk of cardiovascular morbidity and mortality that increases at lower TSH levels. Levels <.1mU/L are beneficial in patients with micro or macroscopic disease. However it may induce tumour growth among patients with aggressive recurrent disease, no benefit was observed in low-intermediate DTC.

Conclusion

Physicians may need to suppress TSH in patients with micro or macroscopic DTC. However, caution is needed in aggressive recurrent disease. The available level of evidence showed no benefit of TSH lowering therapy in low-intermediate disease.

Key Words

TSH suppression, cardiovascular morbidity, mortality, Differentiated thyroid carcinoma

What this review adds:

1. What is known about this subject?

The role of TSH lowering/suppression is controversial.

2. What new information is offered in this review?

T4 therapy may accelerate tumour growth in recurrent aggressive disease. Some patients with DTC are resistant to T4 therapy.

3. What are the implications for research, policy, or practice?

Although TSH suppression is beneficial in DTC with micro or macroscopic disease. However, it may induce or accelerate tumour growth in certain patients.

Introduction

Differentiated thyroid carcinoma (DTC) standard of care is surgery in the form of lobectomy, total thyroidectomy, with completion thyroidectomy in some patients. Because thyroid-stimulating hormone (TSH) can potentially affect the growth of follicular-cell derived thyroid cancer, thyroxine (T4) is given to some patients as suppressive therapy to restore normal TSH.¹ A key feature of the treatment is the TSH lowering in low-risk DTC and suppression in high-risk patients. Suppression of TSH by supra-physiological doses of T4 is a mainstay of long-term management of differentiated thyroid carcinoma for decades. However, clear evidence for its use is lacking. TSH suppression with T4 can adversely affect the patients with DTC in terms of quality of life, cardiovascular outcomes, and bone mineral density.^{2,3} Given the above controversy, we conducted the current review to investigate the current knowledge of TSH suppression and assessing its cardiovascular adverse effects.

Methodology

The literature search and articles selection: A systematic electronic search was conducted in Pub Med, MEDLINE, and the first hundred articles in Google Scholar. The search was limited to articles published during the period 2008-2019 including Epub and ahead of print, with no limitation of language. Animal studies were not included. The terms TSH suppression, differentiated thyroid carcinoma, TSH level, cardiovascular risk, cardiovascular morbidity, cardiovascular mortality, atrial fibrillation, arterial stiffness, and left ventricular volume were used with different combinations. A total of one hundred and eighty-five articles were retrieved. The authors screened the titles and abstracts independently. Only eighteen articles were included in the current review after duplication removal and applying inclusion and exclusion criteria. The author's name, county, year of publication, type of study, number of patients included, the duration of follow-up if applicable, and the results were reported.

The different stages of the review process were shown in the PRISMA chart Figure 1.

Results

Out of one hundred and eighty-five articles, one hundred

and ten manuscripts remain after the removal of duplication and irrelevant articles, and only eighteenth fulfilled the inclusion criteria. There were thirteen observational studies, four reviews, and an experimental study, ten were from Europe, four from Asia, one published in the USA, and two from Latin America. Eight articles touched the benefits of TSH suppression, while the remaining ten assessed the cardiovascular adverse effects. The studies showed increasing cardiovascular mortality, insulin resistance, atherogenic lipid profile, increasing rates of atrial fibrillation, aortic stiffness, and diastolic dysfunction, especially at lower TSH levels. Regarding the benefits of TSH suppression, the review article showed contradicting findings ranged from the individualization of treatment, increasing the tumour growth, and the justification in patients with micro or macroscopic disease. The observational studies were on the side that no benefit of TSH suppression at least in low-risk patients. Tables 1 to 3. The quality assessment of the included studies according to the Ottawa Newcastle Scale were illustrated in Tables 2 and 4.

Discussion

In the current review, Deasy et al.⁴ in their retrospective study (88 patients with DTC) suggested to weigh the risk and benefits when applying TSH suppression, Basu et al.⁵ reviewed the literature and concluded that T4 use in TSH suppression among patient with recurrent, aggressive DTC may contribute to the clinical growth of the tumour, Park et al.⁶ included 466 patients in a retrospective study and showed no benefit of TSH suppression in low-risk DTC, a review published in France⁷ assessed the level of TSH suppression and found that TSH level for patients with micro or macroscopic disease is <0.1mU/L, for other patients, the individual health status, risk of relapse, and clinical follow-up guides the level, another review from the USA⁸ stated that TSH suppression must be weighed against the potential detrimental side-effects of long-term sub-clinical hyperthyroidism, an experimental study from Brazil⁹ showed inheritance resistance to T4. In the present review, two prospective studies^{10,11} with reasonable number of patients (a total of 1791, Newcastle-Ottawa scale=8) and followed for up to 5.6 years showed the TSH level in low-intermediate grade papillary thyroid carcinoma has no effect on short term recurrence, in fact TSH suppression before the first response to treatment assessment does not influence the rate of structural disease. Regarding cardiovascular morbidity, Millat et al.¹² in their case-control study observed Insulin resistance, a hypercoagulable state, and an atherogenic lipid profile in patients with differentiated thyroid cancer. On TSH suppressive therapy,

Klein Hesselink and colleagues published a retrospective and case-control studies.^{13,14} The studies included 4114 patient from Netherland and found an increased rate of atrial fibrillation, cardiovascular and all-cause mortality in patients with DTC, a lower TSH level increased cardiovascular mortality, a cross-sectional longitudinal study¹⁵ observed aortic stiffness among patients on TSH therapy for DTC, the occurrence of AF among DTC patients was supported by a review of literature,¹⁶ it is interesting to note that N-terminal pro Brain Natriuretic Peptide levels are elevated in patients with DTC, and are associated with an increased risk for cardiovascular events and all-cause mortality.¹⁷ Similar findings of heart failure risk were shown by Klein Hesselink et al.¹⁸ who conducted a cohort including 66 patients and followed for five years. Further studies¹⁹ including 8386 patients with DTC on thyroxine therapy found increased morbidity from AF and arrhythmia accountable to TSH suppression below 0.1mU/L. However, cardiovascular mortality was lower among patients due to lower coronary artery disease. More recent studies^{20,21} support the findings of AF and heart failure with prolonged TSH suppression. However, no evidence of increased risk of IHD or HF, a plausible explanation is that the atria contributed to only up to 25 per cent of cardiac output.

Conclusion

In the current review the available evidence suggested that patients with DTC on TSH suppressive therapy are at an increased risk of cardiovascular mortality, AF, aortic stiffness, insulin resistance, a hypercoagulable state, and an atherogenic lipid profile. Furthermore, the cardiovascular risks were more with lower TSH levels. The contradicting evidence regarding heart failure and myocardial factors could be due to not controlling for different confounders. Regarding TSH suppression the review suggested that it is not needed at least for low-intermediate risk DTC, for patients with recurrent, aggressive DTC may even contribute to the clinical growth of the tumour. For patients with the micro or macrovascular disease, a TSH of below 0.1mU/L is justifiable.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)

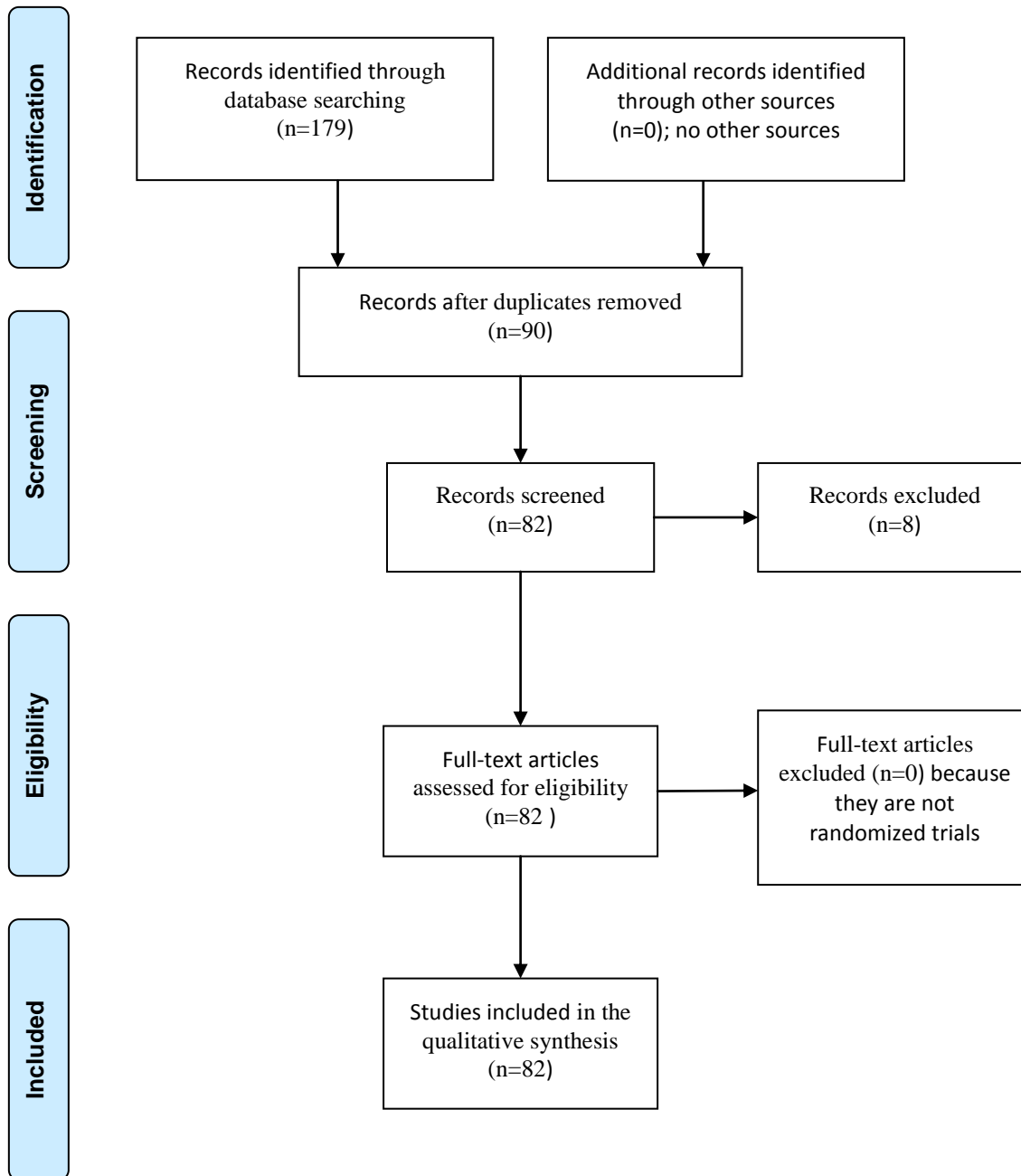


Table 1: The benefits and level of TSH suppression among patients with DTC

Author	Year	Country	Type	No of patients	Duration	Results
Deasy et al.	2010	Ireland	Retrospective	88		Weigh the risk and benefits
Basu et al.	2013	India	Review			T4 use in TSH suppression among patients with recurrent, aggressive DTC may contribute to the clinical growth of the tumour.
Park et al.	2015	Netherlands	Retrospective	446		No benefit of TSH suppression in low-risk DTC
Do Cao et al.	2015	France	A review			TSH level for patients with micro or macroscopic disease is < 0.1mU/L, for other patients, the individual health status, risk of relapse, and clinical follow-up guides the level
Davis et al.	2015	USA	Review			TSH suppression must be weighed against the potential detrimental side-effects of long-term sub-clinical hyperthyroidism.
Santoro et al.	2017	brazil	Experimental study			Higher T ₄ dosage is needed in DTC patients who are carriers of the rs11563250G allele
Lee et al.	2018	Korea	A prospective study	1528	5.6 years	Serum TSH levels did not affect short-term recurrence in patients with low-risk DTC after thyroid lobectomy
Lamartina et al.	2019		A prospective	263	3 years	TSH suppression before the first response to treatment assessment does not influence the rate of structural disease

Table 2: Quality of the selected studies on TSH suppression by using the Newcastle-Ottawa scale

Author	Selection	Compatibility/exposure and outcome	Total score
Deasy et al. et al.	1	4	5
Park et al.	4	3	7
Lee et al.	4	4	8
Lamartina et al.	3	5	8

Table 3: The relationship of long Thyrotrophin releasing hormone (TSH) suppressive therapy and cardiovascular disease among patients with differentiated thyroid carcinoma

Author	Year	Country	Type	No of patients	Duration	Results
Mittal et al.	2012	Nepal	A case-control			Insulin resistance, a hypercoagulable state, and an atherogenic lipid profile were observed in patients with differentiated thyroid cancer.
Klein Hesselink et al. (a).	2013	Netherlands	A retrospective comparative	2096		The risk of cardiovascular and all-cause mortality is increased in patients with DTC, a lower TSH level

						increased cardiovascular mortality
Klein Hesselink et al. (b)	2015	Netherlands	A case-control	2018		Increased atrial fibrillation
Gazdag et al.	2015	Hungary	Cross-sectional longitudinal study	24		Aortic stiffness was observed
Do Cao et al.	2015	France	A review			Atrial fibrillation increased
Klein Hesselink et al. (c)	2017	Netherland	A case-control study	1064		N-terminal pro Brain Natriuretic Peptide levels are elevated in patients with DTC and are associated with an increased risk for cardiovascular events and all-cause mortality.
Klein Hesselink et al. (d)	2017	Netherland	Cohort study	66	5 years	Diastolic dysfunction indicating early cardiac aging was observed
Pajamäki et al.	2018	Finland	Retrospective cohort	8386		Increased morbidity from AF and arrhythmia accountable to TSH suppression below 0.1mU/L. However, cardiovascular mortality was lower among patients due to lower coronary artery disease.
Wang et al.	2018	China	Case-control	105	One year	Prolonged use of TSH suppression leads to suppression of cardiac function
Toulis et al.	2019	UK	Case-control	1259		Increased risk of AF, no evidence of increased risk of IHD or HF

Table 4 Quality of the selected studies on cardiovascular risks among patients with DTC by using the Newcastle-Ottawa scale

Author	Selection	Compatibility/exposure and outcome	Total score
Mittal et al.	1	3	4
Klein Hesselink et al. ²	3	4	7
Klein Hesselink et al. ³	3	5	8
Gazdag et al.	3	4	7
Klein Hesselink et al. ⁶	3	4	7
Klein Hesselink et al. ⁷	3	5	8
Pajamäkiet al.	2	4	6
Wang et al.	4	3	7
Toulis et al.	4	4	8