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Hypothyroidism consequent to thyroidectomy is associated with elevated remnant lipoproteins and cholesterol enrichment of triglyceride-rich lipoproteins: an observational study

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Abstract

Background Hypothyroidism may affect triglyceride-rich lipoprotein (TRL) subfractions and low-density lipoprotein (LDL) and their averaged sizes. The present study aimed to determine whether increases in remnant particles were larger than other TRL subfractions and whether changes in remnant particles were related to changes in the TRL cholesterol/triglyceride ratio.

Methods An observational study was conducted to assess the impact of short term (4–6 weeks) hypothyroidism consequent to thyroidectomy on TRL subfractions, including remnant lipoproteins, LDL subfractions, and the TRL cholesterol and triglyceride content. Seventeen patients were studied: (1) during hypothyroidism, 4–6 weeks after total thyroidectomy for differentiated thyroid carcinoma (thyroid stimulating hormone (TSH) ranging from 59 to 371 mU/L) and free thyroxine (ranging from 0.8 to 6.8 pmol/L) and (2) after approximately 20 weeks of thyroid hormone supplementation, aimed at TSH levels below the reference range (TSH ranging from 0.01 to 2.15 mU/L). TRL, LDL subfractions, and the cholesterol and triglyceride content in TRL were measured by nuclear magnetic resonance spectroscopy.

Results Hypothyroidism led to substantial increases (> 30%, $p < 0.001$) in total cholesterol, LDL cholesterol, non-HighDensity Lipoproteins, triglycerides, TRL particle concentrations, and LDL particle concentrations. Among TRL subfractions, very small TRL particles (24–29 nm), corresponding to remnant lipoproteins, showed the most pronounced reduction (59%, 95% confidence interval (CI): 70–45%) after thyroid hormone supplementation ($P < 0.001$). TRL cholesterol content and the TRL cholesterol/triglyceride ratio were also higher during hypothyroidism ($P < 0.001$). Changes in TRL cholesterol correlated with changes in very small TRL particles ($r = 0.70$, 95% CI: 0.34–0.88, $P = 0.002$).

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Conclusions Profound hypothyroidism confers increases in TRL and LDL particles, with the most pronounced effect on very small TRL (remnant) particles. These effects on remnants coincide with an increase in TRL cholesterol and the TRL cholesterol/triglyceride ratio.

Trial registration number NTR ID 7228, 20-08-2018.

Keywords Thyroid neoplasms, Hypothyroidism, Lipoproteins, LDL, Lipoproteins, VLDL nuclear magnetic resonance spectroscopy, Remnant lipoproteins, thyroid stimulating hormone

Introduction

Given the high prevalence of both thyroid disorders and atherosclerotic cardiovascular disease (ASCVD), their association has been extensively studied for decades. It is commonly appreciated that overt and perhaps also subclinical hypothyroidism represent risk factors for ASCVD [1–3]. Accordingly, a recent Mendelian randomization study using of the UK biobank repository, documented a causal association of hypothyroidism with coronary heart disease, angina pectoris and myocardial infarction, but not with ischemic stroke and peripheral artery disease [4].

Overt hypothyroidism has profound and multifaceted effects on lipoprotein metabolism and intracellular lipid homeostasis, which may at least in part explain effects of hypothyroidism on ASCVD [5–7]. Thyroid hormones are able to promote low density lipoprotein (LDL) receptor-mediated LDL particle clearance. Combined with impaired biliary cholesterol excretion and increased intestinal cholesterol absorption this results in increased LDL cholesterol in hypothyroidism [5–7]. Notably, hypothyroidism also gives rise to elevations in plasma triglycerides [6, 7]. Hypothyroidism is likely to result in enhanced hepatic triglyceride accumulation [8], which represents a driving force for increased production of triglyceride-rich lipoproteins (TRL). In addition, TRL clearance is probably diminished consequent to impaired delipidation by lipases and impaired hepatic removal, with the LDL receptor-related protein 1 (LRP1) playing an important role [6, 7, 9].

In the past few years epidemiological studies have focused on the atherogenic potential of cholesterol carried in TRL, in particular on remnant lipoproteins, as their quantification may improve ASCVD risk classification [10, 11]. Remnant lipoprotein cholesterol is commonly approximated as TRL cholesterol, calculated as the difference between total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol [10, 11]. In addition to specific assays for remnant cholesterol, such as immunoseparation techniques [12], remnant lipoproteins can also be characterized by their size using nuclear magnetic resonance (NMR) spectroscopy. This method allows for the assessment of plasma concentrations of specific TRL and LDL subclasses and their contributions to the total TRL and LDL particle concentrations [13, 14].

Other studies have already shown a decrease in remnant lipoproteins, determined by immunoseparation, in response to levothyroxine treatment in subclinical hypothyroidism [15], and a decrease in non-HDL cholesterol following levothyroxine administration in subclinical and overt hypothyroidism [16]. Using NMR spectroscopy, a cross-sectional study from the ELSA-Brasil cohort demonstrated higher concentrations of very small TRL, corresponding to remnant particles, in subclinical hypothyroidism [17]. Moreover, profound hypothyroidism consequent to thyroidectomy may lead to increases in intermediate density lipoproteins and medium sized TRL [18]. Yet, the extent to which hypothyroidism affects various TRL and LDL subfractions and their averaged sizes remains unknown. In particular, no NMR spectroscopy studies have been carried out to determine comprehensively whether effects of overt hypothyroidism on remnant particles are more pronounced compared to other TRL subfractions.

Hypothyroidism, consequent to total thyroidectomy for differentiated thyroid carcinoma, offers a unique intervention to establish effects of thyroid hormone withdrawal on circulating lipoproteins in humans [19–21]. The present study was initiated to determine the extent to which hypothyroidism consequent to total thyroidectomy affects various NMR-determined plasma TRL subfractions, including remnant lipoprotein particles, LDL subfractions, as well as the TRL cholesterol and triglyceride content in TRL. Specifically, this study aimed to assess whether remnant lipoproteins increase disproportionately compared to other TRL subfractions and whether these changes coincide with increases in the TRL cholesterol-to-triglyceride ratio.

Materials and methods

Participants and study design

We carried out the current observational study among patients with newly diagnosed non-metastasized differentiated thyroid carcinoma (DTC), aged 18–75 years as described in detail elsewhere [19]; inclusion was between 2015 and 2019. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen (registration number 2015/116) and was

registered at the Netherlands Trial Register (NTR ID 7228). Reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22]. All participants gave written informed consent. Exclusion criteria were pregnancy, a history of cardiovascular events, atrial fibrillation and suspicion of distant metastasis. No participants were using lipid-modifying medications (such as statins, fibrates, ezetimibe, or PCSK9 inhibitors).

The present study comprised two outpatient study visits, following Dutch guidelines of DTC treatment, as reported earlier [21]:

a) Between 4 and 6 weeks after total thyroidectomy, under circumstances of hypothyroidism, i.e. at the day before ablative radioactive iodine treatment. This procedure was carried out with thyroid stimulating hormone (TSH) levels being considerably elevated to enhance uptake of radioactive iodine in any potentially remaining thyroid tissue. The Dutch guidelines at the time of this study did not include preference for rTSH over endogenously elevated TSH levels, which was considered the standard procedure at that time.
b) After approximately 20 weeks of thyroid hormone supplementation (liothyronine ($n = 15$; 75 µg daily) or levothyroxine ($n = 2$; 150 and 200 µg daily), which was started the day after radioactive iodine administration. Most participants were started on liothyronine due to its faster suppression of TSH and its shorter half-life, which allows for quicker discontinuation before potential subsequent radioactive iodine diagnostics. Participants were advised by a dietician to keep their nutrient intake and alcohol intake similar from 5 days onwards before each study visit with the exception of avoiding iodine-rich foods before the hypothyroidism visit. Detailed data on diet composition of the individual participants were not recorded. At both study visits, blood pressure, pulse rate, height and weight were measured. Body mass index (BMI) was calculated as weight divided by length squared (kg/m^2). At both study visits, participants were studied after a 10 h fast.

Laboratory methods

Venous blood samples were obtained from an antecubital vein after 10 h of fasting. TSH (reference range 0.27 to 4.20 mU/L) and free thyroxine (FT4) (reference range 12 to 22 pmol/L) were measured using the Roche Modular E170 Analyzer (Roche Diagnostics, Mannheim, Germany). Plasma glucose was measured using a routine procedure. Ethylene diamine tetra-acetic acid (EDTA)-anticoagulated plasma was prepared by centrifugation at 3000 rotations per minute for 15 min at 4 °C and stored at − 80 °C until analysis. EDTA-anticoagulated plasma samples were sent frozen at − 80 °C to Labcorp (Morrisville, NC, USA). At this laboratory, samples were thawed and analyzed using a Vantera® Clinical Analyzer, a fully automated, high-throughput, 400 MHz proton (1 H) NMR spectroscopy platform [13]. Lipoprotein parameters were reported using the LP4 algorithm as previously described [13, 14, 23]. Triglyceride rich lipoprotein (TRL) particles, i.e. very large, large, medium, small, and very small TRL particles (corresponding to remnant lipoproteins or intermediate density lipoprotein particles in an earlier algorithm), and low density lipoprotein (LDL) particles, i.e. large, medium, and small LDL particles (LDLP), were quantified using the conventional deconvolution method and the amplitudes of their spectroscopically distinct lipid methyl group NMR signals [23]. Total TRL particles were calculated as the sum of the concentrations of individual TRL subfractions. Total LDL particles were calculated as the sum of the concentrations of large, medium, and small LDLP. Mean TRL and LDL size were calculated using the weighted averages derived from the sum of the diameters of each subfraction. Estimated ranges of particle diameter for the TRL and LDL subfractions were as follows: very large TRLP, 90–240 nm; large TRLP, 50–89 nm; medium TRLP, 37–49 nm; small TRLP, 30–36 nm; very small TRLP, 24–29 nm; large LDLP, 21.5–23 nm; medium LDLP, 20.5–21.4 nm; and small LDLP, 19–20.4 nm. The cholesterol and triglyceride content in the total TRL fraction were calculated using the same LP4 algorithm by taking into consideration the number of TRL particles and the signals from the cholesteryl ester, cholesterol and triglycerides molecules. Total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and apolipoprotein B (apoB) were determined using the Extended Lipid Panel Assay as described in detail elsewhere [24]. Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL cholesterol. Very large TRL particles were either very low or undetectable, and were, therefore, not reported. Small LDL particles could not be determined in one participant. For this reason, total LDL particles, small LDL particles and LDL size were reported for 16 participants.

Statistical analysis

SPSS 28 (version 28.0, IBM Corp., Armonk, NY, USA) and R version 4.3.0 (Vienna, Austria) (http://cran.r-project.org/) were used for data analysis and visualization. Lipoprotein subfraction concentrations and other continuous variables were deliberately reported as mean ± SD to facilitate comparison with previous studies and across lipoprotein subclasses. Despite some skewness in certain variables, mean ± SD provides a standardized representation that allows for better assessment of relative changes.

Given the small sample size, normality tests have limited reliability, and paired t-tests, which are robust to moderate deviations from normality, were used for comparisons. To ensure validity, we also performed non-parametric Wilcoxon signed-rank tests, which confirmed that all significant results remained unchanged.

Changes are presented with 95% confidence intervals (CI). Pearson correlation coefficients were calculated by linear regression analysis with 95% CI. Two-sided *P*-values < 0.05 were considered to be significant. To assess the robustness of the correlation, we also included multivariable regression analyses using adjustment for age, sex, estimated glomerular filtration rate and body mass index.

Results

We included 17 DTC patients (16 women, aged 46 ± 11 (range 26 to 66) years), of whom 14 had papillary thyroid carcinoma and 3 follicular thyroid carcinoma. Two had a history of hypothyroidism and were treated with levothyroxine before thyroidectomy, another patient was treated for Graves disease 8 years before the study. One participant had type 1 diabetes. None of the participants had distant metastases. Concomitant drug use, i.e. oral contraceptives ($n = 8$), short acting insulin administered via an insulin pump (approximately 45 units per day; $n = 1$), prednisolone (5 mg daily, $n = 1$) were unchanged during the study. None of the participants were current smokers, eight patients were former smokers, all of whom had stopped smoking at least three years prior to study entry. Nine patients (53%) did not consume alcohol, while the remaining eight patients reported an average intake of 1.1 ± 2.0 alcoholic beverages per week. Detailed characteristics of the study population are presented in Table 1.

Mean TSH was 106 (range 59 to 371) mU/L during hypothyroidism and 0.19 (range 0.01 to 2.15) mU/L during thyroid hormone supplementation ($P < 0.001$). 16 of the 17 patents had a TSH level below the reference range during thyroid hormone supplementation. During hypothyroidism mean FT4 was 2.7 (range 0.8 to 6.8) pmol/L. None of the participants had a history of hyperlipidemia. During hypothyroidism, body weight was 82.2 ± 15.1 kg vs. 81.0 ± 16.3 kg during thyroid hormone supplementation, corresponding to a BMI of 27.5 ± 5.0 kg/m^2 and 27.1 ± 5.6 kg/m^2, respectively ($P = 0.03$). Plasma glucose did not significantly change (89 ± 15 mg/dL during hypothyroidism and 96 ± 25 mg/dL during thyroid hormone supplementation; $P = 0.08$). Time span between thyroidectomy and I^{131} administration was 4 weeks in 12, 5 weeks in 3 and 6 weeks in 2 participants (Table S1). There were no significant correlations between the time span between thyroidectomy and blood sampling during

Table 1 Baseline patient characteristics

Parameters for the entire cohort, independent of study visit			
Sex, female, *n (%)*	16 (94)		
Age, *mean ± SD*	46 ± 11		
Insulin use, *n (%)*	1 (5)		
Prednisolone use, *n (%)*	1 (5)		
Oral contraceptive use, *n (%)*	8 (47)		
Smoked, *n (%)*			
Never	9 (53)		
Currently	0		
Formerly	8 (47)		
Daily cigarettes (former smokers), *mean ± SD*	13 ± 7		
Years smoked (former smokers, *mean ± SD*	14.8 ± 14.0		
Years stopped, *mean (min-max)*	18 (3–34)		
Alcohol, *n* yes *(%)*	8 (47)		
Weekly number of alcoholic beverages, *mean ± SD*	1.1 ± 2.0		
Parameters per study visit	**Hypothyroidism (TSH range 59–371 mU/L)**	**Thyroid hormone supplementation (TSH range 0.01–2.15 mU/L)**	***P*-value**
TSH, mU/L	106 ± 75	0.19 ± 0.51	< 0.001
FT4, pmol/L	2.7 ± 1.5	-	-
Systolic blood pressure, mmHg	124 ± 17	127 ± 17	0.23
Diastolic blood pressure, mmHg	81 ± 8.6	79 ± 12.6	0.43
Pulse, rate/min	68 ± 9.0	77 ± 8.3	0.02
Weight, kg	82.2 ± 15.1	81.0 ± 16.3	0.03
BMI, kg/m^2	27.5 ± 4.9	27.1 ± 5.6	0.03
Glucose, mg/dL	89 ± 15	96 ± 25	0.08

The *P*-value refers to the comparison of parameters at the visit of hypothyroidism versus the visit of thyroid supplementation

Abbreviations: BMI: body mass index; FT4: free thyroxine TSH: thyroid stimulating hormone, SD: standard deviation

hypothyroidism with TSH (r=-0.224, P = 0.387); or with FT4 (r=-0.301, P = 0.240).

As shown in Table 2, plasma total cholesterol, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and apoB were all considerably higher during hypothyroidism compared with their levels during thyroid hormone supplementation. The total TRL particle concentration was also substantially higher during hypothyroidism, which was attributable to an increase in medium, small and very small TRL particles. Very large TRL particles were not detectable in most participants in any of the study visits, consistent with the fasting state. Notably, of the TRL subfractions, the most pronounced changes were observed for very small TRL particles, which correspond to remnant particles. As a result, the average TRL size was smaller during hypothyroidism vs. thyroid hormone supplementation. The significant changes in these lipoprotein subfractions and the lack of significant changes in large TRL and small LDL were confirmed by Wilcoxon signed rank tests (not shown). Also when adjusting for BMI by dividing very small TRL particle concentration by the BMI, the very small TRL particle/BMI ratio was much higher during hypothyroidism (6.88 ± 3.36 nmol/L per kg/m^2) compared to its value obtained during thyroid hormone supplementation (2.43 ± 1.1 nmol/L per kg/m^2; P < 0.001) (change -65% (95% CI -89 to -40%). Along with these changes in TRL particles, the cholesterol content and the cholesterol/triglyceride ratio in TRL were higher during hypothyroidism. In line, the relative changes in TRL cholesterol during hypothyroidism where greater than those in TRL triglycerides (P = 0.002) (Table 2). Furthermore, the total LDL particle concentration was higher during hypothyroidism, consequent to increases in large and medium LDL particles. Small LDL particles did not change. As a result, the average LDL size was greater during hypothyroidism vs. during thyroid hormone supplementation (Table 2). Figure 1 shows the plasma total TRL concentration (panel A), very small TRL particles (remnants) (panel B), the total TRL cholesterol content (panel C) and the total TRL cholesterol/triglyceride ratio (panel D) during hypothyroidism and thyroid hormone supplementation. When excluding participants which levothyroxine supplementation, the participant which used insulin and the male participant, leaving 14 participants (due to overlap), essentially similar findings were observed (data not shown). In this subset, BMI was 26.75 ± 4.53 kg/m^2 during hypothyroidism and 26.34 ± 5.15 kg/m^2 during liothyronine supplementation (P = 0.064). Very small TRL particles, TRL cholesterol, TRL triglycerides and

Table 2 Lipoprotein variables of 17 patients with differentiated thyroid carcinoma during hypothyroidism and after 20 weeks of thyroid hormone supplementation

Parameter	Hypothyroidism (TSH range 59–371 mU/L)	Thyroid hormone supplementation (TSH range 0.01–2.15 mU/L)	Change with 95% CI**	*P*-value
Total cholesterol (mg/dL)	256 ± 53	154 ± 21	-39 (-43 to -24)	< 0.001
Non-HDL cholesterol (mg/dL)	185 ± 45	98 ± 9	-56 (-51 to -41)	< 0.001
LDL cholesterol (mg/dL)	145 ± 35	79 ± 17	-45 (-49 to -40)	< 0.001
HDL cholesterol (mg/dL)	71 ± 18	52 ± 11	-18 (-24 to -12)	< 0.001
Triglycerides (mg/dL)	138 ± 47	92 ± 26	-31 (-38 to -25)	< 0.001
Apolipoprotein B (mg/L)	130 ± 31	70 ± 13	-45 (-50 to -40)	< 0.001
Total TRL particles (nmol/L)	279 ± 81	111 ± 38	-58 (-66 to -50)	< 0.001
Very large TRL particles (nmol/L)	ND	ND	ND	ND
Large TRL particles (nmol/L)	1.9 ± 2.8	1.5 ± 1.7	-25 (-53 to 3)	0.34
Medium TRL particles (nmol/L)	14.9 ± 12.3	8.7 ± 6.2	-42 (-47 to -35)	0.018
Small TRL particles (nmol/L)	77.6 ± 50.3	36.0 ± 29.2	-42 (-60 to -24)	0.002
Very small TRL particles (nmol/L)	183 ± 76	64 ± 27	-57 (-70 to -45)	< 0.001
TRL size (nm)	41.9 ± 7.2	45.5 ± 8.5	3.7 (0.8 to 6.6)	0.017
TRL cholesterol (mg/dL)	40 ± 13	19 ± 6	-51 (-59 to -43)	< 0.001
TRL triglycerides (mg/dL)	93 ± 44	53 ± 25	-41 (-50 to -32)	< 0.001
TRL cholesterol/triglyceride ratio	0.47 ± 0.12	0.39 ± 0.10	-16 (-23 to -8)	< 0.001
Total LDL particles (nmol/L)*	1991 ± 432	1197 ± 198	-39(-59 to -28)	< 0.001
Large LDL particles (nmol/L)	823 ± 428	363 ± 151	-38 (-67 to -8)	< 0.001
Medium LDL particles (nmol/L)	736 ± 464	292 ± 271	-46 (-72 to -19)	0.002
Small LDL particles (nmol/L)*	502 ± 259	535 ± 232	16 (-5 to 67)	0.67
LDL size (nm)*	21.4 ± 0.5	21.0 ± 0.4	-0.4 (-0.6 to -0.1)	0.004

Data in mean ± SD. *Small LDL particles could not be determined in 1 participant; total LDL particles and LDL size are therefore calculated in 16 participants **Changes are expressed in mean % change with 95% confidence intervals, except for TRL and LDL size for which the differences are in mean with 95% confidence intervals. Statistical comparisons were done by paired T-tests. Abbreviations: CI, Confidence intervals HDL, high density lipoproteins; LDL, low density lipoproteins; ND: not detectable in most participants in any of the study visits; non-HDL cholesterol: non-High Density Lipoprotein cholesterol; TRL, triglyceride-rich lipoproteins; non-HDL cholesterol is calculated as the difference between total and HDL cholesterol. *P*-values are determined by paired T-test

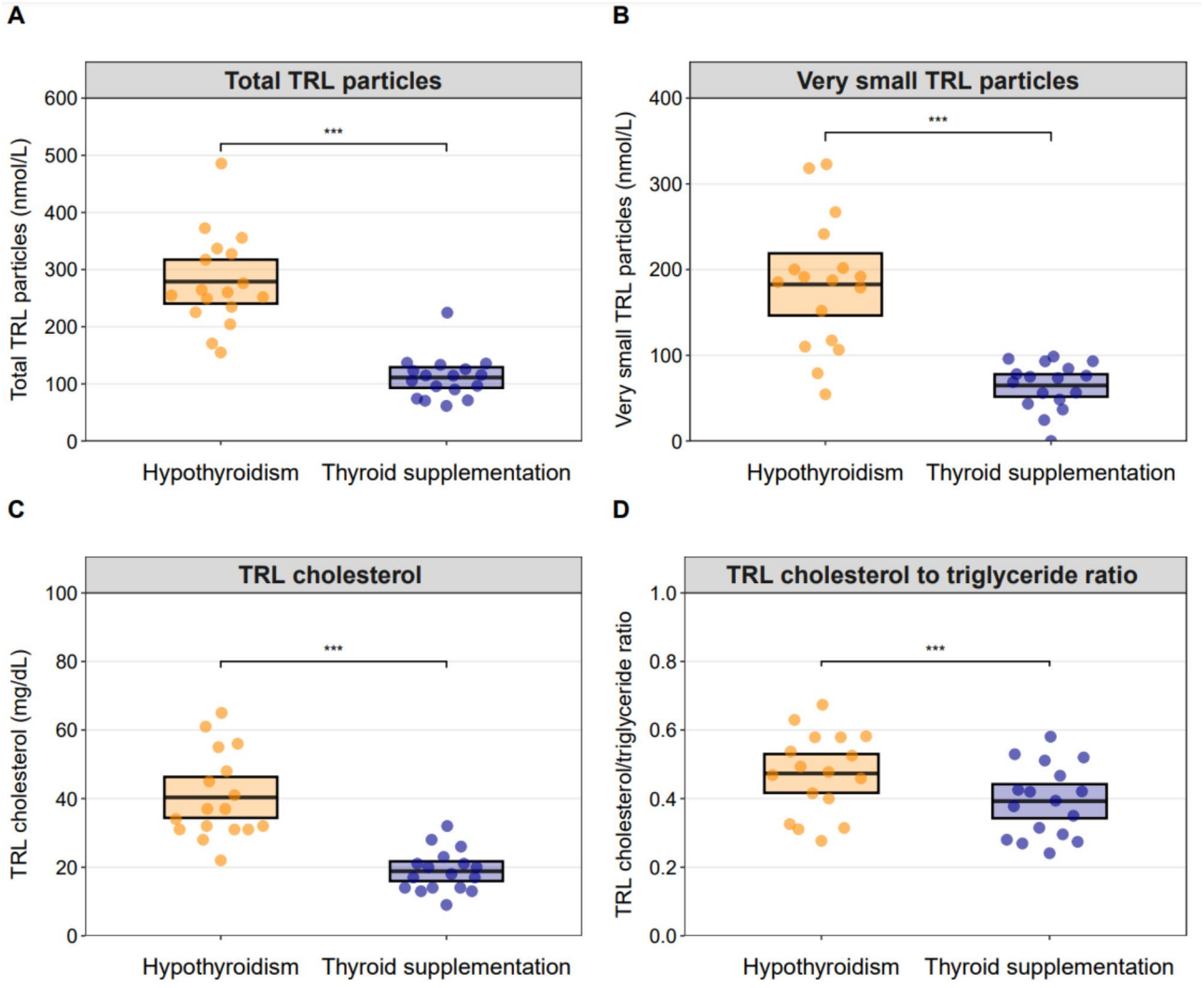

Fig. 1 Plasma total triglyceride-rich lipoprotein (TRL) concentration (**panel A**), very small TRL particles (remnants) (**panel B**), the total TRL cholesterol content (**panel C**) and the total TRL cholesterol/triglyceride ratio (**panel D**) during hypothyroidism (left side) and thyroid hormone supplementation (right side) in 17 patients with differentiated thyroid carcinoma. Dot plots with boxes representing mean and 95% confidence intervals are shown. ***$P < 0.001$

the TRL cholesterol/triglyceride ratio were 188 ± 82 nmol/L, 41 ± 13 mg/dL, 88 ± 43 mg/dL and 0.50 ± 0.11 during hypothyroidism and 69 ± 23 nmol/L ($P < 0.001$), 18 ± 6 mg/dL ($P = 0.012$), 49 ± 24 mg/dL ($P < 0.001$) and 0.41 ± 0.10 ($P = 0.007$), respectively during liothyronine supplementation. All other changes in lipoprotein variables were also similar compared to those obtained in the whole group.

The total TRL particle cholesterol content was correlated with very small TRL particles during hypothyroidism ($r = 0.618$ (95%CI, 0.195 to 0.884); $P = 0.008$), but less so during thyroid hormone supplementation ($r = 0.474$ (95%CI, -0.010 to 0.777); $P = 0.055$) in line with the shift in TRL particle distribution during hypothyroidism. Of note, the changes in the total TRL particle cholesterol content, as well as in the total TRL cholesterol/triglyceride ratio were correlated with the changes in very small TRL particles ($r = 0.702$ (95%CI, 0.335 to 0.884); $P = 0.002$ and $r = 0.615$ (95%CI, 0.191 to 0.846); $P = 0.009$), respectively). These associations were similar when assessed using linear regression analyses with adjustments for age, sex, eGFR and BMI (Table S2). Figure 2 shows the relationships of changes in very small TRL particles with changes in total TRL cholesterol content (panel A) and with changes in total TRL cholesterol/triglyceride ratio (panel B).

Discussion

The present study shows that plasma concentrations of very small TRL particles, corresponding to remnant lipoproteins based on their size, are elevated in profound hypothyroidism compared with their concentrations during thyroid hormone supplementation, aimed at achieving TSH levels below the reference range. Of the

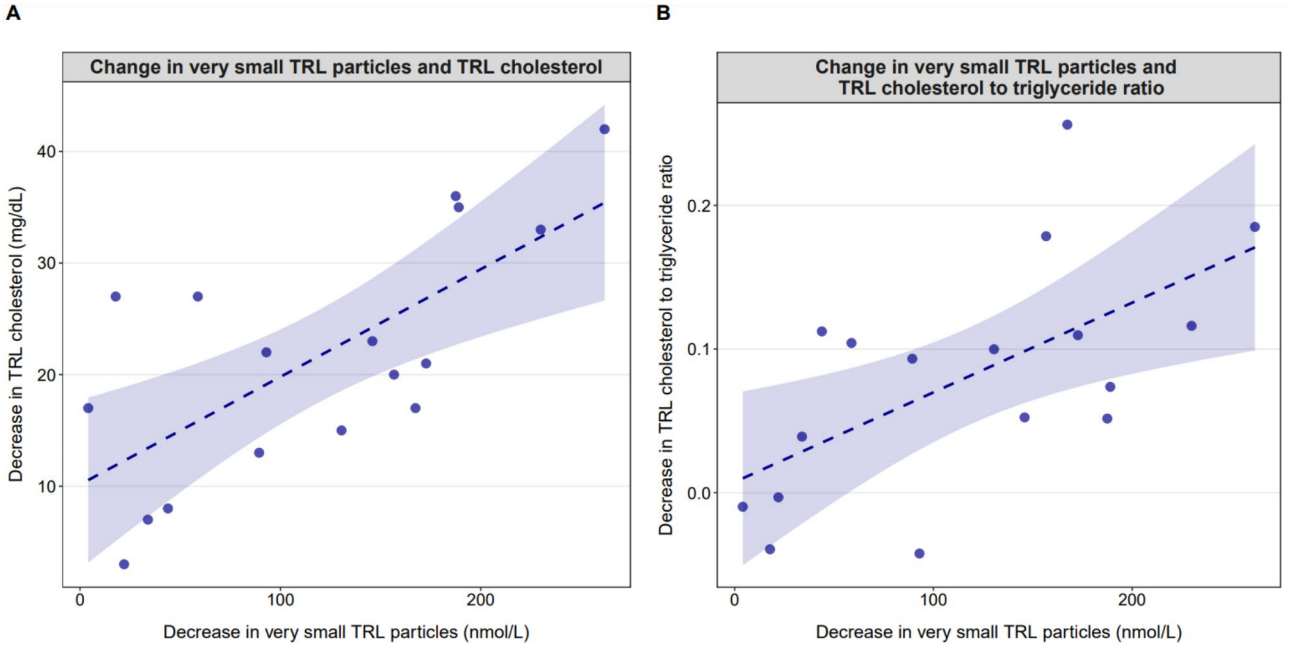

Fig. 2 Relationships between changes in very small TRL particles and total TRL cholesterol content (left **panel**; $r = 0.702$ (95%CI, 0.335 to 0.884); $p = 0.002$) and the total TRL cholesterol/triglyceride ratio (right **panel;**$r = 0.615$ (95%CI, 0.191 to 0.846); $P = 0.009$). Regression lines with 95% confidence intervals are shown

individual TRL subfractions the greatest effect was seen for very small TRL particles resulting in a smaller TRL size during hypothyroidism. Furthermore, the cholesterol content and the cholesterol/triglyceride ratio in the total TRL fraction were higher during hypothyroidism, and the changes in these TRL cholesterol estimates were correlated with the changes in very small TRL particles the during thyroid hormone supplementation. Collectively, the current findings support the notion that thyroid hormone status exerts profound effects on remnant lipoproteins, along with effects on circulating triglycerides, LDL cholesterol, non-HDL cholesterol, apoB, as well as the total TRL and LDL concentrations. We surmise that the predominant effect on very small TRL particles could be regarded as a consequence of delayed TRL delipidation and clearance in hypothyroidism [5–8].

Besides studies using immunoseparation techniques and an NMR study on lipoprotein subfractions in subclinical hypothyroidism [15, 17, 25], two previous studies have reported on NMR-determined lipoprotein subfractions during hypothyroidism consequent to (near) total thyroidectomy for thyroid carcinoma as compared to resumption with levothyroxine [18, 26]. In the study of Pearce et al., TSH levels averaged 73 mU/L during hypothyroidism and 0.74 mU/L after thyroid hormone resumption among 28 DTC patients [26]. In the study of Bagdade et al. TSH levels averaged 63 mU/L during hypothyroidism and 0.49 mU/L after levothyroxine resumption among 13 DTC patients [18]. Although not specified, in both studies several patients were likely to be restudied with levothyroxine while TSH was below the reference range. Notably, lipoprotein subfractions were measured in the same laboratory in these studies as in the present report [18, 26]. However, an early version of the deconvolution algorithm was used in these studies to document lipoprotein subfractions, and TRL cholesterol TRL and triglycerides were not reported. Importantly, very small TRL particles were reported in these studies as intermediate density lipoproteins rather than as very small TRLs. Both Pierce et al. and Bagdade et al. found elevations in intermediate density lipoproteins (IDL) during hypothyroidism, but such different categorization of TRL subfractions (very small TRL particles using the so-called LP4 algorithm vs. IDL being categorized as TRL remnants) precludes direct comparison of TRL size between the present report and these previous studies. Of further relevance, while both studies shown an increase in IDL, there was no comparison regarding the extent of IDL elevations compared to changes TRL subfractions.

The TRL cholesterol concentration averaged 40 mg/dL during hypothyroidism and 19 mg/dL during thyroid hormone supplementation. In comparison, in the Copenhagen General Population Study, remnant cholesterol, corresponding to TRL cholesterol in the current study, amounted to 23 mg/dL [10]. This aligns well with the current finding that TRL cholesterol is considerably elevated during hypothyroidism. Also our findings on LDL cholesterol and triglyceride elevations correspond with previous results in which thyroidectomy for thyroid cancer

was used as an intervention to induce hypothyroidism [19, 20]. With the exception of large TRL particles and small LDL particles, all TRL and LDL subfractions as well as apoB levels were considerably elevated during hypothyroidism as compared to the levels found in the PREVEND study, a general population-based study among participants of predominant North European descent, in which we applied a similar NMR platform and the LP4 algorithm [14]. TRL and LDL particles as well as apoB concentrations during hypothyroidism were also elevated compared to concentrations in a US control population [24]. In addition, average TRL size was smaller during hypothyroidism compared to findings from these general population cohorts [14, 27]. A previous study suggested that hypothyroidism may be associated with a predominance of small, dense LDL particles, as assessed by tube gel electrophoresis [28]. However, in our study, small LDL particles did not differ significantly, consistent with findings from other NMR-based studies [18, 26]. Regarding LDL size, we observed only a minor decrease after thyroid hormone supplementation, suggesting that the increase in LDL cholesterol during hypothyroidism was primarily driven by larger LDL particles rather than a shift toward small, dense LDL. The limited change in LDL size also aligns with the findings of Kim et al. [29], who reported no significant differences in LDL particle size across thyroid function states.

There is a robust association of all-cause mortality with non-HDL cholesterol [30]. Moreover, the association of apoB with incident ASCVD is as strong or perhaps even stronger than that of LDL cholesterol [31, 32]. Likewise, the association of total LDL particle concentration, measured by NMR spectroscopy, with incident cardiovascular disease has been reported to be at least as strong as that of conventional lipid measurements [33, 34]. Interestingly, it has been estimated that on a per particle basis, TRL remnants are approximately 4 times more atherogenic than LDL [35]. Against this background our findings support the contention that the profound elevations in cholesterol rich TRL, remnant particles and LDL particle concentrations together with increases in standard lipids may play an important role in the elevated ASCVD risk in the context of hypothyroidism [2, 3].

Strengths and limitations

The strengths of this study are the extensive NMR data, and that data collection for our study was carried out following the sequence of interventions as indicated by Dutch treatment guidelines for DTC, as operative during the study inclusion period between 2015 and 2019. Limitations are that individual dietary intake data, including macronutrient composition (e.g., carbohydrate, saturated and unsaturated fat, and protein from animal or plant sources), were not collected. Nonetheless, representative data on the habitual dietary intake of Dutch adults are available in a national dietary survey conducted by the National Institute for Public Health and the Environment (RIVM Report 2022 – 0190) [36]. The striking female predominance of DTC explains why most patients included were female [37]. For practical reasons it was not feasible to synchronize study visits with an individualized phase of the menstrual cycle or oral contraceptive use. Consequently, some effects of different phases of the menstrual cycle or oral contraceptives on lipoprotein (sub)factions cannot be excluded. Furthermore, the extent to which profound hypothyroidism affects the various TRL and LDL subfractions reported here do not necessarily hold true for males, and we consider the present findings as preliminary. As this study focuses on remnant lipoproteins, it is important to consider whether dysbetalipoproteinemia could be an underlying lipoprotein abnormality. However, due to its low prevalence and the fact that none of the participants had total cholesterol levels exceeding 200 mg/dL (maximum: 193 mg/dL) or triglycerides exceeding 175 mg/dL (maximum: 149 mg/dL) during thyroid hormone supplementation —thresholds proposed for further dysbetalipoproteinemia evaluation— this diagnosis can essentially be ruled out [38]. Also, in this study we aimed to achieve TSH levels below the reference range, rather than complete TSH suppression with undetectable TSH levels, which was achieved in nearly all patients. Therefore, as in previous studies [18, 26], it cannot be excluded that potential mild over supplementation could have to some extent overestimated the lipoprotein subfraction effects observed. Lastly, the use of T3 instead of T4 limits generalizability, as it bypasses regulated conversion, leading to faster TSH suppression and potentially altering thyroid hormone signaling across tissues.

Conclusion

This study demonstrates that profound hypothyroidism consequent to thyroidectomy gives rise to substantial increases in circulating TRL and LDL particle concentrations. The most pronounced effect was found for very small TRL (remnant) particles. Increases in remnant particles were related to increase in the TRL cholesterol/triglyceride ratio. Given the high atherogenicity of TRL remnants, these findings offer a mechanistic explanation for the increased cardiovascular risk associated with hypothyroidism. The pronounced rise in remnant particles suggests that lipid abnormalities may be present even when conventional lipid levels appear normal. Future research should examine whether similar, though more subtle, changes occur in subclinical hypothyroidism and whether they contribute to long-term cardiovascular risk. These insights may ultimately inform individualized lipid management across the spectrum of thyroid dysfunction.

Abbreviations

Apo	Apolipoprotein
BMI	Body mass index
CI	Confidence intervals
CV	Coefficient of variation
DTC	Differentiated thyroid carcinoma
FT4	Free thyroxine
HDL	High density lipoproteins
LDL	Low density lipoproteins
NMR	Nuclear magnetic resonance
NTR	Netherlands Trial Register
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TRL	Triglyceride-rich lipoproteins
TSH	Thyroid stimulating hormone

Supplementary Information

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Supplementary Material 1

Author contributions

TPL and RPFD developed and formulated the research questions, have full access to the study data and take responsibility for its integrity and the data analysis. AP and RPFD wrote the manuscript. AP, MHL, WTZ, MAC, TPL and RPFD contributed to the acquisition of data, contributed to discussion, draft revision and edited the manuscript. All authors approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen (registration number 2015/116).

Conflicts of interest

MAC is an employee of LabCorp and holds stock in LabCorp. The other authors declare that they have no conflicts of interest.

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