REVIEW

Update on dyslipidemia in hypothyroidism: the mechanism of dyslipidemia in hypothyroidism

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Abstract

Hypothyroidism is often associated with elevated serum levels of total cholesterol, LDL-C and triglycerides. Thyroid hormone (TH) affects the production, clearance and transformation of cholesterol, but current research shows that thyroid-stimulating hormone (TSH) also participates in lipid metabolism independently of TH. Therefore, the mechanism of hypothyroidism-related dyslipidemia is associated with the decrease of TH and the increase of TSH levels. Some newly identified regulatory factors, such as proprotein convertase subtilisin/kexin type 9, angiogenin-like proteins and fibroblast growth factors are the underlying causes of dyslipidemia in hypothyroidism. HDL serum concentration changes were not consistent, and its function was reportedly impaired. The current review focuses on the updated understanding of the mechanism of hypothyroidism-related dyslipidemia.

Key Words

- dyslipidemia
- hypothyroidism
- ANGPTL
- FGF
- PCSK9

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Introduction

Hypothyroidism, including overt and subclinical hypothyroidism is a common disease among people. The former is defined as increased serum thyroid-stimulating hormone (TSH) levels and reduced free peripheral thyroid hormone (TH) concentrations. The latter is characterized by normal free peripheral TH concentrations. The association between thyroid dysfunction and dyslipidemia was first reported in 1930. Since then, it has been gradually recognized that hypothyroidism could cause disorders of lipid metabolism (1), mainly with increased total cholesterol (TC) and LDL-C (2) in blood. Elevated LDL-C can lead to progressive lipid accumulation, plaque formation in the arteries and increase the risk of cardiovascular disease (CVD), the leading cause of death worldwide. Regardless of TSH or TC concentration, cholesterol levels will return to normal (3, 4) and cardiac function improves (5) after T4 replacement treatment. Furthermore, T4 treatment has a more significant impact on blood lipid profiles in overt than subclinical hypothyroidism (6). Therefore, it is exceedingly important to pay attention to the relationship between hypothyroidism and lipid metabolism.

Previous observations have found that the prevalence of overt hypothyroidism is about 4.3% (7) and of subclinical hypothyroidism is about 11.1% (8) among hypercholesterolemic patients, both of which are higher than that of general people. Overt and subclinical hypothyroidism patients with serum TSH >10 mLU/L had an increased risk of CVD and mortality (9). These findings suggested that TH and TSH are two important risk factors for lipid metabolic disorders.

TH is a key regulator of metabolism, development and growth, which plays an important role in regulating the anabolism and catabolism of lipids. However, the deeper mechanism between hypothyroidism and blood lipid profile is still not fully understood, like the signaling pathway of TSH and other regulatory factors involved in lipid disturbance. This review focuses on mechanisms of hypothyroidism related to dyslipidemia, including

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the established mechanisms and the newly identified mechanisms.

Dyslipidemia in hypothyroidism

Hypothyroidism has a different impact on blood lipid components; generally, it tends to increase levels of TC, especially apolipoprotein B (ApoB)-containing lipoprotein cholesterols, like LDL-C and triglyceride (TG) (1, 10, 11), while its influence on ApoA-containing lipoprotein cholesterol, like HDL-C, is uncertain (12). However, the ratios of ApoB to ApoA-containing lipoprotein cholesterols (LDL-C/HDL-C and TG/HDL-C) were consistently higher in hypothyroidism than the euthyroid ones (13, 14, 15). In addition, hypothyroidism patients are more likely to develop postprandial hypertriglyceridemia (16), generally with elevated TG, TG-rich lipoproteins (TRLs) and remnant lipoprotein (RLP).

Hypothyroidism has a different impact on blood lipid profiles. A higher degree of ApoB-containing lipoprotein cholesterols is found in patients with TSH >10 mLU/L compared to those with TSH 4.0–10.0 mLU/L (17, 18, 19). Regardless of the thyroid status, circulating TSH level is always positively correlated with levels of ApoB-containing lipoprotein cholesterols (20, 21, 22, 23, 24, 25). Hence the higher TSH level is, the greater the risks of dyslipidemia are (26). If there is no significant impairment of thyroid function with a low TSH level, blood lipids even improve over time (27). Therefore, we could initially speculate that besides TH, TSH also plays an important role in regulating lipid metabolism.

The mechanism of dyslipidemia in hypothyroidism

Hypothyroidism influences lipid profiles mainly via TH. TH could bind to thyroid hormone receptorβ (THRβ), mainly expressed in the liver, to regulate the expression of downstream target genes (28). The total effect of TSH on TC level includes the direct effect and the indirect effect (TH) (29, 30). Multiple regression analysis showed that the increase of cholesterol levels was closely related to declined TH levels after injection of TSH in levothyroxine-treated thyroidectomized patients (31). TSH alone also can increase TC levels in CVD patients independent of TH (32). It has been reported that TSH regulates cholesterol metabolism through binding to TSH receptors (TSHRs) on the surface of hepatocytes (33) and adipocytes (34). Therefore, current evidence suggests that both TH and TSH affect cholesterol metabolism. Some regulatory factors are involved in cholesterol metabolism regulating as following. The major effect of TH and TSH on lipid metabolism in hypothyroidism has been outlined in Fig. 1.

Hypothyroidism and LDL-C metabolism

Hypothyroidism affects the production and clearance of LDL-C

TH has contradictory effects on cholesterol absorption and production. TH can directly induce the expression of liver HMG-COA reductase (HMGCR), a rate-limiting enzyme in cholesterol synthesis (35), achieving greater cholesterol synthesis (36). Besides binding to THR, TH could activate sterol regulatory element-binding protein 2 (SREBP2) (37), a major transcription factor, and SREBP2 can stimulate the transcription of HMGCR gene. Hence, hypothyroidism can cause reduced cholesterol synthesis by affecting HMGCR. But the effect of TH on the Niemann-Pick C1-like 1 protein (NPC1L1) in the intestine leads to increased cholesterol absorption in hypothyroidism (38). In hypothyroidism, free fatty acid (FFA) oxidation is also reduced, leading to increased very low-density lipoprotein (VLDL) secretion in the liver. TH could enhance β-oxidation of FFA by increasing the autophagy of hepatocytes (39). It could also stimulate carnitine palmitoyltransferase Iα (CPT1A), a rate-limiting β-oxidation enzyme (40). Accordingly, CPT1A mRNA and enzyme activity in the hyperthyroidism animal livers increase significantly (41); CPT1A is inhibited in the hypothyroidism mice (42). TH can also reduce the production of ApoB48 and ApoB100, thus reducing the production of VLDL and chylomicron (CM) (43, 44). Moreover, ApoB48 levels are negatively correlated to TH (45). Overall, the reduction of TH inhibits cholesterol synthesis via HMGCR but promotes the absorption of cholesterol through NPC1L1 and reduces catabolism through β-oxidation.

The LDL receptor (LDLR) is a transmembrane glycoprotein on the hepatocyte surface that recognizes lipoproteins containing ApoB, promoting cholesterol clearance. TH can upregulate the expression of LDLR mRNA through binding to thyroid-responsive element (TRE) of LDLR gene on the hepatocyte surface (46). Meanwhile, SREBP2 binds to the sterol regulatory element (SRE) on the LDLR promoter, thereby promoting the transcription of the LDLR gene (47). Therefore, the number of LDLR and LDL-C clearance rates decreased in hypothyroidism. The combined impact of TH on cholesterol production

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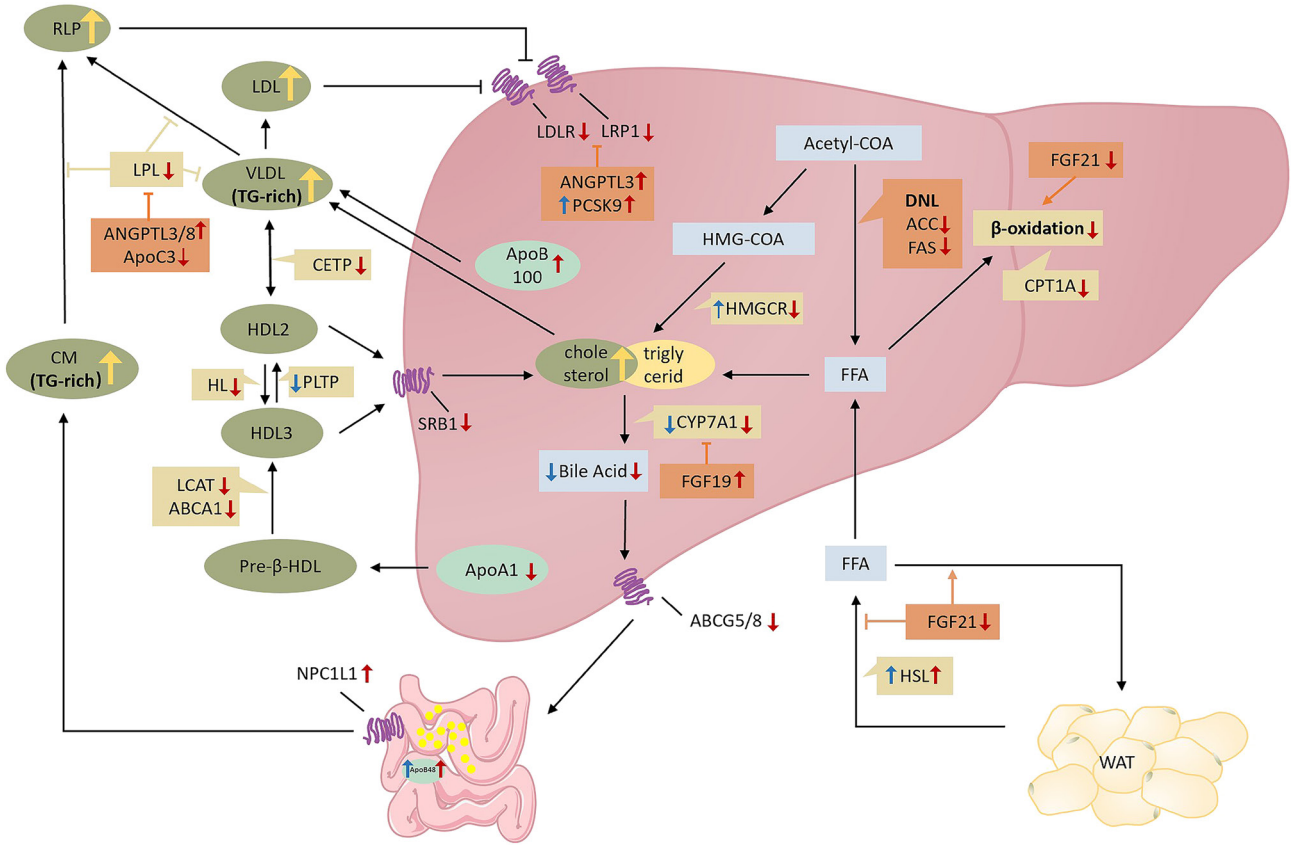

Figure 1

Effect of decreased TH and increased TSH on lipid metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. TH decreases in hypothyroidism and then *de novo* lipogenesis (DNL) and the activity of HMG-COA reductase (HMGCR) reduce, leading to declined cholesterol production, but free fatty acid (FFA) β-oxidation also decreases. TH reduction reduces the activity of cholesterol 7α-hydroxylase (CYP7A1) and ATP-binding cassette transporter G5/8 (ABCG5/8) to reduce cholesterol clearance. In general, triglyceride (TG)-rich very low-density lipoprotein (VLDL) level is increased in hypothyroidism, and the elevation of Niemann-Pick C1-like 1 protein (NPC1L1) concentration leads to an increase of TG-rich chylomicron (CM). The decrease of TH causes the declined function that lipoprotein lipase (LPL) hydrolyzes CM and VLDL, and the clearance of LDL and remnant lipoprotein (RLP) by LDL receptor (LDLR) and LDL receptor-related protein 1 (LRP1) decreases too, so TG level increases. However, the net concentration of HDL is not consistent. TSH mainly results in the increase of proprotein convertase subtilisin/kexin type 9 (PCSK9), HMGCR and hormone-sensitive lipase (HSL) levels and the decrease of CYP7A1. RLP, remnant lipoprotein; ANGPTL3/8, angiogenin-like protein3/8; ApoC3, apolipoprotein C3; CETP, cholesterol transport protein transporter; HL, hepatic lipase; PLTP, phospholipid transfer protein; LCAT, lecithin cholesterol acyltransferase; ABCA1, ATP-binding cassette transporter A1; SRB1, scavenger receptor b1; FGF19/21, fibroblast growth factors 19/21; HMG-COA, 3-hydroxy-3-methyl glutaryl coenzyme A; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; CPT1A, carnitine palmitoyltransferase Iα; WAT, white adipose tissue.

and clearance leads to a net accumulation of serum LDL-C in hypothyroidism.

On the one hand, TSH can directly affect cholesterol synthesis. Mice with liver TSHR knockout had low TC levels, especially serum LDL-C (48). The binding of TSH to TSHR of hepatocyte membrane upregulates the expression and activity of HMGCR through the cAMP/PKA/CREB signaling pathway (49). TSH can also stimulate the expression of SREBP2 to regulate HMGCR (35, 50). In adipocytes, TSHβ elevates HMGCR mRNA levels, and TSHβ expression levels in mice's s.c. adipocytes are directly related to circulating cholesterol levels (51). TSHβ gene expression is also positively correlated with the expression of fatty acid mobilization (CAV1, ENGL1) (52). It has been found that TSH increased the phosphorylation of perilipin and hormone-sensitive lipase (HSL) to increase lipolysis, and circulating FFA increased significantly after TSH injection *in vitro* studies (53). Also, TSH could stimulate the increase of ApoB (31, 45). So, we could speculate that TSH is capable as a stand-alone hormone to produce a physiological response on lipid metabolism and have an effect independent of TH.

On the other hand, TSH plays an important part in LDL clearance. TSH induces PI3K/AKT/SREBP2 and SREBP2/HNF4/ Cholesterol 7α-hydroxylase (CYP7A1) signaling pathways to inhibit the synthesis of hepatic bile

acids through TSHR (54). In patients with hypothyroidism and hypercholesterolemia, serum TSH was significantly negatively correlated with bile acid levels, independent of TH (10). Interestingly, the association between TSH and total serum bile acid was stronger in patients under 65 (55).

The decrease of TH and increase of TSH share similar pathogenic mechanisms of LDL-C accumulation in hypothyroidism, both of which could induce the cholesterol production and inhibit clearance. The effect of TH and TSH on LDL-C in hypothyroidism has been outlined in Fig. 2.

Factors involved in hypothyroidism-related LDL-C elevation

Fatty acids are obtained from the diet or *de novo* lipogenesis (DNL), where acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) play catalytic roles in the liver and adipose tissue (AT). TH regulates the expression of target genes in two different ways: TH could directly upregulate ACC/FAS through TRE (the direct mechanism) (56) or SREBP1/carbohydrate response element-binding protein (ChREBP) (the indirect mechanism). The transcription of SREBP1 is negatively regulated via TRE (56, 57), but TH can also improve the translation efficiency of SREBP1 mRNA through non-genomic actions (58). Then SREBP1 combines with SRE in ACC and FAS genes to stimulate the expression (59, 60). Meanwhile, the inhibition of SREBP1C expression downregulates the expression of HSL gene, thus inhibiting lipid lipolysis (56). It is known that THβ influences the expression of ChREBP in hepatocytes (61) and ACC/FAS genes are positively regulated by ChREBP (62). ChREBP and SREBP1C can regulate each other to some extent (63). These new observations suggest that TH fine-tunes lipid adipogenesis by regulating the expression of SREBP-1C and ChREBP genes respectively.

FGF21is a member of the FGF superfamily. It is mainly released from hepatocytes and is considered as an important endogenous regulator of glucose–lipid metabolism (64), and endogenous FGF21 is mainly released from hepatocytes. When treated with recombinant FGF21, serum TG, VLDL-C and LDL-C of rodents significantly reduced (65, 66). The same situation was observed in the human study: LDL-C and TG were lower and HDL-C was higher in patients using FGF21 analog (67). Chronic treatment with recombinant FGF21 can even reduce

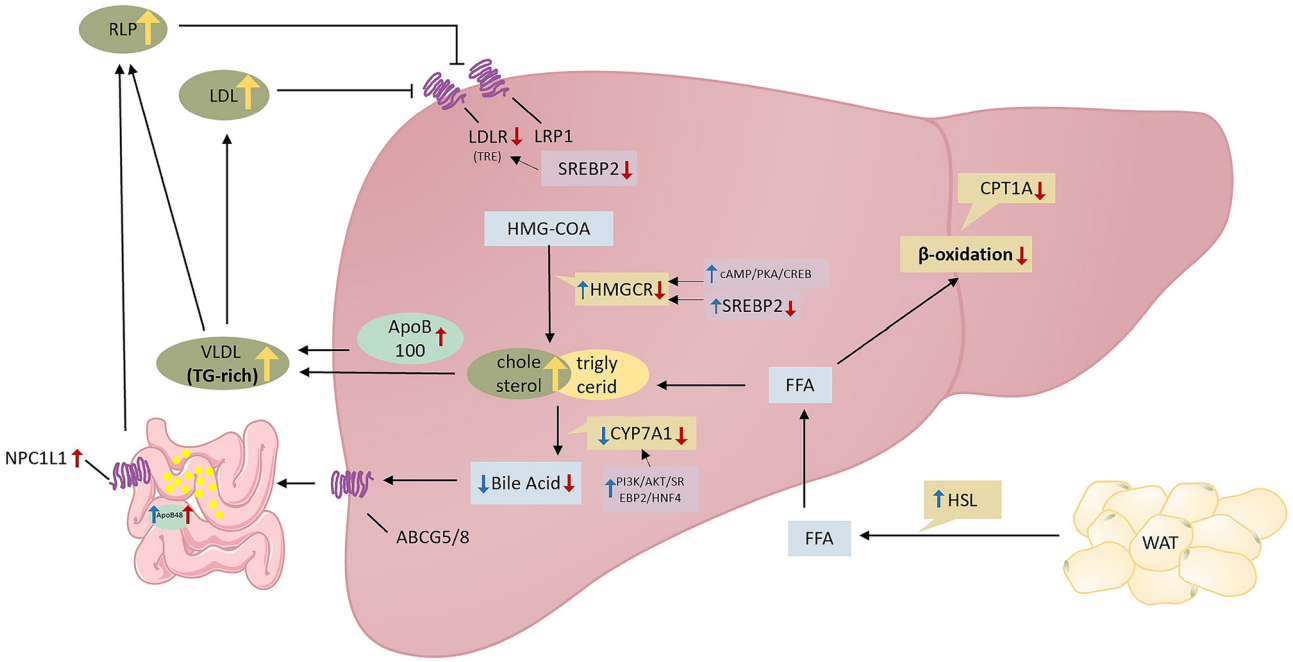

Figure 2
Effect of decreased TH and Increased TSH on LDL-C metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. The reduction of TH inhibits cholesterol synthesis via HMGCR, but the absorption of cholesterol through NPC1L1 increases; the catabolism through β-oxidation and LDL-C clearance through LDL-R decrease. TSH could increase cholesterol synthesis and lipolysis but inhibits the clearance of cholesterol independently. The decrease of TH and increase of TSH induce the net production and inhibit the clearance of LDL-C, thus leading to LDL-C accumulation.

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serum and liver TG levels in diet-induced obese mice by inhibiting SREBP1 (68). FGF21 reduces circulating FFAs by inhibiting lipolysis in white adipose tissue (WAT) (69) and stimulating FFAs uptake into WAT, consequently decreasing the secretion of VLDL in liver (70). FGF21 could also increase TRL disposal in AT (70).

TH increases FGF21 transcription and peptide levels in mice's liver through THRβ binding to TRE in FGF21 intron 2 (71). TH also induces liver FGF21 gene expression to promote β-oxidation by activating AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) in a proliferator-activated receptor α (PPARα)-dependent manner in mice, and the expression of FGF21 reportedly increased in a dose-dependent manner in mice treated with exogenous TH (72, 73). ChREBP also regulates plasma TG levels by regulating FGF21 (74, 75). In turn, peripheral administration of FGF21 could decrease TH levels (76).

Studies have found that FGF21 levels were significantly lower in hypothyroidism patients (77) and increased or did not change in hyperthyroidism patients (78, 79) due to the effect of TH. However, another study has found that the increase of circulating FGF21 levels in hypothyroidism patients is related to serum TSH (80). So, it could be speculated that TH and TSH have contradictory effects on pathogenetic metabolism. Whether TSH could induce the expression of FGF21 needs further exploration.

FGF19, secreted from the ileum after the stimulation of bile acid (81), participates in the negative feedback regulation of bile acid synthesis by inhibiting liver CYP7A1 (82). TH has a direct effect on the secretion of FGF19 (79). Circulating FGF19 levels significantly decrease in hypothyroidism patients and are independently correlated with TSH levels (83). Further studies have shown that SREBP downregulates the transcription and expression of FGF19 (84).

TH could regulate cholesterol synthesis via miRNA, a kind of small regulatory RNA. TH induces the expression of miR-181d in humans, thereby reducing the expression of caudal type homeobox 2 (CDX2), a transcription factor that activates sterol O-acyl transferase 2 (SOAT2). SOAT2 is essential for converting cholesterol into cholesterol ester (CE), and the latter is the preferred form of LDL (85); and TH mediated the reduction of miR-206, so TG and TC in HepG2 cells declined (86). Also, TH could positively regulate hepatic miR-378, leading to the reduction of serum cholesterol levels through promoting bile acid synthetic pathways (87). Recently, a regulatory module containing three miRNAs (miR-34a-5p, miR-24-3p and miR-130a-3p) and four proteins (thioredoxin, selenium-binding protein 2, elongation factor 1β and prosaposin) about hepatic lipid metabolism was identified in subclinical mice (88).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease, binds to the LDLR on the hepatocyte surface, facilitating LDLR degradation in lysosomes and reducing its recycling. PCSK9 could also regulate LDL receptor-related protein 1 (LRP1), which competes with LDLR (89). Studies have shown that TH significantly reduces PCSK9 levels (79). Both SREBP1 and SREBP2 can affect PCSK9 mRNA (90). Studies have found that SREBP2 can bind to the SRE1 site on the PCSK9 promoter (47). The expression of SREBP1C and FAS in liver is involved in circulating PCSK9 and its mRNA levels (91, 92). Combined, TH reduces PCSK9 through SREBPs, thereby increasing the expression of LDLR, promoting the clearance of cholesterol in the plasma and reducing cholesterol levels. Currently, studies have found that TSH is significantly positively correlated with plasma PCSK9, which partly depends on SREBP1C, SREBP2 and HMGCR (93, 94).

Regulatory factories like ACC/FAS of DNL, FGF21 and miR-181d/206 could affect the synthesis of LDL-C, while factories like FGF19 and PCSK9 influence the degradation of LDL-C. The detailed metabolisms are shown in Fig. 3.

Hypothyroidism and hypertriglyceridemia

Hypothyroidism affects TG production and transformation

TG comes from circulating exogenous or intracellular FFAs produced by glycolysis and fat. TH could reduce the production of VLDL-TG in liver (95). When the rate of lipolysis remains unchanged, hypothyroidism will lead to decreased lipid oxidation rates and elevated TG (96). TH could also increase ApoA5 mRNA and protein levels in hepatocytes, leading to a decline of TG (97). TH mainly upregulates the activity of lipoprotein lipase (LPL), which could lead to the lipolysis of TRLs, including CM and VLDL; the decrease of TH leads to the attenuation of these effects, thus promoting the elevation of serum TG in hypothyroidism (98). Studies have shown that impaired hepatic lipase (HL) activity in hypothyroidism patients may also be related to the accumulation of TRL (45). The transfer of TG to HDL is impaired in subclinical hypothyroidism patients (99).

Remnant lipoprotein (RLP) is composed of cholesterol, CE and ApoE-riched smaller particles. TRL particles gradually lose TG, phospholipid, ApoA and ApoC then transfers to RLP after being hydrolyzed by LPL. Existing studies have shown that hypothyroidism is associated with

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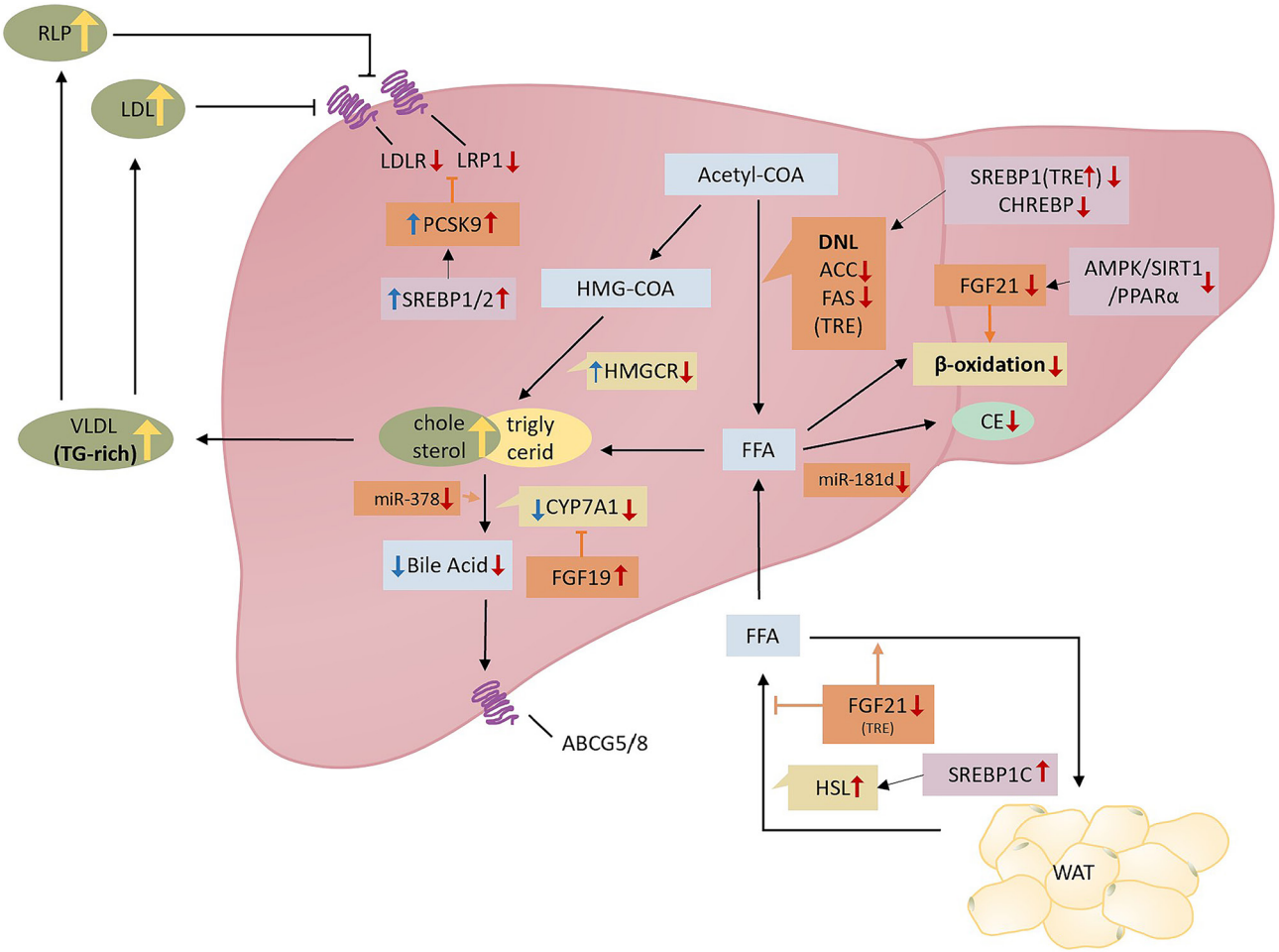

Figure 3
Regulatory factors involved in hypothyroidism-related dyslipidemia. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. ACC/FAS, FGF21 and miR-181d/206 could affect the synthesis of LDL-C, while factors like FGF19 and PCSK9 influence the degradation of LDL-C. In hypothyroidism, FFA synthesis via DNL decrease, and the indirect mechanisms of TH on SREBP1 is stronger than the direct mechanisms through TRE. The oxidation and lipolysis of FFA decreases partly because of hypothyroidism-induced decreased FGF-21. FGF-19 inhibits bile acid synthesis and PCSK9 increases the degradation of LDLR, thus inhibiting the clearance of cholesterol in hypothyroidism.

increased serum RLP levels (100). On the one hand, the excess production of TRL particles in the liver can explain the elevated RLP levels in hypothyroidism patients. On the other hand, LRP1 is expressed on the hepatocyte surface and binds to ApoE, internalizing TRL and contributing to RLP clearance. TH influences the lipid profile by increasing the transcription of LRP1 in mice and humans (101). Interestingly, SREBP1 and SREBP2 could downregulate the transcription of LRP1 in human vascular smooth muscle cells and macrophages through binding to SRE (102, 103). Therefore, hypothyroidism can lead to LRP1 reduction and RLP clearance through SREBP.

TSH could also promote the synthesis of TG. It binds to TSHR to promote TG synthesis in differentiated adipocytes via AMPK/PPARγ/GPAT3 axis (104). TSH could also significantly increase TG levels in hepatocytes in a dose-dependent manner through TSHR/cAMP/PKA/PPARα and PPARα/AMPK/SREBP1C signaling pathways (49, 105). Higher TSH levels in the euthyroid population may affect TG-rich metabolism via ApoE (106), which could explain increased ApoE levels in hypothyroidism patients (107).

Hypothyroidism and newly identified mechanisms factors in TG metabolism

ANGPTL1-8 are secretory glycoproteins composed of an N-terminal helical domain and a C-terminal fibrinogen-like domain. Angptl3 is identified for proteolysis at positions 221–224 to produce N-terminal domains.

TH could inhibit mRNA of ANGPTL3 TRβ dependently (108), and there was a positive correlation between ANGPTL3 and TSH in Graves' disease patients (109). Circulating VLDL-TG and LDL-C declined in ANGPTL3 loss-of-function heterozygotes (110, 111) because some studies have shown that ANGPTL3 at high concentration could inhibit LPL (112, 113). ANGPTL3 cleaves LPL through furin protease (114) and shows reversible inhibition of LPL catalytic activity. However, other studies also found that ANGPTL3 inactivates LPL by catalyzing the irreversible unfolding of its hydrolase domain, which is similar to ANGPTL4 (115). Furthermore, ANGPTL3 deficiency could lead to declined postprandial lipid levels, possibly due to accelerated catabolic metabolism of TRLs and reduced flow of fatty acids into liver (116, 117). One study demonstrated that ANGPTL3 gene siRNAs induced increased expression of LDLR/LRP1 and reduced the secretion of apoB100, resulting in increased uptake of LDL/VLDL (118). However, in another study, it was reported that the use of ANGPTL3 MAB, the reduction of LDL-C could be independent of the LDLR pathway, and it was speculated that the transformation from VLDL to LDL reduced partially because of increased ApoB clearance (111). Circulating ANGPTL3 levels elevated and were positively correlated with HDL-C in hypothyroidism patients (119). ANGPTL 3 acts as an inhibitor of endothelial lipase, which could hydrolyze HDL-phospholipid to reduce plasma HDL levels, and ANGPTL 3 is also involved in promoting the elevation of plasma HDL-C in humans and rodents (120).

ANGPTL8, known as TD26, re-feeding induced in fat and liver, lipasin and betatrophin, is an atypical member of ANGPTL family. It is expressed mainly in liver of humans, while in AT and liver of mice. The TG clearance rate and LPL activity in Angptl8 knockout mice increase significantly, thus reducing the plasma TG levels (121, 122). ANGPTL8 can cooperate with ANGPTL3 to improve the binding of ANGPTL3 to LPL and promote LPL lysis to increase the plasma TG level in mice (123, 124, 125). ANGPTL3 and ANGPTL8 can even promote each other somehow (125). Circulating Angptl8 levels increase in hypothyroidism patients and positively correlate with TSH, TG and TC (119, 122, 126, 127, 128). However, ANGPTL8 mRNA in HepG2 cells is induced by TH (129), and its expression can also be specifically activated in the liver of mice through SREBP1a and SREBP2 (124). These pieces of evidence could suggest that TH and TSH regulate ANGPTL8. TH could also convert lipid droplets through the autophagy process activated by ANGPTL8 to regulate lipid metabolism (129). In addition, the lipid contents in adipocytes significantly reduced after the deletion of ANGPTL8 gene (130). ANGPTL8 protein levels are positively related to TC, LDL-C in patients with morbid obesity and type 2 diabetes (131), but whether it is related to hypothyroidism or not, the answer remains uncertain.

ANGPTL6, also known as AGF, does not bind to angiogenin receptors. In patients with hypothyroidism, serum ANGPTL6 levels increase and are positively correlated with TSH and TC (132). Serum ANGPTL6 levels are also an independent predictor of low HDL and high TG (133). Studies have found that ANGPTL6 could mediate increased expression of PPARα through the extracellular regulated protein kinases/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, leading to increased expression of FGF21, thereby promoting β-oxidation (134). It is possible to predict that TSH could induce FGF21 through ANGPTL6; however, TH has the opposite effect on FGF21 from TSH and the effect prevails, so serum FGF21 level is more prone to decrease in hypothyroidism as mentioned above.

The domain of Angptl4 is similar to Angptl3 (135). But, TH could not inhibit the expression of Angptl4 mRNA (108), and there is no significant change of Angptl4 levels in hypothyroidism (119). So, we could speculate that TH could not influence lipid metabolism through Angptl4.

Serum ApoC3, another LPL inhibitor, was found to decrease in hypothyroidism mice with or without pregnancy (42). The suppressed expression of ApoC3 gene leads to increased LPL activity and decreased plasma TG levels (136). Taken together, ApoC3 decrease leads to LPL increase in the presence of hypothyroidism.

Angptl3/6/8 and ApoC3 play important roles in TG transformation, especially Angptl3 and Angptl8 make a synergic reaction. More basic and epidemiological studies are needed to verify the deeper relationship between Angptl6/FGF21 and TSH. The detailed effects of TH and TSH on TG metabolisms are shown in Fig. 4.

Hypothyroidism and HDL-C metabolism

Thyroid hormone affects HDL levels

HDL synthesis decreases in hypothyroidism. A study has documented a positive relationship between FT4 and plasma pre-β-HDL formation in type 2 diabetes mellitus patients (137). TH strongly induces ApoA1 gene and protein expression (138), thereby increasing cholesterol efflux from peripheral tissues to HDL in reverse cholesterol transport (RCT). Homocysteine levels significantly increase in hypothyroidism mice; and homocysteine can reduce circulating HDL-C by inhibiting ApoA1 protein synthesis, thereby inhibiting RCT (139). However, ApoA1 levels

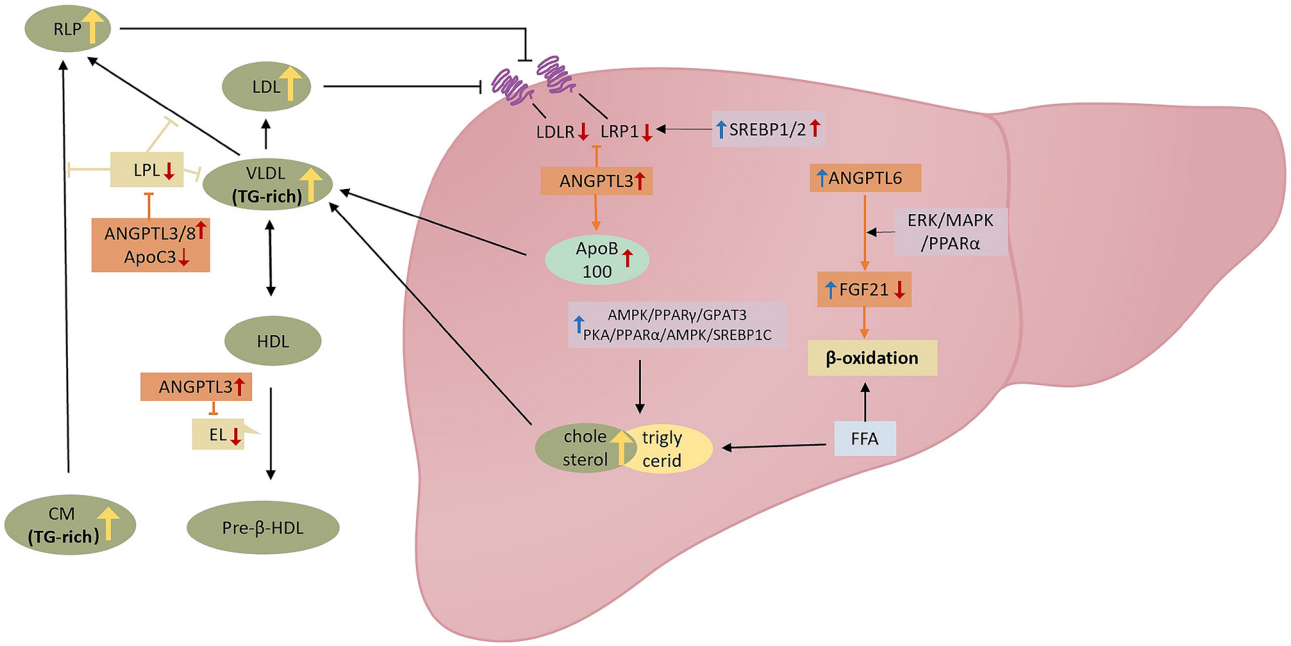

Figure 4
Effect of decreased TH and increased TSH on TG metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. The increase of Angptl3 in hypothyroidism could inhibit LDL degradation via LDL-R and inhibit cholesterol transport via LPL and EL. TSH is related to Angptl6, influencing β-oxidation to some extent.

increase in hypothyroidism patients after thyroidectomy (140, 141). The potential causes of the contradictory result are not clear yet. TH could also stimulate cholesterol efflux from macrophages to HDL via transporter protein ATP-binding cassette transporter A1 (ABCA1) (138). The activity of ABCA1 and lecithin cholesterol acyltransferase decreases in hypothyroidism, which leads to the inhibition of the synthesis and maturation process of HDL particles (142).

The HDL clearance and transformation process decrease in hypothyroidism. TH stimulates HL, thus promoting HDL degradation and changing HDL components (143). Plasma cholesterol transport protein transporter (CETP) concentrations decrease in hypothyroidism, resulting in elevated plasma HDL-C levels (144). TH can increase the transcription of CYP7A1, a rate-limiting enzyme in RCT, thus promoting the transformation of cholesterol into bile acid (145). TH could also stimulate the secretion of bile acid in liver and intestine by stimulating the transcription of ATP-binding cassette transporter G5/8 (ABCG5/ABCG8) in rats (138), which is the last step of RCT (146). Hypothyroidism could inhibit cholesterol clearance by decreasing scavenger receptor b1 (147). These effects of TH on HDL synthesis and clearance counteract each other; therefore, the HDL-C level is not constant.

Patients with a moderate increase in TSH had reduced CETP and phospholipid transfer protein activities, which resulted in decreased HDL2 and elevated HDL3 levels (148). However, in T2DM patients, there is a positive correlation between TSH and CETP, thereby raising the possibility that hyperglycemia has strong effects on the ability of VLDL to accept cholesteryl esters from HDL (149). Hence, HDL-C levels could be affected by numerous conditions. The detailed effects of TH and TSH on HDL levels are shown in Fig. 5.

Hypothyroidism impairs HDL cholesterol efflux capacity

Though HDL levels were not consistent, cholesterol efflux capacity (CEC) was impaired in overt hypothyroidism, reflecting HDL function losses (107, 141). Paraoxonase-1 (PON1) is an important anti-oxidative enzyme that resides on HDL. Recent reports showed that after thyroidectomy, PON1 activity remained unaltered (140) but the PON1/ApoA1 ratio decreased (107). Altogether, hypothyroidism may affect HDL function through several unclear mechanisms.

Even though elevated HDL-C levels could not always protect humans from CVD and mortality, CEC is a

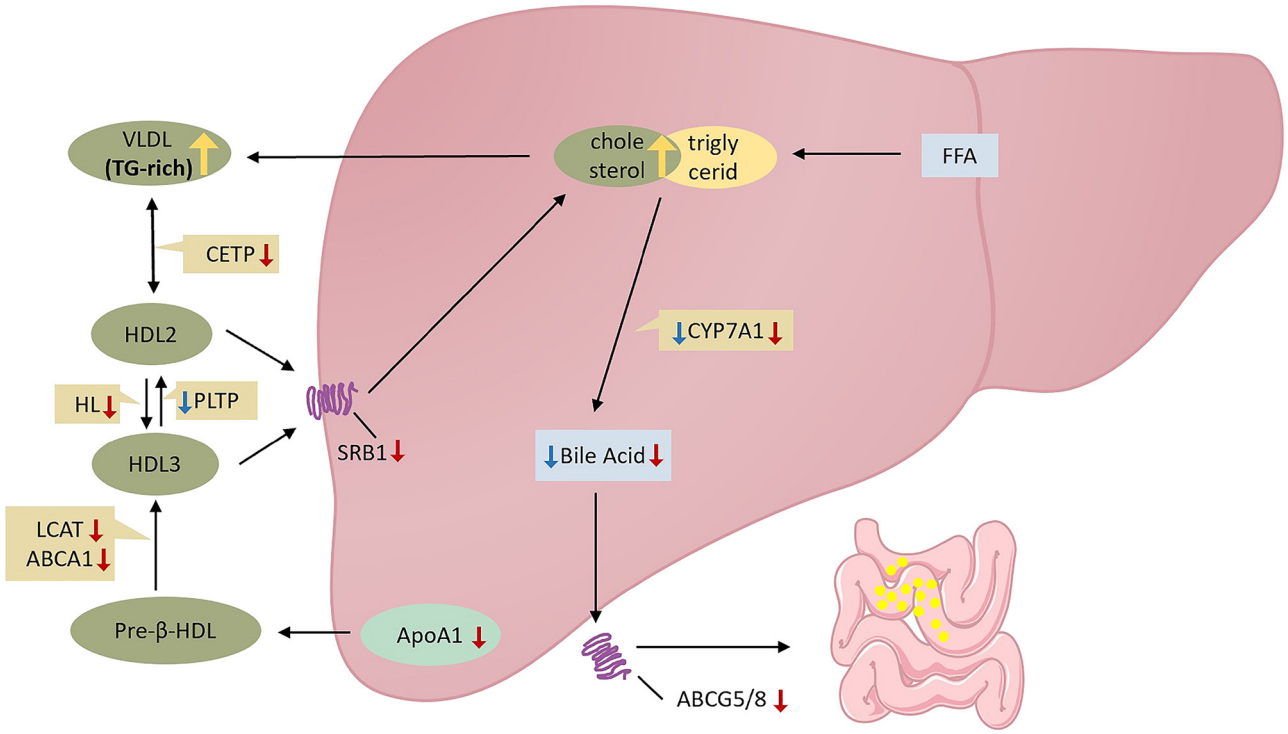

Figure 5
Effect of decreased TH and increased TSH on HDL metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. HDL synthesis via LCAT, ABVA1 and apoA1 enhances but HDL clearance and transformation process decreases in hypothyroidism because of TH-induced decreased HL, CEPT, CYP7A1, ABCG5/8 and SR-B1. Several effects counteract each other; therefore, the HDL-C level is not constant.

biomarker of HDL functionality and is cardioprotective. So what we should pay more attention to is HDL CEC (150).

Conclusion

Besides known TH metabolic pathways, TSH is also shown to be an important factor influencing lipid metabolism *in vitro* and *in vivo*. Either the decrease of TH or the increase of TSH in hypothyroidism could increase LDL-C and TG. HDL levels are not constant because regulating factors counteract each other; however, HDL function, a predictor of cardiovascular risk independent of HDL-C levels, is impaired in hypothyroidism. Hence, we could focus on the mechanism of how TH affects HDL function. Even in normal thyroid and subclinical hypothyroidism, higher TSH levels could affect lipid metabolism through an independent TSH signaling pathway. It seems that keeping TSH at a low normal level to minimize cholesterol concentrations is an important treatment in hypothyroidism from a clinical point of view. Significantly, the main hormone physiological change of hypothyroidism patients comes from TH; and TSH could be influenced by TH negative feedback regulation. Combined, whether TSH metabolic pathway makes up a large proportion of hypothyroidism or not, we need more evidence to figure it out.

Currently, we find that many regulatory factors, like SREBPs, ChREBP, ANGPTLs and FGF19/21, are also involved in lipid metabolism of hypothyroidism. These factors provide potential drug targets for treatments of hypothyroidism-related hyperlipidemia, like Angptl3 inhibitor, Evinacumab. However, the specific mechanism of TH or TSH on some factors has not been clarified yet. For instance, whether TSH could influence cholesterol metabolism through Angptl6 and FGF19 pathways is unclear. So, further basic and epidemiological studies are required to clarify the contradictory change of lipid levels and mechanism of these newly identified factors.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
H X L and D Q P contributed to the study design; H X L wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

References

1 Chen Y, Wu X, Wu R, Sun X, Yang B, Wang Y & Xu Y. Changes in profile of lipids and adipokines in patients with newly diagnosed hypothyroidism and hyperthyroidism. *Scientific Reports* 2016 **6** 26174. (https://doi.org/10.1038/srep26174)
2 Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, *et al.* Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016 **133** e38–e360. (https://doi.org/10.1161/CIR.0000000000000350)
3 Abdel-Gayoum AA. Dyslipidemia and serum mineral profiles in patients with thyroid disorders. *Saudi Medical Journal* 2014 **35** 1469–1476.
4 Zhao M, Liu L, Wang F, Yuan Z, Zhang X, Xu C, Song Y, Guan Q, Gao L, Shan Z, *et al.* A worthy finding: decrease in total cholesterol and low-density lipoprotein cholesterol in treated mild subclinical hypothyroidism. *Thyroid* 2016 **26** 1019–1029. (https://doi.org/10.1089/thy.2016.0010)
5 Scherer T, Wolf P, Winhofer Y, Duan H, Einwallner E, Gessl A, Luger A, Trattnig S, Hoffmann M, Niessner A, *et al.* Levothyroxine replacement in hypothyroid humans reduces myocardial lipid load and improves cardiac function. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** E2341–E2346. (https://doi.org/10.1210/jc.2014-2112)
6 Arinzon Z, Zuta A, Peisakh A, Feldman J & Berner Y. Evaluation response and effectiveness of thyroid hormone replacement treatment on lipid profile and function in elderly patients with subclinical hypothyroidism. *Archives of Gerontology and Geriatrics* 2007 **44** 13–19. (https://doi.org/10.1016/j.archger.2006.01.006)
7 Tagami T, Kimura H, Ohtani S, Tanaka T, Tanaka T, Hata S, Saito M, Miyazaki Y, Araki R, Tanaka M, *et al.* Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia. *Endocrine Journal* 2011 **58** 449–457. (https://doi.org/10.1507/endocrj.k11e-012)
8 Willard DL, Leung AM & Pearce EN. Thyroid function testing in patients with newly diagnosed hyperlipidemia. *JAMA Internal Medicine* 2014 **174** 287–289. (https://doi.org/10.1001/jamainternmed.2013.12188)
9 Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, Abdulazeem H, Aertgeerts B, Beecher D, Brito JP, *et al.* Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ* 2019 **365** l2006. (https://doi.org/10.1136/bmj.l2006)
10 Song Y, Zhao M, Zhang H, Zhang X, Zhao J, Xu J & Gao L. Thyroid-stimulating hormone levels are inversely associated with serum total bile acid levels: a cross-sectional study. *Endocrine Practice* 2016 **22** 420–426. (https://doi.org/10.4158/EP15844.OR)
11 Alsamghan AS, Alsaleem SA, Alzahrani MAS, Patel A, Mallick AK & Sheweita SA. Effect of hypovitaminosis D on lipid profile in hypothyroid patients in Saudi Arabia. *Oxidative Medicine and Cellular Longevity* 2020 **2020** 6640402. (https://doi.org/10.1155/2020/6640402)
12 Heima NE, Eekhoff EMW, Oosterwerff MM, Lips PTA, van Schoor NM & Simsek S. Thyroid function and the metabolic syndrome in older persons: a population-based study. *European Journal of Endocrinology* 2013 **168** 59–65. (https://doi.org/10.1530/EJE-12-0375)
13 Cerbone M, Capalbo D, Wasniewska M, Alfano S, Mattace Raso G, Oliviero U, Cittadini A, De Luca F & Salerno M. Effects of L-thyroxine treatment on early markers of atherosclerotic disease in children with subclinical hypothyroidism. *European Journal of Endocrinology* 2016 **175** 11–19. (https://doi.org/10.1530/EJE-15-0833)
14 Liu FH, Hwang JS, Kuo CF, Ko YS, Chen ST & Lin JD. Subclinical hypothyroidism and metabolic risk factors association: a health examination-based study in northern Taiwan. *Biomedical Journal* 2018 **41** 52–58. (https://doi.org/10.1016/j.bj.2018.02.002)
15 Unal E, Akın A, Yıldırım R, Demir V, Yildiz İ & Haspolat YK. Association of subclinical hypothyroidism with dyslipidemia and increased carotid intima-media thickness in children. *Journal of Clinical Research in Pediatric Endocrinology* 2017 **9** 144–149. (https://doi.org/10.4274/jcrpe.3719)
16 Arikan S, Bahceci M, Tuzcu A, Celik F & Gokalp D. Postprandial hyperlipidemia in overt and subclinical hypothyroidism. *European Journal of Internal Medicine* 2012 **23** e141–e145. (https://doi.org/10.1016/j.ejim.2012.05.007)
17 Martin SS, Daya N, Lutsey PL, Matsushita K, Fretz A, McEvoy JW, Blumenthal RS, Coresh J, Greenland P, Kottgen A, *et al.* Thyroid function, cardiovascular risk factors, and incident atherosclerotic cardiovascular disease: the atherosclerosis risk in communities (ARIC) study. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 3306–3315. (https://doi.org/10.1210/jc.2017-00986)
18 van Vliet NA, Bos MM, Thesing CS, Chaker L, Pietzner M, Houtman E, Neville MJ, Li-Gao R, Trompet S, Mustafa R, *et al.* Higher thyrotropin leads to unfavorable lipid profile and somewhat higher cardiovascular disease risk: evidence from multi-cohort Mendelian randomization and metabolomic profiling. *BMC Medicine* 2021 **19** 266. (https://doi.org/10.1186/s12916-021-02130-1)
19 Yuan C, Sun X, Liu Y & Wu J. The thyroid hormone levels and glucose and lipid metabolism in children with type 1 diabetes: a correlation analysis. *Translational Pediatrics* 2021 **10** 276–282. (https://doi.org/10.21037/tp-20-204)
20 Iqbal AM, Lteif AN & Kumar S. Association between mild hyperthyrotropinemia and hypercholesterolemia in children with severe obesity. *Journal of Pediatric Endocrinology and Metabolism* 2019 **32** 561–568. (https://doi.org/10.1515/jpem-2018-0519)
21 Dahl AR, Iqbal AM, Lteif AN, Pittock ST, Tebben PJ & Kumar S. Mild subclinical hypothyroidism is associated with paediatric dyslipidaemia. *Clinical Endocrinology* 2018 **89** 330–335. (https://doi.org/10.1111/cen.13752)
22 Jin HY. Prevalence of subclinical hypothyroidism in obese children or adolescents and association between thyroid hormone and the components of metabolic syndrome. *Journal of Paediatrics and Child Health* 2018 **54** 975–980. (https://doi.org/10.1111/jpc.13926)
23 Jain RB. Associations between the levels of thyroid hormones and lipid/lipoprotein levels: data from National Health and Nutrition Examination Survey 2007–2012. *Environmental Toxicology and Pharmacology* 2017 **53** 133–144. (https://doi.org/10.1016/j.etap.2017.05.002)
24 Luxia L, Jingfang L, Songbo F, Xulei T, Lihua M, Weiming S, Ying N, Gaojing J, Qianglong N, Yujuan L, *et al.* Correlation between serum TSH levels within normal range and serum lipid profile. *Hormone and Metabolic Research* 2020 **53** 32–40. (https://doi.org/10.1055/a-1191-7953)
25 Kuś A, Marouli E, Del Greco FM, Chaker L, Bednarczuk T, Peeters RP, Teumer A, Medici M & Deloukas P. Variation in normal range thyroid function affects serum cholesterol levels, blood pressure, and type 2 diabetes risk: a mendelian randomization study. *Thyroid* 2021 **31** 721–731. (https://doi.org/10.1089/thy.2020.0393)

26 Chang YC, Hua SC, Chang CH, Kao WY, Lee HL, Chuang LM, Huang YT & Lai MS. High TSH level within normal range is associated with obesity, dyslipidemia, hypertension, inflammation, hypercoagulability, and the metabolic syndrome: a novel cardiometabolic marker. *Journal of Clinical Medicine* 2019 **8** 817. (https://doi.org/10.3390/jcm8060817)

27 Ahi S, Amouzegar A, Gharibzadeh S, Delshad H, Tohidi M & Azizi F. Trend of lipid and thyroid function tests in adults without overt thyroid diseases: a cohort from Tehran thyroid study. *PLoS ONE* 2019 **14** e0216389. (https://doi.org/10.1371/journal.pone.0216389)

28 Chamba A, Neuberger J, Strain A, Hopkins J, Sheppard MC & Franklyn JA. Expression and function of thyroid hormone receptor variants in normal and chronically diseased human liver. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 360–367. (https://doi.org/10.1210/jcem.81.1.8550778)

29 Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, Zhang B, Guan Q, Xu J, Zhang J, *et al*. Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2724–2731. (https://doi.org/10.1210/jc.2012-1133)

30 Geng H, Zhang X, Wang C, Zhao M, Yu C, Zhang B, Wang Y, Ban B & Zhao J. Even mildly elevated TSH is associated with an atherogenic lipid profile in postmenopausal women with subclinical hypothyroidism. *Endocrine Research* 2015 **40** 1–7. (https://doi.org/10.3109/07435800.2013.879166)

31 Beukhof CM, Massolt ET, Visser TJ, Korevaar TIM, Medici M, de Herder WW, Roeters van Lennep JE, Mulder MT, de Rijke YB, Reiners C, *et al.* Effects of thyrotropin on peripheral thyroid hormone metabolism and serum lipids. *Thyroid* 2018 **28** 168–174. (https://doi.org/10.1089/thy.2017.0330)

32 Xu C, Yang X, Liu W, Yuan H, Yu C, Gao L & Zhao J. Thyroid stimulating hormone, independent of thyroid hormone, can elevate the serum total cholesterol level in patients with coronary heart disease: a cross-sectional design. *Nutrition and Metabolism* 2012 **9** 44. (https://doi.org/10.1186/1743-7075-9-44)

33 Zhang W, Tian LM, Han Y, Ma HY, Wang LC, Guo J, Gao L & Zhao JJ. Presence of thyrotropin receptor in hepatocytes: not a case of illegitimate transcription. *Journal of Cellular and Molecular Medicine* 2009 **13** 4636–4642. (https://doi.org/10.1111/j.1582-4934.2008.00670.x)

34 Santini F, Galli G, Maffei M, Fierabracci P, Pelosini C, Marsili A, Giannetti M, Castagna MG, Checchi S, Molinaro E, *et al.* Acute exogenous TSH administration stimulates leptin secretion *in vivo*. *European Journal of Endocrinology* 2010 **163** 63–67. (https://doi.org/10.1530/EJE-10-0138)

35 Zhang X, Song Y, Feng M, Zhou X, Lu Y, Gao L, Yu C, Jiang X & Zhao J. Thyroid-stimulating hormone decreases HMG-CoA reductase phosphorylation via AMP-activated protein kinase in the liver. *Journal of Lipid Research* 2015 **56** 963–971. (https://doi.org/10.1194/jlr.M047654)

36 Choi JW & Choi HS. The regulatory effects of thyroid hormone on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Endocrine Research* 2000 **26** 1–21. (https://doi.org/10.1080/07435800009040142)

37 Shin DJ & Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein-2 (SREBP-2). *Journal of Biological Chemistry* 2003 **278** 34114–34118. (https://doi.org/10.1074/jbc.M305417200)

38 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** 1127–1136. (https://doi.org/10.1053/j.gastro.2008.01.032)

39 Sinha RA, You SH, Zhou J, Siddique MM, Bay BH, Zhu X, Privalsky ML, Cheng SY, Stevens RD, Summers SA, *et al.* Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. *Journal of Clinical Investigation* 2012 **122** 2428–2438. (https://doi.org/10.1172/JCI60580)

40 McGarry JD & Brown NF. The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. *European Journal of Biochemistry* 1997 **244** 1–14. (https://doi.org/10.1111/j.1432-1033.1997.00001.x)

41 Jackson-Hayes L, Song S, Lavrentyev EN, Jansen MS, Hillgartner FB, Tian L, Wood PA, Cook GA & Park EA. A thyroid hormone response unit formed between the promoter and first intron of the carnitine palmitoyltransferase-Ialpha gene mediates the liver-specific induction by thyroid hormone. *Journal of Biological Chemistry* 2003 **278** 7964–7972. (https://doi.org/10.1074/jbc.M211062200)

42 Zhou J, Dong X, Liu Y, Jia Y, Wang Y, Zhou J, Jiang Z & Chen K. Gestational hypothyroidism elicits more pronounced lipid dysregulation in mice than pre-pregnant hypothyroidism. *Endocrine Journal* 2020 **67** 593–605. (https://doi.org/10.1507/endocrj.EJ19-0455)

43 Goldberg IJ, Huang LS, Huggins LA, Yu S, Nagareddy PR, Scanlan TS & Ehrenkranz JR. Thyroid hormone reduces cholesterol via a non-LDL receptor-mediated pathway. *Endocrinology* 2012 **153** 5143–5149. (https://doi.org/10.1210/en.2012-1572)

44 Davidson NO, Powell LM, Wallis SC & Scott J. Thyroid hormone modulates the introduction of a stop codon in rat liver apolipoprotein B messenger RNA. *Journal of Biological Chemistry* 1988 **263** 13482–13485. (https://doi.org/10.1016/S0021-9258(18)68263-8)

45 Mugii S, Hanada H, Okubo M, Masuda D, Takeoka K, Hidaka Y, Ohama T, Matsuyama A, Nakagawa-Toyama Y, Nishida M, *et al.* Thyroid function influences serum apolipoprotein B-48 levels in patients with thyroid disease. *Journal of Atherosclerosis and Thrombosis* 2012 **19** 890–896. (https://doi.org/10.5551/jat.12757)

46 Lopez D, Abisambra Socarrás JF, Bedi M & Ness GC. Activation of the hepatic LDL receptor promoter by thyroid hormone. *Biochimica et Biophysica Acta* 2007 **1771** 1216–1225. (https://doi.org/10.1016/j.bbalip.2007.05.001)

47 Dong B, Singh AB, Fung C, Kan K & Liu J. CETP inhibitors downregulate hepatic LDL receptor and PCSK9 expression *in vitro* and *in vivo* through a SREBP2 dependent mechanism. *Atherosclerosis* 2014 **235** 449–462. (https://doi.org/10.1016/j.atherosclerosis.2014.05.931)

48 Zhou L, Wu K, Zhang L, Gao L & Chen S. Liver-specific deletion of TSHR inhibits hepatic lipid accumulation in mice. *Biochemical and Biophysical Research Communications* 2018 **497** 39–45. (https://doi.org/10.1016/j.bbrc.2018.01.187)

49 Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, Yu C, Qin C, Liu J, Tian X, *et al.* A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. *Hepatology* 2010 **52** 1401–1409. (https://doi.org/10.1002/hep.23800)

50 Liu S, Jing F, Yu C, Gao L, Qin Y & Zhao J. AICAR-induced activation of AMPK inhibits TSH/SREBP-2/HMGCR pathway in liver. *PLoS ONE* 2015 **10** e0124951. (https://doi.org/10.1371/journal.pone.0124951)

51 Moreno-Navarrete JM, Moreno M, Ortega F, Xifra G, Hong S, Asara JM, Serrano JCE, Jové M, Pissios P, Blüher M, *et al.* TSHB mRNA is linked to cholesterol metabolism in adipose tissue. *FASEB Journal* 2017 **31** 4482–4491. (https://doi.org/10.1096/fj.201700161R)

52 Comas F, Lluch A, Sabater M, Latorre J, Ortega F, Ricart W, López M, Fernández-Real JM & Moreno-Navarrete JM. Adipose tissue TSH as a new modulator of human adipocyte mitochondrial function. *International Journal of Obesity* 2019 **43** 1611–1619. (https://doi.org/10.1038/s41366-018-0203-1)

53 Gagnon A, Antunes TT, Ly T, Pongsuwan P, Gavin C, Lochnan HA & Sorisky A. Thyroid-stimulating hormone stimulates lipolysis in adipocytes in culture and raises serum free fatty acid levels *in vivo*. *Metabolism: Clinical and Experimental* 2010 **59** 547–553. (https://doi.org/10.1016/j.metabol.2009.08.018)

54 Song Y, Xu C, Shao S, Liu J, Xing W, Xu J, Qin C, Li C, Hu B, Yi S, *et al.* Thyroid-stimulating hormone regulates hepatic bile acid homeostasis *via* SREBP-2/HNF-4α/CYP7A1 axis. *Journal of Hepatology* 2015 **62** 1171–1179. (https://doi.org/10.1016/j.jhep.2014.12.006)

55 Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM, Zheng SJ, Zhou JC & Xu J. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Medical Science Monitor* 2014 **20** 1432–1441. (https://doi.org/10.12659/MSM.891163)

56 Gambo Y, Matsumura M & Fujimori K. Triiodothyronine enhances accumulation of intracellular lipids in adipocytes through thyroid hormone receptor α via direct and indirect mechanisms. *Molecular and Cellular Endocrinology* 2016 **431** 1–11. (https://doi.org/10.1016/j.mce.2016.04.023)

57 Senese R, Cioffi F, de Lange P, Leanza C, Iannucci LF, Silvestri E, Moreno M, Lombardi A, Goglia F & Lanni A. Both 3,5-diiodo-L-thyronine and 3,5,3′-triiodo-L-thyronine prevent short-term hepatic lipid accumulation via distinct mechanisms in rats being fed a high-fat diet. *Frontiers in Physiology* 2017 **8** 706. (https://doi.org/10.3389/fphys.2017.00706)

58 Gnoni GV, Rochira A, Leone A, Damiano F, Marsigliante S & Siculella L. 3,5,3'triiodo-L-thyronine induces SREBP-1 expression by non-genomic actions in human HEP G2 cells. *Journal of Cellular Physiology* 2012 **227** 2388–2397. (https://doi.org/10.1002/jcp.22974)

59 Han C, Wang J, Li L, Zhang Z, Wang L & Pan Z. The role of insulin and glucose in goose primary hepatocyte triglyceride accumulation. *Journal of Experimental Biology* 2009 **212** 1553–1558. (https://doi.org/10.1242/jeb.022210)

60 Fang K, Wu F, Chen G, Dong H, Li J, Zhao Y, Xu L, Zou X & Lu F. Diosgenin ameliorates palmitic acid-induced lipid accumulation via AMPK/ACC/CPT-1A and SREBP-1c/FAS signaling pathways in LO2 cells. *BMC Complementary and Alternative Medicine* 2019 **19** 255. (https://doi.org/10.1186/s12906-019-2671-9)

61 Gauthier K, Billon C, Bissler M, Beylot M, Lobaccaro JM, Vanacker JM & Samarut J. Thyroid hormone receptor beta (TRbeta) and liver X receptor (LXR) regulate carbohydrate-response element-binding protein (ChREBP) expression in a tissue-selective manner. *Journal of Biological Chemistry* 2010 **285** 28156–28163. (https://doi.org/10.1074/jbc.M110.146241)

62 Sanchez-Gurmaches J, Tang Y, Jespersen NZ, Wallace M, Martinez Calejman C, Gujja S, Li H, Edwards YJK, Wolfrum C, Metallo CM, *et al.* Brown fat AKT2 is a cold-induced kinase that stimulates ChREBP-mediated *de novo* lipogenesis to optimize fuel storage and thermogenesis. *Cell Metabolism* 2018 **27** 195.e6–209.e6. (https://doi.org/10.1016/j.cmet.2017.10.008)

63 Linden AG, Li S, Choi HY, Fang F, Fukasawa M, Uyeda K, Hammer RE, Horton JD, Engelking LJ & Liang G. Interplay between ChREBP and SREBP-1c coordinates postprandial glycolysis and lipogenesis in livers of mice. *Journal of Lipid Research* 2018 **59** 475–487. (https://doi.org/10.1194/jlr.M081836)

64 Liu J, Xu Y, Hu Y & Wang G. The role of fibroblast growth factor 21 in the pathogenesis of non-alcoholic fatty liver disease and implications for therapy. *Metabolism: Clinical and Experimental* 2015 **64** 380–390. (https://doi.org/10.1016/j.metabol.2014.11.009)

65 Adams AC, Halstead CA, Hansen BC, Irizarry AR, Martin JA, Myers SR, Reynolds VL, Smith HW, Wroblewski VJ & Kharitonenkov A. LY2405319, an engineered FGF21 variant, improves the metabolic status of diabetic monkeys. *PLoS ONE* 2013 **8** e65763. (https://doi.org/10.1371/journal.pone.0065763)

66 Véniant MM, Komorowski R, Chen P, Stanislaus S, Winters K, Hager T, Zhou L, Wada R, Hecht R & Xu J. Long-acting FGF21 has enhanced efficacy in diet-induced obese mice and in obese rhesus monkeys. *Endocrinology* 2012 **153** 4192–4203. (https://doi.org/10.1210/en.2012-1211)

67 Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, Kharitonenkov A, Bumol T, Schilske HK & Moller DE. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. *Cell Metabolism* 2013 **18** 333–340. (https://doi.org/10.1016/j.cmet.2013.08.005)

68 Xu J, Lloyd DJ, Hale C, Stanislaus S, Chen M, Sivits G, Vonderfecht S, Hecht R, Li YS, Lindberg RA, *et al.* Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. *Diabetes* 2009 **58** 250–259. (https://doi.org/10.2337/db08-0392)

69 Chen W, Hoo RL-c, Konishi M, Itoh N, Lee PC, Ye HY, Lam KS-l & Xu A. Growth hormone induces hepatic production of fibroblast growth factor 21 through a mechanism dependent on lipolysis in adipocytes. *Journal of Biological Chemistry* 2011 **286** 34559–34566. (https://doi.org/10.1074/jbc.M111.285965)

70 Schlein C, Talukdar S, Heine M, Fischer AW, Krott LM, Nilsson SK, Brenner MB, Heeren J & Scheja L. FGF21 lowers plasma triglycerides by accelerating lipoprotein catabolism in white and brown adipose tissues. *Cell Metabolism* 2016 **23** 441–453. (https://doi.org/10.1016/j.cmet.2016.01.006)

71 Zhang A, Sieglaff DH, York JP, Suh JH, Ayers SD, Winnier GE, Kharitonenkov A, Pin C, Zhang P, Webb P, *et al.* Thyroid hormone receptor regulates most genes independently of fibroblast growth factor 21 in liver. *Journal of Endocrinology* 2015 **224** 289–301. (https://doi.org/10.1530/JOE-14-0440)

72 Adams AC, Astapova I, Fisher FM, Badman MK, Kurgansky KE, Flier JS, Hollenberg AN & Maratos-Flier E. Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPARalpha-dependent manner. *Journal of Biological Chemistry* 2010 **285** 14078–14082. (https://doi.org/10.1074/jbc.C110.107375)

73 Chau MDL, Gao J, Yang Q, Wu Z & Gromada J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway. *PNAS* 2010 **107** 12553–12558. (https://doi.org/10.1073/pnas.1006962107)

74 Iizuka K, Takao K, Kato T, Horikawa Y & Takeda J. ChREBP reciprocally regulates liver and plasma triacylglycerol levels in different manners. *Nutrients* 2018 **10** 1699. (https://doi.org/10.3390/nu10111699)

75 Benhamed F, Denechaud PD, Lemoine M, Robichon C, Moldes M, Bertrand-Michel J, Ratziu V, Serfaty L, Housset C, Capeau J, *et al.* The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. *Journal of Clinical Investigation* 2012 **122** 2176–2194. (https://doi.org/10.1172/JCI41636)

76 Domouzoglou EM, Fisher FM, Astapova I, Fox EC, Kharitonenkov A, Flier JS, Hollenberg AN & Maratos-Flier E. Fibroblast growth factor 21 and thyroid hormone show mutual regulatory dependency but have independent actions *in vivo*. *Endocrinology* 2014 **155** 2031–2040. (https://doi.org/10.1210/en.2013-1902)

77 Wang G, Liu J, Yang N, Hu Y, Zhang H, Miao L, Yao Z & Xu Y. Levothyroxine treatment restored the decreased circulating fibroblast growth factor 21 levels in patients with hypothyroidism. *European Journal of Internal Medicine* 2016 **31** 94–98. (https://doi.org/10.1016/j.ejim.2016.03.028)

78 Xiao F, Zeng J, Huang P, Yan B, Zeng X, Liu C, Shi X, Wang L, Song H, Lin M, *et al.* Independent association of serum fibroblast growth factor 21 levels with impaired liver enzymes in hyperthyroid patients. *Frontiers in Endocrinology* 2018 **9** 800. (https://doi.org/10.3389/fendo.2018.00800)

79 Bonde Y, Breuer O, Lütjohann D, Sjöberg S, Angelin B & Rudling M. Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. *Journal of Lipid Research* 2014 **55** 2408–2415. (https://doi.org/10.1194/jlr.M051664)

80 Lee Y, Park YJ, Ahn HY, Lim JA, Park KU, Choi SH, Park DJ, Oh BC, Jang HC & Yi KH. Plasma FGF21 levels are increased in patients with hypothyroidism independently of lipid profile. *Endocrine Journal* 2013 **60** 977–983. (https://doi.org/10.1507/endocrj.ej12-0427)

81 Lundåsen T, Gälman C, Angelin B & Rudling M. Circulating intestinal fibroblast growth factor 19 has a pronounced diurnal variation and modulates hepatic bile acid synthesis in man. *Journal of Internal*

Medicine 2006 **260** 530–536. (https://doi.org/10.1111/j.1365-2796.2006.01731.x)
82 Angelin B, Larsson TE & Rudling M. Circulating fibroblast growth factors as metabolic regulators – a critical appraisal. *Cell Metabolism* 2012 **16** 693–705. (https://doi.org/10.1016/j.cmet.2012.11.001)
83 Lai Y, Wang H, Xia X, Wang Z, Fan C, Wang H, Zhang H, Ding S, Teng W & Shan Z. Serum fibroblast growth factor 19 is decreased in patients with overt hypothyroidism and subclinical hypothyroidism. *Medicine* 2016 **95** e5001. (https://doi.org/10.1097/MD.0000000000005001)
84 Miyata M, Hata T, Yamazoe Y & Yoshinari K. SREBP-2 negatively regulates FXR-dependent transcription of FGF19 in human intestinal cells. *Biochemical and Biophysical Research Communications* 2014 **443** 477–482. (https://doi.org/10.1016/j.bbrc.2013.11.126)
85 Yap CS, Sinha RA, Ota S, Katsuki M & Yen PM. Thyroid hormone negatively regulates CDX2 and SOAT2 mRNA expression via induction of miRNA-181d in hepatic cells. *Biochemical and Biophysical Research Communications* 2013 **440** 635–639. (https://doi.org/10.1016/j.bbrc.2013.09.116)
86 Zheng Y, Zhao C, Zhang N, Kang W, Lu R, Wu H, Geng Y, Zhao Y & Xu X. Serum microRNA miR-206 is decreased in hyperthyroidism and mediates thyroid hormone regulation of lipid metabolism in HepG2 human hepatoblastoma cells. *Molecular Medicine Reports* 2018 **17** 5635–5641. (https://doi.org/10.3892/mmr.2018.8633)
87 Sun C, Liu W, Lu Z, Li Y, Liu S, Tang Z, Yan Y, Li Z, Feng H, Zhang D, *et al.* Hepatic miR-378 modulates serum cholesterol levels by regulating hepatic bile acid synthesis. *Theranostics* 2021 **11** 4363–4380. (https://doi.org/10.7150/thno.53624)
88 Zhang L, Wu K, Bo T, Zhou L, Gao L, Zhou X & Chen W. Integrated microRNA and proteome analysis reveal a regulatory module in hepatic lipid metabolism disorders in mice with subclinical hypothyroidism. *Experimental and Therapeutic Medicine* 2020 **19** 897–906. (https://doi.org/10.3892/etm.2019.8281)
89 Canuel M, Sun X, Asselin MC, Paramithiotis E, Prat A & Seidah NG. Proprotein convertase subtilisin/kexin type 9 (PCSK9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1). *PLoS ONE* 2013 **8** e64145. (https://doi.org/10.1371/journal.pone.0064145)
90 Lee JS, Mukhopadhyay P, Matyas C, Trojnar E, Paloczi J, Yang YR, Blank BA, Savage C, Sorokin AV, Mehta NN, *et al.* PCSK9 inhibition as a novel therapeutic target for alcoholic liver disease. *Scientific Reports* 2019 **9** 17167. (https://doi.org/10.1038/s41598-019-53603-6)
91 Ruscica M, Ferri N, Macchi C, Meroni M, Lanti C, Ricci C, Maggioni M, Fracanzani AL, Badiali S, Fargion S, *et al.* Liver fat accumulation is associated with circulating PCSK9. *Annals of Medicine* 2016 **48** 384–391. (https://doi.org/10.1080/07853890.2016.1188328)
92 Jing Y, Hu T, Lin C, Xiong Q, Liu F, Yuan J, Zhao X & Wang R. Resveratrol downregulates PCSK9 expression and attenuates steatosis through estrogen receptor α-mediated pathway in L02 cells. *European Journal of Pharmacology* 2019 **855** 216–226. (https://doi.org/10.1016/j.ejphar.2019.05.019)
93 Gong Y, Ma Y, Ye Z, Fu Z, Yang P, Gao B, Guo W, Hu D, Ye J, Ma S, *et al.* Thyroid stimulating hormone exhibits the impact on LDLR/LDL-c via up-regulating hepatic PCSK9 expression. *Metabolism: Clinical and Experimental* 2017 **76** 32–41. (https://doi.org/10.1016/j.metabol.2017.07.006)
94 Yildirim AM, Koca AO, Beyan E, Dogan O, Karakaya S, Aksoz Z & Ertuğrul DT. Association of serum proprotein convertase subtilisin/kexin type 9 (PCSK9) level with thyroid function disorders. *European Review for Medical and Pharmacological Sciences* 2021 **25** 5511–5517. (https://doi.org/10.26355/eurrev_202109_26662)
95 Schaap FG, Rensen PCN, Voshol PJ, Vrins C, van der Vliet HN, Chamuleau RAFM, Havekes LM, Groen AK & van Dijk KW. *ApoAV* reduces plasma triglycerides by inhibiting very low density lipoprotein-triglyceride (VLDL-TG) production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. *Journal of Biological Chemistry* 2004 **279** 27941–27947. (https://doi.org/10.1074/jbc.M403240200)
96 Gjedde S, Gormsen LC, Rungby J, Nielsen S, Jørgensen JOL, Pedersen SB, Riis AL, Weeke J & Møller N. Decreased lipid intermediate levels and lipid oxidation rates despite normal lipolysis in patients with hypothyroidism. *Thyroid* 2010 **20** 843–849. (https://doi.org/10.1089/thy.2009.0212)
97 Prieur X, Huby T, Coste H, Schaap FG, Chapman MJ & Rodríguez JC. Thyroid hormone regulates the hypotriglyceridemic gene APOA5. *Journal of Biological Chemistry* 2005 **280** 27533–27543. (https://doi.org/10.1074/jbc.M503139200)
98 Martínez-Triguero ML, Hernández-Mijares A, Nguyen TT, Muñoz ML, Peña H, Morillas C, Lorente D, Lluch I & Molina E. Effect of thyroid hormone replacement on lipoprotein(*a*), lipids, and apolipoproteins in subjects with hypothyroidism. *Mayo Clinic Proceedings* 1998 **73** 837–841. (https://doi.org/10.4065/73.9.837)
99 Sigal GA, Medeiros-Neto G, Vinagre JC, Diament J & Maranhão RC. Lipid metabolism in subclinical hypothyroidism: plasma kinetics of triglyceride-rich lipoproteins and lipid transfers to high-density lipoprotein before and after levothyroxine treatment. *Thyroid* 2011 **21** 347–353. (https://doi.org/10.1089/thy.2010.0313)
100 Ito M, Takamatsu J, Sasaki I, Hiraiwa T, Fukao A, Murakami Y, Isotani H, Miyauchi A, Kuma K & Hanafusa T. Disturbed metabolism of remnant lipoproteins in patients with subclinical hypothyroidism. *American Journal of Medicine* 2004 **117** 696–699. (https://doi.org/10.1016/j.amjmed.2004.04.027)
101 Moon JH, Kim HJ, Kim HM, Choi SH, Lim S, Park YJ, Jang HC & Cha BS. Decreased expression of hepatic low-density lipoprotein receptor-related protein 1 in hypothyroidism: a novel mechanism of atherogenic dyslipidemia in hypothyroidism. *Thyroid* 2013 **23** 1057–1065. (https://doi.org/10.1089/thy.2012.0457)
102 Costales P, Castellano J, Revuelta-López E, Cal R, Aledo R, Llampayas O, Nasarre L, Juarez C, Badimon L & Llorente-Cortés V. Lipopolysaccharide downregulates CD91/low-density lipoprotein receptor-related protein 1 expression through SREBP-1 overexpression in human macrophages. *Atherosclerosis* 2013 **227** 79–88. (https://doi.org/10.1016/j.atherosclerosis.2012.12.021)
103 Costales P, Aledo R, Vérnia S, Das A, Shah VH, Casado M, Badimon L & Llorente-Cortés V. Selective role of sterol regulatory element binding protein isoforms in aggregated LDL-induced vascular low density lipoprotein receptor-related protein-1 expression. *Atherosclerosis* 2010 **213** 458–468. (https://doi.org/10.1016/j.atherosclerosis.2010.09.034)
104 Ma S, Jing F, Xu C, Zhou L, Song Y, Yu C, Jiang D, Gao L, Li Y, Guan Q, *et al.* Thyrotropin and obesity: increased adipose triglyceride content through glycerol-3-phosphate acyltransferase 3. *Scientific Reports* 2015 **5** 7633. (https://doi.org/10.1038/srep07633)
105 Yan F, Wang Q, Lu M, Chen W, Song Y, Jing F, Guan Y, Wang L, Lin Y, Bo T, *et al.* Thyrotropin increases hepatic triglyceride content through upregulation of SREBP-1c activity. *Journal of Hepatology* 2014 **61** 1358–1364. (https://doi.org/10.1016/j.jhep.2014.06.037)
106 van Tienhoven-Wind LJN, Dallinga-Thie GM & Dullaart RPF. Higher plasma ApoE levels are associated with low-normal thyroid function: studies in diabetic and nondiabetic subjects. *Hormone and Metabolic Research* 2016 **48** 462–467. (https://doi.org/10.1055/s-0042-102883)
107 Jung KY, Ahn HY, Han SK, Park YJ, Cho BY & Moon MK. Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function. *Journal of Clinical Lipidology* 2017 **11** 1347–1353. (https://doi.org/10.1016/j.jacl.2017.08.015)
108 Fugier C, Tousaint JJ, Prieur X, Plateroti M, Samarut J & Delerive P. The lipoprotein lipase inhibitor ANGPTL3 is negatively regulated by thyroid hormone. *Journal of Biological Chemistry* 2006 **281** 11553–11559. (https://doi.org/10.1074/jbc.M512554200)
109 Li H, Xu M, Zhao L, Xia H, Li Y, Hong X, Deng X, Yuan J, Ding Y, Guo C, *et al.* Decreased circulating levels of ANGPTL8 in Graves' disease patients. *Hormones* 2019 **18** 189–195. (https://doi.org/10.1007/s42000-019-00095-8)

110 Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, Natarajan P, Klarin D, Emdin CA, Zekavat SM, *et al.* ANGPTL3 deficiency and protection against coronary artery disease. *Journal of the American College of Cardiology* 2017 **69** 2054–2063. (https://doi.org/10.1016/j.jacc.2017.02.030)

111 Wang Y, Gusarova V, Banfi S, Gromada J, Cohen JC & Hobbs HH. Inactivation of ANGPTL3 reduces hepatic VLDL-triglyceride secretion. *Journal of Lipid Research* 2015 **56** 1296–1307. (https://doi.org/10.1194/jlr.M054882)

112 Reimund M, Kovrov O, Olivecrona G & Lookene A. Lipoprotein lipase activity and interactions studied in human plasma by isothermal titration calorimetry. *Journal of Lipid Research* 2017 **58** 279–288. (https://doi.org/10.1194/jlr.D071787)

113 Morinaga J, Zhao J, Endo M, Kadomatsu T, Miyata K, Sugizaki T, Okadome Y, Tian Z, Horiguchi H, Miyashita K, *et al.* Association of circulating ANGPTL 3, 4, and 8 levels with medical status in a population undergoing routine medical checkups: a cross-sectional study. *PLoS ONE* 2018 **13** e0193731. (https://doi.org/10.1371/journal.pone.0193731)

114 Liu J, Afroza H, Rader DJ & Jin W. Angiopoietin-like protein 3 inhibits lipoprotein lipase activity through enhancing its cleavage by proprotein convertases. *Journal of Biological Chemistry* 2010 **285** 27561–27570. (https://doi.org/10.1074/jbc.M110.144279)

115 Mysling S, Kristensen KK, Larsson M, Kovrov O, Bensadouen A, Jørgensen TJ, Olivecrona G, Young SG & Ploug M. The angiopoietin-like protein ANGPTL4 catalyzes unfolding of the hydrolase domain in lipoprotein lipase and the endothelial membrane protein GPIHBP1 counteracts this unfolding. *eLife* 2016 **5** e20958. (https://doi.org/10.7554/eLife.20958)

116 Minicocci I, Tikka A, Poggiogalle E, Metso J, Montali A, Ceci F, Labbadia G, Fontana M, Di Costanzo A, Maranghi M, *et al.* Effects of angiopoietin-like protein 3 deficiency on postprandial lipid and lipoprotein metabolism. *Journal of Lipid Research* 2016 **57** 1097–1107. (https://doi.org/10.1194/jlr.P066183)

117 Tikkanen E, Minicocci I, Hällfors J, Di Costanzo A, D'Erasmo L, Poggiogalle E, Donini LM, Würtz P, Jauhiainen M, Olkkonen VM, *et al.* Metabolomic signature of angiopoietin-like protein 3 deficiency in fasting and postprandial state. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2019 **39** 665–674. (https://doi.org/10.1161/ATVBAHA.118.312021)

118 Xu YX, Redon V, Yu H, Querbes W, Pirruccello J, Liebow A, Deik A, Trindade K, Wang X, Musunuru K, *et al.* Role of angiopoietin-like 3 (ANGPTL3) in regulating plasma level of low-density lipoprotein cholesterol. *Atherosclerosis* 2018 **268** 196–206. (https://doi.org/10.1016/j.atherosclerosis.2017.08.031)

119 Yang L, Yin R, Wang Z, Wang X, Zhang Y & Zhao D. Circulating Angptl3 and Angptl8 are increased in patients with hypothyroidism. *BioMed Research International* 2019 **2019** 3814687. (https://doi.org/10.1155/2019/3814687)

120 Shimamura M, Matsuda M, Yasumo H, Okazaki M, Fujimoto K, Kono K, Shimizugawa T, Ando Y, Koishi R, Kohama T, *et al.* Angiopoietin-like protein3 regulates plasma HDL cholesterol through suppression of endothelial lipase. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2007 **27** 366–372. (https://doi.org/10.1161/01.ATV.0000252827.51626.89)

121 Izumi R, Kusakabe T, Noguchi M, Iwakura H, Tanaka T, Miyazawa T, Aotani D, Hosoda K, Kangawa K & Nakao K. CRISPR/Cas9-mediated knockout suppresses plasma triglyceride concentrations and adiposity in rats. *Journal of Lipid Research* 2018 **59** 1575–1585. (https://doi.org/10.1194/jlr.M082099)

122 Wang Y, Quagliarini F, Gusarova V, Gromada J, Valenzuela DM, Cohen JC & Hobbs HH. Mice lacking ANGPTL8 (Betatrophin) manifest disrupted triglyceride metabolism without impaired glucose homeostasis. *PNAS* 2013 **110** 16109–16114. (https://doi.org/10.1073/pnas.1315292110)

123 Haller JF, Mintah IJ, Shihanian LM, Stevis P, Buckler D, Alexa-Braun CA, Kleiner S, Banfi S, Cohen JC, Hobbs HH, *et al.* ANGPTL8 requires ANGPTL3 to inhibit lipoprotein lipase and plasma triglyceride clearance. *Journal of Lipid Research* 2017 **58** 1166–1173. (https://doi.org/10.1194/jlr.M075689)

124 Quagliarini F, Wang Y, Kozlitina J, Grishin NV, Hyde R, Boerwinkle E, Valenzuela DM, Murphy AJ, Cohen JC & Hobbs HH. Atypical angiopoietin-like protein that regulates ANGPTL3. *PNAS* 2012 **109** 19751–19756. (https://doi.org/10.1073/pnas.1217552109)

125 Chi X, Britt EC, Shows HW, Hjelmaas AJ, Shetty SK, Cushing EM, Li W, Dou A, Zhang R & Davies BSJ. ANGPTL8 promotes the ability of ANGPTL3 to bind and inhibit lipoprotein lipase. *Molecular Metabolism* 2017 **6** 1137–1149. (https://doi.org/10.1016/j.molmet.2017.06.014)

126 Chung HS, Lee MJ, Hwang SY, Lee HJ, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, *et al.* Circulating angiopoietin-like protein 8 (ANGPTL8) and ANGPTL3 concentrations in relation to anthropometric and metabolic profiles in Korean children: a prospective cohort study. *Cardiovascular Diabetology* 2016 **15** 1. (https://doi.org/10.1186/s12933-015-0324-y)

127 Gusarova V, Banfi S, Alexa-Braun CA, Shihanian LM, Mintah IJ, Lee JS, Xin Y, Su Q, Kamat V, Cohen JC, *et al.* ANGPTL8 blockade with a monoclonal antibody promotes triglyceride clearance, energy expenditure, and weight loss in mice. *Endocrinology* 2017 **158** 1252–1259. (https://doi.org/10.1210/en.2016-1894)

128 Fu Z, Abou-Samra AB & Zhang R. A lipasin/Angptl8 monoclonal antibody lowers mouse serum triglycerides involving increased postprandial activity of the cardiac lipoprotein lipase. *Scientific Reports* 2015 **5** 18502. (https://doi.org/10.1038/srep18502)

129 Tseng YH, Ke PY, Liao CJ, Wu SM, Chi HC, Tsai CY, Chen CY, Lin YH & Lin KH. Chromosome 19 open reading frame 80 is upregulated by thyroid hormone and modulates autophagy and lipid metabolism. *Autophagy* 2014 **10** 20–31. (https://doi.org/10.4161/auto.26126)

130 Ren G, Kim JY & Smas CM. Identification of RIFL, a novel adipocyte-enriched insulin target gene with a role in lipid metabolism. *American Journal of Physiology: Endocrinology and Metabolism* 2012 **303** E334–E351. (https://doi.org/10.1152/ajpendo.00084.2012)

131 Fenzl A, Itariu BK, Kosi L, Fritzer-Szekeres M, Kautzky-Willer A, Stulnig TM & Kiefer FW. Circulating betatrophin correlates with atherogenic lipid profiles but not with glucose and insulin levels in insulin-resistant individuals. *Diabetologia* 2014 **57** 1204–1208. (https://doi.org/10.1007/s00125-014-3208-x)

132 Lim JA, Kim HJ, Ahn HY, Park KU, Yi KH, Park DJ, Jang HC & Park YJ. Influence of thyroid dysfunction on serum levels of angiopoietin-like protein 6. *Metabolism: Clinical and Experimental* 2015 **64** 1279–1283. (https://doi.org/10.1016/j.metabol.2015.06.015)

133 Namkung J, Sohn JH, Chang JS, Park SW, Kim JY, Koh SB, Kong ID & Park KS. Increased serum angiopoietin-like 6 ahead of metabolic syndrome in a prospective cohort study. *Diabetes and Metabolism Journal* 2019 **43** 521–529. (https://doi.org/10.4093/dmj.2018.0080)

134 Kang SG, Yi HS, Choi MJ, Ryu MJ, Jung S, Chung HK, Chang JY, Kim YK, Lee SE, Kim HW, *et al.* ANGPTL6 expression is coupled with mitochondrial OXPHOS function to regulate adipose FGF21. *Journal of Endocrinology* 2017 **233** 105–118. (https://doi.org/10.1530/JOE-16-0549)

135 Ge H, Yang G, Huang L, Motola DL, Pourbahrami T & Li C. Oligomerization and regulated proteolytic processing of angiopoietin-like protein 4. *Journal of Biological Chemistry* 2004 **279** 2038–2045. (https://doi.org/10.1074/jbc.M307583200)

136 TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, *et al.* Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *New England Journal of Medicine* 2014 **371** 22–31. (https://doi.org/10.1056/NEJMoa1307095)

137 van Tienhoven-Wind LJN, Perton FG & Dullaart RPF. *Pre*-β-HDL formation relates to high-normal free thyroxine in type 2 diabetes mellitus. *Clinical Biochemistry* 2016 **49** 41–46. (https://doi.org/10.1016/j.clinbiochem.2015.08.024)
138 Boone LR, Lagor WR, Moya Mde L, Niesen MI, Rothblat GH & Ness GC. Thyroid hormone enhances the ability of serum to accept cellular cholesterol via the ABCA1 transporter. *Atherosclerosis* 2011 **218** 77–82. (https://doi.org/10.1016/j.atherosclerosis.2011.04.028)
139 Yang N, Yao Z, Miao L, Liu J, Gao X, Xu Y & Wang G. Homocysteine diminishes apolipoprotein A-I function and expression in patients with hypothyroidism: a cross-sectional study. *Lipids in Health and Disease* 2016 **15** 123. (https://doi.org/10.1186/s12944-016-0293-5)
140 Sigal GA, Tavoni TM, Silva BMO, Kalil Filho R, Brandão LG & Maranhão RC. Effects of short-term hypothyroidism on the lipid transfer to high-density lipoprotein and other parameters related to lipoprotein metabolism in patients submitted to thyroidectomy for thyroid cancer. *Thyroid* 2019 **29** 53–58. (https://doi.org/10.1089/thy.2018.0190)
141 van der Boom T, Jia C, Lefrandt JD, Connelly MA, Links TP, Tietge UJF & Dullaart RPF. HDL cholesterol efflux capacity is impaired in severe short-term hypothyroidism despite increased HDL cholesterol. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** e3355–e3362. (https://doi.org/10.1210/clinem/dgaa411)
142 Ridgway ND & Dolphin PJ. Serum activity and hepatic secretion of lecithin:cholesterol acyltransferase in experimental hypothyroidism and hypercholesterolemia. *Journal of Lipid Research* 1985 **26** 1300–1313. (https://doi.org/10.1016/S0022-2275(20)34256-5)
143 Kuusi T, Saarinen P & Nikkilä EA. Evidence for the role of hepatic endothelial lipase in the metabolism of plasma high density lipoprotein2 in man. *Atherosclerosis* 1980 **36** 589–593. (https://doi.org/10.1016/0021-9150(80)90251-8)
144 McGowan A, Widdowson WM, O'Regan A, Young IS, Boran G, McEneny J & Gibney J. Postprandial studies uncover differing effects on HDL particles of overt and subclinical hypothyroidism. *Thyroid* 2016 **26** 356–364. (https://doi.org/10.1089/thy.2015.0443)
145 Ness GC & Lopez D. Transcriptional regulation of rat hepatic low-density lipoprotein receptor and cholesterol 7 alpha hydroxylase by thyroid hormone. *Archives of Biochemistry and Biophysics* 1995 **323** 404–408. (https://doi.org/10.1006/abbi.1995.0061)
146 Bonde Y, Plösch T, Kuipers F, Angelin B & Rudling M. Stimulation of murine biliary cholesterol secretion by thyroid hormone is dependent on a functional ABCG5/G8 complex. *Hepatology* 2012 **56** 1828–1837. (https://doi.org/10.1002/hep.25861)
147 Johansson L, Rudling M, Scanlan TS, Lundåsen T, Webb P, Baxter J, Angelin B & Parini P. Selective thyroid receptor modulation by GC-1 reduces serum lipids and stimulates steps of reverse cholesterol transport in euthyroid mice. *PNAS* 2005 **102** 10297–10302. (https://doi.org/10.1073/pnas.0504379102)
148 Skoczyńska A, Wojakowska A, Turczyn B, Zatońska K, Wołyniec M, Rogala N, Szuba A & Bednarek-Tupikowska G. Serum lipid transfer proteins in hypothyreotic patients are inversely correlated with thyroid-stimulating hormone (TSH) levels. *Medical Science Monitor* 2016 **22** 4661–4669. (https://doi.org/10.12659/msm.898134)
149 Triolo M, Kwakernaak AJ, Perton FG, de Vries R, Dallinga-Thie GM & Dullaart RPF. Low normal thyroid function enhances plasma cholesteryl ester transfer in type 2 diabetes mellitus. *Atherosclerosis* 2013 **228** 466–471. (https://doi.org/10.1016/j.atherosclerosis.2013.03.009)
150 Rhainds D & Tardif JC. From HDL-cholesterol to HDL-function: cholesterol efflux capacity determinants. *Current Opinion in Lipidology* 2019 **30** 101–107. (https://doi.org/10.1097/MOL.0000000000000589)

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