EVALUATION OF CARDIOVASCULAR RISK AND MYOCARDIAL PERFUSION IN PATIENTS WITH RADICALLY TREATED DIFFERENTIATED THYROID CARCINOMA AND REPEATED EPISODES OF IATROGENIC HYPOTHYROIDISM

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Abstract

Context. Patients with radically treated differentiated thyroid carcinoma (DTC) undergo multiple episodes of iatrogenously-acquired hypothyroidism for the oncological follow-up. In some patients, this elevates high-sensitive C-reactive protein (hsCRP), a cardiovascular risk biomarker.

Objective. We wanted to determine if there is any correlation between repeated hypothyroidism episodes, elevated hsCRP and an increased cardiovascular risk as stated through myocardial perfusion.

Design. Between July 2014-January 2015, we analyzed serological levels of hsCRP for identifying our patients' cardiovascular risk; we performed a myocardial perfusion scintigraphy to observe the alterations.

Subjects and methods. We included 27 patients (n=27), mean age of 52±10; CI (95%), 14 female, all disease-free after thyroidectomy, radioiodine ablation and chronic thyroid hormone treatment. We assigned the cardiovascular risk category for each patient according to hsCRP levels; all patients underwent a myocardial perfusion scintigraphy in order to determine the cardiac perfusion index (CPI).

Results. hsCRP has been higher in > 65 years old male patients with more than 5 thyroid hormone withholdings. hsCRP is significantly associated with CPI (p=0.001). Spearman's rank correlation indicates a strongly positive linear correlation between these two parameters (r=0.745).

Conclusions. Repeated thyroid hormonal withdrawals in patients with DTC during the long-term follow-up elevated hsCRP at cardiovascular risk levels, having an impact on myocardial perfusion.

Key words: differentiated thyroid carcinoma, myocardial perfusion, hsCRP, thyroid hormone withdrawal, cardiovascular risk.

INTRODUCTION

Radical treatment for patients with differentiated thyroid carcinoma (DTC) consists of

total or near-total thyroidectomy, with or without lymphadenectomy, followed by radioiodine (iodine-131 [I-131]) ablation of the remnant thyroid tissue. The monitoring protocol and the need for subsequent life-long hormonal treatment, depend on each individual's risk of recurrence and mortality (1–5). Monitoring includes clinical examinations, measurement of serum thyroglobulin (Tg) and anti-Tg (ATg) concentrations, neck ultrasound (US) and, if needed, whole-body scintigraphy (WBS) using I-131 (6,7). To accurately conduct oncologic monitoring, serum thyrotropin (TSH) levels must be unsuppressed and markedly increased (8).

TSH concentrations can be increased through thyroid hormone withholding (THW) for 2–6 weeks. However, this iatrogenic-induced hypothyroidism may be associated with a large spectrum of metabolic disorders, as well as cardiovascular consequences.

C-reactive protein (CRP), especially high-sensitivity (hs) CRP (hsCRP), is considered a biomarker of inflammation. Slight but continuously elevated hsCRP has been found to be a marker for increased cardiovascular risk. Moreover, hsCRP concentrations are significantly higher in patients with primary or subclinical hypothyroidism than in euthyroid controls. Myocardial function can also be evaluated by myocardial perfusion scintigraphy. This method, which uses an intravenously injected tracer, is the most widely used imaging procedure in nuclear cardiology.

The associations between hypothyroidism, hsCRP concentration and cardiovascular disease suggested that THW may enhance cardiovascular risk. This correlational study assessed myocardial perfusion rates in radically treated DTC patients who have undergone multiple THWs for I-131 ablation and follow-up and who had increased serum hsCRP

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levels. The study evaluated whether increased hsCRP concentrations due to multiple THW procedures reduced myocardial perfusion, thus enhancing cardiovascular risk.

PATIENTS AND METHODS

Patients

The study included 27 patients with DTC who had undergone radical primary treatment and were followed-up for a minimum 3-years at the “Professor Dr. Ion Chiricuță” Institute of Oncology Cluj-Napoca (IOCN), a Romanian tertiary referral center. Between July 2014 and January 2015, the study cohort was subjected to THW for at least two weeks, enhancing TSH concentrations to >30 mIU/L (9), in order to correctly assess oncological markers values. Other inclusion and exclusion criteria are stated in Table 1.

All patients provided written informed consent for the collection of clinical data and serological samples and for the use of their data in scientific reports. The study protocol was approved by the Ethics Committee of IOCN.

All patients had undergone total or near-total thyroidectomy, followed by THW for four weeks and ablation with a low to median level of I-131 (mean 2.7 ± 1.3 GBq) (10–13). Immediately after radioiodine ablation, patients had TSH concentrations of 0.2–4.2 mIU/L and underwent levothyroxine (LT4) therapy at suppressive doses (target TSH <0.1 mIU/L) until shown to be disease-free. Disease-free status was defined as negative findings on physical examination, neck US, and I-131 whole-body scintigraphy, undetectable Tg (<0.1 µg/L), upon stimulation, and undetectable anti-thyroglobulin antibodies (TgAb) (<115 IU/mL). After patients achieved oncological disease-free status, their LT4 concentration was adjusted to maintain TSH within the lower normal range, 0.4–1.0 mIU/L (14–20).

The first follow-up, 6 weeks after ablation, consisted of a physical examination and measurements of serum TSH and FT4 concentrations. Oncological examinations were performed 6 months after ablation and after THW, and consisted of a physical examination, neck US and measurements of serum concentrations of TSH, stimulated Tg and TgAb.

All subsequent THWs were performed for two weeks, unless TSH was <25 mIU/L or <100 fold lower than its concentration during LT4 therapy, whichever was lower, with the purpose of checking any remnant tumoral tissue presence, even in disease-free patients. If TSH was insufficiently elevated, the THW was extended for an additional two weeks. None of the patients from the study cohort required stimulation with recombinant human TSH (rhTSH). After 6-months, patients were monitored based on their initial and subsequent DTC status. All patients had normal cardiac function, as shown by normal electrocardiograms and cardiac ultrasonography, both when euthyroid and when iatrogenically hypothyroid.

Methods and blood sampling

Blood samples were obtained immediately before the index THW and after 2 weeks of THW. Patients were fasted for a minimum of 12-h and placed in the supine position for 30 minutes prior to blood drawing. Serological analyses were performed immediately after blood drawing, with all analyses performed in the same accredited (ISO 15189) laboratory.

CRP concentrations between 0.15–20 mg/L were measured by a latex-immunoturbidimetry method (Roche Diagnostics, Basel, Switzerland), with intra- and inter-run coefficients of variation of 1.6% and 0.43–5.6%, respectively. Cardiovascular risk was stratified by hsCRP concentrations, as defined by American Heart Association (21), with concentrations <1 mg/L,

Table 1. Study inclusion and exclusion criteria for patients with radically treated differentiated thyroid carcinoma (DTC)

Inclusion criteria	Exclusion criteria
DTC disease-free status	hsCRP >10 mg/L at baseline or at the end of the index THW (1 patient excluded)
Increased TSH concentrations	Prior history of any inflammatory thyroid disease (2 patients excluded)
Never-smoker status	Cardiac history beyond controlled hypertension; dyslipidemia (2 patients excluded)
Free thyroxine (FT4) concentrations before THW within normal range	Evidence of chronic or acute inflammatory processes, including infections (1 patient excluded)
More than 2 THWs before the index THW	

Abbreviations: hsCRP= high-sensitivity C-reactive protein; THW= thyroid hormone withholding; TSH= thyroid-stimulating hormone. Note: the initial cohort had 33 patients, 6 patients were excluded.

Table 2. Descriptive statistics of radically treated differentiated thyroid carcinoma patients, according to cardiovascular risk groups

hsCRP-related cardiovascular risk categories	No. of patients	hsCRP (mg/L), mean $\pm$ SD	CPI, mean $\pm$ SD	THW, median (Q1; Q3)	age (years), mean $\pm$ SD
low cardiovascular risk (<1 mg/L)	12	0.56 $\pm$ 0.25	0.16 $\pm$ 0.39	4 (3; 9.25)	50.17 $\pm$ 10.49
medium cardiovascular risk (1-3 mg/L)	10	1.75 $\pm$ 0.64	1.4 $\pm$ 1.07	5.5 (4; 8)	56 $\pm$ 9.18
high cardiovascular risk (>3 mg/L)	5	4.46 $\pm$ 1.10	1.8 $\pm$ 0.44	6 (3; 11)	50 $\pm$ 10.94

hsCRP – high-sensitivity C-reactive protein;

THW – thyroid hormone withdrawals;

CPI – cardiac perfusion index.

1–3 mg/L, and >3 mg/L defined as low, intermediate, and high cardiovascular risk, respectively. Patients with hsCRP concentrations >10 mg/L were excluded from the study.

Myocardial imaging

Myocardial perfusion scintigraphy was performed on all patients after they became euthyroid, following at least 6 weeks of hormonal treatment after the last THW. Myocardial perfusion was performed at rest, as fixation of the radiopharmaceutical in myocytes was regarded as proportional to blood flow and, therefore, cardiac viability (22).

Patients stopped taking any medication on the morning prior to the examination. Following injection of the radiopharmaceutical tracer, 99mTechnetium-sestamibi (99mTc-sestamibi), at a dose of 740–1100 MBq, patients were allowed sweet liquid and a chologogue lunch. The patient was placed in the dorsal decubitus position, holding the left upper limb above the head, and images were acquired with a SPECT camera (23), with a large field of view, and a low-energy high-resolution (LEHR) collimator. Images were edited using a Butterworth filter, with a cutoff of 0.5, and tridimensionally reconstructed, and were later analyzed in three views: vertical long axis (VLA), horizontal long axis (HLA) and short axis (SA) views. These scintigraphy results were used to calculate myocardial perfusion activity scores. Cardiac perfusion index (CPI) was determined using a 5-point scale, with scores of 0–3 indicating normal, minimally abnormal, moderately abnormal, and severely abnormal perfusion, respectively, and 4 indicating absence of tracer uptake.

Statistics

Data are presented as means $\pm$ standard deviations (SDs) and medians (first-third quartiles), unless stated otherwise. Relationships involving abnormally distributed parameters (e.g. hsCRP, CPI) were determined using non-parametric tests and were expressed using Spearman's rho coefficient. Bivariate analyses using the F test on linear regression model

were performed to determine the effects of age, TSH and hsCRP concentrations, number of prior THW procedures and CPI. In each analysis, one variable (e.g. hsCRP concentration) was considered the dependent variable, and the other parameters (e.g. age, TSH concentration, number of prior THW procedure, and CPI) were independent variables. As chronic iatrogenic hypothyroidism was thought to require at least two THW procedure, the cut-off value was chosen to be at least one previous THW before the index THW. The cut-off values of serological variables were defined by the manufacturer of each testing kit. The results of multivariate analysis are presented as adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). All statistical analyses were performed using SPSS software version 23, for Mac OSX. A P value <0.05 was considered statistically significant.

RESULTS

The study cohort included 13 males (48.1%) and 14 females (51.9%), of mean $\pm$ SD age at baseline of 52 $\pm$ 10 years (95% CI, 48–56 years). All patients had confirmed DTC pathology; their mean $\pm$ SD time from DTC diagnosis was 100.4 $\pm$ 87.6 months.

At baseline, mean $\pm$ SD hsCRP concentration was 1.72 $\pm$ 1.55 mg/L (95% CI, 1.10–2.33 mg/L); number of THW procedures was 17.33 $\pm$ 5.04 (95%CI, 5–8.99); their CPI was 0.92 $\pm$ 0.99 (95% CI, 0.51–1.32), and their TSH concentration was 37.30 $\pm$ 25.82 mIU/L (95% CI, 27–47 mIU/L) (Table 2).

The causal relationships between hsCRP concentration and the other parameters was evaluated using the F-test for linear regressions. hsCRP was significantly associated with CPI (p=0.001), but not with patient age (p=0.198), TSH concentration (p=0.913), or number of THW episodes (p=0.916). Analysis of the relationship between hsCRP and CPI using Spearman's rank correlation coefficient showed that r=0.745, indicating a strongly positive linear correlation (Fig. 1).

Figure 1. Correlation between cardiac perfusion index and high sensitive C-reactive protein (hsCRP), a cardiovascular risk bio-marker, in patients with radically-treated differentiated thyroid carcinoma.

Figure 2. Myocardial perfusion scintigraphy, showing a decreased perfusion of the cardiac muscle (see the arrow).

DISCUSSION

Our study's main finding is that increased hsCRP levels in patients with DTC are associated with a decreased perfusion of the myocardial tissue (Fig. 2). There is a strong, highly significant linear correlation between hsCRP concentration and cardiac perfusion, showing that medium- and high-risk levels of hsCRP were associated with a statistically significant increase in the 5-point CPI.

The incidence of DTC, the most frequent type of endocrine tumor, has increased exponentially over the last decade (24). A better approach to its pathology, including new methods of treatment and monitoring, may benefit patients. Suitable multimodal treatment has increased the 10-year survival rate to over 90%.

It is well known that up to 30% of these patients relapse in 10-15 years intervals from acquiring disease-free status. Therefore, they must undergo life-long follow-up, which includes several THWs (9).

Previous studies (25) have shown that hsCRP levels increase in patients with DTC after repeated THWs. Therefore, increasing hsCRP through repeated THWs may have a deleterious effect on myocardial function due to the reduction of blood supply in the coronary arteries, reducing myocardial perfusion.

Prospective studies have confirmed that patients with elevated hsCRP concentrations are at higher risk of developing coronary artery disease and myocardial infarction than patients with lower hsCRP concentrations. Similarly, hsCRP concentrations are predictive of cardiovascular risk (21).

hsCRP and CPI have been reported higher in male than in female patients and in those >65 than ≤65 years old, indicating that age and gender are important cardiovascular risk factors in DTC patients undergoing THW.

The lipid profile is also altered during THW, associating an elevated TSH with increased values of total cholesterol, LDL cholesterol, and with low HDL cholesterol levels, enhancing the cardiovascular risk. Older patients are likelier to associate elevations of VLDL cholesterol and triglycerides (25).

The limitations of the current study were represented by the small number of cases we included and by the lack of rhTSH, due to economic reasons and availability issues.

Recent international multicenter trials have shown that complete radioiodine ablation has equivalent efficacy in patients receiving rhTSH and those with elevated TSH due to THW (26-29). The general use of rhTSH is constrained by economic reasons and lack of availability in some areas; therefore, there is general interest in identifying patients who may benefit more from rhTSH stimulation than THW.

There are only a few studies that treated this subject. To our knowledge, the present study is the first to show correlations between induced thyroid insufficiency and reduced myocardial perfusion in patients with DTC.

Additional studies are needed to assess hsCRP values and myocardial perfusion in patients treated with rhTSH before oncologic follow-up, evaluating its cardiovascular benefits and protective effect by avoiding thyroid hormone withdrawal.

In conclusion, patients with radically treated DTC frequently present an altered myocardial perfusion rate. This may be caused by an inflammatory state of the coronary arteries due to multiple thyroid hormonal withdrawals, increasing cardiovascular risk in these patients.

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Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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