CLINICAL STUDY

Increased progression of carotid intima media thickness in thyroid peroxidase antibodies-positive rheumatoid arthritis patients

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Abstract

Objective: Autoimmune diseases such as rheumatoid arthritis (RA) and hypothyroidism tend to cluster, and this coexistence amplifies the elevated cardiovascular risk in RA. Whether thyroid peroxidase antibodies (TPOabs) are associated with increased cardiovascular disease (CVD) risk has not been studied extensively. Therefore, this study determined firstly the prevalence of TPOabs in RA and secondly whether TPOabs were associated with CVD. Moreover, this study explored whether TPOabs were related to RA characteristics.

Design and methods: Data from the CARRÉ Study, an ongoing study investigating CVDs and its risk factors in RA ($n=322$), was used to ascertain the prevalence of TPOabs in RA patients. In addition, cardiovascular and RA disease characteristics were compared between TPOabs-positive and -negative patients at baseline and at a second visit after 3 years.

Results: TPOabs were present in 47/322 (15%) RA patients and TSH levels were higher in TPOabs-positive patients (1.40 mU/l) compared with TPOabs-negative patients (1.26 mU/l, $P=0.048$). At baseline and after 3 years no association was observed between TPOabs and (risk factors for) CVD. Regression analyses revealed a significantly larger progression of carotid intima media thickness (cIMT; $\beta=0.13$ mm) in TPOabs-positive compared with TPOabs-negative patients independent of risk factors for cIMT progression. RA disease activity scores (DAS28) were higher in TPOabs-positive compared with TPOabs-negative patients (4.4 vs 3.8 $P=0.018$).

Conclusions: TPOabs were associated with increased cIMT progression. Moreover, an association between TPOabs and DAS28 was observed. Hence, TPOabs seems to have a role in the amplified cardiovascular risk in RA patients.

European Journal of Endocrinology 169 751–757

Introduction

Autoimmune thyroiditis is the most prevalent autoimmune disorder and is characterized by elevated levels of anti-thyroid antibodies in ~70% of the patients (1). Traditionally, autoimmune diseases such as rheumatoid arthritis (RA) and autoimmune thyroiditis were considered separate disorders, but there is emerging evidence that autoimmune diseases share similarities in genetic and immunological origin, and environmental risk factors (2, 3), suggesting that people with one autoimmune disease are at higher risk for another autoimmune disease (4). Coexistence of autoimmune disorders was recently demonstrated for hypothyroidism and RA and, interestingly, this coexistence amplifies the cardiovascular risk (5, 6, 7, 8, 9).

The natural course from preclinical to clinical autoimmune diseases such as hypothyroidism and RA is a slow and multifactorial process (10). Therefore, the evolution from pre- or subclinical disease into clinically overt disease takes years. In RA, the presence of anti-cyclic citrullinated protein antibodies (ACPA) is considered an important predictive factor, as ACPA have already been detected a decade before the onset of RA (11). Moreover, ACPA is an important prognostic factor as ACPA is associated with erosive disease and higher mortality rates (12, 13). Hence, the autoantibody ACPA has clinical value as a predictor for RA and is also an important prognostic factor in RA patients.

Thyroid peroxidase antibodies (TPOabs) have been implicated as important predictive parameters for future autoimmune hypothyroidism (14, 15, 16), but on the

other hand the presence of TPOabs could not be related to prognostic and clinical factors in euthyroid and subclinical hypothyroid patients (17).

Whether the presence of TPOabs (irrespective of thyroid status) is associated with a certain phenotype of RA has not been studied extensively in RA (18). Therefore, the aim of this study was firstly to determine the prevalence of TPOabs in RA and second to determine whether their presence was associated with cardiovascular disease (CVD) or specific parameters of RA.

Subjects and methods

Study population

For this study, we used data from the CARRÉ Study, which is a prospective cohort of patients with RA, in whom cardiovascular events and concurrent risk factors were investigated (19). Briefly, in the CARRÉ investigation a total of 353 patients aged 50–75 years who fulfilled the American College of Rheumatology criteria of 1987 for RA were enrolled (20). Patients were enrolled between 2001 and 2002, and were seen for a second visit between 2004 and 2005 to assess the incidence of risk factors for CVD. This study included RA patients in whom TPOabs could be assessed from baseline samples stored at -80°C ($n=322$). At follow-up of the second visit, data of 256 RA patients were used for the analysis. All patients provided written informed consent and the Jan van Breemen Research Institute/Reade received approval by the local medical ethics committee.

Rheumatoid parameters

All patients with RA attended the outpatient clinic at the Jan van Breemen Research Institute/Reade. These patients were seen by a research physician, and completed a questionnaire recording demographic data, medical, and medication history. A physical examination was performed, including the 28 joint disease activity index score (DAS28) (21). Briefly, DAS28 is a validated instrument to assess the disease activity in RA patients and is a composite of four elements: i) erythrocyte sedimentation rate (ESR); ii) patient's general health or global disease activity on a visual analog scale (VAS) of 100 mm, lower VAS representing better general health; iii) number of swollen joints; and iv) number of painful joints. Furthermore, blood samples were taken to measure the inflammatory and disease-specific parameters: C-reactive protein (CRP) and serological markers (IgM-rheumatoid factor (IgM-RF) and anti-cyclic citrullinated protein antibodies (ACPA)) as previously described (19).

Cardiovascular parameters

Blood pressure, BMI, and waist-to-hip ratio were assessed as previously described (19). During the visit at the outpatient clinic patients' smoking status was classified as never, current, or former smoker by the research physician. Fasting blood samples were taken to assess lipids and glucose levels. The atherogenic index is defined as the total cholesterol:HDL-C ratio. Diabetes was defined as known diabetes mellitus or patients using at least one glucose-lowering agent.

Metabolic syndrome was defined according to the original National Cholesterol Education Program – Third Adult Treatment Panel (NCEPATP III) definition (22). According to this definition patients fulfil the criteria for metabolic syndrome when three or more of the following factors are present:

1. Abdominal obesity: in females waist circumference >88 cm and in males waist circumference >102 cm;
2. Raised blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive medication;
3. Raised TG: ≥ 1.7 mmol/l (150 mg/dl) or use of lipid-lowering drugs;
4. Reduced HDL-C: in females <1.29 mmol/l (50 mg/dl) and in males <1.03 mmol/l (40 mg/dl) or use of lipid-lowering drugs;
5. Raised fasting plasma glucose: ≥ 6.1 mmol/l (110 mg/dl).

CVDs were defined as a verified history of coronary, cerebral, or peripheral arterial diseases. Coronary artery disease included a myocardial infarction, a coronary artery bypass graft procedure, or percutaneous transluminal coronary angioplasty. Cerebral arterial disease was defined as a cerebral vascular accident, a transient ischemic attack, or carotid endarterectomy. Peripheral arterial disease included a peripheral arterial bypass, an ankle/brachial blood pressure index of <0.90 , or leg amputation as a consequence of peripheral arterial disease.

Ultrasonography of the common carotid artery

In this study, the ultrasound analysis of the right common carotid artery was performed by two physicians, who were unaware of the participants' clinical or laboratory characteristics, as previously described (23). Each observer performed a reproducibility test with other experienced observers from the institute before starting to perform measurements. Inter-observer and intra-observer variability were good (variations $<10\%$). Measurements were performed with a 7.5-MHz linear probe connected to a computer equipped with vessel wall movement-detection software and an acquisition system (Wall track system, Pie Medical) that enables measurement of the carotid intima media thickness (cIMT). After localization of the common carotid artery, cross-sectional

measurements were performed 10 mm proximal to the carotid bulb. Sites with mural atherosclerotic plaques were avoided because of difficulty in identifying carotid arterial variables in these regions. The distance between the lumen–intima interface and the leading edge of the media–adventitia interface of the far wall corresponds with cIMT. Measurements of IMT were triggered by echocardiogram to the R-peak of the cardiac cycle. The cIMT was performed in a subset of 105 patients at baseline and in 78 patients after 3 years.

Thyroid parameters

Thyroid status was assessed at baseline samples. Clinical hypothyroidism was defined by a documented medical history of clinical hypothyroidism or the presence of an increased serum TSH (>4.0 mU/l) in the presence of a decreased (<11 pmol/l) serum-free thyroxine (fT₄), as described previously (5). Subclinical hypothyroidism was defined by an increased serum TSH in the presence of a normal (11–25 pmol/l) serum fT₄ and subclinical hypothyroid patients were not treated with levothyroxine (5). TPOabs were determined by immunoassay, using an Immulite 1000 (Siemens, Los Angeles, CA, USA) according to the manufacturer's recommendations. According to these recommendations, the concentration of TPOabs is expressed in IU/ml and is considered elevated when levels are higher than 35 IU/ml.

Statistical analyses

TPOabs prevalence rates were calculated in the CARRE population. Characteristics were compared using Students' *t*-test, Mann–Whitney *U* test, or χ^2 test when appropriate between TPOabs-negative (TPOabs <35 IU/ml) and -positive RA patients. Data were presented as mean ($\pm$ s.d. (=s.d.)) in case of a normally distributed parameter or as median with interquartile range in case of a nonnormally distributed parameter, or as percentage of the total population. Linear regression analyses were carried out with difference in cIMT as outcome measure and TPOabs positivity as independent variable. The model was performed in three steps:

1. step 1 as crude analysis
2. step 2 as step 1 and adjusted for gender, age, and parameters, statistically (or borderline) different variables between TPOabs-positive and -negative patients, i.e. DAS28 at baseline, methotrexate (MTX) use, and IgM-RF positivity (Model 1)
3. step 3 as step 2 and adjusted for (cardiovascular) risk factors for progression in cIMT, i.e. CVD prevalence at baseline, statin use, smoking at baseline, diabetes mellitus at baseline, atherogenic index at baseline, prednisolone use at baseline, hypertension according to NCEPATIII criteria at baseline, and TSH levels at baseline (Model 2).

Analyses were carried out using SPSS software, version 15.0 (SPSS), and *P* values <0.05 were considered statistically significant.

Results

Thyroid status in TPOabs-positive and -negative RA patients

In 322 patients TPOabs status could be assessed: 47 (14.7%) of these patients were TPOabs-positive (see Table 1). TPOabs-positive patients had significantly higher TSH levels than TPOabs-negative patients (median TSH 1.40 and 1.26 mU/l respectively, $P=0.048$). Moreover, TPOabs levels were significantly associated with TSH ($\beta=0.01$, $P<0.001$).

RA characteristics in TPOabs-positive and -negative patients

RA characteristics are shown in Table 1. The TPOabs-positive group showed a significantly higher percentage of females than the TPOabs-negative group (89 vs 62%; $P<0.001$). Mean TPOabs levels were significantly lower in MTX users compared with non-MTX users. A higher percentage of TPOabs-positive was IgM-RF positive, although this did not reach statistical significance. Disease activity scores (DAS28) were higher in TPOabs-positive patients compared with TPOabs-negative patients (4.4 ± 1.3 vs 3.8 ± 1.4 , $P=0.018$). A significant lower percentage of the TPOabs-positive compared with TPOabs-negative RA patients was found in a low disease activity state (DAS28 <3.2), respectively, 16 and 32% (OR: 0.36, 95% CI 0.14–0.88, $P=0.032$). Adjustment for gender, MTX use, and IgM-RF slightly influenced this association (OR: 0.40, 95% CI 0.16–1.0, $P=0.054$).

Cardiovascular risk in TPOabs-positive and -negative patients

As shown in Table 2, no significant differences were found between TPO-positive patients and TPO-negative patients with regard to prior and baseline CVD risk factors. At baseline, cIMT was assessed in 105 randomly selected RA patients; 90 RA patients were TPOabs-negative and 15 RA patients were TPOabs-positive.

CVD risk factors in TPOabs-positive and -negative patients at follow-up

At follow-up, 38 of the 256 (14.8%) RA patients were TPOabs patients. At the second visit, the mean DAS28 was $3.61 (\pm 1.1)$ in TPOabs-positive RA patients and $3.14 (\pm 1.1)$ in TPOabs-negative RA patients ($P=0.020$). Cardiovascular risk factors and CVD are

Table 1 Characteristics in TPOabs-positive and -negative RA patients.

	TPOabs-positive <i>n</i> =47	TPOabs-negative <i>n</i> =275	<i>P</i> value
Demographics			
Age (years)	62.6 (±7.0)	63.0 (±7.7)	0.69
Female (%)	89	62	<0.001
Thyroid status			
TSH (mU/l)	1.40 (0.93–2.81)	1.26 (0.88–1.74)	0.048
Levothyroxine use (%)	8.5	2.1	0.041
Manifested hypothyroid (%)	6.5	3	0.38
Subclinical hypothyroid (%)	11	1	0.002
RA-related baseline characteristics			
DAS28	4.4 (±1.3)	3.8 (±1.4)	0.018
Low disease activity (DAS28 <3.2) (%)	16	32	0.027
ESR (mm/h)	21 (10–40)	17 (9–30)	0.077
CRP (mg/l)	7 (3–30)	7 (3–18)	0.70
RA duration (years)	6 (4–10)	7 (4–10)	0.68
Erosive (%)	77	82	0.41
Rheumatoid factor IgM (IU/ml)	50 (9–150)	31 (10–142)	0.40
Rheumatoid factor IgM positive (%)	81	69	0.091
ACPA (AU/l)	30 (9–450)	50 (10–412)	0.40
ACPA positive (%)	47	51	0.37
Previous DMARDs (<i>n</i>)	2 (1–3)	2 (2–3)	0.15
DMARDs current (<i>n</i>)	1 (1–1)	1 (1–2)	0.14
MTX current (%)	47	60	0.094
Prednisolone current (%)	11	19	0.23

DAS28, disease activity score 28 joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ACPA, anti-cyclic citrullinated protein antibody; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; SSZ, sulphasalazine; HCQ, hydroxychloroquine.

shown in Table 3. More TPOabs-positive patients were using lipid-lowering drugs, as 28% of the TPOabs-positive RA patients compared with 13% of the TPOabs-negative RA patients were using statins ($P=0.043$). In TPOabs-positive patients, cIMT was significantly higher compared with TPOabs-negative RA patients, 0.96 and 0.83 mm respectively. Linear regression analysis revealed higher cIMT progression in levothyroxine naïve TPOabs-positive patients compared with TPOabs-negative patients after (stepwise) adjustment

for gender, age, disease activity at baseline, MTX use, and IgM-RF positivity ($\beta=0.13$, 95% CI 0.004–0.264, $P=0.044$, see Table 4). Additional stepwise adjustment for CVD prevalence at baseline, statin use, smoking at baseline, diabetes mellitus at baseline, atherogenic index at baseline, prednisolone use at baseline, hypertension according to NCEP ATIII criteria at baseline, and TSH levels at baseline did not influence this association ($\beta=0.13$, 95% CI 0.004–0.257, $P=0.043$).

Table 2 Baseline cardiovascular disease risk factors.

	TPOabs-positive <i>n</i> =47	TPOabs-negative <i>n</i> =275	<i>P</i> value
Cardiovascular-related factors			
Prior cardiovascular disease (%)	22	17	0.44
cIMT ^a (mm)	0.82 (±0.15)	0.81 (±0.12)	0.72
Metabolic syndrome NCEP ATIII (%)	27	22	0.48
Smoking status			0.96
Current smoker (%)	29	30	
Never smoker (%)	24	22	
Former smoker (%)	47	48	
BMI (kg/m ²)	26.7 (±5)	26.6 (±5)	0.93
Waist:hip ratio	0.88 (±0.08)	0.89 (±0.08)	0.38
Hypertension NCEP ATIII (%)	53	50	0.75
Atherogenic index	4.5 (±1.6)	4.4 (±1.5)	0.81
Statin use (%)	9	11	0.80
Glucose (mmol/l)	5.1 (4.8–5.8)	5.1 (4.8–5.5)	0.89
Hyperglycemic (>6.1 mmol/l) (%)	16	11	0.37
Diabetes mellitus (%)	0	5	0.24

cIMT, carotid intima-media thickness, ^aperformed in a subset of 105 RA patients; NCEP ATIII, National Cholesterol Education Program – Third Adult Treatment Panel.

Table 3 Cardiovascular risk factors at follow-up in TPOabs-positive and -negative patients.

	TPOabs-positive n=38	TPOabs-negative n=218	P value
Cardiovascular-related factors			
Incident cardiovascular disease (%)	8	7	1.00
cIMT ^a at follow-up (mm)	0.96 (±0.24)	0.83 (±0.14)	0.015
Hypertension NCEP ATIII at follow-up (%)	74	81	0.38
Systolic blood pressure at follow-up (mmHg)	139 (±17)	140 (±22)	0.62
Diastolic blood pressure at follow-up (mmHg)	80 (±8)	81 (±9)	0.67
Total cholesterol at follow-up (mmol)	5.8 (±1.1)	5.5 (±1.1)	0.18
HDL-C at follow-up (mmol)	1.6 (±0.5)	1.6 (±0.6)	0.90
LDL-C at follow-up (mmol)	3.5 (±1.1)	3.3 (±1.0)	0.26
Triglycerides at follow-up (mmol)	1.2 (1.0–1.5)	1.3 (1.0–1.8)	0.43
Atherogenic index at follow-up	4.0 (±1.9)	3.7 (±1.4)	0.44
Statin use at follow-up (%)	28	13	0.043
Hypertriglyceridemia NCEP ATIII at follow-up (%)	20	26	0.53
Low-HDL NCEP ATIII at follow-up (%)	35	28	0.44
Diabetes mellitus at follow-up (%)	0	6	0.092
BMI (kg/m ²)	27.5 (±5.1)	26.8 (±5.0)	0.49

cIMT, carotid intima-media thickness, ^aperformed in a subset of 78 RA patients; NCEP ATIII, National Cholesterol Education Program – Third Adult Treatment Panel.

Discussion

In this study, we found TPOabs to be present in 15% of the RA patients. Moreover, this study observed a clear association between the presence of TPOabs and thyroid status, as ~18% of the TPOabs-positive patients were hypothyroid compared with only 5% of the TPOabs-negative patients. Furthermore, significant higher levels of TSH were observed in TPOabs-positive patients compared with TPOabs-negative patients. These findings are in contrast to the results of a study on 70 Italian RA patients (18), showing no association between thyroid antibody status and hormonal status. However, in a much larger study ($n=2700$) a clear association between TPOabs and TSH levels and future hypothyroidism was seen, which underscores the observations of our study (16). In addition, our study observed a higher percentage of females in the TPOabs-positive group, which is in agreement with the results of the study by Roos *et al.* (16).

Interestingly, TPOabs-positive patients had a significantly higher disease activity, reflected by higher disease activity scores, a lower percentage of low disease activity and higher ESR levels in the TPOabs-positive group. An explanation for this observation might be the sex difference between TPOabs-positive and -negative patients as we observed that adjustment for gender (marginally) influenced the association between disease activity and TPO antibody status, and previous studies already demonstrated a higher disease activity state in females compared with male RA patients (24, 25). Moreover, lower TPOabs levels were found in the MTX users. This is in agreement with the previous observation of our group that MTX use appears to have an important immunomodulating effect on anti-glutamic acid decarboxylase in latent autoimmune diabetes of the adult and concomitant RA (26). Therefore, it is likely that the difference in disease activity between

TPOabs-positive and -negative patients is at least in part explained by a (somewhat) lower MTX use in TPOabs-positive patients. Moreover, this study observed that TPOabs-positive RA patients had higher disease activity scores during follow-up. Although these results are intriguing, the question remains whether the higher disease activity in TPOabs-positive patients is part of their phenotype and whether this results in a more therapy-refractory disease.

Moreover, this study found a larger cIMT progression, a surrogate marker for atherosclerosis in TPOabs-positive patients compared with TPOabs-negative patients. Although the reported cIMT progression difference seems small, these progression rates are clinically relevant as the progression rate is tenfold bigger than the progression rate of placebo arms of large statin trials (27, 28, 29). Previously, similar results were reported in the Rotterdam's study, as a greater incidence

Table 4 Regression coefficients of linear regression analyses in RA patients for IMT progression.

	Model 1	Model 2
TPOabs-positive	0.134*	0.131*
Gender	0.042	0.018
Age	0.000	−0.002
DAS 28	−0.018	−0.022
Rheumatoid factor positive	−0.022	−0.008
Methotrexate use	−0.015	0.008
Prevalent cardiovascular disease		0.146*
TSH		0.051
Prednisolone use		0.054
Statin use		0.033
Hypertension NCEP ATIII		−0.059
Atherogenic index		0.015
Diabetes mellitus		0.122
Smoking		−0.017

* $P<0.05$, NCEP ATIII, National Cholesterol Education – Third Adult Treatment Panel.

of aortic atherosclerosis was observed in TPOabs-positive subclinical hypothyroid patients (30). These observations suggest an atherogenic role of TPOabs. In this respect, it is interesting that a previous study already suggested an atherogenic role for autoimmune thyroiditis as they observed a clear association between Hashimoto thyroiditis in an euthyroid state and cIMT independently of cardiovascular risk factors (31). Also, others observed a clear association between cIMT and hypothyroidism in female RA patients independent of cardiovascular risk factors (32, 33). A mechanism explaining this link may be a state of chronic inflammation in TPOabs-positive patients, which causes endothelial dysfunction, ultimately resulting in atherosclerosis. Indeed, this study observed higher inflammatory states reflected as higher disease activity scores and higher ESR rates in TPOabs-positive patients. Another explanation may be that chronic inflammation is the driving force for the cIMT progression and that TPOabs are just innocent bystanders in this case.

Although the results of this study are intriguing, some limitations have to be taken into account. The first concern is the small sample size of the study, which raises the question whether the results are generalizable to other populations. However, the small sample size might be the explanation for why no associations were observed between thyroid antibody status and (incident) cardiovascular events, as both conditions are relatively uncommon. Therefore it is difficult to reject the null hypothesis, i.e. a type II error. Obviously, a longer follow-up is needed to reveal the association between TPOabs status and incident CVD. Another limitation of this study is the design, as it is known that in studies with an observational design confounding is common. To deal with this multivariable regression, analyses were performed, although residual confounding of unknown and unmeasured variables cannot be excluded.

In conclusion, TPOabs positivity (irrespective of thyroid status) was associated with cIMT progression, although no increased CVD prevalence or incidence after 3 years of follow-up was observed. Moreover, this study shows TPOabs to be associated with disease activity. Hence, TPOabs seem to have a role in the amplified cardiovascular risk in hypothyroid patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement

H G Raterman was responsible for the design of the study, analysis, and interpretation of data and drafting of the manuscript. A E Voskuyl,

S Simsek, B A C Dijkmans, P Lips, W F Lems, and M T Nurmohamed assisted with analysis and interpretation of data and revised the manuscript critically. M J L Peters and V P van Halm were responsible for acquisition of the data, assisted with interpretation of data, and revised the manuscript critically. I M W van Hoogstraten and M W J Schreurs performed laboratory analysis, assisted with interpretation, and revised the manuscript critically.

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Received 18 May 2013

Revised version received 29 August 2013

Accepted 4 September 2013