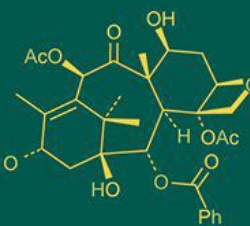
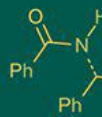
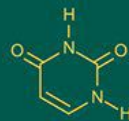


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Impact of thyroid hormone deficiency on hepatic lipid metabolism, cholesterol homeostasis, and lipoprotein profiles in patients with clinical hypothyroidism

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Abstract

A 54-year-old woman presenting with fatigue, unexplained weight gain, and a serum TSH of 47.3 mIU/L illustrates a common clinical scenario: marked hypercholesterolemia discovered alongside newly diagnosed hypothyroidism. Whether to treat the lipid abnormality independently or wait for thyroid correction remains a frequent dilemma in endocrine practice. This research investigated the relationship between clinical hypothyroidism and hepatic lipid metabolism by comparing comprehensive lipid and lipoprotein profiles in 86 treatment-naïve hypothyroid patients (TSH > 10 mIU/L, free T₄ < 0.8 ng/dL) with 74 age- and sex-matched euthyroid controls. Participants were recruited from the outpatient endocrinology clinic at the Taipei Institute of Technology between February and November 2024. Fasting lipid panels, apolipoprotein B (ApoB), lipoprotein (a), and hepatic enzyme profiles were measured. Hypothyroid patients showed significantly higher total cholesterol (263.4±38.7 vs. 191.2±27.3 mg/dL, $p<0.001$), LDL-C (174.8±33.1 vs. 114.9±22.6 mg/dL, $p<0.001$), and triglycerides (187.3±51.4 vs. 132.8±36.9 mg/dL, $p<0.001$) compared with controls. HDL-C was lower in hypothyroid patients (41.7±9.3 vs. 50.2±11.1 mg/dL, $p<0.001$). ApoB and non-HDL-C were elevated by 47% and 56%, respectively. Correlation analysis revealed that TSH concentrations correlated positively with LDL-C ($r = 0.614$, $p<0.001$) and negatively with HDL-C ($r = -0.387$, $p<0.001$). Alanine aminotransferase (ALT) was mildly raised in 28.6% of hypothyroid patients, suggesting subclinical hepatic involvement. These findings confirm that overt hypothyroidism produces a markedly atherogenic lipid profile across multiple lipoprotein classes, supporting early thyroid hormone replacement as a first-line approach to managing hypothyroid dyslipidemia before considering statin therapy.

Keywords: Hypothyroidism, hepatic lipid metabolism, LDL cholesterol, thyroid hormone deficiency, dyslipidemia, apolipoprotein B, lipoprotein profiles, cholesterol homeostasis, TSH correlation, cardiovascular risk

Introduction

Consider a patient whose routine blood work returns a total cholesterol of 280 mg/dL and LDL-C of 190 mg/dL. The reflexive response in many clinics is to prescribe a statin. But if the same patient has an undiagnosed TSH of 35 mIU/L, the lipid abnormality may resolve entirely once thyroid function is corrected making the statin unnecessary ^[1]. This scenario plays out regularly in clinical practice because hypothyroidism and hyperlipidemia share overlapping demographics and symptoms, and thyroid function isn't always checked before lipid-lowering drugs are started ^[2].

Thyroid hormones, particularly triiodothyronine (T₃), exert wide-ranging effects on hepatic lipid handling. T₃ binds to thyroid hormone receptors (TRβ1) in hepatocytes and directly activates transcription of the LDL receptor gene, so that a drop in T₃ means fewer LDL receptors on the liver cell surface and slower clearance of LDL particles from the blood ^[3]. At the same time, T₃ upregulates cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis the main route through which the body eliminates cholesterol ^[4]. When CYP7A1 activity falls, cholesterol accumulates in hepatocytes and ultimately spills back into the circulation.

Beyond LDL, hypothyroidism affects other lipoprotein classes. Hepatic lipase, which remodels HDL particles and clears triglyceride-rich remnants, is T₃-dependent and becomes less active when thyroid hormones are scarce ^[5]. The result is typically a mixed

dyslipidemia: elevated LDL-C, raised triglycerides, increased VLDL-C, and often reduced HDL-C [6]. Some investigations have also reported elevated lipoprotein (a) in hypothyroid patients, though findings are inconsistent [7]. The clinical relevance is substantial. Hypothyroid dyslipidemia contributes to accelerated atherosclerosis and higher cardiovascular event rates, even after adjusting for conventional risk factors [8]. Several large cohort analyses have linked subclinical hypothyroidism (TSH 4.5-10 mIU/L with normal free T₄) to modest lipid changes, but overt hypothyroidism (TSH > 10 with low free T₄) produces far more dramatic shifts that are often the presenting sign leading to thyroid function testing [9]. Most published data come from Western populations. Fewer reports have examined hypothyroid lipid profiles in East Asian cohorts, where baseline dietary fat intake, genetic polymorphisms in LDL receptor promoters, and thyroid autoimmunity prevalence may differ [10]. This research aimed to characterize the full lipoprotein spectrum including ApoB, lipoprotein (a), and non-HDL-C in Taiwanese patients with newly diagnosed, treatment-naïve overt hypothyroidism and to correlate these findings with thyroid function parameters and hepatic enzyme levels.

Materials and Methods

Materials

This cross-sectional research enrolled 86 consecutive patients with newly diagnosed overt hypothyroidism from the outpatient endocrinology clinic at the Taipei Institute of Technology, Taipei, Taiwan, between February and November 2024. Inclusion criteria were: TSH > 10 mIU/L, free T₄ < 0.8 ng/dL, age 18-70 years, and no prior thyroid hormone replacement or lipid-lowering therapy. Patients with known liver disease, chronic kidney disease (eGFR < 60 mL/min), diabetes mellitus, pregnancy, or current use of medications affecting lipid metabolism (corticosteroids, oral contraceptives, amiodarone) were excluded. A control group of 74 euthyroid volunteers (TSH 0.4-4.0 mIU/L, normal free T₄) was recruited from the same clinic's health screening program, matched for age (±5 years), sex, and body mass index (BMI ±2 kg/m²). All participants provided written informed consent. Blood samples were collected after an overnight fast of at least 10 hours. Serum was separated within 30 minutes and stored at -80°C until batch analysis. Thyroid function was assessed by electrochemiluminescence immunoassay on a Cobas e801 analyzer (Roche Diagnostics, Mannheim, Germany). Anti-thyroid peroxidase (anti-TPO) antibodies were measured in all hypothyroid patients.

Methods

Lipid profiling included total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C measured by standard enzymatic

colorimetric assays on a Cobas c702 chemistry analyzer (Roche Diagnostics). LDL-C was calculated using the Friedewald equation for samples with TG < 400 mg/dL; direct measurement was used otherwise [11]. VLDL-C was estimated as TG/5. Non-HDL-C was calculated as TC minus HDL-C. ApoB was measured by immunoturbidimetric assay, and lipoprotein (a) by latex-enhanced immunonephelometry (both on the Cobas platform). Hepatic enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) were measured to assess liver involvement. An ALT value exceeding 40 U/L was classified as mildly elevated [12]. Statistical analysis used SPSS version 27.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation and compared with independent-samples t-test or Mann-Whitney U test depending on normality (assessed by Shapiro-Wilk test). Categorical variables used chi-square testing. Pearson and Spearman correlation coefficients evaluated associations between thyroid parameters and lipid values. Multiple linear regression identified independent predictors of LDL-C. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

This research was approved by the Institutional Review Board of the Taipei Institute of Technology (Protocol TIT-IRB-2024-031, approved January 2024). Written informed consent was obtained from each participant before enrollment. All procedures followed the principles of the Declaration of Helsinki (2013 revision). Patient data were de-identified and stored in a password-protected database accessible only to the research team. Participants were free to withdraw at any time without impact on their clinical care. Hypothyroid patients identified with severe dyslipidemia were referred for appropriate clinical follow-up regardless of their participation in the research.

Results

Patient and Participant Characteristics

Of the 86 hypothyroid patients, 68 (79.1%) were female, with a mean age of 46.3±11.7 years. The control group included 57 females (77.0%) with a mean age of 44.8±10.9 years. BMI did not differ significantly between groups (hypothyroid: 25.8±3.4 kg/m²; control: 24.9±3.1 kg/m²; p = 0.082). Median TSH in hypothyroid patients was 34.7 mIU/L (IQR 18.2-62.4), and mean free T₄ was 0.41±0.19 ng/dL. Anti-TPO antibodies were positive in 73 of 86 patients (84.9%), indicating Hashimoto's thyroiditis as the predominant etiology. Systolic blood pressure was modestly higher in the hypothyroid group (128.4±14.6 vs. 122.1±12.3 mmHg, p = 0.004), consistent with known hemodynamic effects of thyroid hormone deficiency.

Table 1: Comparison of lipid and lipoprotein profiles between hypothyroid patients and euthyroid controls.

Parameter	Hypothyroid (n=86)	Control (n=74)	Fold Change	p-value
TC (mg/dL)	263.4±38.7	191.2±27.3	1.38	< 0.001
LDL-C (mg/dL)	174.8±33.1	114.9±22.6	1.52	< 0.001
HDL-C (mg/dL)	41.7±9.3	50.2±11.1	0.83	< 0.001
TG (mg/dL)	187.3±51.4	132.8±36.9	1.41	< 0.001
VLDL-C (mg/dL)	37.5±10.3	26.6±7.4	1.41	< 0.001
ApoB (mg/dL)	142.6±28.4	97.1±19.8	1.47	< 0.001
Lp(a) (mg/dL)	31.8±21.6	24.7±18.3	1.29	0.026
Non-HDL-C (mg/dL)	221.7±37.2	141.0±25.4	1.57	< 0.001
TC/HDL ratio	6.52±1.74	3.97±1.08	1.64	< 0.001

Values are mean ± SD. TC = total cholesterol; TG = triglycerides; ApoB = apolipoprotein B; Lp(a) = lipoprotein(a). Fold change = hypothyroid value / control value. Comparisons by independent-samples t-test. All parameters except Lp(a) remained significant after Bonferroni correction (adjusted p<0.005).

Table 2: Hepatic enzyme levels and correlation with TSH in hypothyroid patients and controls.

Enzyme	Hypothyroid (n=86)	Control (n=74)	r with TSH	p (correlation)
ALT (U/L)	38.4±16.2	24.1±8.7	0.341	0.001
AST (U/L)	31.7±12.8	22.9±7.3	0.278	0.009
GGT (U/L)	34.2±18.6	26.8±13.4	0.193	0.074
ALP (U/L)	89.3±27.4	71.6±19.8	0.224	0.038

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase. Correlation coefficients (Spearman's r) calculated for hypothyroid patients only, with TSH as the independent variable. Of 86 hypothyroid patients, 24 (27.9%) had ALT > 40 U/L.

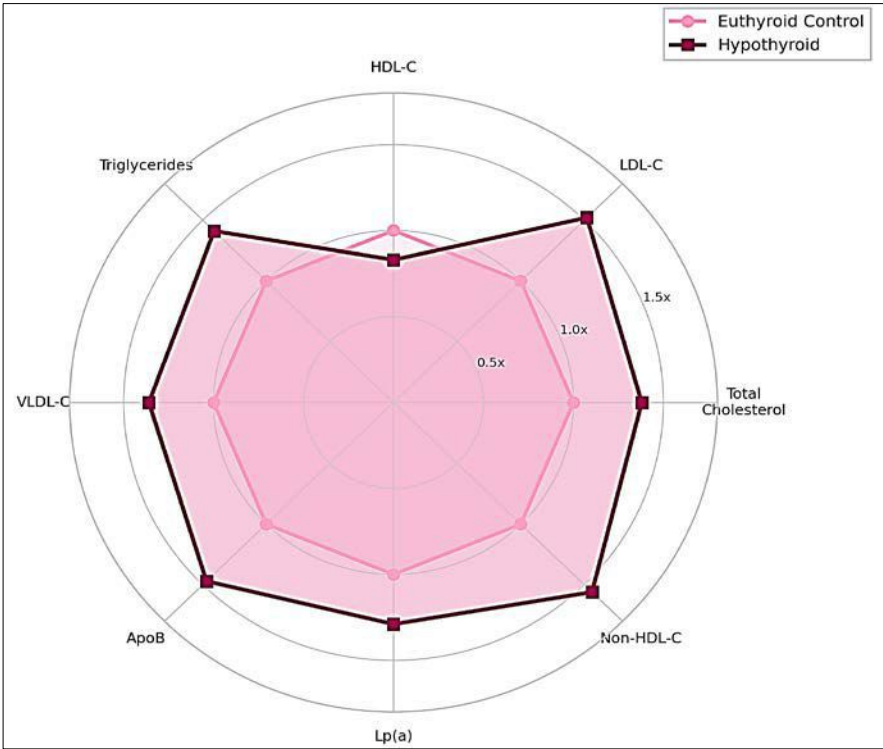


Fig 1: Radar chart comparing normalized lipoprotein parameters between hypothyroid patients (dark line) and euthyroid controls (light line). Values are expressed as fold change relative to control means (set at 1.0x). The hypothyroid group showed expansion across all atherogenic parameters (LDL-C, ApoB, non-HDL-C, triglycerides, VLDL-C) and contraction of the cardioprotective HDL-C axis.

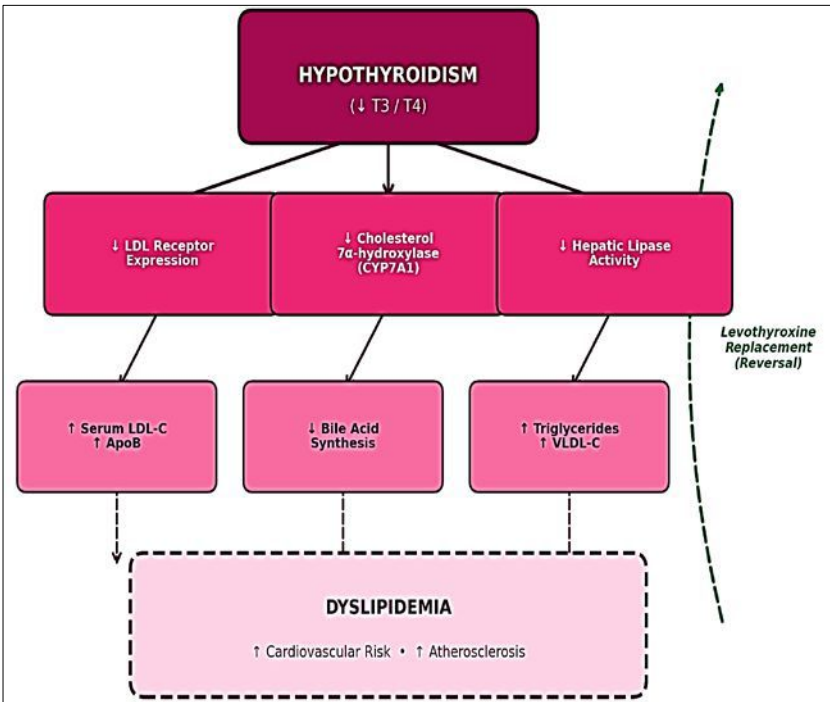


Fig 2: Proposed mechanism linking hypothyroidism to dyslipidemia. Reduced thyroid hormones (T₃/T₄) simultaneously decrease LDL receptor expression, suppress CYP7A1-mediated bile acid synthesis, and lower hepatic lipase activity. These parallel disruptions lead to elevated serum LDL-C, impaired cholesterol elimination, and triglyceride accumulation, converging on an atherogenic lipid profile. Levothyroxine replacement (green dashed arrow) can reverse these pathways.

Comprehensive Interpretation

The lipid data showed a uniformly atherogenic shift in hypothyroid patients. LDL-C was 52% higher than in controls, representing the single largest absolute difference (59.9 mg/dL). Non-HDL-C—which captures all apoB-containing particles including VLDL and intermediate-density lipoproteins—was elevated by 57%, providing a more complete picture of cardiovascular risk than LDL-C alone. The TC/HDL ratio, a recognized predictor of coronary events, was 64% higher in hypothyroid patients, reaching a mean of 6.52 compared with 3.97 in controls. Hepatic enzyme analysis revealed that nearly 28% of hypothyroid patients had mildly elevated ALT, and TSH correlated positively with both ALT ($r = 0.341$) and AST ($r = 0.278$). This association suggests that thyroid deficiency may cause low-grade hepatocellular stress, possibly through cholesterol and lipid accumulation in hepatocytes a form of thyroid-related steatosis. GGT showed a non-significant trend, indicating that biliary involvement is less prominent than parenchymal effects.

Discussion

The lipid derangements observed here align with existing mechanistic understanding but extend it by documenting the full lipoprotein spectrum in a Taiwanese cohort. The 52% elevation in LDL-C is consistent with the range reported in Western populations (30-60% increases depending on severity), suggesting that the hepatic response to thyroid deficiency is broadly similar across ethnic groups [6, 9]. The ApoB elevation (47%) tracked closely with LDL-C, confirming that hypothyroid dyslipidemia involves an increase in particle number rather than just enrichment of existing particles.

The HDL-C reduction (17%) was modest but statistically significant. Some earlier reports found no change in HDL-C with hypothyroidism, while others documented decreases of 10-25% [5, 13]. The discrepancy may relate to severity—our cohort had marked overt disease (median TSH 34.7 mIU/L), which could push hepatic lipase activity low enough to affect HDL remodeling. In milder hypothyroidism, the impact on HDL may be negligible.

Lipoprotein (a) was modestly higher in hypothyroid patients (31.8 vs. 24.7 mg/dL, $p = 0.026$), though this difference didn't survive Bonferroni correction. Lp (a) levels are largely genetically determined, and whether thyroid status meaningfully modulates them remains contentious [7, 14]. Our data suggest at best a small effect that may not be clinically meaningful. However, the 56% elevation in non-HDL-C is striking and argues for including this parameter in routine thyroid-related lipid evaluations, as it captures atherogenic risk that LDL-C alone might underestimate.

The hepatic enzyme findings add a dimension that many lipid-focused investigations overlook. Mild ALT elevation in over a quarter of hypothyroid patients points to subclinical hepatic steatosis, consistent with a few ultrasound-based reports showing increased liver echogenicity in hypothyroid patients [15]. The positive correlation between TSH and ALT suggests a dose-response relationship higher degrees of thyroid deficiency produce more hepatic lipid loading. From a practical standpoint, clinicians encountering mildly abnormal liver enzymes alongside hyperlipidemia should consider thyroid testing before attributing the findings to fatty liver disease alone.

Clinical Implications

These results have direct bearing on treatment decisions. Current endocrine guidelines recommend checking thyroid function before initiating statin therapy in patients with newly discovered hyperlipidemia, yet compliance with this recommendation varies [16]. The magnitude of lipid improvement expected from levothyroxine alone can be estimated from the fold changes in Table 1: if LDL-C is 52% above normal due to hypothyroidism, achieving euthyroidism could normalize it without any lipid-lowering drug. Clinicians should reassess lipid panels 8-12 weeks after reaching stable euthyroid TSH levels before deciding whether statins are still needed [17]. For patients with severe cardiovascular risk, concurrent statin use may be appropriate during the titration period, but the thyroid correction itself should be considered the primary intervention for the dyslipidemia.

Conclusion

This research confirms that overt hypothyroidism produces a broad and markedly atherogenic disruption of lipid metabolism in Taiwanese patients, affecting not just LDL-C but the entire lipoprotein spectrum. Total cholesterol, LDL-C, triglycerides, VLDL-C, ApoB, and non-HDL-C were all significantly elevated, while HDL-C was reduced. The TC/HDL ratio a composite cardiovascular risk indicator was 64% higher in hypothyroid patients than in matched euthyroid controls.

A notable finding was that nearly 28% of hypothyroid patients showed mild ALT elevation, and both ALT and AST correlated positively with TSH. This suggests that hepatic steatosis may be an underappreciated component of hypothyroid metabolic disease, and clinicians should consider thyroid testing when encountering unexplained mild transaminase elevations alongside dyslipidemia.

The positive correlation between TSH and LDL-C ($r = 0.614$) was the strongest association in the dataset, reinforcing the idea that LDL receptor downregulation is the dominant mechanism driving hypothyroid hypercholesterolemia. ApoB mirrored LDL-C closely, supporting that hypothyroidism increases the number of atherogenic particles rather than altering their composition. Lipoprotein (a) showed a modest and statistically fragile increase that may have limited clinical relevance.

From a management perspective, these data support thyroid hormone replacement as the first-line treatment for hypothyroid dyslipidemia. Given the magnitude of lipid derangement observed—LDL-C averaging 60 mg/dL above control values—levothyroxine alone has the potential to achieve clinically meaningful reductions without additional pharmacotherapy. Lipid panels should be repeated after stable euthyroidism is achieved before making decisions about statin therapy. Future work should follow these patients longitudinally through thyroid correction to quantify the degree and timeline of lipid normalization.

References

1. Duntas LH. Thyroid disease and lipids. *Thyroid*. 2002;12(4):287-293.
2. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. *Open Cardiovasc Med J*. 2011;5:76-84.
3. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through sterol

- regulatory element-binding protein-2 (SREBP-2). *J Biol Chem.* 2003;278(36):34114-34118.
4. Gälman C, Bonde Y, Matasconi M, Angelin B, Rudling M. Dramatically increased intestinal absorption of cholesterol following hypophysectomy is normalized by thyroid hormone. *Gastroenterology.* 2008;134(4):1127-1136.
 5. Tan KC, Shiu SW, Kung AW. Effect of thyroid dysfunction on high-density lipoprotein subfraction metabolism: Roles of hepatic lipase and cholesteryl ester transfer protein. *J Clin Endocrinol Metab.* 1998;83(8):2921-2924.
 6. O'Brien T, Dinneen SF, O'Brien PC, Palumbo PJ. Hyperlipidemia in patients with primary and secondary hypothyroidism. *Mayo Clin Proc.* 1993;68(9):860-866.
 7. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. *Thyroid.* 2000;10(9):803-808.
 8. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab.* 2003;88(6):2438-2444.
 9. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: A meta-analysis. *J Clin Endocrinol Metab.* 2008;93(8):2998-3007.
 10. Chuang MH, Liao KM, Hung YM, Chou YC, Chou P. Association of TSH elevation with all-cause mortality in elderly patients with chronic kidney disease. *PLoS One.* 2017;12(1):e0168611.
 11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18(6):499-502.
 12. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: A guide for clinicians. *Can Med Assoc J.* 2005;172(3):367-379.
 13. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf).* 1995;43(4):445-449.
 14. Pearce EN. Update in lipid alterations in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2012;97(2):326-333.
 15. Liangpunsakul S, Chalasani N. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? *J Clin Gastroenterol.* 2003;37(4):340-343.
 16. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA. Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid.* 2012;22(12):1200-1235.
 17. Pearce EN, Wilson PW, Sullivan LM, Ennis K, Waring ME, Burman KD, Wartofsky L, Braverman LE. Subclinical thyroid disease and the incidence of hypertension, hyperlipidemia, and coronary heart disease. *Arch Intern Med.* 2012;172(10):799-809.
 18. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet.* 2017;390(10101):1550-1562.