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Original article

Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects ☆

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ABSTRACT

Objectives: Hypothyroidism is associated with normocytic anaemia. Indeed, a limited number of studies have shown significant associations between free thyroxin (T4) and erythrocyte indices. These studies did not include vitamin B12, folic acid, iron and renal function in the analyses. We therefore studied the association between thyroid hormones and erythrocyte indices in a population-based cohort of older euthyroid subjects, with adjustment for major confounding parameters.

Design: Data, including thyroid hormones and erythrocyte indices, are from the Longitudinal Aging Study Amsterdam (LASA), an ongoing cohort study on predictors and consequences of changes in health in the ageing population in the Netherlands. Multivariable linear regression analyses were applied to study the cross-sectional associations between free T4, thyroid stimulating hormone (TSH) and erythrocyte indices (haemoglobin content, haematocrit, mean cell volume (MCV) and erythrocyte count) in a euthyroid sub-sample. The final models were adjusted for vitamin B12, folic acid, iron levels and renal function.

Results: In 708 euthyroid older subjects, an increase of 5 pmol/L free T4 was associated with a mean increase of 0.12 mmol/L or 0.19 g/dL of haemoglobin, 0.068 10^{12}/L erythrocytes and 0.006 L/L haematocrit ($P=0.007$, $P=0.005$, $P=0.001$, respectively). Free T4 was not significantly associated with MCV ($P>0.05$). TSH appeared not to be associated with any of the erythrocyte indices (all $P>0.05$).

Conclusions: In a cohort of older subjects, free T4, but not TSH, was associated with erythrocyte indices, confirming the role of thyroid hormones in the regulation of erythropoiesis.

1. Introduction

Thyroid hormones have regulatory functions in erythropoiesis [1–8]; however, the mechanisms by which thyroid hormones regulate erythropoiesis are not yet fully elucidated but seem to be multiple in nature. In humans, a limited number of studies have addressed the association of thyroid function with haematological parameters [9–12]. In a case–control study, iron and ferritin levels were lower in 57 women with sub-clinical hypothyroidism than in the 61 euthyroid controls [9], and in a clinical trial, thyroxin treatment was shown to increase erythropoietin levels in 63 women with sub-clinical hypothyroidism, but no significant effects on haemoglobin concentration or haematocrit were observed [10]. In euthyroid subjects, the association between thyroid hormones and erythrocyte indices has been studied recently [11,12]. In the Haemochromatosis and Iron Overload Screening study, the association of free thyroxin (T4) with haemoglobin and red cell distribution width (RDW) was studied in 141 patients with haemochromatosis and 243 healthy controls. In the controls subjects, but not in the patients, free T4 was positively correlated with haemoglobin concentration and negatively correlated with RDW [11]. In that study, no multivariable regression analyses were performed with adjustments for potential confounders. In a population-based cohort of 1011 euthyroid older subjects, significant associations between free T4 and haemoglobin concentration, erythrocyte count and haematocrit were found [12]. In that particular study, no adjustments for other potential confounding factors including nutritional parameters (vitamin B12, folic acid and iron) and renal function were applied in the multivariable linear regression analyses. Indeed, a number of studies have shown that renal function, either expressed as estimated glomerular filtration rate (eGFR) or serum creatinine level, is significantly associated to both thyroid function (TSH) [13–15] and haemoglobin concentration [16]. In addition, some [17,18], but not all studies [19,20], have found a higher prevalence of vitamin B12 and/or folic acid deficiency in patients with hypothyroidism. Nonetheless, additional adjustments for vitamin B12, folic and iron seem appropriate to minimize residual confounding.

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In conjecture with the aforementioned considerations, the objective of the present study was to assess the association of thyroid hormones (free T4 and TSH) with erythrocyte indices in a sample of euthyroid older subjects in a population based cohort with adjustment of renal function and nutritional parameters.

2. Methods

2.1. Study sample and biochemical analyses

Data for this study are from the Longitudinal Aging Study Amsterdam (LASA), an ongoing cohort study on predictors and consequences of changes in health in the ageing population in the Netherlands. The sampling design and data collection methods have been described in detail previously [21,22]. In brief, a random sample of 3107 older men and women (aged 55–85) stratified by age, sex, and urbanization, was enrolled in 1992 or 1993. Recruitment took place in three different regions in the Netherlands. Because of logistical and financial reasons, biochemical analyses in the 1992/1993 baseline cohort were determined in only one of the three data collection regions, resulting in 762 subjects in whom the relevant biochemical data were available (total study population). The present analyses were performed in 708 subjects with thyroid stimulating hormone (TSH) between 0.3 and 4.5 mU/L and free T4 within the reference range, i.e. 11–22 pmol/L (euthyroid study population) as defined previously [23]. The biochemical analyses of TSH, FT4, haematological parameters, vitamin B12, folic acid, iron and creatinine were performed at the Department of Clinical Chemistry at the Isala Clinics in Zwolle, as described previously [23–25]. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) Study equation [26].

All LASA participants provided written informed consent and the ethical review board of the VU University Medical Centre (VUmc) approved the study.

2.2. Statistical analyses

Data are presented as mean with standard deviation (SD) or as median with the interquartile range (IQR) in case of variables with a skewed distribution. Differences between male and female subjects were tested with a Student's *t*-test or a Mann–Whitney-*U* test, as appropriate. The univariable association between variables was calculated with correlation analyses. The association of free T4 in the euthyroid subjects was assessed by multivariable linear regression analyses with the erythrocyte parameters (haemoglobin concentration, haematocrit, erythrocyte count and mean cell volume) as dependent variables, respectively, and free T4 as independent variable. The first model was adjusted for age and sex as confounding variables, the second model was additionally adjusted for vitamin B12, folic acid and iron, and the final model was additionally adjusted for renal function (eGFR). To test whether the association of free T4 and the erythrocyte parameters could be explained by TSH, this parameter was entered as a covariate into the final model. Effect modification of age and sex was tested by adding the appropriate interaction term (age × free T4 and sex × free T4, respectively). Variables with a skewed distribution were entered as log-transformed variables into the analyses.

The statistical analyses were performed with IBM SPSS Statistics version 20.2.0 (IBM, Armonk, New York). A *P*-value of less than 0.05 was considered as statistically significant, except for the interaction term (*P*-value<0.1).

3. Results

3.1. Characteristics of the study population

The study population comprised of 762 subjects of whom 708 were euthyroid (50.7% males). Thirteen of these 708 subjects were on thyroid hormone substitution therapy. The biochemical data of the 708 euthyroid subjects are presented in Table 1. The median TSH in the euthyroid sample was 1.24 (IQR: 0.84–1.80) mU/L with no significant differences between male and female subjects ($P=0.29$). The mean free T4 of the euthyroid sample was 15.0 (SD: 3.0) pmol/L with higher values in males than in females (16.3 (3.0) versus 15.7 (3.0) pmol/L, $P=0.012$). The mean haemoglobin concentration in the euthyroid population was 9.3 (0.8) mmol/L [15 (1.3) g/dL] in males and 8.6 (0.7) mmol/L [14 (1.1) g/dL] in females ($P<0.001$). Haemoglobin concentration was inversely correlated with age in males but not in females ($r=-0.22$; $P<0.001$ and $r=+0.01$; $P=0.85$, respectively). Mean cell volume (MCV) was slightly higher in males than in females (92.4 (4.5) versus 91.6 (4.1) fL; $P=0.021$) and increased with age ($r=+0.13$; $P=0.012$ and $r=+0.15$; $P=0.005$, for males and females, respectively). Erythrocyte count was higher in males than in females (4.8 (0.41) vs 4.6 (0.37) 10^{12}/L; $P<0.001$) and decreased with age in males but not in females ($r=-0.24$; $P<0.001$ and $r=-0.04$; $P=0.44$, for males and females, respectively). Haematocrit was higher in males than in females (0.44 (0.03) vs 0.42 (0.03); $P<0.001$) and decreased with age in males but not in females ($r=-0.19$; $P<0.001$ and $r=-0.04$; $P=0.43$, for males and females, respectively). Vitamin B12 levels did not differ between males and females ($P=0.06$), whereas folic acid and iron levels were lower in females than in males (both $P<0.05$).

3.2. Association of free T4 with erythrocyte indices

The interaction-terms (sex × free T4 and age × free T4) were not statically significant (both *P*-values > 0.1) and therefore the multivariable linear regression analyses were performed in the euthyroid study sample without stratification by sex or age. In the multivariable linear regression analyses, free T4 was positively associated with haemoglobin concentration, erythrocyte count and haematocrit, independent of vitamin B12, folic acid and iron levels (Table 2, Model 2). Free T4 was not associated to MCV. An increase of 5 pmol/L free T4 was associated with a mean increase of 0.12 mmol/L (0.19 g/dL) of haemoglobin, 0.068 10^{12}/L erythrocytes and 0.006 L/L haematocrit. Additional adjustment for eGFR did not affect the models to a significant extent (Table 2, Model 3). The strength of the associations between free T4 and the erythrocyte parameters was not abolished nor lost significance when TSH was added into the models (data not shown). The associations in the total sample (n = 762, euthyroid and non-euthyroid subjects) and analyses in the sample without the subjects on thyroid hormone substitution therapy (n = 695) yielded comparable results with respect to the strength of the associations of free T4 and erythrocyte indices (data not shown). Due to the lack of power, no significant associations were found in the subjects with hypothyroidism or hyperthyroidism (data not shown).

Table 1
Characteristics of the study population.

n	708
Age (years)	68.5 (8.6)
Sex (% males)	50.7%
Thyroid parameters	
TSH, mU/L	1.24 (0.84–1.80)
FT4, pmol/L	15.9 (3.0)
Erythrocyte indices	
Haemoglobin, mmol/L/g/dL	8.9 (0.80)/14 (1.2)
Haematocrit, L/L	0.42 (0.037)
Erythocytes, 10^{12}/L	4.7 (0.41)
MCV, fL	92.0 (4.3)
Nutritional parameters	
Vitamin B12, mmol/L	290 (225–370)
Folic acid, pmol/L	9.3 (7.4–11.0)
Iron, μmol/L	15.4 (5.5)
Renal function	
Creatinine, μmol/L	96.4 (21.0)
eGFR, mL/min	64 (13)

Table 2
Multivariable regression analyses of the association between free T4 (per 5 pmol/L) and erythrocyte parameters.

Parameter	Model 1		Model 2		Model 3	
	b (95% CI)	*P*-value	b (95% CI)	*P*-value	b (95% CI)	*P*-value
Haemoglobin, mmol/L	0.096 (0.04; 0.19)	0.04	0.12 (0.03; 0.20)	0.009	0.12 (0.034; 0.21)	0.007
Haemoglobin, g/dL	0.15 (0.06; 0.31)	0.04	0.19 (0.048; 0.32)	0.009	0.19 (0.055; 0.34)	0.007
Erythrocytes, 10^{12}/L	0.065 (0.017; 0.11)	0.008	0.065 (0.017; 0.11)	0.008	0.068 (0.02; 0.12)	0.005
Haematocrit, L/L	0.006 (0.001; 0.01)	0.008	0.006 (0.002; 0.01)	0.002	0.006 (0.003; 0.01)	0.001
MCV, fL	−0.12 (−0.66; 0.42)	0.66	0.048 (−0.46; 0.55)	0.85	0.012 (−0.40; 0.52)	0.96

Model 1: adjusted for age and sex; Model 2: Model 1 with additional adjustments for iron, vitamin B12 and folic acid; Model 3: Model 2 with additional adjustments for eGFR.

3.3. Association of TSH with erythrocyte indices

In the euthyroid sample, TSH was weakly but significantly associated with erythrocyte count (b = −0.04 (−0.08; −0.005); $P = 0.024$), but not with haemoglobin concentration, haematocrit or MCV (b = −0.06 (95% CI: −0.13; 0.2) mmol/L [b = 0.096 (95% CI: −0.21; 0.32) g/dL]; $P = 0.13$, b = −0.003 (95% CI: −0.006; 0.0002); $P = 0.076$, b = 0.27 (95% CI: −0.13; 0.67); $P = 0.18$, respectively, per 1 mU/L TSH, adjusted for age and sex). The association between TSH and erythrocyte was borderline significant after additional adjustments for iron, folic acid, vitamin B12 and eGFR ($P = 0.054$).

3.4. Additional analyses

Both TSH (per 1 mU/L) and free T4 (per 5 pmol/L) were inversely associated with eGFR (b = −1.7 (−2.9; −0.6); $P = 0.002$, b = −1.5 (−2.9; −0.001); $P = 0.049$, respectively, adjusted for age and sex). Renal function (eGFR) was associated with haemoglobin concentration, haematocrit and erythrocyte count (all $P < 0.05$), but not with MCV ($P > 0.1$).

4. Discussion

In the present study, free T4 was significantly associated with parameters of erythropoiesis, including haemoglobin concentration, haematocrit and erythrocyte count, whereas TSH was not significantly associated with any of these parameters. Our study is, to the best of our knowledge, the second study assessing the relation of thyroid hormones and haematological parameters in a larger population based cohort study. The results of the present study are in line with the study of Bremner and co-workers [12], who showed that free T4 was significantly associated to haemoglobin concentration, erythrocyte count and haematocrit. However, in contrast to the study of Bremner et al., we found no association between free T4 and MCV. In the study of Bremner et al., the regression coefficient of the association of free T4 and haemoglobin converted to change of haemoglobin in mmol/L per 5 pmol/L equalled 0.084 and is comparable to the results in the present study (i.e. 0.12 mmol/L or 0.19 g/dL haemoglobin per 5 pmol/L free T4). Bremner and co-workers also demonstrated significant associations of T3 with the studied erythrocyte indices. Unfortunately, T3 was not determined in the baseline measurements of LASA. Furthermore, TSH was not associated with any of the erythrocyte parameters which is in line with the findings of Bremner and co-workers [12]. We confirmed the association of TSH and free T4 with renal function (eGFR) as demonstrated in recent studies [13–16]. However, in the analysis of free T4 with the erythrocyte parameters (including haemoglobin), the models were not affected by additional adjustments of eGFR.

The mechanisms by which thyroid hormones modulate erythropoiesis are not fully understood. Stimulation of erythropoietin production (EPO), receptor mediated effects in erythrocyte precursors and effects on iron metabolism have been suggested as possible mechanisms [4,5]. These effects can be mediated either via TSH through the TSH receptor, which has been suggested to exist on erythrocytes and erythrocyte precursors, or by metabolic effects mediated by T4 or T3, or both. In the present study, free T4 but not TSH, was significantly associated with haemoglobin concentration, which implies that the metabolic effects of thyroid hormones are regulated by direct or indirect effects of T4 or T3 rather than TSH receptor mediated effects. Indeed, additional adjustments of the final models (Table 2, Model 3) with TSH did not abolish these associations, suggesting that TSH has no mediating effect on the association of free T4 and the erythrocyte indices. Some authors suggest that EPO production or EPO release may be influenced by T4 or T3 levels [28,29]. In a clinical trial in patients with iron deficiency and hypothyroidism, in which patients were treated with either iron or iron in combination with T4, the haemoglobin content increased almost fivefold with the combination treatment as compared to iron alone [10]. These data stress the metabolic importance of T4 in erythropoiesis possibly by synergistic effects on iron metabolism or the production of EPO or other growth factors. Unfortunately, the authors did not measure EPO levels. In vitro, T3 has been shown to be able to augment the release of growth factors from leukocytes that potentiate the erythroid burst-forming unit (BFU-E) proliferation [27]. In a study in mice, Sullivan and McDonald demonstrated that T4 stimulated erythropoiesis probably by a direct, β2-adrenergic receptor-mediated stimulation of red cell precursors [2]. Miska and co-workers showed that oral administration of dried thyroid gland to adult male mice stimulated erythropoiesis. Furthermore, the thyroid pre-treatment increased radiation resistance as revealed by their 30-day survival and higher recovery of peripheral blood cell counts [3].

The strength of the associations is rather small, a change of 5 pmol/L free T4 is associated with an increase of 0.12 mmol/L in haemoglobin concentration and therefore the clinical implications of our findings seem limited. However, our data provide more insight in the role of thyroid hormones in the regulation of erythropoiesis.

This study has several strengths and limitations. The main strength of the study is that the analysis was performed in a well-characterised population-based cohort with measurement of thyroid function and haematological parameters. A possible limitation is the fact that the numbers of subjects with hypothyroidism and hyperthyroidism were too small to be analyzed separately and therefore the association of TSH with erythrocyte indices could not be studied over the full range of thyroid (dys)function. A final limitation is the lack of measurement of ferritin and transferrin in addition to iron to optimally characterize iron deficiency anaemia and anaemia of chronic disease.

5. Conclusion

In conclusion, in the present study significant associations between free T4 and erythrocyte indices, including haemoglobin concentration, haematocrit and erythrocyte count were demonstrated. These results may be relevant for the further understanding of the role of thyroid hormones in the regulation of erythropoiesis.

Learning points

- Free T4, but not TSH, is associated with erythrocyte indices, independent of serum vitamin B12, folic acid and iron levels, and glomerular filtration rate.

- These findings confirm the role of thyroid hormones in the regulation of erythropoiesis.

Conflict of interests

The authors state that they have no conflicts of interest.

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