Cardiovascular Outcomes of Differentiated Thyroid Cancer Patients on Long Term TSH Suppression: A Systematic Review and Meta-Analysis

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Introduction
The global incidence of thyroid carcinoma has been rapidly increasing over the past three decades [1]. This is largely due to increasing diagnostic yield, with unchanged mortality rates [2]. Differentiated thyroid cancer (DTC) accounts for over 95 % of thyroid malignancies [3]. These patients often have an excellent prognosis, with 10-year survival rates exceeding 90 % [4, 5].

DTC patients typically receive partial or total thyroidectomy as curative treatment for their condition [6]. They may also receive radioactive iodine treatment (RAI) to ablate remaining thyroid tissue that was not removed by surgery [6]. Thyroid stimulating hormone (TSH) is known to stimulate proliferation of thyroid cancer cells [3]. Hence patients often receive long term TSH suppression post-surgery in the form of iatrogenic levothyroxine supplementation, to reduce the risk of cancer recurrence and cancer-associated mortality [7].

The most common cause of subclinical hyperthyroidism is iatrogenic levothyroxine treatment, hence a state of exogenous subclinical hyperthyroidism is often induced in DTC patients [8]. There is an increasing body of evidence that suggests this is associated
with increased cardiovascular morbidity and mortality [8, 9]. It is well established that subclinical hyperthyroidism is a risk factor for atrial fibrillation [10, 11]. There are also numerous physiological complications associated with TSH suppressive therapy, such as increased left ventricular mass, tachycardia [12], diastolic dysfunction [13], impaired arterial elasticity [14], and negative prothrombotic changes [15].

Whilst the optimal degree of TSH suppression with regards to cancer recurrence risk is well established, there is a lack of guidelines which optimally correlate TSH suppression and cardiac morbidity [16]. Synthetic dosing requires dynamic reassessment with respect to the individual’s risk of cancer recurrence and cardiovascular health [17]. With the exception of atrial fibrillation, there is limited research investigating the discrete clinical outcomes of TSH suppressed DTC patients. Rather the literature is largely focused on surrogate clinical parameters. This review includes several large cohort studies published since the last systematic review on the topic, hence it better evaluated the cardiovascular clinical outcomes of DTC patients on long-term TSH suppression. It is also the first meta-analysis to offer quantitative estimations of risk. Specifically, this review investigated the cardiovascular morbidity of treatment and whether these patients experienced higher incident rates of cardiovascular disease.

Materials and Methods

Systematic search strategy

The literature search was conducted through Medline (1947 to 22 July 2021), Embase (1946 to 22 July 2021), and CENTRAL (1991 to 22 July 2021). Search terms included numerous keywords pertaining to the cardiovascular outcomes of DTC patients on long-term TSH suppression (Supplementary Fig. 1S). The search was adapted for the databases CINAHL and Scopus. Further papers were identified from previous systematic reviews relevant to the topic.

Study selection – Inclusion/exclusion criteria

The study selection followed the PRISMA guidelines. No formal study protocol was lodged. Two reviewers (JY and SE) used Endnote to collate the results from the literature search and duplicates were deleted. The results were initially screened by title and abstract. Full texts were subsequently retrieved and screened for inclusion into the review.

Eligibility criteria for studies included those which investigated DTC patients who received long-term TSH suppression as part of their treatment regimen. Further, the studies were included if results were reported as measures of discrete cardiovascular clinical outcomes such as incident atrial fibrillation, stroke, ischaemic heart disease, heart failure, cardiovascular mortality, all-cause mortality, etc.

Studies that did not meet all these criteria were excluded. Specifically, studies that investigated patients with poorly differentiated thyroid cancer, non-cancer thyroid conditions and patients on short-term TSH suppression were excluded. Studies that reported their results in clinical parameters of cardiovascular disease as opposed to discrete clinical outcomes such as echocardiographic findings, heart rate variability were also excluded. Furthermore, animal studies and non-English studies were excluded. There was no restriction on publication type or date.

Data extraction, analysis, and quality assessment

Data were extracted from the relevant included studies and compiled into a master excel spreadsheet stratified into demographic and outcome features. The demographic data included: i) author, ii) year, iii) country of publication, iv) baseline data collection year, v) type of study, vi) length to follow up, vii) total participants, viii) study group, ix) control group, x) male/female ratio, xi) age participants, xii) measure used (age), and xiii) TSH levels measured. If TSH levels were not available, it was assumed that patients were TSH suppressed as per the relevant country’s national guidelines.

The following data were extracted from included studies: i) reported study effects, ii) measure used, iii) effect size, iv) lower 95 % CI, v) upper 95 % CI, vi) reference category, vii) analysis adjusted, and viii) adjusted for what measures.

Two independent reviewers (JY and RK) performed a risk of bias and quality assessment of included studies using the Newcastle-Obtawa Scale, which evaluated the three domains of patient selection, comparability, and outcome. Scores ranged from 0–9 and studies with scores of 6 or greater were considered high quality (Supplementary Table 1S). Consensus was reached for all differences.

Statistical analysis

Review manager 5.4.1 was utilised for data analysis. The studies were combined by the generic inverse-variance method on the natural logarithms of hazard ratios (HR). Hazard ratios (HR) were reported with 95 % confidence intervals. If specific hazard ratios were not reported in a paper, these were generated from available raw data, that is, number of participants and events in the study and control groups. Some of the papers reported follow up in median and other reported follow up in median. So, we took a median of the combined means and medians to obtain length to follow up. Test of overall effects and statistically significant results were reported with pooled hazard ratios.

Meta-analysis was performed on outcomes assessed by more than two studies. The χ² test was used to assess heterogeneity, and this was quantified with the I² value. Heterogeneity was characterised as: I² < 25% none; I² 25–49% low; I² 50–74% medium; I² > 75% high. Both random and fixed effect models were used for the meta-analysis depending on the I² value. Random effect models were used for medium to high I² values and fixed effect models were used for low to medium I² values. Significance level was set at <0.05. Funnel plots were created with RevMan 5.4.1 to assess for potential publication bias and small study effects (Supplementary Fig. 2S).

Results

The systematic search yielded 130 papers once the duplicates were removed. These studies were screened by title and abstract, of which 100 were excluded and 30 were sought for retrieval. 29 full text studies were reviewed, and one full text was unable to be retrieved. 19 studies did not fulfil the inclusion criteria. 10 studies
were included into the review. The PRISMA diagram is shown in Fig. 1.

Of the included papers, six were European studies [18–23], three were from the US and Canada [24–26], and one was from South Korea [27]. All studies were published within the previous decade. Nine papers were cohort studies, and one paper was a cross-sectional study (Table 1). The quality of included studies was assessed as high via the Newcastle-Ottawa scale (Supplementary Table 1S). There was a total of 195,879 patients and 204,595 controls across the papers. Median length to follow up was 8.6 years. Table 2 summarises key characteristics of the included papers.

**Cardiovascular morbidity**

All studies investigated cardiovascular morbidity or mortality. The outcomes and key findings are summarised in Table 2. The subjects were DTC patients undergoing long-term TSH suppression therapy. Unless stated otherwise, controls were healthy, non-TSH suppressed individuals with findings adjusted for age, sex, and variable degrees of social and cardiovascular risk factors. Two papers used population based cohorts, without specified numbers of control subjects, as the reference group [23, 24]. In two other papers, the control groups were non-TSH suppressed DTC patients [25, 26]. The reference categories and details of analysis adjustment are summarised in Supplementary Table 3S. Heterogeneity ranged between 16–98 % across outcomes (Fig. 2–6).

**Cardiovascular and all-cause mortality**

Two studies reported on cardiovascular mortality and three studies reported on all-cause mortality (Fig. 2) [18, 21, 22]. Hesselink et al. reported increased cardiovascular mortality among 524 DTC patients [18]. Pajamaki et al. reported decreased cardiovascular mortality among 901 DTC patients [21]. All-cause mortality was significantly increased among DTC patients (4434 patients, HR 2.04, 95 % CI 1.02, 4.07).
Atrial fibrillation

Atrial fibrillation (AF) was measured in eight studies (Fig. 3) [19–24, 26, 27]. No occurrences of AF were observed in a study of 66 DTC patients, hence, it was not included in the statistical analysis [20]. Risk of AF was significantly increased among DTC patients compared to controls (194 212 patients, HR 1.58, 95 % CI 1.40, 1.77). Suh et al. demonstrated a dose dependent effect whereby increased doses of levothyroxine (TSH suppression) lead to an increased risk of AF [27].

Stroke/cerebrovascular disease

Five studies reported on ischaemic heart disease (Fig. 5) [21–23, 25, 27]. There was no difference in ischaemic heart disease (IHD) risk between DTC patients and controls (194 170 patients, HR 1.07, 95 % CI 0.99, 1.16).

Heart failure

Three studies investigated occurrence of heart failure in DTC patients (Fig. 6). There was no difference in HF incidence between DTC patients and controls (10 810 patients, HR 0.99, 95 % CI 0.78, 1.26).
Other CVD outcomes

The study by Pajamaki et al. also investigated a number of other cardiovascular outcomes not previously mentioned. These included hypertension, arteriovenous disease, valvular disease, cardiomyopathies, and disease of the pulmonary arteries in their group of 901 patients and 4485 controls [21]. For all outcomes, there was no difference in incidence between TSH suppressed DTC patients and healthy controls [21]. The study showed an increased risk of all arrhythmias in the DTC cohort compared to controls. Further, when pooling the cardiovascular outcomes together the study demonstrated a significantly increased risk of cardiovascular morbidity in DTC patients [21].

Park et al. also investigated several other cardiovascular outcomes, namely hypertension, arterial disease, and venous disease. The study showed that DTC patients receiving TSH suppression therapy were at increased risk of hypertension and disease of the arteries, arterioles and capillaries, when compared to DTC patients who did not receive TSH suppressive therapy [25]. There was no difference in incidence of venous disease between TSH suppressed and non-TSH suppressed patients [25].

Degree of TSH suppression and cardiovascular outcomes

There was variability in the degree of TSH suppression and the way in which it was measured across studies, different guidelines of suppression were used depending on where the study was conducted (Supplementary Table 2S). Three studies showed no relationship between degree of TSH suppression and incidence/prevalence of AF [19, 24, 26]. The degree of TSH suppressive therapy was difficult to interpret some of the studies. Touil et al. assumed TSH suppression to be within British guidelines, however not all TSH measurements of the patients were available, hence the extent of suppressive therapy was not reported [22]. Similarly, Zoltek et al. assumed TSH suppression to be in line with Swedish national guidelines, although specific measurements were not reported [23]. Suh et al. measured levothyroxine dose as a proxy marker for the degree of TSH suppression [27]. This study showed a dose dependent increase in AF, stroke and IHD incidence with increasing levothyroxine dose [27]. Another study reported that lower TSH levels were associated with increased cardiovascular mortality [18]. Further, Pajamaki et al. reported increased CVD morbidity in patients with TSH levels below 0.1 mIU/l [21]. Park et al. demonstrated an association between TSH suppression and increased risk of hypertension and arterial disease [25]. These findings are summarised in Supplementary Table 2S.

Discussion

The primary aim of this study was to better evaluate discrete cardiovascular outcomes in TSH suppressed DTC patients. The results demonstrated a number of adverse cardiovascular diseases associated with long term DTC management. Although there is a paucity of studies investigating discrete adverse cardiovascular events in the given setting, this review has included two large population-based cohort studies [23, 27], which have not been included in previous qualitative reviews, and also affords quantitative data.
Table 1 | Overview of Included studies.

| Authors [Ref] | Year | Country | Baseline data collection year–year of DTC diagnosis | Type of study | Length to follow up (Years) | #Study group | #Control group | M/F | Age of participants (Years) | SD age participants (Years) | Measure Used | Age of participants at study start | TSH levels measured | Age of participants | SD age participants | TSH levels measured |
|---------------|------|---------|-----------------------------------------------|--------------|---------------------------|-------------|----------------|-----|--------------------------|--------------------------|-------------|---------------------------|----------------------|----------------|----------------|----------------------|----------------|
| Abonowara et al. [24] | 2012 | Canada | 2009–2010 | Cross-sectional | 11.0 | 136 | 136 | NR | 18/118 | 52 | Mean | Yes | Mean | Yes | 14 | 14 | Mean | 48.6 | 4.8 |
| Klein Hesselink et al. [19] | 2015 | Netherlands | 1980–2010 | Cohort | 8.7 | 2081 | 518 | NR | 1562 | 1572 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Klein Hesselink et al. [18] | 2013 | Netherlands | 1980–2010 | Cohort | 8.5 | 2096 | 518 | NR | 1572 | 1572 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Park et al. [25] | 2018 | USA | 2000–2006 | Cohort | 6.5 | 771 | 465 | NR | 666 | 666 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Pajamaki et al. [21] | 2019 | Finland | 1981–2002 | Cohort | 8.5 | 36848 | 901 | NR | 1003 | 1003 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Suh et al. [27] | 2019 | South Korea | 2004–2016 | Cohort | 5.0 | 14312 | 3009 | NR | 11930 | 11930 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Toulis et al. [22] | 2020 | UK | 1996–2006 | Cohort | 6.5 | 77 | 465 | NR | 666 | 666 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Wang et al. [26] | 2019 | Sweden | 2000–2006 | Cohort | 6.3 | 306 | 306 | NR | 666 | 666 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |
| Zoltek et al. [23] | 2020 | Sweden | 1987–2013 | Cohort | 9.6 | 6900 | NR | NR | 1312 | 1312 | Mean | Yes | Median | 33 | 3 | Yes | 49 | 16 |

This study demonstrated that DTC patients experience increased rates of AF. Pathophysiological mechanisms involve the positive chronotropic and dromotropic effects of exogenous thyroxine administration and subsequent iatrogenic subclinical hyperthyroidism [28]. Thyroid hormone excess is associated with an increased resting heart rate, impaired ventricular relaxation and increased left ventricular mass which leads to elevated left atrial pressures [12, 28]. Increased atrial ectopic activity is also associated with thyrotoxicosis [28]. All of these factors may contribute to the increased rates of AF in DTC patients.

Table 2 | Investigated outcomes and key findings of papers.

<table>
<thead>
<tr>
<th>Authors [Ref]</th>
<th>Outcomes studied</th>
<th>Significant positive findings vs. control/reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abonowara [24]</td>
<td>AF</td>
<td>Increased prevalence AF</td>
</tr>
<tr>
<td>Hesselink [19]</td>
<td>AF</td>
<td>Increased incidence AF</td>
</tr>
<tr>
<td>Klein Hesselink [18]</td>
<td>CVD Mortality, All Cause Mortality</td>
<td>Increased incidence CVD mortality and all cause mortality</td>
</tr>
<tr>
<td>Klein Hesselink [20]</td>
<td>AF</td>
<td>Nil</td>
</tr>
<tr>
<td>Park [25]</td>
<td>HTN, Heart Disease, Cerebrovascular Disease, Disease of Arteries/Arterioles/Capillaries, Venous and Lymphatic Disease</td>
<td>Increased incidence HTN and arterial disease</td>
</tr>
<tr>
<td>Pajamaki [21]</td>
<td>CVD Mortality, CVD Morbidity, All Cause Mortality, All Arrhythmias, AF, HF, HTN, Cerebrovascular Disease, Vascular Disease, CAD, Cardiomyopathy/Valvular Disease, Pulmonary Artery Disease</td>
<td>Increased incidence AF, all arrhythmias, CVD morbidity Reduced CVD mortality</td>
</tr>
<tr>
<td>Suh [27]</td>
<td>AF, Stroke, CHD</td>
<td>Increased incidence AF, stroke, CHD</td>
</tr>
<tr>
<td>Toulis [22]</td>
<td>AF, All Cause Mortality, Stroke, HF, IHD</td>
<td>Increased incidence AF, stroke, all cause mortality</td>
</tr>
<tr>
<td>Wang [26]</td>
<td>AF</td>
<td>Nil</td>
</tr>
<tr>
<td>Zoltek [23]</td>
<td>AF, Stroke, IHD, HF, Cerebrovascular Disease, Ischaemic Heart Attack</td>
<td>Increased incidence AF, cerebrovascular disease</td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation; CVD: Cardiovascular disease; HTN: Hypertension; HF: Heart failure; CAD: Coronary artery disease; CHD: Coronary heart disease; IHD: Ischaemic heart disease.
Risk of stroke was increased in DTC patients, and Suh et al. further demonstrated a dose-dependent increased risk of stroke with increasing TSH suppressive therapy [27]. A central mechanism underlying this association is the increased rates of AF in DTC patients. It is well established that AF predisposes to cardiac thrombus formation and hence may lead to a greater risk of ischaemic stroke [29]. Suh et al. also demonstrated an increased risk of stroke independent of atrial fibrillation, suggesting that other pathophysiological mechanisms may be in effect. It is plausible that hypercoagulability, systolic hypertension and increased arterial stiffness associated with iatrogenic hyperthyroidism may be partially responsible for the increased rates of stroke in DTC patients [30].

The two papers investigating CVD mortality produced opposing findings. Pajamaki et al. reported a decreased CVD mortality in DTC patients [21]. This was attributed to the excellent survival rates associated with DTC [4, 5, 31], combined with the lifelong follow up of DTC patients, which encourages continued interaction with the medical community [21]. Further, patients that die due to cancer are unable to reach a cardiovascular endpoint hence resulting in lower cardiovascular mortality [32]. Conversely, Hesselink et al. showed increased cardiovascular mortality in DTC patients [18]. Although the pathophysiological mechanisms are not clearly understood, it may be associated with increased left ventricular mass, AF and decreased diastolic function in TSH suppressed patients [13, 14, 33]. There were numerous methodological differences between the studies. Hesselink et al. controlled for cardiovascular risk factors whereas Pajamaki et al. did not. The two cohorts were subject to differing degrees of TSH suppression, and length to follow-up was over twice as long in the study by Pajamaki et al. Further studies are required to better evaluate this outcome. All-cause mortality was significantly increased in DTC patients. It is possible that elements of both CVD mortality and cancer related mortality contributed to this.

DTC patients were found to be at a mildly higher risk of IHD than controls, although this was not statistically significant. Four of five studies showed no evidence of difference. The only positive significant finding was demonstrated by Suh et al., which had marked greater statistical power than the other studies, with a sample size of 182,419 as opposed to 11,751 combined across the other papers. Suh et al. also demonstrated a dose-dependent increase in IHD risk with increasing levothyroxine administration [27]. It was proposed that the possible underlying mechanisms are similar to those affecting ischaemic stroke risk in the TSH suppressed, that is, systolic hypertension, hypercoagulability, increased arterial stiffness and enhanced LDL oxidation [30, 34].

Surprisingly, no difference in heart failure risk was appreciated between DTC patients and controls. It is possible that the subclinical nature of hyperthyroidism experienced by patients is not sufficient to cause overt clinical heart failure. Investigation of clinical parameters may better elucidate this association. It has been shown that left ventricular ejection fraction decreases with TSH suppression lasting over 12 months [35]. Regarding other outcomes, Park et al. showed an increase in hypertension and arterial disease in TSH suppressed patients [25], attributing this to the myocardial and vascular function impairment associated with long term suppression [14]. Further studies are required to better characterise the additional outcomes investigated by Pajamaki et al. [21].

This review also demonstrates that the association of adverse cardiovascular outcomes in DTC patients is multifactorial and not only attributable to TSH suppressive therapy. Surprisingly, three studies showed no difference between TSH levels and risk of AF [19, 24, 26]. This finding may be due to underpowered studies coupled with varied degrees of TSH suppression between patients [19, 24, 26]. Further, there is possible surveillance bias associated with subclinical paroxysmal AF which may lead to an underestimation of AF incidence [19]. Conversely, four studies demonstrate an increased cardiovascular morbidity and mortality in patients that were TSH suppressed [18, 21, 25, 27]. Two further studies assumed TSH suppression to adhere to national guidelines, however numerical TSH measurements were not recorded or attainable [22, 23]. Hence in these papers it is difficult to draw specific conclusions between TSH suppression and cardiovascular disease.

It is of note that although Hesselink et al. did not find a relationship between TSH levels and AF, they did demonstrate that an increased cumulative dose of RAI was associated with an increased incidence of AF [19]. Similarly, two other studies found patients treated with RAI to be at higher risk of cardiovascular morbidity compared to those who did not receive RAI [21, 25]. All patients in the study by Zoltek et al. received both TSH suppression and RAI therapy. However, these subgroups were not stratified in their analyses, hence it is difficult to deduce an association between cardiovascular morbidity and either of the therapies [23]. Further, Hesselink et al. [18] and Wang et al. [26] adjusted for RAI in their analyses. The ionising radiation in RAI therapy has the capacity to facilitate endothelial dysfunction and thus increase the risk of atherosclerotic disease [36, 37]. It has also been proposed that the cycling from subclinical hyperthyroidism to hypothyroidism, when withdrawing thyroxine therapy to allow RAI therapy, may contribute to rhythm disturbances [19]. Thus to adequately interpret the effects of TSH suppressive therapy there is a need to adjust analyses for concomitant RAI therapy.

Limitations

There are a few limitations associated with this review. Significant heterogeneity exists across studies with respect to treatment regimes, outcome variables, demographic features, follow up, control cohorts, pre-existing comorbidities, and subsequent adjustment of analyses. Different studies conducted their own adjustment analyses and it was not standardised across the included studies.

Hence it was not unexpected that the I² values for the outcomes in the meta-analysis were largely in the medium to high range. It was difficult to conduct subgroup or sensitivity analyses based on differing degrees of TSH suppression due to the existing heterogeneity and variable reporting of TSH levels. This could be performed in future reviews if the included papers contained more accurate reporting of TSH levels. In addition, the outcomes of AF, IHD and stroke were skewed towards the findings of Suh et al. as their sample size was significantly larger than any other study in this review.

The definition for TSH suppression varied significantly between studies and it is known that patients are stratified to differing degrees of TSH suppression based on their risk of cancer recurrence, such that higher risk patients tend to be treated with more aggressive TSH suppressive therapy and are more likely to receive RAI.
[6, 7]. Changing guidelines for TSH suppression are also unaccounted with baseline data collection ranging from 1970 to 2016 across the studies in this review. Further, when reporting degree of TSH suppression, two studies assumed suppressive therapy to be within national guidelines [22, 23]. Without reported TSH values, this assumes concordant treatment paradigms across each study’s respective country as well as patient compliance. Further, Suh et al. measured levothyroxine dose as a proxy marker for TSH suppression, however serum levels of TSH may vary with metabolism, age, sex, weight, and a number of other variables [27]. Similarly, patient compliance with medication was not considered in this study.

Another limitation of the review exists in the differing definitions of cardiovascular outcomes between studies. With respect to cerebrovascular disease, two studies reported on cerebrovascular disease [21, 25], whilst two others reported specifically on stroke [22, 27]. Further, Zoltek et al. defined separate subgroups for cerebral infarction and cerebrovascular disease [23]. For the purposes of this review, both stroke and cerebrovascular disease were combined as an outcome. The study by Park et al. did not have a specific ischaemic heart disease subgroup but rather a broader ‘heart disease’ subgroup [25]. This was combined into the subgroup titled ‘ischaemic/coronary heart disease’ in this review hence all occurrences were assumed to be IHD related.

Conclusion

This study found that DTC patients who are subject to long term TSH-suppression are at higher risk of adverse cardiovascular outcomes, specifically AF, stroke, and all-cause mortality. However, there was significant diversity in study methodology and presentation of findings. Further investigation through larger scale, prospective studies with similar methodology, stringent measurement of TSH levels and adequate adjustment for confounders and comorbidities would better characterise the effects of TSH suppression therapy in DTC patients. Notwithstanding, TSH suppressive therapy for DTC patients requires dynamic assessment and follow up with respect to cardiovascular health. Patients and clinicians must be aware of these increased risks and hence a high clinical suspicion of cardiovascular disease is warranted in TSH-suppressed DTC patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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