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ORIGINAL ARTICLE

Relationship of thyroid hormone levels and cardiovascular events in patients with type 2 diabetes

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Abstract Alterations in thyroid hormone levels are found associated with inflammation in patients with non-thyroidal illness (NTIS) and are common in patients with type 2 diabetes mellitus (T2DM). Inflammation has also been linked with development of cardiovascular events (CVE) in T2DM. Our objective was to assess whether thyroid hormone abnormalities typical of NTIS in patients with T2DM are related to inflammation and CVE. This was a cross-sectional study of 140 subjects; 70 with T2DM and 70 as a control group paired by age, sex and body mass index (BMI). We recorded age, sex, BMI, waist/hip ratio, diabetes duration, HbA1c, CVE history, serum amyloid A (SAA), TSH, total (T) and free (F) T4 and T3, reverse T3 (rT3) and TT3/rT3 ratio. Patients with T2DM had lower levels of TT4 ($p = 0.012$), TT3 ($p < 0.001$), FT3 ($p < 0.001$) and TT3/rT3 ($p = 0.002$). They also showed higher FT4 ($p < 0.001$) and similar TSH levels ($p = 0.627$) compared to the control group. SAA levels correlated positively with rT3 ($r = 0.45$; $p < 0.001$) and inversely with TT3/rT3 ($r = -0.38$; $p = 0.001$). Patients with T2DM and history of CVE had higher rT3 ($p = 0.006$) and lower TT3/rT3 ($p = 0.002$), along with higher SAA levels ($p = 0.002$) than patients without this characteristic. Multiple logistic regression showed that factors independently associated with CVE were older age (OR = 1.159, 95 % CI 1.011–1.329), male sex (OR = 4.391, 95 % CI 1.081–17.829) and higher TT3/rT3 (OR = 0.993, 95 % CI 0.987–0.999). We have confirmed the presence of NTIS in T2DM. We also showed that thyroid hormone abnormalities are associated to inflammatory activity and to CVE in these patients.

Keywords Non-thyroidal illness · Low T3 · Inflammation · Type 2 diabetes · Cardiovascular disease

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Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease that presents more often in individuals with obesity and insulin resistance [1, 2]. These characteristics are often associated with increased systemic inflammation, resulting in a higher risk for cardiovascular events (CVEs) [3].

Inflammatory markers such as C-reactive protein (CRP) reflect CVE and are used in clinical decision-making [4]. The serum amyloid A (SAA) is a pro-inflammatory marker synthesized in the liver in response to interleukin-6 and tumour necrosis factor-α and is known to complement CRP in predicting CVE, as its levels are lower in patients with T2DM before ischaemic events and increase thereafter [5, 6].

The non-thyroidal illness syndrome (NTIS) is a condition characterized by low levels of T3 and sometimes T4 with concurrently normal or low levels of TSH, and has been described in patients with T2DM linked to poor glycaemic control [7, 8]. The aetiology of NTIS has been associated to increased inflammatory activity in non-critically ill patients [9, 10].

As inflammation is involved in both NTIS and CVE, we hypothesized that (1) thyroid hormone abnormalities typical of NTIS would be present in patients with T2DM and

(2) these alterations would be associated with the presence of CVE in these patients.

Subjects and methods

This was a cross-sectional study involving 140 participants, of which 70 patients were with T2DM and the other 70 formed a control group. The control group was selected among persons in the same socio-economical strata as the patients with T2DM, and were paired by age, sex and body mass index (BMI). Patients with T2DM were further classified in subgroups with or without previous history of CVE. Subjects between 40 and 75 years of age fitting the exclusion criteria were selected if willing to participate in the study. All the participants were from an iodine-sufficient area.

Exclusion criteria were previous history of thyroid disease, thyroid nodules, use of levothyroxine, positive antithyroid antibodies, acute illnesses, history of illnesses associated with a pro-inflammatory state (i.e. inflammatory and/or auto-immune conditions) and diseases associated with NTIS such as renal impairment (creatinine clearance <60 ml/min/m^2), hepatic failure (abnormal coagulation tests or low albumin levels), heart failure (stages 3 and 4 according to NYHA classification), chronic obstructive pulmonary disease, cancer and history of acute myocardial infarction and stroke <6 months previously. Patients using medications known to alter thyroid hormone levels or those who were exposed to iodine containing contrasts less than a year previously were also excluded. Patients were consecutively selected during routine clinic appointments, based on the above-mentioned criteria from April to October 2012. Owing to the tertiary referral nature of our institution, 15 % of potential participants with T2DM were selected due to the presence of exclusion criteria in the majority of patients under care in the University Hospital. Only one patient eligible to enter the study refused consent, for personal reasons.

Clinical data were recorded by chart review and consisted of: age, gender, time since diabetes diagnosis, therapy (oral drugs, insulin alone or combination), waist/hip ratio (WHR), BMI, presence of hypertension (defined by treatment of this condition or a previous record of blood pressure >130/80 mmHg), smoking habit, cardiovascular disease and microvascular complications of diabetes (nephropathy, neuropathy, retinopathy).

Cardiovascular events were defined as a history of unstable angina, previous myocardial infarction or myocardial revascularization, stroke, history of reported lower limb claudication, lower extremity amputation or documented ischaemia (ankle-brachial index <0.9 in one or both legs).

Laboratory measurements consisted of fasting glycaemia, HbA1c, serum TSH, total (T) and free (F) T4 and T3, reverse T3 (rT3), TT3/rT3 ratio and SAA. A morning blood sample was collected from an antecubital vein, immediately processed and the serum was stored at −80 °C for subsequent analysis.

TSH and FT4 were measured by electrochemiluminescence assay (Roche Hiachi-Elecsys Cobas, USA—reference values (RV): TSH: 0.45–4.5 mIU/l; FT4: 0.9–1.8 ng/dl). TT4 (RV: 4.5–12.5 μg/dl), TT3 (RV: 86–187 ng/dl), FT3 (RV: 1.4–4.4 pg/ml) and rT3 (RV: 0.09–0.350 ng/ml) were measured by radioimmunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, USA). All intra-and inter-assay coefficient of variations were <9 %.

SAA was measured by ELISA (Anogen, Ontario, Canada—RV: 1–5 μg/ml; sensitivity 1.1 ng/ml; coefficient of variation <10 %). Fasting glycaemia was analysed using the hexokinase method (RV: 70–100 mg/dl) and HbA1c by high-performance liquid chromatography (RV: 4–5.7 %).

Conversion from mass to SI units: TT4: μg/dl × 12.87 = nmol/l; FT4: ng/dl × 12.87 = pmol/l; TT3: ng/dl × 0.01536 = nmol/l; FT3: pg/ml × 1.536 = pmol/l; rT3: ng/ml × 1.54 = nmol/l; glucose: mg/dl ÷ 18 = mmol/l.

The study was approved by the University Ethics in Research Committee and conducted in according to the Declaration of Helsinki. All the participants were explained the nature of the study and written informed consent was obtained from all subjects.

Statistical methods

Descriptive analysis of clinical and laboratorial parameters was done by measurements of position and dispersion for continuous variables and by frequency tables for categorical variables.

Comparison of serum thyroid hormone concentrations and the inflammatory marker between two groups was performed with the Mann–Whitney test and comparison of the same variables between the 3 therapy type groups was done with the Kruskal–Wallis test.

Association between two clinical categorical variables was assessed with the Chi Square test or Fischer's exact test, as appropriate. Associations among thyroid hormone concentrations, inflammatory markers and clinical parameters were examined with Spearman's correlation coefficient.

Factors associated to cardiovascular disease in patients with T2DM were assessed by logistic regression analysis. The multivariate model included all variables that showed $p < 0.1$ in univariate analysis.

All analyses were done with SPSS Statistical Package (IBM Corp., USA) version 20.0. Significance was set at 5 % ($p < 0.05$) for all tests.

Table 1 Participants' demographical and clinical characteristics

	Patients with diabetes	Control group	*p*
Age (years)	60 (53.0–63.3)	54.5 (50–61)	0.11
Sex (men/women)	26/44 (37.1/62.9)	26/44 (37.1/62.9)	1.0
Weight (kg)	76.5 (67–92)	73.5 (66.8–86.3)	0.29
Height (m)	1.62 (1.54–1.68)	1.61 (1.55–1.67)	0.97
BMI (kg/m^2)	30 (25.9–34.6)	28.6 (25.7–33.3)	0.31
Waist (cm)	102.5 (89–112)	95 (86–106.3)	0.017
Hip (cm)	101 (94.5–107)	104 (99–114)	0.002
Waist/hip ratio	0.99 (0.93–1.06)	0.89 (0.84–0.95)	<0.001
Smoking	7 (10)	2 (2.9)	0.17
Hypertension	53 (75.7)	11 (15.7)	<0.001
Statin use	48 (68.6)	6 (8.6)	<0.001
Cardiovascular disease	18 (25.7)	4 (5.7)	0.002
Time since event (years)	3.5 (1.2–5.7)	2.7 (1.3–4.1)	0.678
Ischaemic heart disease	11 (61)	3 (75)	0.02
Stroke	5 (28)	1 (25)	0.07
Lower limb ischaemia	2 (11)	0	0.09

Data are shown as median (interquartile range) or number (%)

BMI body mass index

Results

Participants' characteristics

Clinical and demographical characteristics as well as information on cardiovascular disease of all subjects and their respective comparisons are summarized in Table 1.

In patients with T2DM, median (interquartile range) time since diabetes diagnosis was 12 years (5.8–18 years), median HbA1c was 8.35 % (7.3–10.0 %) and median fasting glycaemia was 146 mg/dl (109–193 mg/dl). Median total cholesterol, LDL- and HDL-cholesterol and triglycerides were 185 mg/dl (150–215 mg/dl), 103 mg/dl (81–127.3 mg/dl), 40.5 mg/dl (35–50.3 mg/dl) and 142.5 (93.2–205.8 mg/dl), respectively. Sixty-eight percent of patients with T2DM were using statins at the time of data collection. As for therapy, 30.4 % of patients were on oral drugs only, 14.3 % on insulin alone and 54.3 % on combination therapy. Regarding microvascular complications, 60 % of patients presented diabetic retinopathy, 45.7 % had neuropathy and 52.9 % diabetic nephropathy. One quarter of patients ($n = 18$) had a history of cardiovascular disease.

Comparison of thyroid hormone levels and inflammatory markers between patients with T2DM and the control group

Patients with T2DM had lower levels of TT4 ($p = 0.012$), TT3 ($p < 0.001$), FT3 ($p < 0.001$) and TT3/rT3 ($p = 0.02$) and higher levels of FT4 ($p < 0.001$). The difference in SAA levels approached but did not reach statistical significance ($p = 0.051$). There were no differences in levels of other hormonal variables between patients with T2DM and the control group. Of note, TSH was similar in both ($p = 0.625$) even in the face of lower T3 levels in patients with T2DM. Hormonal and SAA levels in both groups and their respective comparison are shown in Table 2.

Regarding associations between inflammation and thyroid hormone levels in patients with T2DM, we found significant associations between SAA and WHR ($r = 0.24$; $p = 0.048$), rT3 ($r = 0.45$; $p < 0.001$) and TT3/rT3 ($r = -0.38$; $p = 0.001$).

Comparative analysis in the subgroups of patients with type 2 diabetes with and without previous cardiovascular events

Patients with a history of CVEs ($n = 18$) were older (62.5 vs. 58 years; $p = 0.029$), showed higher WHR (1.05 vs. 0.98; $p = 0.028$) and had higher SAA levels (27.42 vs. 12.85 μg/ml; $p = 0.002$). Moreover, these patients presented higher rT3 levels (0.270 vs. 0.200 ng/ml; $p = 0.006$) and lower TT3/rT3 (262.98 vs. 393.11; $p = 0.002$). Differences in HbA1c and time of diabetes diagnosis between both subgroups approached but did not reach statistical significance (9.45 vs. 8.10 %; $p = 0.081$ and 15.5 vs. 12 years; $p = 0.078$, respectively). Comparison of all clinical and laboratorial variables between subgroups with T2DM is summarized in Table 3.

Patients with T2DM and CVE showed higher SAA (27.42 vs. 10.73 mg/dl; $p = 0.001$), rT3 (0.270 vs. 0.212 ng/ml; $p = 0.014$) and FT4 levels (1.32 vs. 1.08 ng/dl; $p = 0.001$) along with lower TT3 (72.24 vs. 89.97 ng/ml; $p = 0.002$), FT3 (1.91 vs. 2.41 pg/ml; $p = 0.033$) and TT3/rT3 (262.98 vs. 447.92; $p = 0.001$) when compared to the control group, Fig. 1.

Table 2 Hormonal and inflammatory variables in patients with type 2 diabetes and the control group

	Patients with diabetes	Control group	*p*
TSH (mIU/l)	2.25 (1.53–3.44)	1.98 (1.35–3.32)	0.63
Total T4 (μg/dl)	6.45 (5.37–7.53)	7.15 (6.24–7.99)	0.012
Free T4 (ng/dl)	1.26 (1.13–1.44)	1.08 (0.98–1.29)	<0.001
Total T3 (ng/ml)	77.28 (68.55–91.76)	89.97 (83.29–104.47)	<0.001
Free T3 (pg/ml)	1.95 (1.59–2.34)	2.41 (1.93–2.76)	<0.001
Reverse T3 (ng/ml)	0.230 (0.155–0.291)	0.212 (0.145–0.315)	0.54
Total T3/reverse T3	360.2 (256.7–461.6)	447.9 (273.3–681.4)	0.02
Serum amyloid A (μg/ml)	14.68 (5.92–26.04)	10.72 (3.67–19.11)	0.051

Data are shown as median (interquartile range)

Table 3 Clinical and laboratorial characteristics of patients with type 2 diabetes with and without previous cardiovascular events

	Patients with CVE	Patients without CVE	*p*
Age (years)	62.5 (57.8–64.5)	58 (48.5–63)	0.029
Sex (men/women)	6/12 (33/67)	14/38 (27/73)	0.004
Weight (kg)	89.8 (76–96.7)	74.1 (65.5–87)	0.012
Height (m)	1.65 (1.57–1.74)	1.59 (1.53–1.67)	0.027
BMI (kg/m^2)	31.1 (27.9–34.7)	28.7 (25.3–34.3)	0.271
Waist (cm)	107.5 (98.5–113.5)	99 (88.3–110.5)	0.117
Hip (cm)	101 (96.5–107.3)	100.5 (94–106.8)	0.711
Waist/hip ratio	1.05 (0.99–1.09)	0.98 (0.92–1.04)	0.028
HbA1c (%)	9.45 (8.1–10.52)	8.1 (7.3–9.17)	0.081
Fasting glycaemia (mg/dl)	179 (114–226)	144 (107–182)	0.181
Nephropathy	12 (67)	25 (48)	0.273
Retinopathy	14 (77.8)	28 (53.8)	0.097
Neuropathy	11 (61.1)	21 (40.4)	0.172
Smoking	3 (16.6)	4 (7.7)	0.363
Hypertension	18 (100)	35 (67.3)	0.004
Statin use	14 (77.8)	34 (65.4)	0.391
Total cholesterol (mg/dl)	158 (145.5–214.8)	187.5 (152.5–215)	0.39
LDL cholesterol (mg/dl)	90.5 (77.8–126)	109 (82–127.8)	0.33
HDL cholesterol (mg/dl)	37 (33.8–44.5)	41 (35.2–52.5)	0.168
Triglycerides (mg/dl)	121 (86–223.5)	148 (99.8–198)	0.643
TSH (mIU/L)	1.9 (1.4–3.61)	2.29 (1.49–3.38)	0.667
Total T4 (μg/dl)	6.99 (5.37–7.88)	6.41 (5.28–7.34)	0.436
Free T4 (ng/dl)	1.33 (1.16–1.52)	1.26 (1.13–1.4)	0.172
Total T3 (ng/ml)	72.24 (62.9–90.83)	79 (69.2–92.58)	0.382
Free T3 (pg/ml)	1.91 (1.59–2.36)	1.98 (1.56–2.36)	0.737
Reverse T3 (ng/ml)	0.270 (0.231–0.379)	0.200 (0.147–0.279)	0.006
Total T3/reverse T3	262.98 (219.80–390.19)	393.10 (298–528.15)	0.002
Serum amyloid A (μg/ml)	27.48 (10.6–34.88)	12.85 (5.2–24.5)	0.002

Data are shown as median (interquartile range) or number (%)

BMI body mass index

When comparing patients with T2DM and no CVE history, we found significant lower serum levels of TT4 (6.41 vs. 7.15 μg/dl; $p = 0.007$), TT3 (78.99 vs. 89.97 ng/ml; $p < 0.001$) and FT3 (1.98 vs. 2.41 pg/ml; $p < 0.001$), and higher levels of FT4 (1.25 vs. 1.08 ng/dl; $p < 0.001$). In this comparison, there were no differences in SAA levels ($p = 0.410$), rT3 ($p = 0.649$) or TT3/rT3 ratio ($p = 0.253$), Fig. 2.

Regression analysis for cardiovascular disease in patients with type 2 diabetes

Univariate regression analysis showed that the predictors for CVEs with $p < 0.1$ were WHR (OR = 1.801, 95 % CI 0.988–3.282; $p = 0.055$), age (OR = 1.115, 95 % CI 1.011–1.229; $p = 0.029$), male sex (OR = 5.429, 95 % CI 1.709–17.244; $p = 0.004$), diabetic retinopathy (OR = 3.0, 95 %

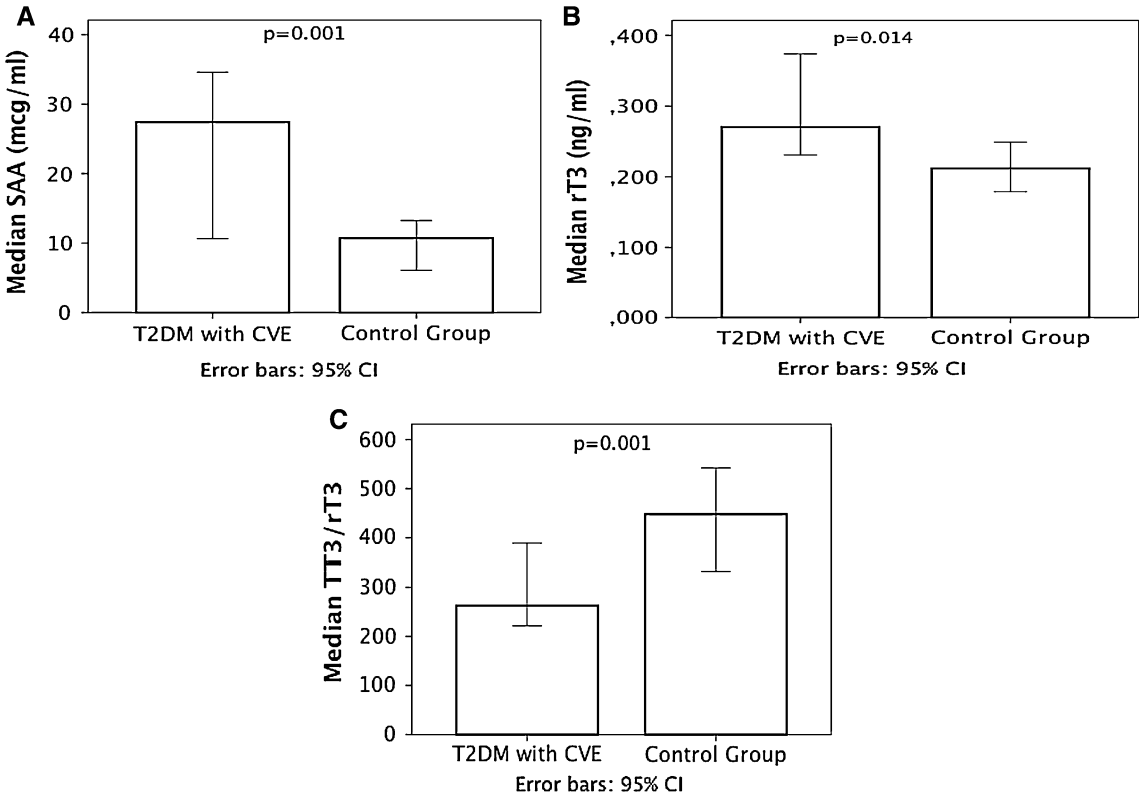

Fig. 1 Median serum levels of SAA (**a**), rT3 (**b**) and TT3/rT3 (**c**) between patients with type 2 diabetes and cardiovascular disease (T2DM with CVE) and the control group. *Error bars* represent 95 % confidence intervals on the medians

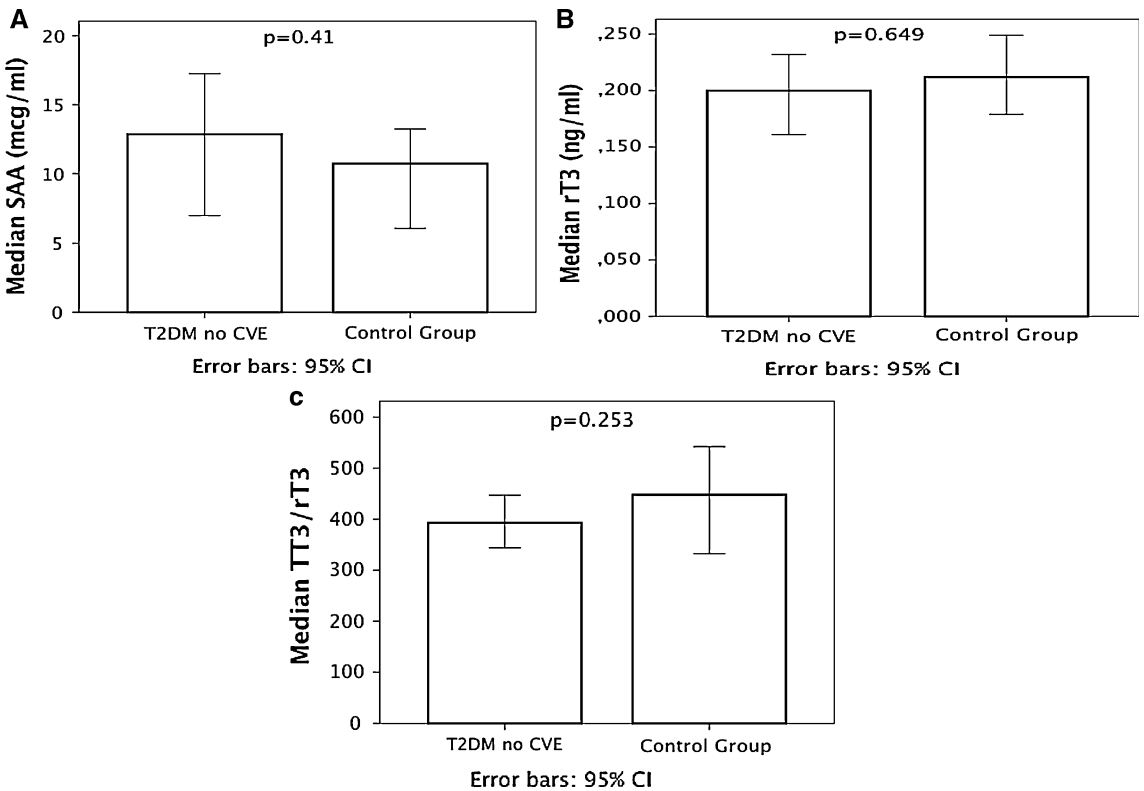

Fig. 2 Median serum levels of SAA (**a**), rT3 (**b**) and TT3/rT3 (**c**) between patients with type 2 diabetes and no cardiovascular disease history (T2DM no CVE) and the control group. *Error bars* represent 95 % confidence intervals on the medians

Table 4 Multiple logistic regression analysis for the cardiovascular disease in patients with type 2 diabetes

Variable	OR	95 % CI	*p*
Male sex	4.391	1.081–17.829	0.038
Age	1.159	1.011–1.329	0.034
Higher waist/hip ratio	1.034	0.414–2.583	0.942
Retinopathy	0.367	0.066–2.036	0.252
Higher TT3/rT3	0.993	0.987–0.999	0.032
Higher serum amyloid A	1.046	0.993–1.103	0.089

OR odds ratio, *95 % CI* 95 % confidence intervals for the odds ratio

CI 0.870–10.343; $p = 0.082$), higher TT3/rT3 (OR = 0.994, 95 % CI 0.989–0.998; $p = 0.009$) and higher SAA (OR = 1.053, 95 % CI 1.010–1.097; $p = 0.016$).

Multivariate regression analysis showed that the factors independently associated with CVEs were male sex (OR = 4.391, 95 % CI 1.081 = 17.829; $p = 0.038$), older age (OR = 1.159, 95 % CI 1.011–1.239; $p = 0.034$) and higher TT3/rT3 (OR = 0.993, 95 % CI 0.987–0.999; $p = 0.032$), Table 4.

Discussion

In T2DM, a more pronounced inflammatory activity has been related to an increased risk for CVEs [3, 11, 12]. As inflammation is related to both thyroid hormone abnormalities in NTIS and CVEs in T2DM, we hypothesized that there would be an association between thyroid hormone abnormalities typical of NTIS and CVE in patients with T2DM. In this study, patients with previous CVEs had higher rT3 levels and a lower TT3/rT3 ratio, findings characteristic of NTIS [13].

Importantly, differences in TT3/rT3 appeared only when patients were subdivided by the presence of CVE. Comparison between patients with T2DM and no CVE with the control group showed differences only in TT4, TT3 and FT3, with no differences in rT3, TT3/rT3 or SAA. On the other hand, patients with CVE had higher levels of SAA and lower TT3/rT3 than the control group and than patients with T2DM but no CVE, showing that the differences in rT3, TT3/rT3 and SAA were mediated by the presence of CVE. Furthermore, our regression models showed that the ratio of TT3/rT3, a sensitive indicator of NTIS, was associated with CVE, even after adjustments for other possible confounders derived from univariate models.

In addition, this study showed that patients with T2DM had lower levels of TT4, TT3 and FT3 and higher levels of FT4 than subjects without diabetes paired by age, sex and BMI, concurrently with normal serum TSH levels. These findings are consistent with NTIS in these patients. The low TT3/rT3 ratio confirms our diagnosis. The higher levels of FT4 and low FT3 could be a consequence of changes in deiodinase activity, leading to impaired conversion of thyroxine to the biologically active T3. Decreased activity of type 2 deiodinase has been associated to diabetes [14], and is believed to be of major importance in the pathophysiology of NTIS in critically ill patients and in those with chronic diseases in an outpatient setting [15, 16]. Thyroid hormone abnormalities that resemble NTIS have been described in patients with type 1 and type 2 diabetes, and were related to glycaemic control [17, 18].

We believe the low TT4 levels in face of higher FT4 could be due to the old age and high BMI of the participants. Age and weight gain, and especially the central distribution of fat, have been associated with higher insulin levels, which could lead to lower levels of thyroid hormone binding globulin [19]. Thus, the association of decreased synthesis of carrier proteins allied to impaired conversion of T4 to T3 would hypothetically result in a pattern of higher FT4 and low TT4 and T3.

In patients with NTIS, the pro-inflammatory process has a central role in the pathophysiology of thyroid hormone abnormalities [20, 21]. It is partially responsible for changes in T3 levels and for the hypothalamic-pituitary component of NTIS, which can be recognized by the inappropriately normal TSH in face of low T3 levels [22]. T2DM has been documented as an inflammatory disease in the last decades, associated to increased visceral adipose tissue and insulin resistance [11, 23].

In our study, we were able to identify a significant positive correlation between SAA and rT3 and inverse for SAA and TT3/rT3. SAA is an acute-phase inflammatory protein synthesized in the liver in response to interleukin-6 and tumour necrosis factor-α [6]. SAA was also positively correlated to WHR. Higher WHR is known to be a good clinical surrogate for visceral adiposity and is positively associated with insulin resistance [24]. It has been shown that the main source of pro-inflammatory mediators in patients with T2DM is the visceral adipose tissue [25].

We found no correlation between HbA1c and TT3 or FT3 levels and we thus believe that inflammatory process from increased visceral adipose tissue is a more significant contributor to thyroid hormone imbalances in T2DM than glycaemic control. Previous studies assessing thyroid hormone levels in diabetes have only included patients in poor glycaemic control or recently diagnosed. The reason why we did not find such association between HbA1c and

thyroid hormone levels is perhaps related to the fact that our patients had a better (although not ideal) mean HbA1c. This could also be an explanation for the absence of differences in rT3 levels in the comparison of patients with T2DM and the control group, which could be demonstrated only in those with a history of previous CVE, and, consequently, more pronounced inflammatory activity.

However, our study has some limitations. The case–control design does not allow conclusions on causality. Although we were able to identify differences in thyroid hormone levels between subjects with and without T2DM, larger, prospective researches are needed to confirm our findings. Nevertheless, we found significant correlations between the inflammatory variable and thyroid hormone levels associated with CVE. We thus believe these findings, although preliminary, warrant further investigation on larger studies that are capable of more powerful statistical analysis. We aimed at a first step analysis of the association between thyroid hormone imbalances in T2DM and CVE, because this relationship had not been demonstrated so far.

In conclusion, we have confirmed previous works showing that patients with T2DM have lower serum levels of thyroid hormone and normal TSH levels, which is evidence for the presence of NTIS in this condition. Moreover, we were able to show that these differences in thyroid hormone levels are associated to inflammatory activity and related to a history of CVE in these patients. We believe these results should encourage further research to confirm our findings in larger, prospective studies and to assess the clinical utility of thyroid hormone measurements in T2DM for predicting CVE, especially when compared to available laboratory markers.

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Conflict of interest The authors have nothing to declare.

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