Improvement of Thyroid Function in Hypothyroid Patients with Rheumatoid Arthritis After 6 Months of Adalimumab Treatment: A Pilot Study

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is characterized by high levels of cytokines such as tumor necrosis factor (TNF). TNF appears to have an etiologic role in thyroid dysfunction, and thyroid dysfunction is a common comorbidity in RA. Anti-TNF treatment might limit thyroid dysfunction. Thus, changes in thyroid hormones were studied during TNF-blocking therapy in patients with RA.

Methods. At baseline and after 6 months' treatment with adalimumab, thyroid function [thyroid-stimulating hormone (TSH), free thyroxine (fT4), and antibodies against thyroid peroxidase (TPOabs)] were assessed in 138 consecutive adalimumab-treated patients with RA who were naive for TNF-blocking agents. Patients were categorized as hypothyroid, hyperthyroid, or euthyroid. In these groups, changes in thyroid function were determined.

Results. Prevalences of hypothyroidism, hyperthyroidism, and TPOabs were 13%, 5%, and 15%, respectively. After 6 months, TPOabs decreased from 267 to 201 IU/ml ($p = 0.048$). In hypothyroid patients without concomitant L-thyroxine, a trend for declining levels of TSH was observed. Subgroup analysis revealed that in patients who were hypothyroid and TPOabs-positive and L-thyroxine-naive, TSH levels decreased significantly, from 12.5 (interquartile range 6.7–18.4) to 7.1 (interquartile range 4.9–13.8) mU/l ($p = 0.043$).

Conclusion. Anti-TNF treatment improves thyroid function in hypothyroid patients with RA (especially in those who are L-thyroxine-naive and TPOabs-positive), providing further evidence that inflammatory cytokines such as TNF have a pathogenic role in thyroid dysfunction. (First Release Nov 15 2010; J Rheumatol 2011;38:247–51; doi:10.3899/jrheum.100488)

Key Indexing Terms:
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The manifestations of rheumatoid arthritis (RA) extend beyond symmetrical inflammation of the joints. Accumulating evidence supports an increased risk for comorbid conditions such as osteoporosis, cardiovascular diseases, and underlying cardiovascular risk factors such as hypothyroidism[1,2,3,4]. Treatments such as tumor necrosis factor (TNF)-blocking agents effectively reduce disease activity as well as radiological joint progression[5]. The effect of TNF-blocking agents on thyroid hormone metabolism is not well known, although antibodies against thyroid peroxidase (TPOabs) seem not to be influenced by adalimumab treatment[6]. Interestingly, a recent case report describes the decrease in thyroid hormonal requirements in a patient with synovitis, acne, pustolosis, hyperostosis and osteitis syndrome and concomitant hypothyroidism[7]. Another report described the development of Graves' disease during treatment with adalimumab[8]. In addition, both hyperthyroid and hypothyroid patients have higher serum concentrations of TNF-α in comparison with euthyroid controls[9]. Moreover, TNF infusion results in severe hypothyroidism and declining levels of triiodothyronine (T3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH)[10,11]. Hence, TNF

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appears to play an etiologic role in the development of thyroid disorders. Therefore, we hypothesize that TNF-blocking agents might induce changes in thyroid metabolism with subsequent improvement of thyroid function in patients with thyroid dysfunction.

MATERIALS AND METHODS

Patient recruitment and treatment. Patients with RA who are TNF-blocking agent-naive (n = 138) were recruited from a cohort of 188 consecutive patients with RA treated with the TNF-blocking agent adalimumab at the Department of Rheumatology of the Jan van Breemen Institute, Amsterdam. The characteristics of this cohort have been described[12]. All patients fulfilled the American College of Rheumatology 1987 revised criteria for RA[13], and all patients needed to have active disease according to the Dutch consensus statement on the initiation and continuation of TNF-blocking therapy in RA[14]. In all patients, blood samples were obtained and disease activity was assessed at baseline and after 28 weeks of adalimumab treatment using the 28-joint disease activity score (DAS28)[15]. All patients provided written informed consent and the study was approved by the medical ethics committee.

Thyroid status. In all patients, thyroid status, including TSH, fT4, and TPOabs, was assessed from serum samples. Patients were categorized into 3 groups: (1) euthyroid, defined as a normal thyroid function; (2) hypothyroid, defined as TSH > 4.0 mU/l, fT4 < 10 pmol/l, or a known diagnosis of hypothyroidism; and (3) hyperthyroid, defined as TSH < 0.30 mU/l, fT4 > 24 pmol/l, or a known diagnosis.

Laboratory measurements. Baseline laboratory measures included IgM rheumatoid factor (RF) by in-house ELISA and anticitrullinated protein antibodies (ACPA) by ELISA (second-generation anti-CCP ELISA, Axis Shield, Dundee, UK) as described[12]. Serum TSH, fT4, and TPOabs levels were assessed by an electrochemiluminescence immunoassay using an in-house Cobas® analyzer according to the manufacturer's instruction. Serum was incubated on a biotinylated medium, then in the next incubation step streptavidin-coated microparticles were added. This reaction mixture is aspirated into the measuring cell and a voltage was applied to induce chemiluminescent emission, measured by a photomultiplier. The ultimate response is determined by a calibration curve. According to the manufacturer's instructions, the cutoff level for positivity for TPOabs was set at 34 IU/ml. In biochemical hyperthyroid patients with RA, antibodies directed against TSH receptor (TRabs) were determined in serum using a commercial ELISA (Medizym® T.R.A., Medipan, Dahlewitz/Berlin, Germany), according to the manufacturer's instructions. TRabs values > 1.6 IU/l were considered positive.

Statistical analysis. The characteristics of the patients with RA were expressed as mean with SD or median with interquartile range, where appropriate. The 2 groups of patients with RA who had thyroid dysfunction were compared with euthyroid patients with RA for RA-related variables (i.e., IgM RF status, ACPA status, C-reactive protein, erythrocyte sedimentation rate, DAS28, and concomitant prednisolone or disease-modifying antirheumatic drug use) with Students' t test, Mann-Whitney U test, chi-squared test, or Fisher's exact test, where appropriate.

To evaluate differences in thyroid function during treatment, a paired t test was used in case of a normally distributed variable, or the Wilcoxon signed-rank test in case of a non-normally distributed variable. To evaluate whether the difference in thyroid function differed between the thyroid groups, linear regression analyses were performed. All analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics. At baseline, 18 patients with RA (13%) were hypothyroid, 7 (5%) were hyperthyroid, and 21 (15%) were positive for TPOabs. Baseline characteristics for the adalimumab-treated patients with RA, stratified for thyroid status, are shown in Table 1.

Baseline characteristics were similar among hypothyroid and euthyroid patients with RA, although the use of concomitant prednisolone was more frequent and in higher dosages in hypothyroid patients. Hyperthyroid patients used more concomitant prednisolone compared to euthyroid patients (86% vs 28%; p = 0.0040). The other disease characteristics and demographics did not differ significantly between hyperthyroid and euthyroid patients.

Changes in thyroid function after 6 months. Overall, TSH levels decreased significantly in the total group from 1.5 (IQR 0.94–2.3) to 1.3 (IQR 0.93–2.0) mU/l (p = 0.0014). No changes were observed in fT4 levels.

TSH decreased from 4.1 (IQR 2.3–6.1) to 3.5 (IQR 2.0–6.6) mU/l in the hypothyroid group (n = 18, p = 0.064; Table 2). Linear regression analyses showed a significantly larger decrease in TSH levels in hypothyroid patients with RA compared to euthyroid patients with RA (ß = –0.85, 95% CI –1.39 to –0.30, p = 0.003). Adjustment for prednisolone use did not change our results (ß = –0.94, 95% CI –1.49 to –0.40, p = 0.001). Testing for effect modification revealed that the effect on the change in TSH was different in the hypothyroid group with and without L-thyroxine use (p = 0.040). In fact, a significantly larger decrease in TSH levels was observed in the L-thyroxine-naive hypothyroid group (n = 10) compared to the L-thyroxine-naive euthyroid group (n = 113; ß = –1.45, 95% CI –2.12 to –0.77, p < 0.0005).

In the hypothyroid group without concomitant L-thyroxine use, TSH levels decreased in 8 of the 10 hypothyroid patients with RA (Figure 1). Moreover, 2 of these patients (20%) became biochemically euthyroid. No statistically different changes were observed in fT4 levels. In the hyperthyroid group, no statistically different changes were observed in levels of TSH and fT4.

Changes in thyroid function after 6 months in TPOabs-positive patients with RA. In TPOabs-positive patients (n = 21), TPOabs levels decreased significantly from 267 (IQR 95–367) to 201 (IQR 79–335) IU/ml (p = 0.048).

In the hypothyroid TPOabs-positive patients (n = 11), median TPOabs levels decreased from 325 (IQR 265–562) to 282 (IQR 201–452) IU/ml, and in the euthyroid TPOabs-positive patients, TPOabs levels changed from 114 (IQR 72–270) to 108 (IQR 33–213; not significant when comparing hypothyroid with euthyroid, Table 2). Comparing TSH values in TPOabs-positive patients, levels changed significantly from 3.9 IU/ml (range 2.0–12.5) to 3.5 IU/ml (range 2.4–7.1; p = 0.041). When comparing changes in TSH levels in hypothyroid patients with euthyroid patients, a borderline significant change was seen in hypothyroid patients (ß = –1.62, 95% CI –3.39 to 0.15, p = 0.07). No significant changes were observed in fT4 levels.

In TPOabs-positive hypothyroid patients without concomitant L-thyroxine use (n = 5), fT4 levels increased sig-

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Table 1. Baseline characteristics of patients with rheumatoid arthritis (n = 138) stratified for thyroid group. Continuous variables are presented as means with SD in cases of normal distribution or as medians with interquartile ranges in cases of non-normal distribution.

Characteristics	Hypothyroid, n = 18	Euthyroid, n = 113	Hyperthyroid, n = 7	p†	p*
Age, yrs	57 ± 11	54 ± 12	56 ± 10	0.29	0.64
Women, %	78	75	100	1.0	0.20
Disease duration, yrs	8 (6–18)	7 (3–15)	8 (3–22)	0.19	0.86
IgM RF-positive, %	56	55	86	0.99	0.24
IgM RF levels, IU/ml	40 (14–142)	35 (11–72)	68 (31–105)	0.47	0.19
ACPA-positive, %	83	73	86	0.56	0.68
ACPA levels, AU/ml	1320 (158–3300)	402 (33–1550)	1000 (218–2210)	0.12	0.41
Erosive disease, %	78	81	86	0.76	1.0
Current prednisone use, %	50	28	86	0.065	0.0040
Prednisone dosage, mg/day	3 (0–10)	0 (0–5)	5 (4–6)	0.020	0.011
Current MTX use, %	78	78	86	1.0	1.0
MTX dosage, mg/wk	15 (4–25)	20 (10–25)	15 (7.5–25)	0.23	0.38
No. DMARD used	4 (3–4)	3 (2–3)	3 (2–6)	0.066	0.47
DAS28	5.2 ± 1.4	5.1 ± 1.1	5.4 ± 1.4	0.65	0.47
ESR, mm/h	24 (17–56)	22 (11–41)	17 (9–26)	0.46	0.60
CRP, mg/l	13 (7–32)	12 (6–27)	18 (7–40)	0.76	0.47

† Hypothyroid vs euthyroid. * Hyperthyroid vs euthyroid vs euthyroid. RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AU: arbitrary units.

Table 2. Levels of thyroid-stimulating hormone (TSH), free thyroxine, and antibodies against thyroid peroxidase during 6 months of adalimumab treatment, stratified for thyroid group.

	Hypothyroid, n = 18		Euthyroid, n = 113		Hyperthyroid, n = 1	
	T = 0	T = 6 Months	T = 0	T = 6 Months	T = 0	T = 6 Months
TSU, mU/l	4.1 (2.3–6.1)	3.5 (2.0–6.6)†	1.4 (0.9–2.1)	1.3 (0.9–1.8)*	0.5 (0.3–1.0)	0.5 (0.3–1.6)
fT4, pmol/l	16.8 ± 4.6	16.7 ± 3.8	17.7 ± 2.4	17.5 ± 2.3	22.2 ± 3.4	21.5 ± 3.6
TPOabs-positive, %	61	67	8	6	14	14
TPOabs, IU/ml	325 (265–562)	282 (201–452)	114 (72–270)	108 (33–213)	73 (73–73)	49 (49–49)
L-thyroxine use, %	44	44	0	0	14	14
L-thyroxine dosage, μg	87.5 (59–100)	87.5 (59–100)	0	0	100	100

* $p < 0.05$ compared to baseline. † $p < 0.10$ compared to baseline. ft4: free thyroxine; TPOabs: antibodies against thyroid peroxidase.

nificantly from 12.6 pmol/l (± 1.6) to 13.4 pmol/l (± 1.3; p = 0.039). TSH levels decreased in all hypothyroid patients from 12.5 mU/l (range 6.7–18.4) to 7.1 mU/l (range 4.9–13.8; p = 0.043; Figure 2). Moreover, one of these TPOabs-positive and L-thyroxine-naive patients (20%) became biochemically euthyroid.

DISCUSSION

Our study demonstrates that in anti-TNF-naive patients with RA and hypothyroidism, thyroid function can be improved with the TNF-blocking agent adalimumab. Our data give indirect evidence that inflammatory cytokines such as TNF may play key roles in the development of clinical thyroid dysfunction.

Literature regarding inflammatory markers such as cytokines and established hypothyroidism is scarce. In patients with Hashimoto thyroiditis, levels of TNF have been described as increased. Since TNF upregulates adhesion molecules and human leukocyte antigen class II molecules, it promotes antigen presentation to activated T lymphocytes[9,16]. In this way, elevated TNF levels might exacerbate the autoimmune processes involved in the pathogenesis of autoimmune thyroiditis.

Although this hypothesis seems plausible, the precise involvement of cytokines such as TNF and interleukin 6 (IL-6) in thyroid dysfunction remains unknown. However, it is generally accepted that these cytokines influence the conversion of T4 to T3 and thereby also affect the release of TSH[17]. Indeed, in patients in an intensive care setting, often characterized by high levels of inflammatory markers, the development of thyroid disturbances, also known as non-thyroidal illness syndrome (NTIS), is well known, although an intrinsic disease of the hypothalamic-pituitary-thyroid axis is absent in these patients[17]. In addition, NTIS is temporary and resolves when patients are cured.

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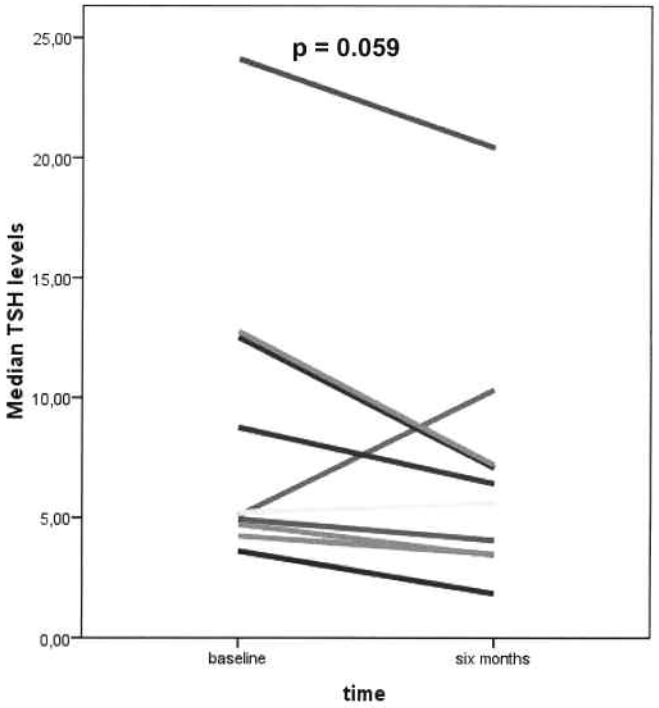

Figure 1. Changes in thyroid-stimulating hormone (TSH) levels in hypothyroid patients with RA who are not using L-thyroxine (n = 10).

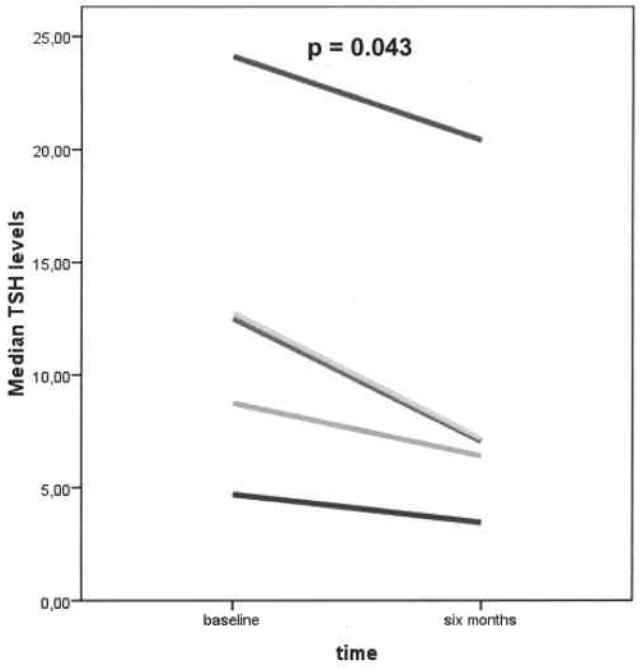

Figure 2. Changes in thyroid-stimulating hormone (TSH) levels in thyroid peroxidase antibody-positive hypothyroid patients with RA who are not using L-thyroxine (n = 5).

More intriguing is the report by Caturegli and Kimura, in which they propose a nonclassical hypothesis for the development of autoimmune hypothyroidism derived from a mouse model[18]. In this model they propose that chronic exposure to inflammatory cytokines such as TNF, interferon, and IL-6 results in an immune-mediated chronic inhibition of thyroid function and thyroid atrophy with clinical features of hypothyroidism. To acquire more scientific and clinical support for this hypothesis, overt hypothyroidism must be a common comorbidity in chronic inflammatory diseases such as RA and systemic lupus erythematosus as a consequence of the inflammatory burden of these patients. Hypothyroidism is more prevalent in patients with these rheumatic diseases compared to healthy controls[3,19]. On the other hand, this hypothesis implicates clinical relevance, as this alternative model suggests that autoimmune hypothyroidism may be a reversible condition in at least the subset of patients where the pathogenesis of hypothyroidism is inflammation-mediated. In our study investigating the influence of TNF-blocking agents on thyroid metabolism, we found that in most (8 of 10) L-thyroxine and TNF-blocking agent-naive hypothyroid patients with RA, TSH levels decreased after 6 months of adalimumab treatment. However, one patients experienced dramatically increased TSH levels, but additional analysis revealed that this hypothyroid patient with RA was not responding to adalimumab because of antibodies against adalimumab and had no detectable levels of it. Moreover, this was the only one of the 10 hypothyroid patients with increasing inflammatory measurements after 6 months of adalimumab treatment compared to baseline (data not shown). When we look at the subgroup of TPOabs-positive, L-thyroxine-naive, and anti-TNF-naive hypothyroid patients with RA, all had decreased TSH levels, suggesting that anti-TNF treatment may have a substantial effect on the hormonal disturbances in autoimmune thyroid disorders.

Several study limitations are noted. First, thyroid function was assessed at only 2 timepoints, as the study was designed as a pilot study. To determine a pathogenic role of inflammatory cytokines and thyroid dysfunction, a larger placebo-controlled study with more than 2 timepoints is needed to rule out the common statistical phenomenon known as regression to the mean. Second, in this cohort only 20% of the hypothyroid patients become euthyroid after 6 months and therefore the extent of the clinical implications of our findings remains to be established.

Our study showed for the first time that in patients with hypothyroidism, thyroid function improves with TNF-inhibiting treatment, providing further evidence that inflammatory cytokines such as TNF in addition to genetic factors are important (at least in a subset of patients) in the development of clinical hypothyroidism. We encourage groups studying other inflammatory diseases to investigate the pathogenic role of inflammatory cytokines for the development of thyroid disorders. Moreover, our study highlights that TNF-blocking agents such as adalimumab might have (unknown) pleiotropic effects, i.e., not only antiinflammatory

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but also endocrine and metabolic actions, indicating that continuous monitoring for unexpected, rare adverse events is warranted.

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