The Effect of Endocrine Disorders on Lipids and Lipoproteins

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ABSTRACT

Endocrine disorders and the administration of various hormones can alter lipid metabolism and plasma lipid levels, which may increase or decrease the risk of atherosclerotic cardiovascular disease. In many instances the literature is not consistent with various studies reporting different results. These differences may be due to a variety of factors such as the differences in the severity of the disease state, differences in the duration of the disease, underlying genetic factors that differ between individuals and populations, differences in environmental factors such as diet, the presence of other abnormalities that can alter lipid metabolism such as obesity or diabetes, and other unrecognized factors that could influence the expression and manifestation of various endocrine disorders on lipid parameters. Prolactinomas are associated with an increase in total and LDL cholesterol levels. Growth hormone deficient patients often have an increase in total cholesterol, LDL cholesterol, and triglyceride levels and a decrease in HDL cholesterol levels, whereas growth hormone therapy decreases total cholesterol and LDL cholesterol but increases Lp(a) levels. Acromegaly is associated with an increase in Lp(a) levels as seen in growth hormone therapy, but paradoxically similar to growth hormone deficiency, acromegaly is accompanied by an increase in plasma triglycerides and a decrease in HDL cholesterol levels. Hypothyroidism leads to an increase in total cholesterol, LDL cholesterol, and Lp(a) levels and normal or increased triglycerides and HDL cholesterol. In contrast, hyperthyroidism is characterized by decreases in total cholesterol, LDL cholesterol, and Lp(a) levels, as well as HDL cholesterol levels. Patients with endogenous Cushing's syndrome typically display an increase in total and LDL cholesterol, and triglycerides, while the administration of glucocorticoids frequently also increases HDL cholesterol levels. Men with low testosterone levels may have high LDL cholesterol and triglyceride levels and decreased HDL cholesterol levels, although this relationship is confounded by obesity and the metabolic syndrome, a common cause of male hypogonadism. Androgen deprivation therapy results in an increase in LDL cholesterol, triglycerides, and Lp(a) and a decrease in HDL cholesterol. The effect of testosterone replacement therapy on plasma lipids and lipoproteins is modest and variable but high dose androgen therapy used by athletes can markedly decrease HDL cholesterol and also reduce Lp(a)

levels. The loss of estrogens (postmenopausal females) is associated with a modest increase in LDL cholesterol with either no change or a small decrease in HDL cholesterol. Estrogen administration decreases LDL cholesterol and Lp(a) levels while increasing triglycerides and HDL cholesterol levels but these effects are dependent on the dose and route of administration (transdermal has smaller effects than oral). Concurrent progesterone treatment has little or no effect on the decrease in LDL cholesterol induced by estrogen administration but may blunt the estrogen effect on HDL cholesterol and triglyceride levels depending on the androgenicity of the progesterone. The polycystic ovarian syndrome is associated with increases in LDL cholesterol, triglycerides, and Lp(a) and decreases in HDL cholesterol. The dyslipidemia that occurs with prolactinomas, growth hormone deficiency, Cushing's syndrome, male hypogonadism, androgen deprivation therapy, polycystic ovarian syndrome, and the loss of estrogens may contribute to an increased risk of atherosclerotic cardiovascular disease.

INTRODUCTION

Endocrine disorders and the administration of various hormones can alter lipid metabolism and plasma lipid levels, which may increase or decrease the risk of atherosclerotic cardiovascular disease. In this chapter we will discuss the effects of a number of endocrine disorders on lipid metabolism and plasma lipid and lipoprotein levels. It is worth noting that in many instances the literature is not consistent with various studies reporting different results. These differences may be due to a variety of factors such as the differences in the severity of the disease state, differences in the duration of the disease, underlying genetic factors that differ between individuals and populations, differences in environmental factors such as diet, the presence of other abnormalities that can alter lipid metabolism such as obesity or diabetes, and other unrecognized factors that could influence the expression and manifestation of various endocrine disorders on lipid parameters. In describing the alterations in lipid metabolism and plasma lipid and lipoprotein levels induced by various endocrine disorders we have tried to describe the typical alterations that have been most consistently observed, recognizing that these changes have not been observed in certain published reports and cannot be extrapolated to individual patients.

PROLACTINOMA

Effect of Prolactinomas on Lipid and Lipoprotein Levels

Most studies have shown that patients with a prolactinoma have modestly elevated plasma total cholesterol and LDL cholesterol levels (1-7). In some studies plasma triglyceride levels are also elevated (1,2,4,8,9). HDL cholesterol levels have been reported to be decreased in some studies (7,9,10). Most studies have primarily included female patients with prolactinomas but dyslipidemia is also observed in men with hyperprolactinemia (4).

Table 1. Effect of Hyperprolactinemia on Lipid and Lipoprotein Levels

Total Cholesterol	Increase
LDL-C	Increase
HDL-C	No Change or Decrease
Triglycerides	No Change or Increase

The mechanisms accounting for the alterations in plasma lipid levels are not clear but could be related to a number of factors. First, prolactin may have direct effects on lipid metabolism. For example, prolactin decreases lipoprotein lipase activity in human adipose tissue and plasma lipoprotein lipase activity is decreased in patients with prolactinomas (2,11). Second, elevated prolactin levels are associated with decreased estrogen levels in women, a change that is known to be associated with elevated LDL cholesterol and decreased HDL cholesterol levels. Third, elevated prolactin levels are associated with obesity, which could adversely affect plasma lipid levels (1). Finally, with large prolactinomas the secretion of growth hormone may be impaired, which can result in abnormal plasma lipid levels (2).

Lowering prolactin levels with dopamine agonists, such as bromocriptine or cabergoline, has been shown to decrease plasma total and LDL cholesterol levels and in some instances triglycerides (1,6,7,12-17). However, it is unclear if this effect is solely due to lowering prolactin levels or to other effects of dopamine agonists. The administration of dopamine agonists to patients without prolactinomas has also been shown to induce changes in plasma lipid levels (18).

Risk of Cardiovascular Disease

In patients with prolactinomas, carotid-intima media thickness has been shown to be increased (8,9). Moreover, a positive association of serum prolactin concentrations with all-cause and cardiovascular mortality and events has been reported (19,20). This increase in cardiovascular mortality has been particularly noted in males with elevated prolactin levels (21,22). These results suggest that hyperprolactinemia might increase the risk of atherosclerotic cardiovascular disease. While prolactin induced abnormalities in lipids could contribute to this increased risk, it should be recognized that elevated prolactin levels also induce other metabolic abnormalities such as obesity, insulin resistance, and alterations in glucose metabolism that could accelerate atherosclerosis.

GROWTH HORMONE DEFICIENCY

Effect of Growth Hormone Deficiency on Lipid and Lipoprotein Levels

Dyslipidemia is commonly observed in adults with growth hormone deficiency (23-30). Plasma total cholesterol, LDL cholesterol, and triglyceride levels are elevated while HDL cholesterol levels are decreased. LDL size and Lp(a) levels in controls and in growth hormone deficient patients are similar to controls (26,27,31). It should be recognized that growth hormone deficiency leads to increased adiposity, which may be an important contributor to dyslipidemia (32). However, even when controlling for BMI, dyslipidemia is still present in growth hormone deficient patients (23).

Table 2. Effect of Growth Hormone Deficiency on Lipid and Lipoprotein Levels

Total Cholesterol	Increase
LDL-C	Increase
HDL-C	Decrease

Triglycerides	Increase
Lp (a)	No change

Effect of Growth Hormone Therapy on Lipid and Lipoprotein Levels

Numerous studies have examined the effect of growth hormone replacement therapy on serum lipid levels. A meta-analysis by Newman and colleagues reported on the effect of low dose growth hormone replacement (<0.7mg/day; seven studies) and high dose growth hormone replacement (>0.7mg/day; sixteen studies) involving over 1000 subjects (33). In both the low dose and high dose groups, growth hormone replacement therapy decreased total and LDL cholesterol levels but did not significantly affect either HDL cholesterol or triglyceride levels. LDL cholesterol levels were decreased by 11.3%. A meta-analysis of 37 trials by Maison et al also found that total and LDL cholesterol levels were decreased with no significant changes in triglycerides or HDL cholesterol by growth hormone treatment (34). In a few studies, HDL cholesterol levels have been observed to increase with growth hormone therapy (28,35,36). For example, in a 15 year long term perspective study growth hormone therapy reduced LDL cholesterol and increased HDL cholesterol levels, while having no significant effect on triglyceride levels (37). The ability of growth hormone therapy to decrease LDL cholesterol levels occurs even when patients are on statin therapy (38). Moreover, the decrease in LDL cholesterol levels with growth hormone treatment correlates with baseline LDL cholesterol levels (i.e. the higher the LDL cholesterol the greater the decrease with growth hormone treatment) (39). Interestingly growth hormone treatment increases Lp(a) levels (36,40-46). Of note, studies have shown that treatment with growth hormone increases Lp(a) levels while treatment with IGF-1 decreases Lp(a) levels (47). Whether this increase in Lp(a) levels will enhance the risk of cardiovascular disease is unknown.

Table 3. Effect of Growth Hormone Therapy on Lipid and Lipoprotein Levels	
Total Cholesterol	Decrease
LDL-C	Decrease
HDL-C	No Change or Increase
Triglycerides	No Change
Lp (a)	Increase

Mechanism for the Changes in Lipids and Lipoproteins in Growth Hormone Deficiency

LDL CHOLESTEROL

Studies have shown that growth hormone increases the expression of hepatic LDL receptors (48,49). As a consequence, the clearance of LDL cholesterol is accelerated by growth hormone treatment (50,51). Thus, the increase in total cholesterol and LDL cholesterol levels in growth hormone deficient patients

is likely due to a decrease in hepatic LDL receptors and therefore with growth hormone administration the number of LDL receptors increases leading to a decrease in plasma LDL levels. Notably, in a patient with homozygous familial hypercholesterolemia, devoid of functional LDL receptors, growth hormone treatment did not result in a decrease in LDL cholesterol levels, whereas in growth hormone deficient patients, normal subjects, and patients with heterozygous familial hypercholesterolemia treatment with growth hormone resulted in a decrease in LDL cholesterol levels (50). This observation further demonstrates the importance of LDL receptors in mediating the decrease in LDL cholesterol levels in response to growth hormone administration.

TRIGLYCERIDES

In growth hormone deficient patients there is an increase in hepatic VLDL production and a reduction in VLDL clearance, which together could lead to an increase in plasma triglyceride levels (52). Growth hormone therapy stimulates VLDL secretion and increases VLDL clearance, which is likely due to its effects in up-regulating low density lipoprotein receptors, leading to a neutral effect on plasma triglyceride levels (53). The enhancement in VLDL secretion by growth hormone treatment is likely facilitated by the well-recognized ability of growth hormone to stimulate lipolysis in adipose tissue, which will provide fatty acids for the synthesis of triglycerides in the liver and enhance VLDL production (54). Growth hormone increases fatty acid oxidation but this may not be able to offset the increased lipolysis and VLDL production (55).

LIPOPROTEIN (a)

In transgenic mice expressing the human apolipoprotein (a) gene, growth hormone administration increases the mRNA levels of apolipoprotein (a) and plasma levels of apolipoprotein (a) (56). The increased production of apolipoprotein (a) induced by growth hormone could account for the increase in Lp(a) levels induced by growth hormone treatment.

Risk of Cardiovascular Disease

Several observational studies have found that patients with hypopituitarism on conventional replacement therapy have an increased mortality that is primarily due to cardiovascular and cerebrovascular disease (57-61). Additionally, the risk of myocardial infarctions is increased in hypopituitarism (57,62). Moreover, increased coronary artery calcifications and carotid intima-media thickness have been observed in patients with growth hormone deficiency (29,63-70). It is likely that the dyslipidemia that commonly occurs in growth hormone deficient patients contributes to this increased risk of cardiovascular disease. However, growth hormone deficient patients also display an increase in visceral adiposity, insulin resistance, impaired glucose metabolism, an increased prevalence of the metabolic syndrome, and an increased pro-inflammatory state with elevations in C-reactive protein and inflammatory cytokines, which could also contribute to an increased risk of cardiovascular disease (35).

Whether treating growth hormone deficient patients with growth hormone replacement therapy reduces the risk of cardiovascular disease is uncertain, as there are no long-term randomized outcome studies. There are however a number of observational studies. Svensson and colleagues reported that in patients with hypopituitarism on growth hormone replacement therapy the risk of myocardial infarctions was decreased but the occurrence of cerebrovascular events appeared to be increased compared to untreated patients (57). Bengtsson and colleagues reported that morbidity was not increased in patients with growth hormone deficiency who were treated with growth hormone compared to the general population

and was even reduced compared to untreated patients (71). Holmer et al reported that in growth hormone deficient patients, the risk of nonfatal stroke declined in males and females and nonfatal cardiac events decreased in males treated with growth hormone replacement therapy (72). Finally, van Bunderen et al reported that growth hormone deficient men receiving growth hormone treatment had a mortality rate similar to the background population but women had an increase in cardiovascular mortality (73). Together these results suggest that growth hormone therapy may reduce the risk of cardiovascular disease.

In non-randomized trials a decrease in carotid intima-media thickness was observed in growth hormone deficient patients treated with growth hormone (64,67,68,70,74-76). Other similar studies have not shown a decrease in carotid intima-media thickness with growth hormone treatment [61]. Furthermore, in Brazilian patients with lifelong isolated growth hormone deficiency, treatment with growth hormone increased carotid intima-media thickness (77).

Thus, at this time it is uncertain whether growth hormone replacement therapy will have beneficial effects on long term outcomes. Randomized outcome trials will be required to definitively answer this question.

ACROMEGALY

Effect of Acromegaly on Lipid and Lipoprotein Levels

In patients with acromegaly an increase in plasma triglyceride levels and a decrease in HDL cholesterol levels have been frequently observed (78-88). In one large retrospective study of 307 newly diagnosed patients with acromegaly, 33% of patients were noted to have elevated triglyceride levels (>150mg/dl) while 17% of men and 62% of women had low HDL cholesterol levels defined by metabolic syndrome criteria (89). The effect of acromegaly on total cholesterol and LDL cholesterol levels has been variable (78,79,81-84,86-88,90-93). However, an increase in small dense LDL levels and apolipoprotein B levels may be seen (85-87,94). Additionally, an increase in Lp(a) levels has been reported in several studies (87,92,95-97).

Table 4. Effect of Acromegaly on Lipid and Lipoprotein Levels

Total Cholesterol	Variable
LDL-C	Variable
HDL-C	Decrease
Triglycerides	Increase
Lp (a)	Increase

Treatment of acromegaly that normalizes growth hormone and IGF-1 levels typically results in a decrease in plasma triglyceride levels and an increase in HDL cholesterol levels (82,83,87,97-103). Additionally, small dense LDL and Lp(a) levels may also decrease (87,90,95-97,99-101).

Mechanism for the Changes in Lipids and Lipoproteins in Acromegaly

TRIGLYCERIDES

The increase in plasma triglycerides has been shown to be associated with an increased triglyceride production rate (80). Treatment with growth hormone stimulates VLDL secretion, which is likely facilitated by the ability of growth hormone to enhance lipolysis that will provide fatty acids for the synthesis of triglycerides in the liver, thereby enhancing VLDL production (53,54). In addition, several studies have shown that lipoprotein lipase activity is decreased in patients with acromegaly, which could decrease the clearance of triglyceride rich lipoproteins (79,104,105). It is likely that the insulin resistance and abnormal glucose metabolism that frequently occurs in patients with acromegaly also contributes to the abnormalities in triglyceride metabolism.

HDL CHOLESTEROL

LCAT, CETP, hepatic lipase, and phospholipid transfer protein have all been reported to be decreased in patients with acromegaly (86,88,94). Whether these changes account for the decrease in HDL cholesterol levels is uncertain. A decrease in LCAT, CETP, and hepatic lipase could result in a decrease in reverse cholesterol transport (106).

LIPOPROTEIN (a)

In transgenic mice expressing the human apolipoprotein (a) gene, growth hormone administration increases the mRNA levels of apolipoprotein (a) and plasma levels of apolipoprotein (a) (56). The increased production of apolipoprotein (a) induced by growth hormone could account for the increase in Lp(a) levels in patients with acromegaly. Of note studies have shown that treatment with growth hormone increases Lp(a) levels however treatment with IGF-1 decreases Lp(a) levels (47).

Risk of Cardiovascular Disease

Cardiovascular disease is increased in patients with acromegaly but much of this is related to acromegalic cardiomyopathy, valvular heart disease, and arrhythmias (107,108). It remains uncertain whether atherosclerotic cardiovascular disease is increased (107,108). A study using the German Acromegaly Registry did not observe an increase in myocardial infarctions or strokes in 479 patients with acromegaly compared to the general population (109). Several studies have shown an increase in carotid intima-media thickness in patients with acromegaly (82,83,110-114). However, a study by Otsuki and colleagues showed that if one controls for risk factors carotid intima-media thickness in patients with acromegaly was similar to matched controls (115). In contrast, Ozkan and colleagues found that carotid intima-media thickness in patients with acromegaly was still increased even in matched controls (114). Several studies have shown that the treatment of acromegaly results in a decrease in carotid intima-media thickness (82,83,112,116). In contrast to the results seen in studies of carotid intima-media thickness, studies of coronary artery calcium score in patients with acromegaly have not consistently shown an increase in atherosclerosis. While Cannavo et al have shown an increase in coronary artery calcium, other studies have not shown an increase (117-120). In the study of Herrmann et al the coronary artery calcium score directly correlated with disease duration suggesting that patients with long standing acromegaly are more likely to develop atherosclerosis (121). Thus, whether acromegaly increases atherosclerosis and atherosclerotic cardiovascular disease events requires further investigation.

HYPOTHYROIDISM

Effect of Hypothyroidism on Lipid and Lipoprotein Levels

It has been recognized since the 1930s that hypothyroidism results in an increase in plasma

cholesterol levels (122). Indeed, along with protein bound iodine, cholesterol levels were followed as a marker for treatment before radioimmunoassays were developed for TSH and FT4. The lipid profile of hypothyroid patients is characterized by an increase in total and LDL cholesterol levels (122). LDL cholesterol levels can be strikingly elevated, sometimes raising the suspicion of familial hypercholesterolemia. Hypothyroidism can also unmask familial dysbetalipoproteinemia (Type III hyperlipidemia) (123-125). In most studies there is not an increase in small dense LDL (122). It should be routine clinical practice to determine thyroid function in patients with significant elevations in LDL cholesterol to rule out hypothyroidism as the cause of the hypercholesterolemia. The effect of hypothyroidism on HDL cholesterol levels is variable with either no change or a modest increase in HDL cholesterol levels but there is a more consistent increase in the concentration of HDL 2 particles (122,126). Similarly, hypothyroidism has either no effect or modestly increases plasma triglyceride levels (122). Of note, Lp(a) levels are also increased in hypothyroid patients (122,127-131). In a study of 295 patients with overt hypothyroidism 56% had elevations in LDL cholesterol, 34% had elevated LDL cholesterol and elevated triglyceride levels, 1.5% had elevations only in triglycerides, and 8.5% had no lipid abnormalities (132). Patients with secondary hypothyroidism were more likely to have elevations in both LDL cholesterol and triglyceride levels in this study (132). However, other studies have not observed a difference in the dyslipidemia in patients with primary or secondary hypothyroidism (133). In general, the changes in lipids and lipoprotein induced by hypothyroidism are pro-atherogenic and are more severe with severe hypothyroidism. Restoration of thyroid function improves the lipid abnormalities towards normal (122,132,134,135).

Table 5. Effect of Hypothyroidism on Lipid and Lipoprotein Levels

	Overt Hypothyroidism	Subclinical Hypothyroidism
Total Cholesterol	Increase	Normal to increased
LDL-C	Increase	Normal to increased
HDL-C	Normal to slightly increased	No change
Triglycerides	Normal to increase	Normal to increased
Lp(a)	Increase	No change
Apo B	Increase	Increase
Apo A-I	Increase	No change

Subclinical Hypothyroidism

The effects of subclinical hypothyroidism on lipid and lipoprotein levels have been highly variable with some studies showing changes similar to what is observed in patients with overt hypothyroidism and other studies showing no differences in patients with subclinical hypothyroidism compared to controls (136,137). These differences are likely related the types of patients included in the studies with variables such as age, ethnicity, duration of hypothyroid dysfunction, and the presence of other metabolic abnormalities such as insulin resistance (138). One key variable is the degree of thyroid dysfunction with studies that

included patients with higher TSH levels (>10mIU/L) more likely to show that subclinical hypothyroidism is associated with abnormalities in lipid and lipoprotein levels (137).

An important issue in patients with subclinical hypothyroidism is whether one should treat with thyroid hormone replacement or just observe. Because of this uncertainty it has been of great interest to determine if the lipid profile in patients with subclinical hypothyroidism improves with thyroid hormone treatment. A large number of studies have explored this issue but the results have likewise been inconsistent with some studies showing potentially beneficial changes in the lipid profile and other studies showing no changes with treatment of subclinical hypothyroidism (136,137). A recent review also did not find firm evidence of a beneficial effect on the lipid profile with thyroid hormone treatment in patients with subclinical hypothyroidism (139). It is likely that the patients with higher TSH levels and higher LDL cholesterol levels will benefit from treatment with L-thyroxine (140).

Risk of Cardiovascular Disease in Subclinical Hypothyroidism

A major issue in patients with subclinical hypothyroidism is whether they are at increased risk of developing cardiovascular disease. Some but not all meta-analyses have suggested that subclinical hypothyroidism is associated with a small increase in cardiovascular risk particularly in young patients and patients whose TSH is greater than 10mIU/L (136,141-144). The length of time that a patient is hypothyroid and the degree of elevation of cholesterol may be important factors. Whether thyroid treatment lowers this risk is uncertain with some observational studies reporting a benefit and others reporting no benefit (136,137,145). No randomized outcome studies have addressed whether treatment with thyroid hormone will reduce cardiovascular events in patients with subclinical hypothyroidism and without such studies it is difficult to be certain whether thyroid hormone replacement is indicated.

In patients with subclinical hypothyroidism carotid intima-media thickness (cIMT) is increased and two meta-analysis found that thyroid hormone treatment reduced cIMT suggesting a possible beneficial effect on atherosclerosis (146-148). This decrease in cIMT was associated with a reduction in plasma lipid levels. However, it should be noted that a recent randomized study of 185 subjects with subclinical hypothyroidism (TSH 6.35mIU/L) did not find any difference in cIMT after 18 months in the thyroid hormone treated group compared to the placebo group (149). Only a small number of studies have examined coronary calcium scores but the limited data suggest an increase in coronary calcium in individuals with subclinical hypothyroidism (150-152)

It is recommended by the American Thyroid Association, and the American Association of Clinical Endocrinologists that subclinical hypothyroidism should be treated when the TSH level is >10 mIU/L (145). Routine treatment for patients with TSH levels between 4.5 and 10mIU/L is not recommended but one can decide to initiate therapy based on individual factors, such as antibodies and symptoms (145). There are no recommendations by these societies to treat with thyroid hormone replacement for the purpose of correcting abnormal lipid and lipoprotein levels or reducing cardiovascular risk. Since randomized clinical trials have not consistently shown a lipid-lowering benefit with thyroid hormone therapy in patients with subclinical hypothyroidism (TSH < 10mIU/L), patients with significant hyperlipidemia, should be treated with lifestyle changes and lipid-lowering medications.

Mechanism for the Changes in Lipids and Lipoproteins in Hypothyroidism

Thyroid hormone regulates the expression and activity of a number of key enzymes and receptors that regulate lipid and lipoprotein levels.

LDL CHOLESTEROL

The primary mechanism by which hypothyroidism results in elevated total cholesterol and LDL cholesterol levels is via a decrease in LDL receptor levels in the liver. Thyroid hormone stimulates the expression of LDL receptors and in hypothyroidism the number of hepatic LDL receptors is reduced leading to the decreased clearance of circulating LDL (122,153-158). This decreased clearance of LDL accounts for the increase in plasma LDL levels. Thyroid hormone stimulates LDL receptor expression by increasing SREBP-2 and/or by direct effects on the LDL receptor promoter (159,160). Finally, PCSK9 levels are increased with hypothyroidism, which would further contribute to a decrease in hepatic LDL receptor levels by accelerating the catabolism of LDL receptors (161).

In addition to the effects on the LDL receptor levels, other changes induced by thyroid hormone may also contribute to the increases in LDL cholesterol levels in hypothyroid patients. Studies in LDL receptor deficient mice (LDL receptor knock-out mice) have shown that thyroid hormone administration lowers LDL cholesterol levels despite the absence of LDL receptors (162,163).Thyroid hormone also stimulates the conversion of cholesterol to bile acids by increasing cholesterol 7 alpha hydroxylase, the initial enzyme in bile acid synthesis, and in hypothyroid patients a decrease in bile acid synthesis could contribute to an increase in LDL cholesterol levels (161,163-166). Furthermore, the expression of ABCG5 and ABCG8, the transporters that mediate the movement of cholesterol from the hepatocyte into the bile, are also stimulated by thyroid hormone (167,168). In addition, studies by Goldberg and colleagues demonstrated that thyroid hormone decreases apolipoprotein B production and hence in hypothyroidism there could be an increase in apolipoprotein B synthesis (162). Finally, studies have shown that hypothyroidism is associated with increased intestinal cholesterol absorption that is due to an increase in NPC1L1 (167). Thus, a number of potential pathways could contribute to the increased LDL cholesterol that occurs in hypothyroidism.

TRIGLYCERIDES

As noted above hypothyroidism has only modest effects on plasma triglyceride levels. Several but not all studies have shown that thyroid hormone stimulates lipoprotein lipase activity (169-174). A decrease in lipoprotein lipase activity could lead to the decreased clearance of triglyceride rich lipoproteins accounting for the increase in plasma triglyceride levels in hypothyroidism. Moreover, studies have shown that thyroid hormone stimulates the expression of apolipoprotein A-V, which potentiates the activity of lipoprotein lipase, and is associated with decreases in plasma triglyceride levels (175). Additionally, thyroid hormone decreases angiopoietin-like proteins 3 and 8, inhibitors of lipoprotein lipase, and the levels of angiopoietin-like proteins 3 and 8 are elevated in hypothyroid patients which could lead to a decrease in lipoprotein lipase activity (176,177). Lastly, hypothyroidism increases hepatic VLDL-TG secretion rate, which could also contribute to elevations in plasma triglyceride levels (178).

HDL CHOLESTEROL

As noted above hypothyroidism has only modest effects on plasma HDL cholesterol levels. However, thyroid hormone might be having effects on HDL metabolism that are not reflected in HDL cholesterol levels, as a number of key proteins involved in HDL metabolism and reverse cholesterol transport are regulated by thyroid hormone. Specifically, CETP or

cholesterol ester transfer, hepatic lipase, LCAT, and SR-B1 are increased by thyroid hormone and are decreased in hypothyroidism (168,169,171,174,179-186). A decrease in CETP, hepatic lipase, LCAT, and SR-B1 would be anticipated to result in a decrease in reverse cholesterol transport (106). Moreover, sera from animals treated with thyroid hormone have the increased ability to facilitate the efflux of cholesterol from macrophages to HDL via ABCA1 (187).

LIPOPROTEIN (a)

The mechanism for the increase in Lp(a) is unknown.

HYPERTHYROIDISM

Effect of Hyperthyroidism on Lipid and Lipoprotein Levels

In hyperthyroidism total cholesterol and LDL cholesterol levels are decreased (122,188). Additionally, HDL cholesterol and Lp(a) levels are also decreased (122,188) (Table 6). The effect on triglyceride levels is variable and triglyceride levels may be increased, decreased, or unchanged (122,188). Restoration of euthyroidism results in the normalization of lipid and lipoprotein levels.

Table 6. Effect of Hyperthyroidism on Lipid and Lipoprotein Levels

Total Cholesterol	Decrease
LDL-C	Decrease
HDL-C	Decrease
Triglycerides	Variable
Lp(a)	Decrease
Apo B	Decrease
Apo A-I	Decrease

Given the beneficial effects of thyroid hormone on lipid and lipoprotein levels, consideration has been given to treating patients with thyroid hormone/thyroid hormone analogues to reduce cardiovascular disease. The Coronary Drug Project examined the use of D-thyroxine for lipid lowering in patients with cardiovascular disease. While D-thyroxine was effective in lowering LDL cholesterol levels, it was also associated with an increase in cardiovascular deaths and the trial was therefore stopped early (189). More recently there have been efforts by the pharmaceutical industry to develop thyroid hormone analogs and mimetics that would have the beneficial effects of thyroid hormone on lipids and lipoproteins without inducing the harmful effects of excess thyroid hormone (190).

Mechanism for the Changes in Lipids and Lipoproteins in Hyperthyroidism

Thyroid hormone regulates the expression and activity of a number of key enzymes and receptors that regulate lipid and lipoprotein levels. For details see section on hypothyroidism.

LDL CHOLESTEROL

The decrease in LDL cholesterol levels is primarily due to an increase in hepatic LDL receptors resulting in the accelerated clearance of circulating LDL (122). This increase in LDL receptors is due to thyroid hormone stimulating the increased expression of LDL receptors (122,159,160). In addition, hyperthyroidism leads to a decrease in PCSK9, which will lead to a decrease in the degradation in LDL receptors contributing to the increase in LDL receptors (161).

Studies in LDL receptor deficient mice (LDL receptor knock-out mice) have shown that thyroid hormone administration lowers LDL levels despite the absence of LDL receptors, indicating that factors in addition to up-regulation of the LDL could contribute to the decrease in circulating LDL [167, 168]. Thyroid hormone stimulates the elimination of cholesterol from the body by increasing the conversion of cholesterol into bile acids and increasing the biliary secretion of bile acids and cholesterol (161,165,166,191). Thyroid hormone also diminishes intestinal absorption of dietary cholesterol (167). Finally, thyroid hormone decreases apolipoprotein B production and hence hyperthyroidism could result in a decrease in apolipoprotein B synthesis [167]. The significance of these changes in contributing to the decrease in LDL cholesterol is unknown.

HDL CHOLESTEROL

A number of key proteins involved in HDL metabolism and reverse cholesterol transport are regulated by thyroid hormone. Specifically, CETP, hepatic lipase, LCAT, and SR-B1 are increased by thyroid hormone (168,169,171,174,179-186). An increase in CETP, hepatic lipase, LCAT, and SR-B1 would be anticipated to result in a decrease in HDL cholesterol and an increase in reverse cholesterol transport (106). Moreover, sera from animals treated with thyroid hormone have the increased ability to facilitate the efflux of cholesterol from macrophages to HDL via ABCA1 (187).

LIPOPROTEIN (a)

The mechanism for the decrease in Lp(a) is unknown. Studies have shown that decreases in PCSK9 activity can reduce Lp(a) levels so perhaps the thyroid hormone induced decrease in PCSK9 plays a role (161,192).

CUSHING'S SYNDROME

Effect of Cushing's Syndrome on Lipid and Lipoprotein Levels

It is difficult to state the true prevalence of hyperlipidemia in patients with Cushing's syndrome due to the fact that cut-offs used to establish the presence of hyperlipidemia vary among different studies and the number of patients in these studies have been relatively small. Additionally, the severity of the Cushing's syndrome is also a key variable. Nevertheless, it is apparent that dyslipidemia is a common feature of Cushing's syndrome with an elevation in plasma triglycerides and total cholesterol due to an increase in circulating VLDL and LDL (193-199). The elevation in total and LDL cholesterol levels correlates with the severity of the Cushing's syndrome (193,195). The central obesity that characterizes Cushing's syndrome likely contributes to the dyslipidemia with patients who have central obesity more likely to have alterations in lipid levels (199). Additionally, if Cushing's syndrome is associated with diabetes this can further alter lipid and lipoprotein levels (200). These alterations in lipid and lipoprotein levels improve or normalize after treatment and lowering of the elevated cortisol levels (193,201). The effect of Cushing's syndrome on HDL cholesterol is more variable with increases and decreases in HDL cholesterol both being reported in different studies

(193,194). Finally in one small study Lp(a) levels were not altered in patients with Cushing's syndrome (202), while in another small study Lp(a) levels were increased (199).

Most series report improvement in hyperlipidemia with correction of elevated cortisol levels, though a complete normalization of lipid parameters is frequently not achieved (193). In a longitudinal study, 25 patients had a significant decrease in LDL cholesterol levels after one year of normalization of cortisol levels, but levels still remained higher than healthy controls, albeit similar to BMI-matched controls (198). Similarly, in a cross-sectional study carried out 5 years after cure or control of pituitary Cushing's disease, levels of total and LDL cholesterol were similar to levels found in BMI-matched controls, but higher than in normal controls (199).

Table 7. Effect of Cushing's Syndrome on Lipid and Lipoprotein Levels

Total Cholesterol	Increase
LDL-C	Increase
HDL-C	Variable
Triglycerides	Increase
Lp (a)	No change or Increased
Apo B	Increase
Apo A-I	Variable

In patients without inflammatory disorders, the administration of glucocorticoids has variable effects on the lipid profile; HDL cholesterol levels are typically increased with the magnitude of change in plasma triglyceride and LDL cholesterol varying among studies (203-205). In patients with inflammatory diseases, the effect of glucocorticoids on lipids is confounded by the marked anti-inflammatory effects of glucocorticoids. Inflammation affects lipid and lipoprotein levels and thus reducing inflammation per se can affect the lipid response to glucocorticoid treatment (206). Similarly, the effect of glucocorticoids on lipids following transplantation or the treatment of other medical conditions is also difficult to interpret due to the simultaneous use of other medications and the response of the underlying medical conditions. Furthermore, the dose and route of administration of the glucocorticoids can be an important variable, as low doses often have minimal effects on triglyceride, LDL cholesterol, and HDL cholesterol levels while high doses tend to increase serum triglyceride, LDL cholesterol, and HDL cholesterol levels.

Table 8. Effect of Glucocorticoid Treatment on Lipid and Lipoprotein Levels

Total Cholesterol	Increase
LDL-C	No Change or Increase
HDL-C	Increase

Triglycerides	No Change or Increase

Mechanism for the Changes in Lipids and Lipoproteins in Cushing's Syndrome

The mechanisms by which excess glucocorticoids induce changes in lipid and lipoprotein metabolism have not been precisely elucidated and the literature on this topic is often contradictory (207,208). Below we will review some of the potential mechanisms that could account for the observed changes.

LDL CHOLESTEROL

A single study in rats has shown that glucocorticoids decrease hepatic LDL receptor expression (209). However, this glucocorticoid effect on LDL receptor expression was not seen by Galman and colleagues (167). Intriguingly, Galman and colleagues reported that ACTH stimulation of the adrenals did decrease the expression of both hepatic LDL receptors and SR-B1 receptors, suggesting that hormones other than glucocorticoids secreted by activated adrenal glands might have effects on liver receptors (210). Whether this plays a role in the increase in plasma LDL cholesterol levels seen in some individuals with Cushing's syndrome is unknown.

TRIGLYCERIDES

Glucocorticoid administration stimulates hepatic fatty acid synthesis by increasing the activity of acetyl CoA carboxylase and fatty acid synthesis (207,211-214). In addition, glucocorticoids also stimulate the enzymes required for the synthesis of triglyceride in the liver (215-217). The increase in hepatic triglyceride levels leads to the decreased degradation of Apo B and an increase in the formation and secretion of VLDL (207,208,214,218-220). Moreover, in patients with Cushing's syndrome VLDL production rates are increased, while VLDL clearance is not altered, indicating that hepatic overproduction of VLDL accounts for the increase in serum triglyceride levels (201). This increase in VLDL production could also contribute to the increase in LDL cholesterol levels in patients with Cushing's syndrome (201).

In addition to glucocorticoids increasing hepatic fatty acid synthesis, in acute experimental models, glucocorticoids also increase adipose tissue lipolysis resulting in an increase in circulating free fatty acid levels (207,208,221-227). Glucocorticoids increase the expression of adipose tissue triglyceride lipase and hormone sensitive lipase, two of the key enzymes that mediate the breakdown of triglycerides into free fatty acids in adipose tissue (222,225,228,229). Furthermore, glucocorticoids also stimulate adipose tissue lipolysis by increasing cAMP levels, which stimulates the activation of protein kinase A (PKA) leading to the phosphorylation of hormone sensitive lipase and perilipin (221,225). However, studies have shown that chronic elevations in glucocorticoids do not increase adipose tissue lipolysis; thus it is not clear whether increased transport of fatty acids from adipose tissue to liver contributes to the increased formation and secretion of VLDL by the liver (208,230,231)

HDL CHOLESTEROL

Studies have shown that glucocorticoids increase the synthesis and secretion of Apo A-I by direct effects on the Apo A-I promoter that are mediated via the glucocorticoid receptor (232,233). The increased production of Apo A-I could lead to an increase in HDL cholesterol. Furthermore, glucocorticoids decrease hepatic lipase activity and increase LCAT activity,

which could also contribute to an increase in HDL cholesterol levels (234).

Risk of Cardiovascular Disease

Patients with Cushing's syndrome have a higher mortality rate than age and gender matched controls, which is mainly due to an increased risk of cardiovascular disease (235-238). Notably this increased mortality risk remains even after remission of Cushing's syndrome, but is reduced compared to persistent disease (238,239). Furthermore studies have shown that the hazard ratio for myocardial infarctions was 3.7 and for strokes was 2.0 in patients with Cushing's syndrome (240). Moreover, patients with Cushing's syndrome have an increase in carotid intima-media thickness, which persists after remission of the disease (198,199,241-243). Additionally, coronary artery calcium, a marker of atherosclerosis, is also increased in patients with Cushing's syndrome and also persists after disease remission (244,245). Thus, it is quite clear that Cushing's syndrome increases the risk and occurrence of atherosclerotic cardiovascular disease. It is likely that the dyslipidemia that accompanies Cushing's syndrome contributes to the increase in atherosclerotic cardiovascular disease, but it must be recognized that Cushing's syndrome also induces other abnormalities that are highly associated with an increased risk of atherosclerotic cardiovascular disease such as central obesity, diabetes, insulin resistance, hypercoagulability, and hypertension (246,247). It is therefore likely that the increase in atherosclerotic cardiovascular disease seen in patients with Cushing's syndrome is multifactorial.

Effect of Drugs Used to Treat Cushing's Syndrome on Lipid Levels

Ketoconazole is used to treat patients with Cushing's syndrome. It is an anti-fungal imidazole derivative that blocks several steps in cortisol biosynthesis thereby lowering serum cortisol levels. However, ketoconazole is also an inhibitor of cholesterol biosynthesis, acting directly by blocking the conversion of methyl sterols to cholesterol and indirectly by suppressing cholesterol synthesis via feedback inhibition of HMG-CoA reductase by sterol intermediates (248,249). In the past, ketoconazole had been used to treat patients with familial hypercholesterolemia before the widespread use of statins, as it reduced total, intermediate density cholesterol, LDL cholesterol, and apoB levels by approximately 25% (250). Thus, its use to control hypercortisolism may have a beneficial effect on lipid and lipoprotein levels.

It is important to recognize that ketoconazole also interferes with metabolism of many drugs through the inhibition of several hepatic P450 enzymes. Simvastatin, lovastatin, and atorvastatin are all metabolized by cytochrome P450 CYP3A4, and thus, their plasma concentrations and risk of myotoxicity are greatly increased with concomitant ketoconazole therapy (251). Pravastatin, pitavastatin, and rosuvastatin are preferable as their plasma concentrations are not significantly increased by CYP3A4 inhibitors (251).

Mitotane is used for treatment of adrenal carcinoma or intractable Cushing's disease and results in adrenocortical atrophy and necrosis and inhibits steroidogenesis. Mitotane raises circulating cholesterol, LDL cholesterol, and apolipoprotein B levels (252,253). In one report no changes in triglycerides, HDL cholesterol, apoA-1, or Lp(a) levels were observed (252), while in another report modest increases in triglycerides and marked increases in HDL cholesterol occurred (253). The increase in LDL cholesterol levels has been shown to be reversed by treatment with simvastatin (252). In a case report

mitotane increased LDL cholesterol levels as high as 300mg/dl (254).

Mifepristone, a potent antagonist of glucocorticoid and progesterone receptors, lowers HDL cholesterol and apolipoprotein AI levels (255). The mechanism for this decrease in HDL cholesterol is unknown. In a small study short-term administration of mifepristone reduced serum triglyceride levels, which correlated with increases in adipose tissue lipoprotein lipase activity (256).

TESTOSTERONE

Effect of Testosterone on Lipid and Lipoprotein Levels

ENDOGENOUS TESTOSTERONE LEVELS

Numerous observational (epidemiological) studies have shown that serum testosterone levels directly correlate with HDL cholesterol and apolipoprotein A-I levels (i.e. subjects with low serum testosterone levels have lower HDL cholesterol and apolipoprotein A-I levels) (257-263). Moreover, low serum testosterone levels are inversely correlated with total cholesterol, LDL cholesterol, apolipoprotein B, and triglyceride levels (i.e. subjects with low testosterone levels have higher total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides) (258,262-264). Thus, individuals with low serum testosterone levels have a pro-atherogenic lipoprotein pattern with low HDL cholesterol levels and high triglyceride and LDL cholesterol levels.

Not unexpectedly, given the low HDL cholesterol levels and high triglyceride levels, individuals with low serum testosterone levels are more likely to have the metabolic syndrome (263,265,266). It should be recognized that these associations do not necessarily imply that the low serum testosterone levels are causative. For example, it is likely that obesity and related metabolic abnormalities, such as type 2 diabetes, lead to both the abnormal lipid pattern and the low serum testosterone levels. Indeed, obesity is associated with low testosterone and weight loss restores testosterone levels (266-270). Thus, observational studies may be confounded.

Table 9. Correlation of Testosterone Levels with Lipid and Lipoprotein Levels

HDL-C	Positive (low T = lower)
LDL-C	Negative (low T = higher)
Triglycerides	Negative (low T = higher)
Non-HDL-C	Negative (low T = higher)
Lp(a)	Negative (low T = higher)

ANDROGEN DEPRIVATION THERAPY

Studies of the effect of androgen deprivation therapy not only constitute a clinically relevant state but also provide an alternative approach to understanding the effects of low testosterone levels on lipid and lipoprotein levels. In contrast to the associations in observational studies, most studies of androgen deprivation therapy have shown an increase in plasma HDL cholesterol and apolipoprotein A-I levels (271-278). This increase occurs very rapidly within 2 weeks of lowering serum testosterone levels (271). Furthermore, this increase in HDL cholesterol is inhibited if one simultaneously administers testosterone demonstrating that this increase is due to the suppression of testosterone levels (276). In addition, androgen deprivation therapy is also associated with an elevation of LDL cholesterol, non-HDL cholesterol, Lp(a), and triglyceride levels (272-275,277,279-281). The increase of Lp(a) is notable as

the metabolism of Lp(a) often does not parallel the metabolism of LDL.

Table 10. Effect of Androgen Deprivation Therapy on Lipid and Lipoprotein Levels	
HDL-C	Increase
LDL-C	Increase
Triglycerides	Increase
Non-HDL-C	Increase
Lp(a)	Increase

TESTOSTERONE TREATMENT

There have been several meta-analyses that have examined the effect of testosterone treatment on lipid and lipoprotein levels but the results have been variable. Baseline differences, type of therapy, and duration of therapy may contribute to the differing results. A meta-analysis by Whitsel and colleagues demonstrated that total cholesterol, LDL cholesterol, and HDL cholesterol levels decreased after *intramuscular* testosterone treatment, but triglyceride levels did not change (282). A meta-analysis by Isidori also demonstrated a decrease in HDL cholesterol levels, but found no change in LDL cholesterol with testosterone treatment (both *intramuscular and transcutaneous*) (283) . Similarly, a meta-analysis by Fernández-Balsells and colleagues demonstrated a decrease in HDL cholesterol levels but no change in LDL cholesterol or triglyceride levels with testosterone treatment (both *intramuscular and transcutaneous administration*) (284). A meta-analysis by Haddad et al failed to demonstrate any significant changes in HDL cholesterol, LDL cholesterol, or triglyceride levels (285). A recent meta-analysis by Corona and colleagues did not find changes in HDL cholesterol levels but reported small decreases in total cholesterol and triglycerides (286). Finally, a non-randomized long term trial (8 years) of intramuscular testosterone therapy in patients with pre-diabetes resulted in a decrease in body weight and a decrease in A1c that was accompanied by decreases in LDL and non-HDL cholesterol and triglyceride levels and increases in HDL cholesterol levels compared to an untreated comparison group suggesting that long-term therapy might be beneficial on lipids by effecting body weight and glucose homeostasis (287).

The reason for the differences between these meta-analyses is likely due to the fact that the changes in lipid and lipoprotein levels induced by testosterone treatment are relatively small and variable depending upon the patient population studied, the route and dose of testosterone administration, the duration of therapy, the specific testosterone preparation (whether or not it can undergo aromatization to estrogens), and perhaps other unrecognized factors. For example, the reductions in HDL cholesterol appear to be greater in patients whose baseline HDL cholesterol levels are high (283,284). Additionally, transdermal testosterone treatment appears to have less effect on HDL cholesterol levels than intramuscular administration (288). High dose testosterone treatment appears to more consistently lower HDL cholesterol levels than does low dose treatment (289). For example, testosterone enanthate 200mg IM every week used in a contraception study resulted in a relatively robust 13% decrease in HDL cholesterol levels (290). Similarly, raising serum testosterone levels to higher levels produces greater decreases in LDL cholesterol levels (289). Finally, using testosterone preparations that are not converted to estrogens or simultaneously blocking aromatization can lead to more profound decreases in HDL cholesterol and LDL cholesterol levels, which can be

attributed to estrogens having effects on lipid and lipoprotein levels that counterbalance the effects of androgens (estrogens increase HDL cholesterol and decrease LDL cholesterol) (291,292). **The important clinical point is that in the typical androgen deficient patients that we treat with the usual testosterone therapy will have only modest or no changes in plasma lipid and lipoprotein levels.** The minimal effect of testosterone therapy was clearly demonstrated in a large randomized double-blind trial of 788 males over the age of 65 with low testosterone levels who were treated with either testosterone gel to normalize testosterone levels or placebo for 1 year (293). In this trial HDL cholesterol (adjusted mean difference, -2.0 mg/dL; $P < 0.001$), and LDL cholesterol were both slightly decreased (adjusted mean difference, -2.3 mg/dL; $P = 0.051$) from baseline with no change in triglyceride levels in the testosterone treated individuals.

While treatment of typical older hypogonadal men with testosterone therapy has only modest to no effects on plasma lipids and lipoproteins, the use of high dose androgenic steroids in young men for the purpose of increasing muscle mass and strength can have profound effects. In a study by Webb and colleagues of 14 individuals taking high dose androgenic steroids, HDL cholesterol levels were markedly reduced to 29mg/dl, which was less than 50% of the mean HDL cholesterol when exogenous steroids were not used (61mg/dl) (294). Additionally in these individuals LDL cholesterol levels were also higher on androgenic steroids (150mg/dl) than off of androgenic steroids (125mg/dl) (294). Similarly, Hurley and colleagues demonstrated that androgen use by eight bodybuilders and four powerlifters lowered HDL cholesterol levels by 55% and raised LDL cholesterol levels by 61% (295). In a double blind cross-over study anabolic steroids, which may not have androgenic effects, induced a 25-27% decrease in HDL cholesterol levels, which returned towards normal 6 weeks after cessation of drug use (296). Thus, if one sees an athletic male with unexpectedly low HDL cholesterol levels one should suspect androgen and/or anabolic steroid use, which is often obtained as a dietary supplement or as a pharmaceutical from an unregulated source.

There are a number of potential explanations why the changes in lipid and lipoprotein levels are greater in athletes using androgenic steroids. First, the doses used by the athletes are much higher than used in typical testosterone replacement. Second, the androgenic steroids used are often different and more potent (for example nandrolone-decanoate and oxandrolone). Often the compounds used are not converted to estrogen by aromatase and therefore their effects on serum lipid levels will not be counterbalanced by estrogen formation [265, 272]. Third, aromatase inhibitors are sometimes used simultaneously in combination with the androgenic steroids. Lastly, young athletes are often lean and have little adipose tissue and thus low aromatase activity. There can be individual patient variation in aromatase activity with obese older individuals having increased aromatase activity compared to young athletic individuals (297). As noted earlier, the conversion of testosterone to estrogens by aromatase may blunt the effects of testosterone as estrogens will increase HDL cholesterol levels and decrease LDL cholesterol levels. Together it is likely that these factors account for the more robust changes in lipids and lipoprotein levels induced by androgens in young athletes.

TRANSGENDER MALES

Testosterone therapy in transmen results in increases in total cholesterol, LDL cholesterol, and triglyceride levels and a decrease in HDL cholesterol levels (298-300). These changes are likely due to the combination

of an increase in testosterone and a decrease in estrogen.

LIPOPROTEIN (a)

There is a trend towards a higher incidence of clinically significant elevations in Lp(a) levels in men with low testosterone levels (301). Additionally, reductions in serum testosterone levels by orchiectomy or treatment with GnRH antagonists results in an increase in Lp(a) levels (278,302). Conversely, several studies have shown that testosterone administration decreases Lp(a) levels and the effect is more robust in individuals who have high baseline Lp(a) levels (290,303,304). Moreover, it has been shown that simultaneously administering testosterone with an aromatase inhibitor does not markedly reduce the ability of testosterone to decrease Lp(a) levels, indicating that the conversion of testosterone to estrogens does not account for this effect suggesting a direct action of testosterone (303). Lp(a) is a pro-atherogenic lipoprotein so testosterone induced decreases should be beneficial.

SUMMARY

The most consistent effects of androgen therapy on lipid and lipoprotein levels are to decrease HDL cholesterol and Lp(a) levels. These effects are most apparent with high dose testosterone therapy. The decreases in HDL cholesterol and Lp(a) levels with testosterone therapy are consistent with the increases seen with androgen deprivation therapy. However, both types of treatment result in changes that are the opposite of those seen in the observational studies, suggesting that the observational studies are confounded. However, high potency androgen therapy in young healthy men tends to increase LDL cholesterol levels and markedly decrease HDL cholesterol levels (305).

Table 11. Effect of Testosterone Therapy on Lipid and Lipoprotein Levels	
HDL-C	Decreased or No Change
LDL-C	Decrease
Triglycerides	No consistent change
Lp(a)	Decrease

Mechanism for the Testosterone Induced Lipid and Lipoprotein Changes

HDL CHOLESTEROL

The decrease in HDL cholesterol levels with testosterone administration has been attributed to increases in the expression of SR-B1 in the liver and increases in plasma hepatic lipase activity. In Hep G2 cells, the addition of testosterone increased the mRNA and protein levels of SR-B1 and hepatic lipase but had no effect on the expression of apolipoprotein A-I or ABCA1 (306). Moreover, androgen administration increased plasma hepatic lipase activity but had little effect on lipoprotein lipase (291,307-310). An increase in SR-B1in the liver will facilitate the transfer of cholesterol from HDL particles into the hepatocyte, decreasing plasma HDL cholesterol levels (106). An increase in hepatic lipase activity will increase the hydrolysis of triglycerides and phospholipase on HDL, resulting in the formation of smaller HDL particles, the release of Apo A-I, and increased Apo A-I degradation leading to a decrease in plasma HDL levels (106). Thus, the increase in SR-B1 and hepatic lipase induced by androgens could account for the decrease in HDL cholesterol levels seen with testosterone treatment. There is the potential that the increase in SR-B1 is protective in atherosclerosis as it enhances reverse cholesterol transport from HDL (106).

LDL CHOLESTEROL

The mechanism by which testosterone therapy might affect LDL cholesterol levels is uncertain. It has been shown that testosterone can antagonize the ability of estrogens to stimulate LDL receptor expression in the liver, which could lead to a decrease in hepatic LDL receptors and an increase in plasma LDL cholesterol levels (311).

LIPOPROTEIN (a)

The mechanism by which testosterone treatment lowers Lp(a) levels is unknown.

Risk of Cardiovascular Disease

In the Endocrinology of Male Reproduction section of Endotext the chapter by Yeap and colleagues ("Androgens and Cardiovascular Disease in Men"), extensively reviews the literature on the linkage of testosterone and cardiovascular disease (312). Therefore, we will only briefly summarize the relevant information.

ENDOGENOUS TESTOSTERONE LEVELS

There have been numerous cross sectional studies of testosterone levels in patients with coronary artery disease vs. controls and the results have varied (313). Some studies have shown no association while other studies have found low testosterone levels in patients with coronary artery disease. The majority of prospective studies have shown that cardiovascular disease occurs more frequently in subjects with low testosterone levels (313). Whether the low testosterone is causative or a biomarker of poor cardiovascular health (e.g., obesity, metabolic syndrome, diabetes) cannot be determined from these types of observational studies.

ANDROGEN DEPRIVATION THERAPY

In a meta-analysis by Zhao and colleagues of population-based observational studies comparing androgen deprivation therapy in patients with prostate cancer vs. controls with prostate cancer, six studies were identified with a total of 129,802 androgen deprivation therapy patients and 165,605 controls (314). In this analysis, cardiovascular disease was increased by 10% and cardiovascular mortality by 17% in the androgen deprivation therapy patients. In a meta-analysis by Carneiro and colleagues of 126,898 prostate cancer patients in four cohort studies and 10,760 prostate cancer patients in nine randomized controlled trials, these authors found that cardiovascular events were increased two fold in the androgen deprivation groups (315). When only the randomized trials were analyzed, the relative risk was increased 1.55-fold in the androgen deprivation patients. Finally, a meta-analysis by Bosco of eight observational studies reported a relative risk of 1.57 for fatal and non-fatal cardiovascular disease in patients with prostate cancer treated with GnRH agonists (316). These and other results indicate that the risk of cardiovascular disease is increased in men undergoing androgen deprivation therapy, despite the increase in HDL cholesterol (313).

TESTOSTERONE TREATMENT

There have been a large number of observational studies of the risk of cardiovascular disease in men treated with testosterone replacement and the results have been inconsistent, with some studies showing that testosterone increases the risk while other studies have shown no increase in risk (313). Interestingly, in a very large retrospective study of 544,115 testosterone treated patients it was reported that men treated with intramuscular testosterone had an increased risk of cardiovascular events (1.26) and death (1.34), whereas individuals treated with either

testosterone gel or patch did not have an increased risk (317).

With regards to randomized trials, the Testosterone in Older Men with Mobility Limitations Trial (TOM trial) reported an increase in cardiovascular events with testosterone treatment (318). This trial studied 209 men with an average age of 74 years who had a high baseline prevalence of cardiovascular disease (53%) and major cardiovascular risk factors (diabetes 24%, hypertension 85%, and hyperlipidemia 63%). In this trail subjects were treated with high doses of testosterone gel that resulted in high serum testosterone levels. Although 23 subjects in the testosterone group and 5 in the placebo group had a cardiovascular-related adverse event, it should be recognized that many of these cardiovascular events were not atherosclerotic; only 7 men in the testosterone group and 1 in the placebo group had an atherosclerosis related event. Of note, a similar trial using lower doses of testosterone did not observe an increase in cardiovascular events (319). Additionally, a recent randomized trial with 308 men 60 years or older with low or low-normal testosterone levels demonstrated that treatment with testosterone gel for 3 years did not result in a significant difference in the rates of increase in either common carotid artery intima-media thickness or coronary artery calcium (320). In contrast, a randomized trial demonstrated that testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm3 to 232 mm3 vs 317 mm3 to 325 mm3, respectively; estimated mean difference, 41 mm3; 95% CI, 14 to 67 mm3; P = .003) with no difference in progression of coronary calcium scores (321). It should be noted that baseline plaque volume differed between the testosterone and placebo group, which complicates interpretation of these results.

With the exception of one meta-analysis by Xu et al (322), most meta-analyses of randomized clinical trials of testosterone therapy have not demonstrated a statistically significant difference in the occurrence of cardiovascular events (284,285,323-328). Of note, one meta-analysis explored the effect of the route of administration of testosterone and reported that oral testosterone treatment significantly increased cardiovascular risk (RR = 2.20), while neither intramuscular nor transcutaneous delivery (gel or patch) significantly altered cardiovascular risk (323).

To definitively determine the effect of testosterone replacement therapy on cardiovascular disease will require a large randomized outcome trial similar to the Women's Health Initiative. At this time no such study has been initiated.

SUMMARY

While the data consistently show that androgen deprivation therapy increases the risk of atherosclerotic cardiovascular disease, the effect of testosterone administration is unclear.

FEMALE SEX STEROID HORMONES

Effect of Female Sex Steroid Hormone on Lipid and Lipoprotein Levels

PREMENOPAUSAL WOMEN

The plasma lipid profile of premenopausal women is less pro-atherogenic than the lipid profile in men (329-332). Specifically, HDL cholesterol levels are increased (approximately 10mg/dl higher in women), while LDL cholesterol and non-HDL cholesterol levels are slightly lower compared to male values (329-332). Additionally plasma triglyceride levels are also decreased and the average size of LDL particles is

increased in premenopausal women compared to men (329-332).

Notably most of these differences emerge during puberty. Prior to puberty the lipid profiles of girls and boys are very similar but during puberty HDL cholesterol levels in boys decrease while in girls the HDL cholesterol levels do not change (329-332). Additionally, during puberty triglyceride levels increase in boys with no change in triglyceride levels occurring in girls. LDL cholesterol levels are similar in boys and girls before and during puberty but after age 20 LDL cholesterol increase in both males and females but the increase is greater in males resulting in a modest difference in LDL cholesterol levels between the sexes (329-332).

Table 12. Comparison of Lipid and Lipoprotein Levels in Premenopausal Women Compared to Men

Lipids/Lipoprotein	Premenopausal Women Compared to Men
LDL-C	Lower
HDL-C	Higher
Triglycerides	Lower
Non-HDL-C	Lower

POSTMENOPAUSAL WOMEN

The changes in lipids and lipoproteins that occur during menopause are relatively small and therefore the results reported in the literature are variable (329-332). Cross-sectional studies tend to show a greater shift towards a pro-atherogenic lipid profile after the menopause whereas in longitudinal studies the changes are smaller (329-332). In post-menopausal women increases in LDL cholesterol are reported in most, but not all studies, and the composition of LDL shifts towards smaller dense LDL particles (329-332). HDL cholesterol levels tend to be stable but some studies have reported small decreases (329-332). Following surgical menopause the above changes tend to be more rapid and robust and in this setting Lp(a) levels have been reported to increase; however, during natural menopause the change in Lp(a) is very modest (333,334). It is important to recognize that during menopause there are changes in factors in addition to the loss of sex steroid hormones that can alter lipid and lipoprotein levels. Menopause is associated with increases in total and central body fat and a decrease in insulin sensitivity, which are well recognized to affect lipid and lipoprotein metabolism (32).

Table 13. Effects of Menopause on Lipid and Lipoproteins

Lipids/Lipoproteins	Postmenopausal vs Premenopausal
LDL-C	Increase
HDL-C	No change or small decrease
Lp(a)	No change or increase

TRANSGENDER FEMALES

In a systemic review and meta-analysis it was reported that in male-to-female individuals, serum TG levels were increased without changes in LDL or HDL cholesterol levels (300). In contrast, a recent large observational study of hormone therapy in 294 transwomen reported that LDL cholesterol (−6.0%; 95% CI, −8.6 to 3.6), HDL cholesterol (−9.3%; 95% CI,

−11.4 to −7.3), and triglycerides (−10.2%; 95% CI, −14.5 to −5.9) all decreased (298).

ESTROGEN TREATMENT

The effects of oral estrogen treatment on lipids and lipoproteins have been recognized for many years (329,331,335,336). Estrogen administration increases HDL cholesterol levels by 5-15% and decreases LDL cholesterol levels by 5-20% (329,331,335,336). In addition, estrogens also increase triglycerides but in patients with genetic or acquired abnormalities in triglyceride metabolism estrogen therapy can precipitate marked hypertriglyceridemia and even the chylomicronemia syndrome (337). In women with normal baseline triglycerides an approximate 10-15mg/dl increase in triglycerides occurs with estrogen therapy (329,331,335,336). If the increase in triglycerides is substantial, it leads to a decrease in LDL size (i.e. formation of small dense LDL). Not unexpectedly, estrogens induce an increase in apolipoprotein A-I levels and a decrease in apolipoprotein B levels. Lp(a) levels are also decreased by 20-25% by estrogen therapy (329,331,335,336). The effects of oral estradiol are similar to that of oral conjugated equine estrogens (Premarin).

Table 14. Effect of Oral Estrogen Treatment on Lipid and Lipoproteins

Lipids/Lipoproteins	Estrogen Treatment
LDL-C	Decrease
HDL-C	Increase
Triglycerides	Increase
Lp(a)	Decrease

Transdermal estrogen administration has less of an effect on lipid and lipoproteins (329,331,335,336,338). The increase in HDL cholesterol and the decrease in LDL cholesterol are markedly blunted (329,331,335,336,338). Importantly, the effect of transdermal estrogen on triglycerides is minimal and therefore in patients with baseline abnormalities in triglyceride metabolism, the use of transdermal estrogen therapy is preferred (329,331,335,336,338). In some studies, treatment with transdermal estradiol has actually decreased plasma triglyceride levels (339). The lack of a robust effect on lipids with transdermal estrogen preparations is likely due to decreased exposure of the liver to estrogen compared with oral therapy.

ESTROGEN AND PROGESTERONE TREATMENT

Progestins generally have androgen like effects on lipid and lipoproteins and therefore progestin administration decreases HDL cholesterol and triglyceride levels but has little or no effect on LDL cholesterol levels (329,331,335,336). Thus, when combined with estrogen therapy, the estrogen/progesterone preparation blunts the characteristic estrogen induced increase in HDL cholesterol levels without affecting the estrogen induced reduction in LDL cholesterol levels (329,331,335,336). In many but not all studies, progesterone also blunts the estrogen induced increase in triglyceride levels (329,331,335,336,340). In contrast, progesterone appears to either slightly augment or have no effect on the ability of estrogens to decrease Lp(a) levels (335). It is important to note that the effect of adding progesterone is dependent on both the dose and the androgenicity of the particular progesterone used. Godsland analyzed a large number of studies and found in order of least to most potent progesterone affecting lipid levels the following; dydrogesterone and medrogestone, progesterone,

cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate (335).

The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial randomly assigned 875 healthy postmenopausal women to 1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 days/month; (4) CEE, 0.625 mg/d plus continuous MPA, 2.5 mg/day; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/day for 12 days/month (340). The effects on plasma lipid and lipoproteins are shown in table 15, which demonstrates that the addition of medroxyprogesterone but not progesterone blunts the estrogen induced increase in HDL cholesterol without affecting the decrease in LDL cholesterol levels. In this particular study medroxyprogesterone did not blunt the estrogen induced increase in triglyceride levels.

Table 15. The Effect of Estrogen with or without Progesterone on Plasma Lipid and Lipoprotein Levels (PEPI Trial)

	Placebo	CEE only	CEE+MPA (cyc)	CEE+MPA (con)	CEE+MP(cyc)
HDL-C	-1.2%	5.6%	1.6%	1.2%	4.1%
LDL-C	-4.1%	-14.5%	-17.7%	-16.5%	-14.8%
Triglycerides	-3.2%	13.7%	12.7%	11.4	13.4%

Another study evaluated the effect of hormone replacement on lipid and lipoprotein levels in women with hyperlipidemia (341). In that study, 58 women with a baseline total cholesterol level of 305mg/dl and LDL cholesterol of 212mg/dl were randomly assigned to treatment with 1.25 mg conjugated estrogen plus medroxyprogesterone acetate 5 mg/day or simvastatin 10 mg daily. The results of this trial are shown in table 16 and demonstrate that statins are more effective in lowering LDL cholesterol levels and have a similar effect on HDL cholesterol as hormone replacement therapy. While statins lower triglyceride levels, hormone replacement therapy increases triglycerides. Of note, hormone replacement therapy markedly lowers Lp(a) levels whereas statin treatment has no effect, on this highly atherogenic particle.

Table 16. Effect of Hormone Replacement Therapy vs. Statin Treatment on Lipid and Lipoprotein Levels

Lipids/Lipoproteins	Hormone Replacement	Simvastatin
Total cholesterol	14% decrease	26% decrease
LDL-C	24% decrease	36% decrease
HDL-C	7% increase	7% increase
Triglycerides	29% increase	14% decrease
Lp(a)	27% decrease	1% increase

Considerable variation is seen in the response to hormone replacement therapy. This is likely accounted for by different preparations used, route of administration, dosing regimen (cyclic vs. continuous), difference in hormone status prior to treatment, baseline lipid levels, dietary differences, the presence or absence of other metabolic abnormalities, genetic background, etc. (329,335,336). The studies by Tsuda and colleagues showing that the apolipoprotein E phenotype influences the response of LDL to hormonal therapy provide an example of how genetic background can influence response (342). Women

with the E2/E2 or E2/E3 genotype demonstrated the largest LDL cholesterol decreases while women with the E4/E4 or E4/E3 genotype had only a small change in LDL cholesterol levels in response to hormonal replacement therapy. Another example of the role of genetics are studies showing that polymorphisms of the estrogen receptor-alpha gene may be associated with an augmented HDL cholesterol rise with estrogen therapy (343). It is important to note that women who receive cyclic combined therapy (estrogen and progesterone) may have fluctuations in lipoprotein concentrations depending upon the phase of the cycle and it is therefore important to consistently measure lipids during the same hormonal phase, especially when considering starting medications for hyperlipidemia.

POLYCYSTIC OVARY SYNDROME (PCOS)

Women with PCOS characteristically have low HDL cholesterol levels and increased plasma triglyceride levels (344,345). Additionally, LDL cholesterol and non-HDL cholesterol levels are also increased with the LDL being predominantly small dense LDL (344,345). A meta-analysis of 24 studies reported that in women with PCOS triglyceride levels were increased by 26mg/dl, LDL cholesterol by 12mg/dl, non-HDL cholesterol by 19mg/dl and HDL cholesterol was decreased by 6mg/dl (346). The prevalence of elevated Lp(a) levels is also increased in women with PCOS (344,345). It should be noted that the lipid changes in women with PCOS are observed even when the women are not overweight or obese (344,345). In studies of age and weight matched women, the women with PCOS still have lower HDL cholesterol levels and increased triglycerides, LDL cholesterol, and non-HDL cholesterol levels compared to the controls (344,345). The lipid abnormalities in PCOS are likely multifactorial with increases in androgens, decreases in estrogens, obesity, alterations in fat location, insulin resistance, alterations in glucose homeostasis, genetics, and perhaps other factors all contributing to the lipid abnormalities (344,345). Serum PCSK9 concentrations were higher in PCOS patients than normal controls, which could contribute to the increase in LDL cholesterol levels (347).

Table 17. Lipid and Lipoprotein Levels in Polycystic Ovarian Syndrome	
LDL-C	Increase
HDL-C	Decrease
Triglycerides	Increase
Non-HDL-C	Increase
Lp(a)	Increase

Mechanisms for the Female Sex Steroid Induced Lipid and Lipoprotein Changes

ESTROGENS

There are several effects of estrogen that could lead to an increase in HDL cholesterol levels. First, studies have shown that estrogens stimulate the expression of apolipoprotein A-I, which will lead to an increased synthesis of apolipoprotein A-I and the increased formation of HDL (331,348-352). Second, estrogen therapy decreases hepatic lipase activity, which will decrease the hydrolysis of triglyceride and phospholipids on HDL particles, which could potentially result in a decrease in the catabolism of HDL (353-355). Finally, estrogens suppress the expression of SR-B1 in the liver, which will decrease the transfer of cholesterol from HDL particles into the hepatocyte increasing plasma HDL cholesterol levels (356). Based on kinetic studies it is likely that the

predominant effect of estrogens is to increase the production of HDL, which is mediated by an increase in apolipoprotein A-I production (331,348-352). The net result may be protective from atherosclerosis.

The decrease in LDL cholesterol induced by estrogen treatment is accounted for by an increase in LDL clearance (331,357-360). Studies have shown that estrogens increase the expression of hepatic LDL receptors (361-364). Additionally, estrogens reduce PCSK9 levels, which would decrease the degradation of LDL receptors (365,366). Together, this would increase the number of hepatic LDL receptors leading to the accelerated clearance of LDL and a reduction in plasma LDL cholesterol levels.

The increase in plasma triglyceride levels induced by estrogen treatment is due to the increased production and secretion of VLDL particles (331,351,360,367-369). The mechanism by which estrogens decrease Lp(a) levels is unknown.

PROGESTINS

Many of the adverse effects of progestins on lipid and lipoproteins, such as decreasing HDL cholesterol levels, are thought to be due to activation of the androgen receptor (i.e. androgenic actions) (370). The considerable variation of progestins in influencing lipid and lipoprotein metabolism are related to their androgenic potency. For detailed information on the effect of testosterone and other androgens on lipid and lipoprotein metabolism see the section above on the mechanism for the testosterone induced lipid and lipoprotein changes.

Risk of Cardiovascular Disease

PREMENOPAUSAL WOMEN

It has been recognized for many years that the risk of cardiovascular disease in premenopausal women is very low and substantially lower than in men of similar age (371-373). There is an approximate 10-year delay in the development of cardiovascular disease in women compared to men. The relative contribution of the less pro-atherogenic lipid profile in women to this sex difference in cardiovascular disease risk is likely important but remains uncertain.

POSTMENOPAUSAL WOMEN

After the menopause, the risk of cardiovascular disease increases in women (371,372). Of particular note, premature menopause is associated with an increased risk of developing cardiovascular disease, indicating that age is not the sole factor contributing to the increased risk in postmenopausal women (374-377).

HORMONE REPLACEMENT THERAPY

Numerous observational studies have suggested that hormone replacement therapy reduces the risk of cardiovascular disease (378-384). Based on those data, therapeutic trials of hormone replacement therapy were undertaken to see if therapy would prevent or decrease cardiovascular disease. Surprisingly, the randomized clinical trial outcome studies have not demonstrated a decrease in cardiovascular events.

HERS Trial

The HERS trial was a randomized, blinded, placebo-controlled secondary prevention trial in 2763 women with known coronary artery disease who were postmenopausal with an intact uterus, with a mean age of 66.7 years (385). Patients were randomized to either 0.625 mg of conjugated equine estrogens plus continuous 2.5 mg of medroxyprogesterone acetate or

placebo with an average duration of follow-up of 4.1 years. As expected, LDL cholesterol levels were decreased by 11% and HDL cholesterol levels were increased by 10% in the hormone treated group. Despite these changes, there were no significant differences between the groups in the primary outcome (nonfatal myocardial infarction or CHD death) or in any of the secondary cardiovascular outcomes (coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease). Interestingly, there were more CHD events in the hormone group in year 1 but fewer in years 4 and 5 compared to the placebo group. An unblinded extension of the HERS trial for an additional 2.7 years (HERSII) found that the lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow-up. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with pre-existing cardiovascular disease (386). As expected, hormone therapy decreased Lp(a) levels and in a post hoc analysis there was a suggestion that individuals with high baseline Lp(a) levels and individuals who had a robust decrease in Lp(a) with hormone therapy had a reduction in cardiovascular events (387). Of course, these results are not definitive and suggest the need for further focused trials of hormone therapy in postmenopausal women with elevated Lp(a) levels.

Women's Health Initiative- Estrogen/Progesterone Therapy

The Women's Health Initiative (WHI) examined the effect of hormone replacement therapy in women with and without an intact uterus. The WHI included a randomized primary-prevention trial of conjugated equine estrogens (CEE) (0.625 mg per day) plus continuous medroxyprogesterone acetate (MPA) (2.5 mg per day) or placebo in 16,608 postmenopausal women with an intact uterus who were 50 to 79 years of age at base line (388). As expected, hormone therapy lowered LDL cholesterol levels by 12.7% and increased HDL cholesterol levels by 7.3% and triglycerides by 6.9%. Despite these changes, after a mean follow-up of 5.2 years (planned duration, 8.5 years), the data and safety monitoring board recommended terminating the trial because the overall risks exceeded the benefits. Combined hormone therapy was associated with a hazard ratio for nonfatal myocardial infarction or death due to CHD of 1.24 in the hormone treated group. Similar to the HERS trial an increased risk of cardiovascular events was greatest in the first year of hormone therapy (HR 1.81).

Women's Health Initiative- Estrogen Alone Therapy

In women without a uterus, the WHI carried out a randomized, double-blind, placebo-controlled trial of 0.625mg per day of conjugated equine estrogen (CEE) or placebo in 10,739 postmenopausal women, aged 50-79 years of age (389). As expected, the CEE group demonstrated a significant decrease in LDL cholesterol compared to placebo group (−13.7% vs –1.0%, P<.001) and a much larger increase in HDL cholesterol (15.1% vs 1.1%, P<.001). Additionally, large increases in triglyceride levels were observed in the CEE group (25.0% vs 3.0%, P<.001). After an average follow-up of 6.8 years, the estimated hazard ratio for nonfatal myocardial infarction or CHD death in the CEE vs placebo was 0.91 (0.75-1.12). However, the incidence of stroke was increased by 39% in the CEE group (P=.007).

These two initial reports of the results of the WHI coupled with the HERS trial indicated that hormone replacement therapy was not effective in reducing atherosclerotic cardiovascular disease events in a broad spectrum of postmenopausal women.

Women's Health Initiative- Extension

In 2013 a report was published that extended the follow-up of both the estrogen alone and the combined estrogen/progesterone protocols of the WHI to 13 years (390). It should be noted that after the intervention phase ended only a very small percentage of subjects continued hormonal therapy (<4%). During the cumulative 13-year follow-up, the hazard ratios for nonfatal myocardial infarction or coronary death were 1.09 for CEE plus MPA and 0.94 for CEE alone compared with the placebo groups (both NS). During the 13-year follow-up the hazard ratios for stroke were higher in the hormone therapy groups compared with the placebo groups (HR, 1.16 for CEE plus MPA; HR, 1.15 for CEE alone). Although with cessation of hormonal therapy the risk of atherosclerotic cardiovascular disease appeared to diminish, due to the open label nature of this analysis these data are difficult to interpret. Notably, there was no evidence for a "legacy effect" of cardiovascular benefit or harm after discontinuing hormone therapy. Thus, even with longer follow-up hormonal therapy did not demonstrate a reduction in atherosclerotic cardiovascular disease.

The Subject Age or Time Since Menopause Hypothesis

The WHI results, coupled with those of the HERS trial, have been translated into a recommendation that hormone replacement therapy not be used for cardiovascular disease prevention, that it not be started unless needed for postmenopausal symptom relief, and that it be terminated as soon as possible after obtaining symptom relief. This official interpretation is not accepted, however, by some gynecologists and lipidologists because studies have suggested a more nuanced approach (391). For example, further analysis of the WHI results have suggested that age and/or time from menopause influences the effect of hormonal therapy on atherosclerotic cardiovascular disease events (390). In individuals 50-59 years of age who started hormone treatment with estrogen alone, there was a 40% reduction in coronary heart disease that was borderline statistically significant (p=0.08). In older individuals treated with estrogen alone there was no reduction or even a slight increase in coronary heart disease. In the 50-59 years of age group on estrogen alone, there was a 45% reduction in myocardial infarctions whereas in the 70-79 years of age group, there was a 24% increase in events. In the estrogen-progestin trial the age effect was not observed (Table 18).

Table 18. Effect of Age of Starting Hormone Therapy on Coronary Events in Women's Health Initiative

Endpoint and Age at Study Entry	Estrogen-Progestin	Estrogen Alone
Coronary Heart Disease	Relative Risk	Relative Risk
50-59yrs	1.34	0.60
60-69yrs	1.01	0.95
70-79yrs	1.31	1.09
Myocardial Infarction		
50-59yrs	1.32	0.55
60-69yrs	1.05	0.95
70-79yrs	1.46	1.24
Coronary Revascularization		
50-59yrs	1.03	0.56
60-69yrs	0.85	1.13

70-79yrs	1.08	1.07

A separate, somewhat different age-subgroup analyses from the WHI showed an increase in both coronary heart disease and stroke only in women who started HRT after age 70, while in those age 60-70, there was an increase in stroke but no change in coronary heart disease (392). In further contrast, in those who started hormone therapy before 60 there was no change in stroke, a trend towards decreased coronary heart disease in the CEE study, a trend towards improved global health index in the CEE study, and a statistically significant decrease in total mortality in both studies combined. In fact, there was a trend towards less harm and/or greater benefit in all major endpoints with decreasing age at treatment onset (392).

The age effect is further supported by a meta-analysis of 23 trials with 39,049 women, which showed that hormone therapy significantly reduced CHD events in younger women (OR 0.68 [confidence interval (C I), 0.48 to 0.96]), but not in older women (OR 1.03 [CI, 0.91 to 1.16]) (393). Additionally, a more recent randomized trial in 1006 healthy women aged 45-58 who were recently postmenopausal demonstrated that hormonal therapy decreased an end point of death, myocardial infarction, or heart failure by 39% and myocardial infarction by 55% (394). The more clearly positive results may have been due to inclusion of younger women who were closer to the menopause (average 50 years of age and 0.7 years postmenopausal) than in the WHI study. Taken together, these results suggest that younger women who have recently undergone menopause may have either a decrease or no change in atherosclerotic cardiovascular disease when on hormonal therapy. In contrast, hormonal therapy in older women who have been postmenopausal for many years appears to increase the risk of atherosclerotic cardiovascular disease.

A possible explanation for the effect of age and/or time since menopause on the response to hormonal therapy could be the extent of underlying vascular disease (395). Younger women are more likely to have “healthy” vessels and in these circumstances hormonal therapy is beneficial. In contrast, in older women who may already have underlying atherosclerosis, treatment with hormonal therapy is not beneficial but rather may be harmful. Further support for this hypothesis is provided by subgroup analyses in the WHI showing that women without risk factors for atherosclerosis appear to benefit from hormone therapy (396,397). For example, in women with LDL cholesterol levels less than 130mg/dl or without the metabolic syndrome, hormone therapy is beneficial. However, in women with LDL cholesterol levels greater than 130mg/dl or with the metabolic syndrome, hormone therapy increases the risk of coronary heart disease (Table 19).

Table 19. Effect of Baseline Risk Factors on Coronary Heart Disease Risk

	Odds Ratio for Hormone Therapy Effect	P, interaction
LDL cholesterol (mg/dl)		
<130	0.66	0.03
>130	1.46	
LDL/HDL ratio		
<2.5	0.60	0.002
>2.5	1.73	

Metabolic Syndrome		
No	0.97	0.03
Yes	2.26	

Apart from these considerations of age at treatment onset, there appears to be a strong temporal pattern of risk for cardiovascular disease relative to the time course of hormone therapy. In both the HERS and WHI studies an increase in cardiovascular events occurred during the first year of hormone therapy followed by a decrease with continued treatment (398). Interestingly, a similar temporal pattern was seen in the observational Nurses Health Study (399). One can speculate that the increase in coagulation factors induced by hormone therapy might account for this early increase in cardiovascular events. In a separate but related point, observational studies have shown worse outcomes for women who have stopped hormone therapy vs. those who have continued hormone therapy (379). There has never been a randomized trial of hormone therapy discontinuation vs. continuation of hormone therapy so in patients doing well on hormone therapy it is unclear whether stopping therapy will markedly affect the risk of cardiovascular disease.

EFFECT OF HORMONE THERAPY ON ATHEROSCLEROSIS

Given the absence of definitive results in the clinical outcome studies, further insights may be gained by examining studies of anatomical atherosclerotic changes. Several studies have explored the effect of hormonal therapy on the progression of atherosclerosis measured by quantitative coronary angiography, carotid intima-media thickness (CIMT), or coronary calcium scores (CAC). In patients with pre-existing coronary artery disease, hormone replacement therapy did not affect the progression of coronary atherosclerosis or CIMT (400-403). Another study of healthy menopausal women aged 42 to 58 years between 6 and 36 months from last menses without prior CVD events who had a CAC score less than 50 Agatston units reported that CIMT and CAC changes were not significantly different in the hormonal or placebo groups (404). In contrast, in one study of women without pre-existing atherosclerotic disease, hormone replacement therapy slowed the rate of progression of CIMT (405). These observations support the clinical outcome studies that have shown that women with pre-existing atherosclerotic cardiovascular disease do not benefit from hormone therapy. In contrast, in women without pre-existing atherosclerotic cardiovascular disease, hormone therapy may be beneficial or neutral depending upon the particular study.

In the WHI estrogen alone trial, coronary artery calcium scores were measured in women between 50-59 years of age at study entry (404). The mean coronary-artery calcium score after trial completion was lower in women receiving estrogen therapy (83.1A) than in women receiving placebo (123.1A) ($P = 0.02$). This indicates that calcified-plaque burden in the coronary arteries was lower in younger women assigned to estrogen also supporting the hypothesis that estrogen therapy reduces the progression of atherosclerosis in women who are recently menopausal and do not have pre-existing atherosclerosis.

Hodis and colleagues randomly assigned 643 healthy postmenopausal women who were stratified according to time since menopause (<6 years [early postmenopause] or ≥10 years [late postmenopause]) to receive either oral 17β-estradiol plus progesterone for 10 days of each 30-day cycle or placebo (406). In support of the WHI results, in women who were less

than 6 years past menopause, the mean CIMT increased by 0.0078 mm per year in the placebo group versus 0.0044 mm per year in the estradiol group (P=0.008) while in women who were 10 or more years past menopause the rate of CIMT progression in the placebo and estradiol groups were similar. Coronary-artery calcium, total stenosis, and plaque did not differ significantly between the placebo group and either early or late postmenopausal group on hormonal therapy. Nevertheless, these observations suggest a difference in response to hormonal replacement therapy depending on duration of time since menopause.

In summary, in older women or women with pre-existing atherosclerosis, the data demonstrates that hormone therapy is not beneficial and is likely harmful. In younger women or women without pre-existing atherosclerosis studies suggest that hormone therapy is either modestly beneficial or neutral.

ORAL CONTRACEPTIVES

A Cochrane review has recently addressed the effect of oral contraceptives on atherosclerotic cardiovascular disease (407). They reported that oral contraceptive use did not increase the risk of myocardial infarction or ischemic stroke compared with non-users. The risks did not vary according to the generation of progestogen or according to progestogen type. However, the risk of myocardial infarction or ischemic stroke appeared to increase with higher doses of estrogen. The risk of myocardial infarction or ischemic stroke was only increased in women using oral contraceptives containing ≥ 50 µg of estrogen. In another meta-analysis of progesterone only contraceptives there did not appear to be an increase in the risk of myocardial infarctions (408). Additionally, another recent meta-analysis reported an increase in ischemic strokes but no increase in myocardial infarctions with oral contraceptive use (409). It should be noted that earlier meta-analyses have reported an increased risk of myocardial infarctions and ischemic strokes, which may be related to differences in the composition of the products and doses being used in the past in oral contraceptives (410,411). Thus, oral contraceptives with higher doses of estrogen likely increase cardiovascular disease risk.

POLYCYSTIC OVARY SYNDROME (PCOS)

A recent meta-analysis of five case-control studies and five cohort studies involving a total of 104,392 subjects found that PCOS was associated with a significant increased risk of cardiovascular disease (OR = 1.30) (412). Another smaller meta-analysis reported a 2-fold risk of arterial disease for patients with PCOS compared to women without PCOS (413). In contrast, in a study of cardiovascular events in 309 women with PCOS vs. 343 women without PCOS followed for a mean duration of 23.7 years an increase in cardiovascular disease was not observed (414). Of note the population of patients with PCOS in this study did not have diabetes or dyslipidemia and their BMI was only slightly greater than the controls (29.4 kg/m2 vs 28.3 kg/m2). In a recent review it was noted that an increased prevalence of cardiovascular disease in women with PCOS has not been conclusively demonstrated (415). It has been proposed that the increased risk of cardiovascular disease in women with PCOS is mainly observed in women who are obese and/or have diabetes (416). A meta-analysis of studies comparing carotid intima-media thickness (CIMT) in individuals with PCOS vs. controls reported that women with PCOS have a higher mean CIMT compared with non-PCOS controls (417). Most but not all studies have shown that women with PCOS have higher coronary calcium scores than controls (418-422). In PCOS it is likely that many factors, such as decreased estrogen levels, increased testosterone levels, insulin resistance, hypertension, obesity, alterations in glucose homeostasis, etc., could

contribute to the increased cardiovascular risk in addition to a pro-atherogenic lipid profile and differences in the prevalence of various cardiovascular risk factors in patients with PCOS could account for the variable risk of cardiovascular events.

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