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Effects of endocrine disorders on lipids and lipoproteins

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Endocrine diseases may be associated with dyslipidaemia and may increase atherosclerotic cardiovascular disease (ASCVD) risk. This chapter describes changes in lipids and lipoproteins in diseases of the pituitary, thyroid, adrenal glands, ovaries, and testes, the mechanisms for these changes, ASCVD risk in these endocrine disorders, and whether treatment of the endocrine disorder improves the lipid profile and reduces ASCVD risk. Acromegaly, GH deficiency, Cushing syndrome, chronic glucocorticoid replacement, hypothyroidism, PCOS and male hypogonadism can increase LDL-C and/or TG. Marked reductions in LDL-C are associated with hyperthyroidism, and extremely low HDL-C levels with testosterone and/or other anabolic steroid abuse. Acromegaly, GH deficiency, Cushing syndrome, and chronic glucocorticoid replacement are associated with increased ASCVD risk. Treatment of acromegaly, GH deficiency, hypothyroidism, Cushing syndrome, and testosterone deficiency reduce LDL-C, although statin therapy may still be needed. Effects on ASCVD are not known.

Hormones influence lipid and lipoprotein metabolism, and it is not surprising that endocrine diseases affect the lipid profile and may increase atherosclerotic cardiovascular disease (ASCVD) risk. Table 1 summarizes changes in low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and lipoprotein (a) [Lp (a)] in disorders of the pituitary, thyroid adrenal, and reproductive glands. This chapter describes changes in lipids in endocrine diseases, the

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Table 1
Lipids and lipoproteins in endocrine disorders.

Disorder	Lipid, lipoprotein parameter mg/dL			
	LDL-C	HDL-C	TG	Lp (a)
Pituitary				
Adult GH deficiency	↑	Normal or ↓	Normal or ↑	NC
Acromegaly	NC or ↑	Normal or ↓	↑	↑
Thyroid				
Overt hypothyroidism	↑	Normal or ↑	Normal or ↑	NC or ↑
Subclinical hypothyroidism	NC or ↑	Normal or ↓	Normal	NC
Overt Hyperthyroidism	↓	Normal or ↓	Normal or ↑	↓
Adrenal				
Cushing syndrome	NC or ↑	Normal or ↓	↑	NC or ↑
Chronic glucocorticoids	NC or ↑	Normal or ↑	Normal or ↑	–
Female reproductive hormones				
Premenopausal women vs men	Slightly lower	Higher	Lower	–
Post-menopause vs pre-menopause	Higher	NC or slightly lower	NC	NC or ↑
Hormone therapy post- menopause	↓	↑	↑	↓
PCOS	NC or ↑	↓	↑	↑
Male gonadal disorders				
Male hypogonadism	↑	Normal or ↓	↑	Normal or ↑
Testosterone replacement	NC or ↓	NC or ↓	NC or ↓	↓
Testosterone/anabolic steroid abuse	↑	↓↓	NC or ↓	↓

GH growth hormone, PCOS polycystic ovary syndrome.NC no change, ––Data insufficient, ↓ Decrease, ↓↓ Marked decrease, ↑ Increase. The normal range for HDL-C is ≥ 1.0 mmol/L (40 mg/dL) in men, and ≥1.29 mmol/L (50 mg/dL) in women. The upper limit of the normal range for TG is 1.7 mmol/L (150 mg/dL).

underlying mechanisms for these changes, and the effect of treatment of the endocrine disease on dyslipidaemia and ASCVD risk. This topic is the subject of the 2020 Endocrine Society Clinical Practice Guideline "Lipid Management in Patients with Endocrine Disorders." [1].

Pituitary diseases

Adult growth hormone (GH) deficiency

Growth hormone (GH) is an anabolic peptide which regulates metabolism of carbohydrates, proteins and lipids in adults, and also cartilage and bone growth in children. Adult GH deficiency is commonly associated with hypopituitarism which has been associated with a 2-fold increase in CVD death [2,3], increased fat mass, decreased exercise capacity, cardiovascular disease (CVD), and dyslipidaemia.

Lipid and lipoprotein alterations and mechanisms

Dyslipidaemia in GH deficiency, is characterized by elevated total cholesterol (TC) and LDL-C, decreased HDL-C, increased TG [4–6] and in some cases small dense LDL particles [7]. GH administration upregulates LDL receptors, suggesting that increased LDL-C in GH deficiency may be caused by fewer LDL receptors [8,9]. Elevated TG may be caused by increased hepatic VLDL production, and reduced VLDL clearance [10]. Several studies found that long term GH replacement reduced TC and LDL-C, increased or did not change HDL-C, and did not alter TG [5,11–15]. LDL-C reduction is of a lower magnitude compared to statins. In a meta-analysis of 22 double blind, placebo-controlled trials, including over 1100 patients, GH treatment significantly increased lean body mass, decreased fat mass, and reduced TC and LDL-C. Reduction in LDL-C was 11% [13]. In two small studies of patients with GH deficiency, GH treatment was associated with increased Lp (a) levels compared to baseline [16,17].

ASCVD risk

In observational studies GH replacement has been associated with lower risk of stroke [18] and other cardiovascular events [15,19]. Long term randomized controlled trials (RCTs) are needed to establish whether GH replacement reduces ASCVD morbidity and mortality.

Management

A lipid profile is recommended at the initial visit. If the patient has GH deficiency and hypopituitarism, CVD risk factors should be assessed and treated because of increased CVD morbidity and mortality in hypopituitarism. Statin treatment should be considered in adults with LDL-C above 1.8 mmol/L (70 mg/dL) [1].

Acromegaly

Lipid and lipoprotein alterations and mechanisms

Acromegaly is commonly due to a pituitary adenoma that hyper-secretes GH. GH excess may be present for many years before diagnosis. Dyslipidaemia may be attributed to GH excess, glucose intolerance, diabetes mellitus, and excess body fat. Mild to moderate hypertriglyceridaemia, potentially caused by decreased TG clearance and increased very low density lipoprotein (VLDL) synthesis is the most common lipid abnormality [20,21]. GH stimulates lipolysis, providing FFA for VLDL synthesis. GH also inhibits lipoprotein lipase which decreases clearance of TG-rich lipoproteins [22–24]. GH regulates the response to insulin, and glucose intolerance may contribute to hypertriglyceridemia. Low HDL-C may be due to decreased lecithin cholesteryl acyl transferase (LCAT), cholesteryl ester transfer protein (CETP) and hepatic lipase [25,26], which could potentially reduce reverse cholesterol transport. TC and LDL-C are usually unchanged, although increased small dense LDL-C has been reported [27]. Lp(a) levels may be high, which could contribute to ASCVD.

Various studies reported effects of acromegaly treatment on lipids. Surgery reduced TG to normal and had no effect on TC and LDL-C [28–30]. Octreotide reduced TG and LDL-C and increased HDL-C [27,31]. Partial control of GH excess was associated with reduction in LDL-C, TG and Lp (a) [32]. The GH receptor antagonist pegvisomant increased TC and LDL-C [33,34]. Reduced Lp (a) has been reported after successful treatment with surgery or somatostatin analogs [27,28,35].

Risk of ASCVD

Acromegaly is associated with 2–3 fold increased morbidity and mortality [36]. Cardiac diseases include cardiomyopathy, diastolic and systolic dysfunction, arrhythmias, valvular diseases, and accelerated atherosclerosis. Type 2 diabetes and hypertension may occur. It is not known whether excess GH contributes to the increased risk of ASCVD in acromegaly.

Lipid Management

A lipid profile should be obtained at the first visit, before and after treatment, and periodically thereafter. Persistent hypertriglyceridaemia, and inappropriately high LDL-C for the level of ASCVD risk should be managed according to standard guidelines. A statin, as adjunct to lifestyle changes (diet and physical activity), should be considered post treatment if LDL-C remains above 1.8 mmol/L (70 mg/dL) [1].

Hypothyroidism and hyperthyroidism

The effects of thyroid hormones on lipid homeostasis are complex and involve transcriptional regulation of genes for lipogenesis and post translational regulation of enzymes, transporters, carrier proteins, and cell signaling proteins involved in lipid metabolism [37,38]. Thyroid hormones increase free fatty acids by lipolysis of fat depots and dietary fat, and stimulate free fatty acid uptake by the liver, and hepatic lipogenesis The liver synthesizes and secretes VLDL, which is enzymatically modified in the circulation to LDL-C. Thyroid hormones also upregulate the LDL receptor which clears cholesterol through the liver. In hypothyroidism, reduced LDL-C clearance leads to high levels of LDL-C [37,39].

Thyroid hormones also increase activity of enzymes that metabolize lipoproteins such as hepatic lipase, CETP and LCAT [40].

Lipid and lipoprotein alterations and mechanisms

Hypothyroidism

Overt hypothyroidism is associated with elevated TC and LDL-C, no change or small increase in HDL-C, and normal to increased TG. Lp (a), apolipoprotein B (apoB) and LDL oxidation may be increased [41,42]. T_3 induces HMG CoA reductase and upregulates hepatic LDL receptor gene expression, thus reducing LDL clearance [37]. The changes in lipids, along with reduced endothelial function and increased coagulation, may increase ASCVD risk.

Studies of patients with hyperlipidemia found that the proportion of patients with overt hypothyroidism ranged between 1.4% and 13% [43,44].

In subclinical hypothyroidism, defined as thyroid stimulating hormone (TSH) 4–10 mIU/L, TC and LDL-C may be increased or unchanged, although the increase is of a lower magnitude compared to overt hypothyroidism. HDL-C is usually normal, and TG normal or increased.

Hyperthyroidism

In overt hyperthyroidism that is not transient, TC and LDL-C are decreased, TG are normal and HDL-C unchanged or decreased. Apolipoprotein A (apo A), Apo B and Lp(a) are decreased. Thyroid hormone increases cholesterol metabolism by stimulating LDL receptor gene synthesis [45] upregulating LDL receptor number [39], increasing HMG Co A reductase mRNA and activity [46,47], and increasing activity of enzymes that metabolize lipoprotein.

Risk of ASCVD in thyroid dysfunction

The relationship of thyroid hormone dysfunction with abnormalities in the cardiovascular system, such as congestive heart failure in hypothyroidism and atrial fibrillation in hyperthyroidism, has been known for many years; however, the effects and pathophysiologic mechanisms require further research [48]. QT prolongation in hypothyroidism rarely leads to torsades de pointes [49]. Overt hypothyroidism is associated with changes in risk factors for ASCVD [50]. Studies evaluating subclinical hypothyroidism and ASCVD have yielded conflicting results [51–54]. A meta-analysis reported that subclinical hypothyroidism (TSH 4.5–19.9 mIU/L) was associated with increased CHD events and CHD mortality in persons with higher TSH levels, especially those with TSH $\geq$10 mIU/L [53]. Another study of patients with subclinical hypothyroidism found less definitive results and concluded that subclinical hypothyroidism may be associated with a modest increased risk of CHD and mortality [52]. RCTs are needed to determine whether treatment of subclinical hypothyroidism with thyroid hormone will reduce cardiovascular risk.

Hyperthyroidism is associated with atrial fibrillation, factors that increase thrombogenesis, increased carotid intima-media thickness and increased cerebrovascular events [50]. The etiology of the cerebrovascular disease may be multifactorial.

Management

Hypothyroidism

Hypothyroidism should be ruled out in individuals with high LDL-C before treatment of dyslipidaemia with lipid lowering medications. Re-assessment of lipids, and delay of treatment of dyslipidaemia until after the patient is euthyroid is warranted. A meta-analysis of 79 trials in adults, most with a follow-up period of 1–12 months (including RCTs and observational studies with a comparator group) evaluated the effects of thyroxine on lipids in adults with overt and subclinical hypothyroidism, comparing post-intervention to pre-intervention levels (Tables 2 and 3) [55]. In adults with overt hypothyroidism, mean reduction in LDL-C after thyroid hormone treatment was 1.06 mmol/L (41 mg/dL) or 24% of baseline LDL-C (Table 2). .Elevated LDL-C before treatment with thyroxine and the marked statistically significant reduction in LDL-C with treatment form the basis of the Endocrine Society

Table 2
Meta-analysis of studies of hypothyroidism and hyperthyroidism: Change in lipids and lipoproteins after treatment.

Disorder	No. Studies	Mean lipid concentration mg/dl	
Overt Hypothyroidism, Treatment with LT4		Baseline	Change Post Treatment
Total cholesterol	72	260.3	−58.4
LDL-C	55	168.8	−41.1
HDL-C	57	54.3	−4.1
TG	60	147.3	−27.3
ApoA	25	163.8	−12.6
ApoB	25	131.9	−34.0
Lp(a)	15	27.0	−5.6
Overt Hyperthyroidism, Treatment with surgery, RAI, anti- thyroid medicationrowhead			
Total cholesterol	31	158.7	44.5
LDL-C	29	89.2	31.1
HDL-C	32	46.5	5.5
TG	30	110.1	7.26
Apo A	12	142.6	15.6
Apo B	13	71.9	26.1
Lp(a)	10	16.7	4.2

To convert Total cholesterol, LDL-C, HDL-C to mmol/L, divide by 38.67. To convert TG to mmol/L divide by 88.6. Studies contained varied population characteristics, severity of thyroid dysfunction and duration of follow-up. Adapted from Kotwal, A. et al. [55].

guideline recommendation to rule out hypothyroidism as a secondary cause of hypercholesterolemia, and to delay lipid treatment until the lipid profile has been assessed when the patient is euthyroid [1].

In the meta-analysis by Kotwal et al., in 74 studies, LDL-C was significantly reduced by 0.28 mmol/L (11 mg/dL), which represents 8% of baseline, in adults with subclinical hypothyroidism treated with thyroid hormone (Table 3) [55]. TC and TG were also significantly lower after thyroid hormone treatment, while HDL-C increased slightly and the change was not statistically significant. In 18 studies of subclinical hypothyroidism, LDL-C increased by 0.05 mmol/L (1.8 mg/dL) in patients given placebo or no treatment. Based on these data the Endocrine Society 2020 guideline suggests consideration of thyroxine treatment in patients with subclinical hypothyroidism (TSH <10 miU/L) as a means of

Table 3
Meta-analysis of Studies of Subclinical Hypothyroidism: Changes in Lipids and Lipoproteins after Levothyroxine (LT4) Therapy or either Placebo or Observation (No Treatment).

Disorder	No. Studies	Mean lipid concentration mg/dl	
Subclinical Hypothyroidism, Treatment with LT4		Baseline	Change Post Treatment or Placebo/observation
Total cholesterol	79	217.4	−12.0
LDL-C	74	139.5	−11.1
HDL-C	76	51.8	0.15
TG	76	124.5	−4.5
ApoA	26	154.1	0.4
ApoB	31	115.2	−6.6
Lp(a)	23	23.1	−2.0
Subclinical Hypothyroidism, Observation or Placebo			
Total cholesterol	19	209.6	0.79
LDL-C	18	126.9	1.8
HDL-C	18	52.7	−0.1
TG	19	123.4	1.0
Apo A	10	151.7	1.7
Apo B	10	121.3	−2.7
Lp(a)	7	26.95	−1.7

To convert Total cholesterol, LDL-C, HDL-C to mmol/L, divide by 38.67. To convert TG to mmol/L divide by 88.6. Studies contained varied population characteristics, severity of thyroid dysfunction and duration of follow-up. Adapted from Kotwal, A. et al. [55].

reducing LDL-C, taking into account the patient's age and general health, and whether the patient has CVD [1].

Hyperthyroidism

In hyperthyroidism LDL-C appears "normal"; however, treatment of hyperthyroidism by surgery, radioactive iodine, or medications, increases LDL-C. It is important to assess the lipid profile in patients with hyperthyroidism after successful treatment. The 2020 meta-analysis discussed earlier, evaluated 32 studies that assessed lipids after treatment of overt hyperthyroidism by anti-thyroid medication, radioiodine, or surgery [55]. Total cholesterol, LDL-C and HDL-C significantly increased. The increase in TG was not statistically significant. In 29 studies, mean LDL-C increased by 0.8 mmol/L (31 mg/dL) from a mean baseline of 2.3 mmol/L (89 mg/dL), showing that treatment of hyperthyroidism worsens the lipid profile. Treatment of subclinical hyperthyroidism did not change lipids. These data support the Endocrine Society guideline recommendation for evaluation of the lipid profile in patients with hyperthyroidism after the patient is euthyroid [1]. Changes have been seen as early as 3 months.

Adrenal disorders

Cushing syndrome

Lipid and lipoprotein alterations and mechanisms

Cushing syndrome is caused by excess cortisol and may be associated with central obesity, glucose intolerance, diabetes, hypertension, a hypercoagulable state, and dyslipidaemia. The latter has an estimated prevalence of 38%–71% [56]. Dyslipidaemia manifests as increased TC and LDL-C, normal or increased HDL-C, and increased TG (Table 1).

Lipid and lipoprotein changes are related to direct and indirect effects of glucocorticoids on liver and adipose tissue [57,58]. Glucocorticoids stimulate synthesis of fatty acids and TG in the liver, leading to increased VLDL synthesis and secretion. Increased circulating VLDL may contribute to increased LDL-C levels. Glucocorticoids also increase synthesis and secretion of ApoA1, which could increase HDL-C [59,60]. Although short term elevations in cortisol stimulate lipolysis, chronic cortisol excess as in Cushing syndrome stimulates lipogenesis and fat storage. Patients with central obesity and/or diabetes more commonly have lipid changes.

Risk of ASCVD

The higher risk of ASCVD morbidity and mortality in Cushing syndrome is related to multiple factors, including the metabolic syndrome. It is estimated that more than half of patients with Cushing syndrome have hypertension, one third have obesity and 20%–47% have diabetes [61]. One study found a 2.2- fold increase in mortality [62]. CVD is the most common cause of death. In 343 patients with Cushing syndrome evaluated before diagnosis, and during treatment, the risk of MI (HR 3.7; 95% CI 2.4–5.5) and stroke (HR 2.0; 95% CI 1.3–3.2) were significantly increased [61]. Patients in remission have better outcomes than those with persistent disease [62].

Management

Monitoring the lipid profile (periodically before and after treatment) is recommended. Treatment will improve lipids and lipoproteins, but not necessarily result in optimal levels [57,63,64]. In adults with persistent Cushing syndrome after treatment, statin therapy to reduce LDL-C should be considered regardless of the CV risk score. Statins will improve lipids in patients with Cushing syndrome; however, the effect of statins on CVD outcomes in this population has not been studied. In patients with limited life expectancy, statins might not be appropriate.

Several medications for Cushing syndrome affect lipids. Ketoconazole inhibits cholesterol synthesis and may lower LDL-C and apoB by 25% [57]. Ketoconazole also inhibits cytochrome P 450 3A4 (cyp 3A4) and increases plasma levels of statins metabolized by Cyp3A4, thus increasing the risk of myopathy [65]. These statins are simvastatin, lovastatin and to a lesser extent atorvastatin. In patients taking ketoconazole, statins not metabolized by Cyp 3A4 should be considered. Mitotane, which may be used

for refractory Cushing syndrome and adrenal cortical cancer, inhibits cortisol synthesis and commonly causes elevated cholesterol and TG [66]. Elevations in cholesterol of more than 60% have been observed and can be treated with statins [67]. Mifepristone, an antagonist of glucocorticoid and progesterone receptors, lowers HDL-C and apo A-I, by an unknown mechanism [68].

Chronic glucocorticoid therapy

Lipid and lipoprotein alterations and mechanisms

Chronic glucocorticoid therapy may increase TC, LDL-C, HDL-C and TG [69–71]. Effects on lipids vary according to dose, route of administration, duration of treatment, comorbidities, and medications. A study of glucocorticoid replacement therapy in 2424 patients with hypopituitarism, and secondary adrenal insufficiency, found a dose dependent increase in TC, LDL-C, and TG in those taking doses equivalent to hydrocortisone $\geq$20 mg daily compared to hydrocortisone <20 mg daily [72].

Risk of ASCVD

Observational data suggest an association between chronic glucocorticoid therapy and ASCVD. In one study patients using glucocorticoids (>10 mg prednisolone daily) had a greater risk for MI (OR 2.15; 95% CI 1.45–3.14) compared to non-users [73]. ASCVD outcome trials in patients taking chronic glucocorticoid therapy are lacking.

Management

The threshold for the glucocorticoid dose that causes lipid abnormalities and increased ASCVD risk is not known. It is important to use glucocorticoids for replacement at the lowest doses needed. Therapy with glucocorticoids above replacement doses may be necessary in patients with inflammatory diseases. The ASCVD risk in these patients may be increased because of the inflammatory disease. In patients taking glucocorticoids at higher doses, assessment of the lipid profile and ASCVD risk factors is recommended. Treatment of dyslipidaemia should consider that chronic glucocorticoid therapy above replacement doses enhances ASCVD risk.

Menopause, and hormone replacement

Oestrogens and androgens regulate lipid metabolism in the liver through gene transcription and signaling pathways to receptors [74]. One of the principal effects of oestrogen is the production of TG rich VLDL particles in the liver, in response to FFA delivery. Oestrogen also upregulates LDL receptors and improves hepatic insulin sensitivity [75]. Oestrogen acts through the steroid nuclear receptors oestrogen alpha and beta, and may promote or inhibit gene transcription [76,77]. Oestrogens also signal through G-protein coupled Estrogen Receptor (GPER), which is expressed in multiple organs including the liver [78,79]. More research is needed to understand how these receptors contribute to gene expression in the liver and ASCVD.

Lipid and lipoprotein alterations and mechanisms

Pre-menopausal women

Premenopausal women have a less atherogenic lipid profile in comparison to men, and notably HDL-C levels that are about 0.26 mmol/L (10 mg/dL) higher because of the decrease in HDL-C in boys during puberty. In the cross-sectional German health survey of 13,676 children and adolescents (KIGGS 2003–2006), mean HDL-C concentrations in boys at Tanner stage 1 were 1.55 mmol/L (60 mg/dL) and at Tanner stage 5, 1.3 mmol/L (51.9 mg/dL) [80]. In girls HDL-C remained stable: 1.51 mmol/L (58.4 mg/dL) and 1.48 mmol/L (57.6 mg/dL) at Tanner stages 1 and 5, respectively [80]. LDL-C increases after age 20, with LDL-C levels slightly greater in males compared to females [81–84]. These changes result in differences in the lipid profile in premenopausal adult woman compared to adult men, with higher levels of HDL-C, slightly lower TG and LDL-C and larger LDL particles in premenopausal women.

Post-menopausal women

After menopause, LDL-C increases by a small amount, LDL particles become small and dense, and HDL-C may decrease. Lp(a) may not change or may increase slightly [81,82,84] Increased body fat and visceral fat, and associated insulin resistance may also affect lipids and lipoproteins [85].

Oestrogen and progesterone treatment had a small effect on LDL-C in. HERS (Heart and Estrogen Replacement Study), a randomised placebo-controlled trial in postmenopausal women with coronary heart disease (CHD). Mean LDL-C decreased by 14% to 3.2 mmol/L (125 mg/dL) after one year of treatment with oral oestrogen plus progesterone, and increased by 3% to 3.6 mmol/L (140 mg/dL) in the placebo group [86]. Transdermal oestrogen may also increase LDL-C and decrease HDL-C, but the magnitude of the effect is smaller.

Risk of ASCVD

ASCVD risk is increased in post-menopausal women and continues to increase with age. The risk is higher in women who reach menopause early (before the age of 40–44) [87].

Observational data suggested that hormone therapy (HT) during menopause is associated with reduced ASCVD risk. However, two RCTS, HERS [86] and WHI (Women's Health Initiative) [88] found that oral HT (oral conjugated equine oestrogens 0.625 mg either alone or in combination with medroxyprogesterone acetate 2.5 mg) increased CHD events, stroke and venous thromboembolism, especially in women more than 10 years from the onset of menopause [89,90]. Adverse cardiovascular events were significantly increased in younger women, but the risk was lower [89].

A Cochrane database review of 19 RCTs evaluating oral HT, including WHI, concluded that HT in PMP women overall (those treated in early and in late menopause) has little CVD benefit for either primary or secondary prevention and may cause harm [91]. However, in subgroup analyses by age at initiation of treatment, women who started hormone therapy less than 10 years after the menopause had lower mortality, and coronary heart disease (non-fatal MI and CVD death), although these women had increased risk of venous thromboembolism [91]. In women who started HT ten years or more after menopause, there was little effect on death or CHD, but the risk of stroke and venous thromboembolism were increased. The route of administration of HT impacts its effects on CVD. Current evidence suggests that transdermal HT is not associated with increased risk of venous thromboembolism [92] or stroke [93]. Taken together these data suggest that in healthy postmenopausal women younger than 60 years old, and in women within 10 years of menopause, the benefits of hormone therapy for vasomotor symptoms outweigh the risks [94].

Management

The lipid profile should be monitored in pre-menopausal women taking oral contraceptives to detect elevations in TG, especially in women with a genetic predisposition to hypertriglyceridaemia [95,96]. TG above 5.64 mmol/L (500 mg/dL), increase the risk of pancreatitis; and the risk markedly increases with TG above 11.28 mmo/L (1000 mg/dL). Severe hypertriglyceridaemia and pancreatitis were not observed in one study of postmenopausal women taking oral HT [97].

To reduce ASCVD in postmenopausal women, statins are the treatment of choice.

For women who start menopause before the age of 45 years old, lipids and other risk factors should be assessed and treated because of the increased ASCVD risk associated with early menopause.

Polycystic ovary syndrome

Lipid and lipoprotein alterations and mechanisms

PCOS, which affects women of reproductive age, is diagnosed when two of the following abnormalities are present: excess androgen production (diagnosed clinically and/or biochemically), ovulatory dysfunction, and multiple ovarian cysts [98]. Women with PCOS may have insulin resistance and

metabolic syndrome. Dyslipidaemia is common, occurring in as many as 75% of women in the US [99] and may be related to excess androgens, visceral adiposity, insulin resistance as well as genetic and environmental factors. The lipid profile in anovulatory women is atherogenic and similar to that seen in the metabolic syndrome, with normal or increased LDL-C, low HDL-C, increased TG, and small dense LDL particles [100–104]. Women who ovulate may have lipid changes of a lower magnitude, or normal lipids [105,106].

Risk of ASCVD

Women with PCOS may have risk factors for ASCVD including components of the metabolic syndrome and abdominal obesity. The prevalence of metabolic syndrome in U.S. Caucasian women with PCOS has been estimated to be 34%–46% [107]. It is not known whether women with PCOS have increased ASCVD morbidity and mortality [108,109].

Management

At diagnosis a fasting lipid panel is recommended to assess dyslipidaemia and ASCVD risk. The lipid panel should be repeated during hormonal treatment. Statins may be used, as adjunct to lifestyle therapy, to reduce LDL-C and TG, with the caveat to not use statins during pregnancy [110–112]. Some studies reported that statins decrease androgen levels [110,113,114], although the evidence is not sufficient to recommend statins for that purpose. Statins may worsen insulin resistance, but the data are conflicting [112,113,115].

Male hypogonadism and testosterone replacement

Lipid and lipoprotein alterations and mechanisms

Testosterone levels directly correlate with HDL-C and apoA1 levels and inversely correlate with TC, LDL-C, TG and apo B. Men with hypogonadism and low testosterone concentrations generally have low HDL-C, and increased LDL-C and TG [40,116,117]. Male hypogonadism is associated with increased ASCVD risk and features of the metabolic syndrome, such as increased waist circumference and insulin resistance.

Testosterone in replacement doses has either no effect on lipids or a small effect [118]. HDL-C remains low, and LDL-C unchanged or slightly decreased. Insulin resistance may improve with testosterone replacement [119–121].

Testosterone and other androgens activate hepatic lipase, which hydrolyzes phospholipids and TG in HDL-C, leading to small HDL particles, release and degradation of ApoA-1, and reduced plasma HDL-C [122–124]. Another mechanism is increased Scavenger receptor B1 (SR-B1) in the liver, which facilitates cholesterol transfer from HDL particles into the hepatocyte, thus decreasing plasma HDL-C [125].

Risk of ASCVD

Some studies suggest that testosterone replacement increases ASCVD risk. More data are needed.

Management

It is appropriate to use testosterone in replacement doses in symptomatic male patients with low testosterone levels [126]. Testosterone should not be used to improve dyslipidaemia or reduce ASCVD risk [1].

Testosterone and anabolic steroid abuse

Lipid and lipoprotein alterations

High doses of testosterone, which may be used off label to improve muscle strength and athletic performance, have a greater effect on lipids compared to replacement doses. In 14 individuals taking high dose androgens, HDL-C levels were reduced from 1.6 mmol/L (61 mg/dL) to 0.75 mmol/L (29 mg/dL) [127]. In a double blind cross over trial of anabolic steroids, HDL-C was reduced by 25–27% and returned to normal 6 weeks after steroid discontinuation [128]. In another study, high doses of androgens reduced HDL-C by 50% to a mean level of 0.59 mmol/L (23 mg/dL) and raised LDL-C by more than 50% to 4.9 mmol/L (188 mg/dL) [129].

Management

In patients with very low HDL-C (below 0.78 mmol/L [30 mg/dL]), the use of supraphysiological doses of testosterone and/or other anabolic steroids should be suspected and evaluated by biochemical testing. These patients may also have erythrocytosis. Use of high doses of androgens will suppress the hypothalamic pituitary testicular axis, and recovery may take a year. Stopping these androgens may result in a withdrawal syndrome characterized by depression, anxiety and a loss of self-esteem which can last from weeks to months [130–132].

Gender-affirming hormone therapy

Lipid and lipoprotein alterations

Limited data are available about effects of sex steroid use on lipids in transgender individuals. A meta-analysis of 29 studies found that in male transgender individuals, receiving androgen therapy, TG and LDL-C were significantly increased at $\geq$ 24 months [133]. The mean increase was 0.24 mmol/L (21.4 mg/dL) for TG and 0.46 mmol/L (17.8 mg/dL) for LDL-C. HDL-C was significantly reduced, by a mean of 0.22 mmol/L (8.5 mg/dL) at $\geq$24 months.

In female transgender individuals receiving estrogen, TG was significantly higher at $\geq$24 months with a mean level of 0.36 mmol/L (31.9 mg/dL) and LDL-C and HDL-C were not changed. However, in cross sectional studies that compared female transgender individuals with control groups, LDL-C was significantly lower and significant changes in TG and HDL-C were not found [133].

Risk of ASCVD

Insufficient data are available to evaluate potential effects of gender affirming hormone therapy on CVD morbidity and mortality [133].

Summary

Endocrine hormones affect lipid and lipoprotein metabolism. GH deficiency, acromegaly, Cushing syndrome, chronic glucocorticoid replacement and hypothyroidism may elevate LDL-C and TG, and lower HDL-C. These diseases are associated with increased cardiovascular risk, which could be related to the hormone abnormality and/or dyslipidaemia. It is important to assess lipids in all these disorders. The increased risk of ASCVD in people with Cushing syndrome and chronic glucocorticoid replacement, warrant treatment with statins if LDL-C is above 1.8 mmol/L (70 mg/dL). Treatment of endocrine diseases may reduce LDL-C and/or TG, although dyslipidaemia may remain. Thyroid hormone treatment of overt and subclinical hypothyroidism reduces LDL-C. Treatment of hyperthyroidism raises LDL-C. Therefore, in patients with hypo- or hyper-thyroidism, the lipid profile should be repeated when thyroid function is normal.

Post-menopausal women as a group have increased ASCVD risk, compared to premenopausal women, although in postmenopausal women within 10 years after menopause, the risk of CHD may be unchanged or possibly decreased, while the risk of venous thromboembolism is increased. Several RCTs show that oestrogen (and progestin) therapy in older women (more than 10 years after the menopause), is associated with increased risk of stroke, venous thromboembolism and CHD. Male hypogonadism is associated with small changes in lipids and lipoproteins, which may improve with testosterone therapy; however testosterone should be used for symptomatic hypogonadism and not for LDL-C reduction. Men, and women, who take supra-physiological doses of testosterone and/or other anabolic steroids (usually to build muscle and enhance athletic performance) have very low HDL-C which should alert the endocrinologist to steroid abuse. Changes in lipids and lipoproteins associated with gender affirming hormone therapy require further investigation.

More research is needed on the mechanisms of dyslipidaemia in endocrine disorders, and the effects of treatment of the endocrine disease on dyslipidaemia and ASCVD.

Practice points

- In adults with **GH deficiency**, use statins, rather than GH replacement to lower LDL-C.
- Use a statin as adjunct to lifestyle measures if LDL-C > 70 mg/dL in patients with **acromegaly** post treatment.
- Before treating dyslipidaemia, rule out **hypothyroidism**.
- Re-assess the lipid profile after treatment of **hyperthyroidism**, when the patient is euthyroid.
- In adults with persistent **Cushing syndrome** post treatment, consider statin therapy regardless of the CV risk score.
- Assess the lipid profile and ASCVD risk factors to determine whether lipid lowering therapy (statins) in patients taking **chronic glucocorticoid therapy** would be beneficial.
- In **post-menopausal women**, use statins, rather than hormone therapy to reduce LDL-C and ASCVD risk.
- In adults with very low HDL-C, suspect use of supraphysiological doses of **testosterone and/or other anabolic steroids**.

Research agenda

- Clinical trials to determine the best management of overt and subclinical hypothyroidism in men and women, with and without ASCVD
- CVD outcomes trials to evaluate effects of GH replacement in GH deficient adults
- Evaluation of ASCVD risk in men and women taking chronic glucocorticoids at replacement levels and above replacement levels
- Effect of statins on insulin resistance and diabetes in women with PCOS
- Long term effects of anabolic steroids in men and women, and safe and effective treatments for withdrawal syndrome and infertility
- Effects of gender affirming hormone therapy on lipids, lipoproteins and ASCVD risk

References

*[1] Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2020;105(12):3613–82.
[2] Tomlinson JW, Holden N, Hills RK, et al. Association between premature mortality and hypopituitarism. West midlands prospective hypopituitary study group. Lancet 2001;357(9254):425–31.
[3] Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. Endocr Rev 2010;31(3):301–42.
[4] Giovannini L, Tirabassi G, Muscogiuri G, et al. Impact of adult growth hormone deficiency on metabolic profile and cardiovascular risk [Review]. Endocr J 2015;62(12):1037–48.

[5] Thomas JD, Monson JP. Adult GH deficiency throughout lifetime. Eur J Endocrinol 2009;161(Suppl 1):S97–106.
[6] Colao A, Di Somma C, Spiezia S, et al. The natural history of partial growth hormone deficiency in adults: a prospective study on the cardiovascular risk and atherosclerosis. J Clin Endocrinol Metab 2006;91(6):2191–200.
[7] Rizzo M, Trepp R, Berneis K, et al. Atherogenic lipoprotein phenotype and low-density lipoprotein size and subclasses in patients with growth hormone deficiency before and after short-term replacement therapy. Eur J Endocrinol 2007; 156(3):361–7.
[8] Parini P, Angelin B, Lobie PE, et al. Growth hormone specifically stimulates the expression of low density lipoprotein receptors in human hepatoma cells. Endocrinology 1995;136(9):3767–73.
[9] Rudling M, Norstedt G, Olivecrona H, et al. Importance of growth hormone for the induction of hepatic low density lipoprotein receptors. Proc Natl Acad Sci U S A 1992;89(15):6983–7.
[10] Cummings MH, Christ E, Umpleby AM, et al. Abnormalities of very low density lipoprotein apolipoprotein B-100 metabolism contribute to the dyslipidaemia of adult growth hormone deficiency. J Clin Endocrinol Metab 1997;82(6): 2010–3.
[11] Elbornsson M, Gotherstrom G, Bosaeus I, et al. Fifteen years of GH replacement improves body composition and cardiovascular risk factors. Eur J Endocrinol 2013;168(5):745–53.
[12] Maison P, Griffin S, Nicoue-Beglah M, et al. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. J Clin Endocrinol Metab 2004; 89(5):2192–9.
[13] Newman CB, Carmichael JD, Kleinberg DL. Effects of low dose versus high dose human growth hormone on body composition and lipids in adults with GH deficiency: a meta-analysis of placebo-controlled randomized trials. Pituitary 2015;18(3):297–305.
[14] Gotherstrom G, Svensson J, Koranyi J, et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. J Clin Endocrinol Metab 2001; 86(10):4657–65.
[15] Svensson J, Fowelin J, Landin K, et al. Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. J Clin Endocrinol Metab 2002;87(5):2121–7.
[16] Eden S, Wiklund O, Oscarsson J, et al. Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. Arterioscler Thromb 1993;13(2):296–301.
[17] O'Halloran DJ, Wieringa G, Tsatsoulis A, et al. Increased serum lipoprotein(a) concentrations after growth hormone (GH) treatment in patients with isolated GH deficiency. Ann Clin Biochem 1996;33(Pt 4):330–4.
[18] Holmer H, Svensson J, Rylander L, et al. Nonfatal stroke, cardiac disease, and diabetes mellitus in hypopituitary patients on hormone replacement including growth hormone. J Clin Endocrinol Metab 2007;92(9):3560–7.
[19] Schneider HJ, Klotsche J, Wittchen HU, et al. Effects of growth hormone replacement within the KIMS survey on estimated cardiovascular risk and predictors of risk reduction in patients with growth hormone deficiency. Clin Endocrinol 2011;75(6):825–30.
[20] Christ ER, Cummings MH, Albany E, et al. Effects of growth hormone (GH) replacement therapy on very low density lipoprotein apolipoprotein B100 kinetics in patients with adult GH deficiency: a stable isotope study. J Clin Endocrinol Metab 1999;84(1):307–16.
[21] Moller N, Vendelbo MH, Kampmann U, et al. Growth hormone and protein metabolism. Clin Nutr 2009;28(6): 597–603.
[22] Murase T, Yamada N, Ohsawa N, et al. Decline of postheparin plasma lipoprotein lipase in acromegalic patients. Metabolism 1980;29(7):666–72.
[23] Twickler TB, Dallinga-Thie GM, Zelissen PM, et al. The atherogenic plasma remnant-like particle cholesterol concentration is increased in the fasting and postprandial state in active acromegalic patients. Clin Endocrinol 2001; 55(1):69–75.
[24] Takeda R, Tatami R, Ueda K, et al. The incidence and pathogenesis of hyperlipidaemia in 16 consecutive acromegalic patients. Acta Endocrinol 1982;100(3):358–62.
[25] Boero L, Manavela M, Merono T, et al. GH levels and insulin sensitivity are differently associated with biomarkers of cardiovascular disease in active acromegaly. Clin Endocrinol 2012;77(4):579–85.
[26] Beentjes JA, van Tol A, Sluiter WJ, et al. Low plasma lecithin:cholesterol acyltransferase and lipid transfer protein activities in growth hormone deficient and acromegalic men: role in altered high density lipoproteins. Atherosclerosis 2000;153(2):491–8.
[27] Arosio M, Sartore G, Rossi CM, et al. LDL physical properties, lipoprotein and Lp(a) levels in acromegalic patients. Effects of octreotide therapy. Italian Multicenter Octreotide Study Group. Atherosclerosis 2000;151(2):551–7.
[28] Oscarsson J, Wiklund O, Jakobsson KE, et al. Serum lipoproteins in acromegaly before and 6-15 months after transsphenoidal adenomectomy. Clin Endocrinol 1994;41(5):603–8.
[29] Reyes-Vidal C, Fernandez JC, Bruce JN, et al. Prospective study of surgical treatment of acromegaly: effects on ghrelin, weight, adiposity, and markers of CV risk. J Clin Endocrinol Metab 2014;99(11):4124–32.
[30] Briet C, Ilie MD, Kuhn E, et al. Changes in metabolic parameters and cardiovascular risk factors after therapeutic control of acromegaly vary with the treatment modality. Data from the Bicetre cohort, and review of the literature. Endocrine 2019;63(2):348–60.
[31] Cohen R, Chanson P, Bruckert E, et al. Effects of octreotide on lipid metabolism in acromegaly. Horm Metab Res 1992; 24(8):397–400.
[32] Delaroudis SP, Efstathiadou ZA, Koukoulis GN, et al. Amelioration of cardiovascular risk factors with partial biochemical control of acromegaly. Clin Endocrinol 2008;69(2):279–84.
[33] Parkinson C, Drake WM, Wieringa G, et al. Serum lipoprotein changes following IGF-I normalization using a growth hormone receptor antagonist in acromegaly. Clin Endocrinol 2002;56(3):303–11.
[34] Sesmilo G, Fairfield WP, Katznelson L, et al. Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. J Clin Endocrinol Metab 2002;87(4):1692–9.
[35] Maffei P, Sicolo N, Plebani M. Lipoprotein(a) in acromegaly. Ann Intern Med 1999;130(6):537–8.

[36] Bengtsson BA, Eden S, Ernest I, et al. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand 1988;223(4):327–35.
*[37] Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol 2018; 14(5):259–69.
[38] Sinha RA, Bruinstroop E, Singh BK, et al. Nonalcoholic fatty liver disease and hypercholesterolemia: roles of thyroid hormones, metabolites, and agonists. Thyroid 2019;29(9):1173–91.
[39] Chait A, Bierman EL, Albers JJ. Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. J Clin Endocrinol Metab 1979;48(5):887–9.
*[40] Feingold KR, Brinton EA, Grunfeld C. The effect of endocrine disorders on lipids and lipoproteins. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA); 2020.
[41] Diekman T, Demacker PN, Kastelein JJ, et al. Increased oxidizability of low-density lipoproteins in hypothyroidism. J Clin Endocrinol Metab 1998;83(5):1752–5.
[42] Oge A, Sozmen E, Karaoglu AO. Effect of thyroid function on LDL oxidation in hypothyroidism and hyperthyroidism. Endocr Res 2004;30(3):481–9.
[43] Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160(4):526–34.
[44] Tagami T, Kimura H, Ohtani S, et al. Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia. Endocr J 2011;58(6):449–57.
[45] Lopez D, Abisambra Socarras JF, Bedi M, et al. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochim Biophys Acta 2007;1771(9):1216–25.
[46] Ness GC, Lopez D, Chambers CM, et al. Effects of L-triiodothyronine and the thyromimetic L-94901 on serum lipoprotein levels and hepatic low-density lipoprotein receptor, 3-hydroxy-3-methylglutaryl coenzyme A reductase, and apo A-I gene expression. Biochem Pharmacol 1998;56(1):121–9.
[47] Choi JW, Choi HS. The regulatory effects of thyroid hormone on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Endocr Res 2000;26(1):1–21.
[48] Cappola AR, Desai AS, Medici M, et al. Thyroid and cardiovascular disease: research agenda for enhancing knowledge, prevention, and treatment. Thyroid 2019;29(6):760–77.
[49] Schenck JB, Rizvi AA, Lin T. Severe primary hypothyroidism manifesting with torsades de pointes. Am J Med Sci 2006; 331(3):154–6.
*[50] Razvi S, Jabbar A, Pingitore A, et al. Thyroid hormones and cardiovascular function and diseases. J Am Coll Cardiol 2018;71(16):1781–96.
[51] Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006; 295(9):1033–41.
[52] Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008;148(11):832–45.
[53] Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304(12):1365–74.
[54] Chaker L, Baumgartner C, den Elzen WP, et al. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: an individual participant data analysis. J Clin Endocrinol Metab 2015;100(6):2181–91.
*[55] Kotwal A, Cortes T, Genere N, et al. Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis. J Clin Endocrinol Metab 2020;105(12).
[56] Sharma ST, Nieman LK, Feelders RA. Comorbidities in Cushing's disease. Pituitary 2015;18(2):188–94.
[57] Arnaldi G, Scandali VM, Trementino L, et al. Pathophysiology of dyslipidemia in Cushing's syndrome. Neuroendocrinology 2010;92(Suppl 1):86–90.
[58] de Guia RM, Herzig S. How do glucocorticoids regulate lipid metabolism? Adv Exp Med Biol 2015;872:127–44.
[59] Saladin R, Vu-Dac N, Fruchart JC, et al. Transcriptional induction of rat liver apolipoprotein A-I gene expression by glucocorticoids requires the glucocorticoid receptor and a labile cell-specific protein. Eur J Biochem 1996;239(2): 451–9.
[60] Taylor AH, Raymond J, Dionne JM, et al. Glucocorticoid increases rat apolipoprotein A-I promoter activity. J Lipid Res 1996;37(10):2232–43.
[61] Dekkers OM, Horvath-Puho E, Jorgensen JO, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab 2013;98(6):2277–84.
[62] Clayton RN, Raskauskiene D, Reulen RC, et al. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab 2011;96(3):632–42.
[63] Colao A, Pivonello R, Spiezia S, et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 1999;84(8):2664–72.
[64] Faggiano A, Pivonello R, Spiezia S, et al. Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 2003; 88(6):2527–33.
*[65] Newman CB, Preiss D, Tobert JA, et al., on behalf of the American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health, Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, and Stroke Council. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2018;38:e38–81.
[66] Hescot S, Seck A, Guerin M, et al. Lipoprotein-free mitotane exerts high cytotoxic activity in adrenocortical carcinoma. J Clin Endocrinol Metab 2015;100(8):2890–8.
[67] Greenman Y. Management of dyslipidemia in Cushing's syndrome. Neuroendocrinology 2010;92(Suppl 1):91–5.
[68] Page ST, Krauss RM, Gross C, et al. Impact of mifepristone, a glucocorticoid/progesterone antagonist, on HDL cholesterol, HDL particle concentration, and HDL function. J Clin Endocrinol Metab 2012;97(5):1598–605.

[69] Ettinger Jr WH, Hazzard WR. Prednisone increases very low density lipoprotein and high density lipoprotein in healthy men. Metabolism 1988;37(11):1055–8.
[70] Zimmerman J, Fainaru M, Eisenberg S. The effects of prednisone therapy on plasma lipoproteins and apolipoproteins: a prospective study. Metabolism 1984;33(6):521–6.
[71] Negera E, Tilahun M, Bobosha K, et al. The effects of prednisolone treatment on serological responses and lipid profiles in Ethiopian leprosy patients with Erythema Nodosum Leprosum reactions. PLoS Neglected Trop Dis 2018;12(12): e0007035.
[72] Mazziotti G, Formenti AM, Frara S, et al. Management of endocrine disease: risk of overtreatment in patients with adrenal insufficiency: current and emerging aspects. Eur J Endocrinol 2017;177(5):R231–48.
[73] Varas-Lorenzo C, Rodriguez LA, Maguire A, et al. Use of oral corticosteroids and the risk of acute myocardial infarction. Atherosclerosis 2007;192(2):376–83.
[74] Palmisano BT, Zhu L, Eckel RH, et al. Sex differences in lipid and lipoprotein metabolism. Mol Metabol 2018;15:45–55.
*[75] Palmisano BT, Zhu L, Stafford JM. Role of estrogens in the regulation of liver lipid metabolism. Adv Exp Med Biol 2017; 1043:227–56.
[76] Bjornstrom L, Sjoberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol Endocrinol 2005;19(4):833–42.
[77] Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. Curr Genom 2006;7(8):497–508.
[78] Sharma G, Prossnitz ER. G-Protein-Coupled estrogen receptor (GPER) and sex-specific metabolic homeostasis. Adv Exp Med Biol 2017;1043:427–53.
[79] Nilsson S, Gustafsson JA. Estrogen receptors: therapies targeted to receptor subtypes. Clin Pharmacol Ther 2011;89(1): 44–55.
[80] Schienkiewitz A, Truthmann J, Ernert A, et al. Age, maturation and serum lipid parameters: findings from the German Health Survey for Children and Adolescents. BMC Publ Health 2019;19(1):1627.
[81] Bittner V. Lipoprotein abnormalities related to women's health. Am J Cardiol 2002;90(8A):77i–84i.
[82] Phan BA, Toth PP. Dyslipidemia in women: etiology and management. Int J Womens Health 2014;6:185–94.
[83] Wang X, Magkos F, Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. J Clin Endocrinol Metab 2011;96(4):885–93.
[84] Cifkova R, Krajcoviechova A. Dyslipidemia and cardiovascular disease in women. Curr Cardiol Rep 2015;17(7):609.
[85] Akahoshi M, Soda M, Nakashima E, et al. Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. Atherosclerosis 2001;156(1):157–63.
[86] Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280(7):605–13.
[87] Zhu D, Chung HF, Dobson AJ, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health 2019;4(11):e553–64.
[88] Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349(6):523–34.
[89] Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013; 310(13):1353–68.
[90] Harman SM, Vittinghoff E, Brinton EA, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. Am J Med 2011;124(3):199–205.
*[91] Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015;(3):CD002229.
[92] Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ 2019;364:k4810.
[93] Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. Stroke 2016;47(7):1734–41.
*[94] Mehta J, Manson JE. Menopausal hormone therapy and hypertension: minimizing risk. Menopause 2021;28(11): 1201–2.
[95] Aljenedil S, Hegele RA, Genest J, et al. Estrogen-associated severe hypertriglyceridemia with pancreatitis. J Clin Lipidol 2017;11(1):297–300.
[96] Goldenberg NM, Wang P, Glueck CJ. An observational study of severe hypertriglyceridemia, hypertriglyceridemic acute pancreatitis, and failure of triglyceride-lowering therapy when estrogens are given to women with and without familial hypertriglyceridemia. Clin Chim Acta 2003;332(1–2):11–9.
[97] Tetsche MS, Jacobsen J, Norgaard M, et al. Postmenopausal hormone replacement therapy and risk of acute pancreatitis: a population-based case-control study. Am J Gastroenterol 2007;102(2):275–8.
[98] McCartney CR, Marshall JC. CLINICAL PRACTICE. Polycystic ovary syndrome. N Engl J Med 2016;375(1):54–64.
[99] Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001;111(8):607–13.
[100] Berneis K, Rizzo M, Lazzarini V, et al. Atherogenic lipoprotein phenotype and low-density lipoproteins size and subclasses in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92(1):186–9.
[101] Valkenburg O, Steegers-Theunissen RP, Smedts HP, et al. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. J Clin Endocrinol Metab 2008;93(2):470–6.
[102] Dejager S, Pichard C, Giral P, et al. Smaller LDL particle size in women with polycystic ovary syndrome compared to controls. Clin Endocrinol 2001;54(4):455–62.
[103] Pirwany IR, Fleming R, Greer IA, et al. Lipids and lipoprotein subfractions in women with PCOS: relationship to metabolic and endocrine parameters. Clin Endocrinol 2001;54(4):447–53.

[104] Wild RA, Rizzo M, Clifton S, et al. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2011;95(3):1073–9. e1071-1011.
[105] Rizzo M, Berneis K, Hersberger M, et al. Milder forms of atherogenic dyslipidemia in ovulatory versus anovulatory polycystic ovary syndrome phenotype. Hum Reprod 2009;24(9):2286–92.
[106] Roe A, Hillman J, Butts S, et al. Decreased cholesterol efflux capacity and atherogenic lipid profile in young women with PCOS. J Clin Endocrinol Metab 2014;99(5):E841–7.
[107] Barber TM, Dimitriadis GK, Andreou A, et al. Polycystic ovary syndrome: insight into pathogenesis and a common association with insulin resistance. Clin Med 2016;16(3):262–6.
[108] Schmidt J, Landin-Wilhelmsen K, Brannstrom M, et al. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab 2011;96(12):3794–803.
[109] Fauser BC, Tarlatzis BC, Rebar RW, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97(1):28–38 e25.
[110] Sathyapalan T, Kilpatrick ES, Coady AM, et al. The effect of atorvastatin in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled study. J Clin Endocrinol Metab 2009;94(1):103–8.
[111] Raval AD, Hunter T, Stuckey B, et al. Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev 2011;(10):CD008565.
[112] Puurunen J, Piltonen T, Puukka K, et al. Statin therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2013; 98(12):4798–807.
[113] Raja-Khan N, Kunselman AR, Hogeman CS, et al. Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. Fertil Steril 2011;95(5):1849–52.
[114] Sathyapalan T, Smith KA, Coady AM, et al. Atorvastatin therapy decreases androstenedione and dehydroepiandrosterone sulphate concentrations in patients with polycystic ovary syndrome: randomized controlled study. Ann Clin Biochem 2012;49(Pt 1):80–5.
[115] Rashidi B, Abediasl J, Tehraninejad E, et al. Simvastatin effects on androgens, inflammatory mediators, and endogenous pituitary gonadotropins among patients with PCOS undergoing IVF: results from a prospective, randomized, placebo-controlled clinical trial. J Invest Med 2011;59(6):912–6.
[116] Oppenheim DS, Greenspan SL, Zervas NT, et al. Elevated serum lipids in hypogonadal men with and without hyperprolactinemia. Ann Intern Med 1989;111(4):288–92.
[117] Agledahl I, Skjaerpe PA, Hansen JB, et al. Low serum testosterone in men is inversely associated with non-fasting serum triglycerides: the Tromso study. Nutr Metabol Cardiovasc Dis : Nutr Metabol Cardiovasc Dis 2008;18(4):256–62.
[118] Huo S, Scialli AR, McGarvey S, et al. Treatment of men for "low testosterone": a systematic review. PLoS One 2016; 11(9):e0162480.
[119] Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006;154(6):899–906.
[120] Kapoor D, Aldred H, Clark S, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007;30(4):911–7.
[121] Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011;34(4):828–37.
[122] Tan KC, Shiu SW, Kung AW. Alterations in hepatic lipase and lipoprotein subfractions with transdermal testosterone replacement therapy. Clin Endocrinol 1999;51(6):765–9.
[123] Sorva R, Kuusi T, Taskinen MR, et al. Testosterone substitution increases the activity of lipoprotein lipase and hepatic lipase in hypogonadal males. Atherosclerosis 1988;69(2–3):191–7.
[124] Herbst KL, Amory JK, Brunzell JD, et al. Testosterone administration to men increases hepatic lipase activity and decreases HDL and LDL size in 3 wk. Am J Physiol Endocrinol Metab 2003;284(6):E1112–8.
[125] Langer C, Gansz B, Goepfert C, et al. Testosterone up-regulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. Biochem Biophys Res Commun 2002;296(5):1051–7.
[126] Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical Practice guideline. J Clin Endocrinol Metab 2018;103(5):1715–44.
[127] Webb OL, Laskarzewski PM, Glueck CJ. Severe depression of high-density lipoprotein cholesterol levels in weight lifters and body builders by self-administered exogenous testosterone and anabolic-androgenic steroids. Metabolism 1984;33(11):971–5.
[128] Kuipers H, Wijnen JA, Hartgens F, et al. Influence of anabolic steroids on body composition, blood pressure, lipid profile and liver functions in body builders. Int J Sports Med 1991;12(4):413–8.
[129] Hurley BF, Seals DR, Hagberg JM, et al. High-density-lipoprotein cholesterol in bodybuilders v powerlifters. Negative effects of androgen use. JAMA 1984;252(4):507–13.
[130] Pope Jr HG, Wood RI, Rogol A, et al. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev 2014;35(3):341–75.
[131] Gronbladh A, Nylander E, Hallberg M. The neurobiology and addiction potential of anabolic androgenic steroids and the effects of growth hormone. Brain Res Bull 2016;126(Pt 1):127–37.
*[132] Anawalt BD. Diagnosis and management of anabolic androgenic steroid use. J Clin Endocrinol Metab 2019;104(7): 2490–500.
[133] Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. J Clin Endocrinol Metab 2017;102(11):3914–23.