Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-026-02862-y

CONSENSUS STATEMENT

Dyslipidemias associated with endocrine disorders: a position statement of the working group of the nutrition hormones and metabolism club of the italian society of endocrinology (SIE)

Giovanna Muscogiuri[1,2,3] · Manuela Albertelli[4,5] · Giorgio Arnaldi[6] · Luigi Barrea[10] · Giuseppe Bellastella[7] · Marco Bonomi[8,9] · Marina Caputo[11] · Massimiliano Caprio[12,13] · Angelo Cignarelli[14] · Ludovico Di Gioia[15,16] · Francesco Frasca[18] · Davide Ferrari[17] · Alessandra Gambineri[19,20] · Valentina Gasco[21] · Federico Gatto[22,23] · Annalisa Giandalia[24] · Roberta Giordano[25,26] · Marco Infante[27] · Andrea Isidori[17] · Pasqualino Malandrino[28] · Gianluca Occhi[29] · Rosario Pivonello[30,31] · Nunzia Prencipe[21] · Flavia Prodam[32] · Chiara Simeoli[33] · Ludovica Verde[3,34] · Linda Vignozzi[35,36] · Salvatore Cannavò[24,37] · Francesco Giorgino[14] · Annamaria Colao[1,2] · Gianluca Aimaretti[38] · Diego Ferone[4,5] · Sebastio Perrini[15,16]

Received: 13 January 2026 / Accepted: 12 March 2026

Abstract

Purpose Dyslipidemias are highly prevalent metabolic disturbances and represent a major driver of atherosclerotic cardiovascular disease. Beyond primary forms, numerous endocrine diseases induce secondary dyslipidemias that substantially modify lipid metabolism and contribute to cardiometabolic risk. This Position Statement of the Nutrition Hormones and Metabolism Club of the Italian Society of Endocrinology (SIE) aims to provide an updated, evidence-based synthesis of the pathophysiology, biochemical profile, and clinical impact of dyslipidemias associated with endocrine disorders.

Methods A comprehensive review of current literature was performed, integrating epidemiological, mechanistic, and clinical data on lipid alterations across major endocrine diseases. Expert consensus was used to interpret evidence and formulate recommendations for clinical practice.

Results Distinct and disease-specific dyslipidemic patterns were identified across conditions involving the hypothalamic–pituitary, thyroid, adrenal, gonadal, and GH/IGF-1 axes. Disorders such as acromegaly, growth hormone deficiency, hypothyroidism, hyperthyroidism, Cushing's syndrome, male and female hypogonadism, congenital adrenal hyperplasia, and polycystic ovary syndrome exhibit characteristic lipid abnormalities driven by hormonal dysregulation. These alterations contribute to increased cardiometabolic risk yet are frequently underrecognized and suboptimally managed. Early identification and tailored intervention may significantly improve outcomes.

Conclusion Endocrine-related dyslipidemias represent a clinically relevant but often overlooked contributor to cardiovascular risk. By summarizing current evidence and expert perspectives, this Position Statement aims to support clinicians in improving diagnosis, risk stratification, and management of lipid disorders associated with endocrine diseases, fostering a multidisciplinary approach to cardiometabolic prevention.

Keywords Endocrine disorders · Dyslipidemia · Cardiometabolic risk · Hormonal regulation · Lipid metabolism · Secondary dyslipidemias

Extended author information available on the last page of the article

Published online: 22 May 2026

Introduction

Dyslipidemias are among the most common metabolic abnormalities encountered in clinical practice and represent a major risk factor for atherosclerotic cardiovascular disease (ASCVD). In addition to primary, genetic, or multifactorial forms, a broad spectrum of secondary dyslipidemias may arise from endocrine disorders that directly or indirectly affect lipid metabolism.

Endocrinopathies profoundly influence body composition, energy balance, and the regulation of lipoprotein synthesis, catabolism, and clearance. Alterations in the hypothalamic–pituitary, thyroid, adrenal, gonadal, and growth hormone/ insulin-like growth factor 1 (GH/IGF-1) axes can each lead to distinctive lipid abnormalities, often differing from those observed in primary dyslipidemias. These alterations may represent early biochemical indicators of unrecognized endocrine disease or contribute substantially to the increased cardiovascular (CV) risk associated with endocrine dysfunction.

Accurate identification of dyslipidemias secondary to endocrine disorders is therefore essential to guide differential diagnosis and inform targeted therapeutic strategies. Treating the underlying endocrinopathy frequently results in significant improvement or normalization of the lipid profile, potentially reducing or optimizing the need for lipid-lowering medications.

This Position Statement from the Metabolism Club of the Italian Society of Endocrinology (SIE) provides an evidence-based overview of the pathophysiological mechanisms, biochemical characteristics, and management strategies of the main secondary dyslipidemias associated with endocrine disorders. Specifically, it addresses dyslipidemia in acromegaly, growth hormone deficiency, hypothyroidism, hyperthyroidism, Cushing's syndrome, male and female hypogonadism, congenital adrenal hyperplasia (CAH), and polycystic ovary syndrome (PCOS).

Acromegaly

Pathophysiological mechanisms

Acromegaly is a chronic endocrine disorder characterized by persistent GH hypersecretion, most commonly due to a GH-secreting pituitary adenoma, leading to elevated circulating levels of IGF-1 [1, 2]. The chronic exposure to GH and IGF-1 excess exerts profound effects on carbohydrate and lipid metabolism, primarily through actions on skeletal muscle, liver, and adipose tissue [1, 3]. Physiologically, GH acts as a counter-regulatory hormone to insulin, promoting anabolic processes during fasting by favoring lipid oxidation and inhibiting glucose uptake, while insulin predominates in the postprandial state [4]. In contrast, IGF-1 exerts insulin-like metabolic effects, enhancing glucose uptake and lipid synthesis [5]. The interplay and imbalance of these two hormones underpin the metabolic disturbances observed in acromegaly.

GH binding to its receptor (GH-R) triggers receptor dimerization and activation of the Janus kinase 2 (JAK2), initiating several intracellular signaling cascades, including signal transducer and activator of transcription (STAT), phosphatidylinositol 3-kinase (PI3-K), and mitogen-activated protein kinase (MAPK) pathways [6]. These pathways mediate GH's pleiotropic effects on growth and metabolism. The lipolytic action of GH was first described in the 1940s, when an inverse correlation between GH levels and adiposity was observed [7]. Under physiological fasting conditions, GH promotes lipolysis and lipid oxidation, shifting energy substrate utilization toward lipids, as evidenced by increased circulating free fatty acids (FFAs), 3-hydroxybutyrate, and glycerol [4, 8]. GH inhibits lipoprotein lipase (LPL), the enzyme responsible for hydrolyzing triglycerides (TG) in chylomicrons and very low-density lipoproteins (VLDLs), thereby limiting fatty acid storage in adipose tissue and contributing to elevated circulating lipid levels [9]. Conversely, IGF-1 facilitates FFA uptake into hepatocytes and adipocytes and stimulates lipogenesis, although its lipogenic effects are less pronounced [10, 11].

In acromegaly, sustained GH excess results in continuous lipolysis, increased plasma FFAs, and enhanced hepatic gluconeogenesis. The elevated FFAs interfere with insulin-mediated glucose uptake in peripheral tissues, promoting insulin resistance—the metabolic hallmark of active acromegaly [3, 12, 13]. The abundance of FFAs also provides substrates for hepatic TG synthesis and VLDL overproduction [6, 14]. In parallel, IGF-1 may reduce high density lipoprotein cholesterol (HDL-C) esterification by downregulating lecithin-cholesterol acyltransferase (LCAT) activity, as suggested by the inverse correlation between IGF-1 and LCAT levels [15]. These processes collectively contribute to the pro-atherogenic metabolic profile observed in acromegaly.

GH excess also promotes a pro-inflammatory state within adipose tissue. Overexpression of inflammatory adipokines, including visfatin and interleukin-6 (IL-6), induces local macrophage infiltration and systemic inflammation, further aggravating insulin resistance [16]. Although patients with active acromegaly often exhibit increased lean body mass and reduced overall adiposity, their adipose tissue displays an "inflammatory" molecular phenotype [1, 17].This paradox highlights that metabolic dysfunction in acromegaly is not driven by fat quantity but rather by its altered endocrine function. Chronic inflammation, oxidative stress, and lipid

derangements are thought to underlie the elevated CV morbidity and mortality associated with this condition [15, 18].

Beyond adipose tissue, GH and IGF-1 dysregulation also affect hepatic lipid metabolism. GH promotes TG synthesis and secretion, while IGF-1 modulates lipoprotein remodeling. Elevated levels of atherogenic lipoprotein(a) [Lp(a)] and small dense low density lipoprotein (LDL) particles have been associated with GH excess, correlating directly with disease activity [19, 20]. Additionally, increased apolipoprotein A-I (ApoA-I) and apolipoprotein E (ApoE) levels have been observed, suggesting compensatory alterations in lipoprotein transport and reverse cholesterol flux [19, 20]. Together, these molecular and metabolic changes delineate a distinctive pathophysiological framework where chronic GH and IGF-1 excess drive lipolysis, hepatic lipid turnover, insulin resistance, and low-grade inflammation—establishing the metabolic signature of acromegaly.

Laboratory abnormalities

Acromegaly is associated with a distinctive pattern of dyslipidemia and metabolic abnormalities that differ substantially from those seen in other endocrine disorders. Dyslipidemia is highly prevalent, affecting about 60% of patients regardless of GH and IGF-1 concentrations [21]. The most frequent alterations include mild-to-moderate hypertriglyceridemia and reduced HDL-C, while total cholesterol (TC) and LDL cholesterol (LDL-C) levels are typically normal or only slightly elevated. These findings reflect the complex metabolic effects of chronic GH excess and contribute to the increased CV risk observed in this population [22].

Hypertriglyceridemia is reported in approximately 30–40% of patients, with a threefold higher prevalence than in the general population and no significant sex-related differences [3, 23]. HDL-C concentrations are frequently reduced, particularly in those with active disease, and this decline tends to be more pronounced in postmenopausal women [3, 23] In contrast, LDL-C values are often normal or even reduced in untreated acromegaly, a finding attributed to the GH-induced upregulation of hepatic LDL receptor (LDL-R) activity, which enhances LDL clearance [24]. Studies on apolipoprotein profiles have yielded conflicting results—some report increased ApoE and ApoA-I [20], whereas others show no differences in ApoA-I or apolipoprotein B (ApoB) levels [25].

Qualitative alterations in lipoprotein subclasses are also characteristic of acromegaly. Patients often exhibit an increased proportion of small, dense LDL particles, which are more susceptible to oxidation and strongly associated with atherogenesis [26, 27]. Elevated Lp(a) concentrations are found in a significant subset of patients, with untreated acromegaly showing approximately threefold higher levels than healthy controls [20, 28]. Importantly, these abnormalities may persist even when standard lipid values appear normal, emphasizing the importance of advanced lipid profiling for accurate CV risk assessment.

The severity of lipid alterations closely correlates with disease activity. Patients with active acromegaly display more pronounced dyslipidemia [20, 29], while biochemical remission—achieved through surgery or pharmacological therapy—typically leads to reductions in TG and Lp(a) and increases in HDL-C [26, 29–31]. Nonetheless, certain qualitative alterations, such as the predominance of small dense LDL (sd-LDL) particles, may persist despite biochemical control [26, 27].

The underlying mechanisms are multifactorial. GH excess inhibits LPL and hepatic TG lipase, impairing TG -rich lipoprotein clearance and HDL formation [20, 27]. Increased hepatic LDL-R expression explains the often-normal LDL-C levels [24]. Moreover, altered adipokine secretion—including reduced chemerin and dysregulated leptin—along with elevated inflammatory markers such as interleukin-6 and C-reactive protein, contributes to a pro-inflammatory, pro-atherogenic milieu [24].

Standard lipid testing may underestimate CV risk, as it fails to capture these persistent qualitative lipid abnormalities [29, 32]. Advanced lipidomic analyses have revealed that active acromegaly paradoxically presents with reduced intrahepatic lipid (IHL) content despite insulin resistance, whereas biochemical control increases IHL alongside improved insulin sensitivity, suggesting dynamic GH-dependent modulation of hepatic lipid metabolism [33, 34]. Additionally, alterations in hepatic mitochondrial function and lipid saturation—specifically increased ATP synthesis and decreased unsaturated-to-saturated fatty acid ratios—indicate complex metabolic remodeling beyond conventional lipid markers [33, 34].

Altogether, the biochemical phenotype of acromegaly reflects both quantitative and qualitative dyslipidemia, inflammatory activation, and altered energy metabolism. Evidence from cross-sectional, interventional, and case–control studies across diverse populations supports this distinctive pattern [29, 35, 36]. Variability in LDL-C responses and lipid subfraction distribution, influenced by genetic background, disease duration, and comorbidities [33, 37, 38], underscores the limitations of standard lipid panels. A personalized laboratory assessment—integrating traditional lipid measurements, advanced lipoprotein characterization, and metabolic biomarkers—represents a more accurate approach to risk stratification in acromegalic patients Table 1.

Table 1 Typical lipid panel in acromegaly

Parameter	Change	Mechanism
TC	↔ or slightly ↓	Upregulation of hepatic LDL-R enhances LDL clearance despite increased lipid flux
LDL-C	↔ or slightly ↓	Increased LDL-R expression accelerates ApoB-containing lipoprotein catabolism
HDL-C	↓	Reduced LPL and altered hepatic lipase impair HDL maturation ($HDL_2 \rightarrow HDL_3$ shift)
TG	Mild–moderate ↑	Reduced LPL activity and increased VLDL secretion due to GH excess
LDL particle quality	↑ sd-LDL	TG enrichment and lipoprotein remodeling generate smaller, denser particles
ApoB	↔ or slightly ↓	Enhanced LDL clearance may offset increased production
ApoA-I	↔ or ↓	Impaired HDL synthesis associated with GH excess and insulin resistance
Lp(a)	↑	GH-stimulated hepatic synthesis; may normalize after biochemical control

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; GH, growth hormone.

Medical treatment

Following the most recent Consensus on the diagnosis and treatment of acromegaly comorbidities, the management of dyslipidemia in patients with acromegaly should adhere to general population guidelines, with treatment goals adjusted for other metabolic comorbidities, such as diabetes mellitus and hypertension [35].

Accordingly, diet and appropriate lifestyle interventions remain a cornerstone in managing dyslipidemia in these patients [39]. In this regard, it should be noted that patients with acromegaly are often affected by arthropathy-related pain and joint dysfunction, resulting in significant limitations in mobility, daily functioning and decreased exercise capacity [35]. In addition, diabetes mellitus, present in approximately 30% of the acromegaly population [1], increases CV risk (moderate, high or very high, depending on the presence of disease-related complications) with an LDL target of < 55–70 mg/dL, often requiring pharmacological treatment [40]. Furthermore, the presence of established CV diseases (particularly coronary artery disease and stroke, present in 9.8% and 4.3% of population at acromegaly diagnosis) places these individuals in a very high CV risk category, requiring a more stringent LDL-C target (< 55 mg/dL) [40]. For patients with acromegaly who have not experienced CV events and do not have diabetes (thus considered apparently healthy from a dyslipidemic standpoint) the use of the use of SCORE2 or SCORE2-OP risk charts, according to age, may be helpful [40]. However, even in this contest, the presence of arterial hypertension (found in 30–60% of patients with acromegaly) contributes to increased CV risk [35].

In this population, normalization of GH/IGF-1 levels is frequently associated with improvements in lipid profiles, particularly reductions in TG and increases in HDL-C, as demonstrated by both retrospective and prospective studies involving patients treated surgically or with medical therapies [31, 41]. The agents currently used to treat acromegaly differ in their effects on lipid metabolism. First-generation somatostatin receptor ligands (fg-SRLs) appear to partially replicate the metabolic improvements seen after surgical remission, including reductions in TG and increases in HDL-C [31, 41]. Some data also suggest a lowering effect on ApoB levels. These effects appear more evident with long-acting octreotide compared to lanreotide [31]. However, such metabolic changes are likely secondary to disease control rather than direct pharmacological action [31].

Pasireotide, despite its well-recognized hyperglycemic effect, showed a dose-dependent reduction in TG in early studies involving healthy volunteers [12]. Nevertheless, real-world data in patients with acromegaly have not confirmed a clinically meaningful effect on lipid profiles, with only modest and transient changes observed, primarily in HDL-C increases [12].

Dopamine agonists, such as cabergoline, have been associated with favorable metabolic effects in patients with prolactinomas, including improvements in glucose and lipid metabolism, but specific data in the setting of acromegaly remain sparse and inconclusive [42].

The effects of pegvisomant on lipid metabolism are variable: some studies report increases in total and LDL-C alongside significant reductions in Lp(a), whereas others show no substantial change in lipid parameters[43]. This heterogeneity likely reflects individual differences in baseline metabolic status and other modifying factors [43].

Overall, improvements in lipid profiles among patients with acromegaly are closely tied to biochemical disease control, rather than direct drug effects. Therefore, no specific recommendations currently exist regarding the choice of therapy based on the presence or absence of dyslipidemia.

To date, data from only one clinical trial are available regarding the efficacy of lipid-lowering therapy in patients with acromegaly [44]. In a 3-month, double-blind, placebo-controlled, crossover trial in eleven patients, treatment with atorvastatin 10 mg daily significantly reduced total cholesterol, LDL-C, VLDL-C, ApoB, and the estimated 10-year risk of coronary heart disease, with no significant changes in HDL-C or TG [44].

No other studies have specifically assessed the efficacy and safety of other statins or novel lipid-lowering agents in the acromegaly population. However, some studies have shown that GH decreases circulating PCSK9 levels, increasing hepatic LDL-Rs [45]. This may help explain why GH-lowering therapies alone are often insufficient to improve LDL-C profiles in patients with acromegaly. It also suggests a potential role for PCSK9 inhibitors as add-on to acromegaly-treatment in managing dyslipidemia in this setting [45].

In summary, prospective and long-term studies are lacking to definitively establish whether acromegaly independently increases CV risk when matched for other risk factors. No specific recommendations exist regarding LDL-C targets or the use of lipid-lowering or GH-targeted therapies in this context. As such, the suggestions outlined in the 2020 Consensus remain applicable, recommending alignment with the lipid management guidelines developed for the general population-.

Nutritional intervention

As described above, mild to moderate hypertriglyceridemia and low HDL-C are the most frequent lipid alterations in patients with acromegaly. Total-C and LDL-C are frequently unchanged, although levels of sd-LDL-C and high Lp(a) have been reported [46]. No dedicated clinical trials on specific nutritional interventions have been conducted until now.

According to guidelines on acromegaly management, dyslipidemia, including through nutrition, should follow guidelines for the general population. The goals should take into account CV risk stratification, considering the presence of other comorbidities or risk factors, such as diabetes, hypertension, age, sex, family history, or smoking habits [35].

Few studies have investigated nutritional habits in acromegaly, reporting a higher intake of carbohydrates (mainly from ultra-processed food) and trans fats, and a lower intake of fresh fruits and vegetables than normal controls [47]. Whether these food choices are related to the primary disease should be investigated, but a correct food history to suggest a decreased intake of unhealthy food is the first step in the nutritional management of dyslipidemia. In particular, sugars, sugar-sweetened soft drinks, fruit juices, and trans fats should be avoided, and saturated fats should be less than 10% of the total daily caloric intake to improve the lipid profile. Foods rich in omega-3 fatty acids (fatty fish, avocado), viscous fiber (oats, legumes, citrus), and plant stanol and sterol intake (vegetable oils, nuts, seeds, whole grains, fruits, vegetables, and legumes) should be encouraged to decrease TG.

In general, patients with cardio-metabolic diseases should maintain their weight, or decrease it in the presence of overweight or obesity, and perform physical activity and structured exercise interventions, according to European Society of Cardiology (ESC), American Diabetes Association (ADA), and European Association for the Study of Diabetes (EASD) Guidelines [48–50]. A Mediterranean-style eating pattern improves lipids, and if it is rich in extra virgin olive oil or nuts, as in the Prevención con Dieta Mediterránea (PREDIMED) study, it reduces the ASCVD risk more than a low-fat diet, as demonstrated in the CORDIOPREV study [51, 52]. This is important since acromegalic patients have a high risk of ASCVD [46]. The planetary health diet, introduced by the EAT-Lancet Commission, seems to be associated with favorable lipid profiles [53]. The Dietary Approaches to Stop Hypertension (DASH) diet is a further option since it has been demonstrated to reduce TG levels and increase HDL-C compared to no intervention or usual care [54]. Generally, we could hypothesize that these results are reproducible also in patients with acromegaly, although likely with different ranges of risk reductions.

No evidence exists on fasting regimens. Short-term fasting did not result in an increase in FFAs in acromegalic patients [55], unlike long-term experiments [56]. Coopmans et al. investigated the role of an eucaloric ketogenic diet in a small group of 11 patients with active acromegaly [57]. Although diabetes improved, no findings on the effects on the lipid profile have been published, discouraging its use for this aim at this moment [57].

GH deficiency

Pathophysiological mechanisms

GH exerts wide-ranging effects on body composition, energy balance, and intermediary metabolism, acting as a key regulator of lipolysis, lipid oxidation, and overall nutrient partitioning [58, 59]. Consequently, GH deficiency (GHD) profoundly affects metabolic homeostasis, leading to increased visceral adiposity, unfavorable lipid profiles, and heightened CV risk. Patients with GHD typically present with elevatedTC, LDL-C, and ApoB concentrations, while changes in TG and HDL-C are generally modest. These atherogenic abnormalities arise from the absence of GH's direct regulatory effects on lipoprotein metabolism and its indirect modulation of adipose tissue function, hepatic lipid turnover, and insulin sensitivity [58, 59].

GH normally promotes lipolysis by activating hormone-sensitive lipase (HSL) in adipose tissue and by modulating the expression of Cell Death-Inducing DFF45-like Effector (CIDE) proteins, which regulate lipid droplet fusion

and lipid storage [60]. Lipolysis of TG stored in adipocytes increases circulating FFAs levels, providing energy substrates to peripheral tissues and enhancing hepatic availability of FFAs and glycerol for TG and ApoB-containing lipoprotein synthesis [60]. In the liver, GH stimulates VLDL production and secretion, while also upregulating the expression of LDL-Rs, promoting the clearance of LDL, intermediate-density lipoproteins (IDL), and VLDL remnants [61, 62]. Furthermore, GH inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of endogenous cholesterol synthesis, thereby reducing hepatic cholesterol production [61, 62]. GH also influences bile acid metabolism by inducing cholesterol-7α-hydroxylase (C7αOH), a key enzyme in bile acid synthesis and cholesterol excretion through the enterohepatic pathway [63].

In GHD, the absence of these coordinated actions results in reduced lipolysis, accumulation of visceral fat, and impaired lipid turnover [60]. The consequent increase in fat mass and decrease in lean body mass exacerbate insulin resistance, which further impairs lipoprotein metabolism [60]. Insulin resistance inhibits LPL activity, reducing the clearance of VLDL-ApoB and promoting its conversion into LDL particles. Simultaneously, the downregulation of hepatic LDL-Rs reduces LDL and VLDL removal, contributing to increased plasma levels of ApoB-containing lipoproteins and stimulating compensatory activation of HMG-CoA reductase. Together, these mechanisms lead to the characteristic dyslipidemic pattern of GHD: elevated total and LDL-C, with variable TG and HDL-C alterations.

Although the effects of GH on HDL metabolism remain incompletely understood, evidence suggests that GHD impairs reverse cholesterol transport and cholesterol esterification due to altered cholesteryl ester transfer protein (CETP) activity [64, 65]. Dysregulation of CETP limits the exchange of cholesteryl esters between HDL, VLDL, and LDL, thereby reducing hepatic cholesterol uptake and contributing to low HDL functionality. Moreover, adipose tissue dysfunction in GHD amplifies pro-atherogenic mechanisms through the dysregulated secretion of inflammatory cytokines and adipokines such as leptin, which influence insulin sensitivity and lipid storage [64, 65]. The interplay between GH and adipokine signaling represents a critical, yet incompletely elucidated, axis in the metabolic complications of GHD.

Genetic variability may further modulate the metabolic phenotype of GHD [66]. Specific single nucleotide polymorphisms (SNPs) in genes related to lipid metabolism—including CETP (rs708272, rs3764261, rs1800775), ApoE (rs7412), and ApoB (rs693)—have been associated with variations in total and LDL-C levels in adults with GHD [66]. Such findings underscore the importance of gene–hormone interactions in determining individual susceptibility to dyslipidemia.

Importantly, GH replacement therapy has been shown to ameliorate many of these metabolic alterations [67]. Numerous studies and meta-analyses, including a systematic review of 37 randomized, placebo-controlled trials, demonstrate that GH replacement reduces total and LDL-C levels, increases lean body mass, and decreases fat mass, with variable effects on HDL-C. These data confirm GH's crucial role in maintaining lipid homeostasis and body composition [67]. Collectively, the evidence supports the view that GHD induces a multifactorial atherogenic dyslipidemia, driven by reduced lipolysis, impaired hepatic lipid clearance, and systemic insulin resistance, thereby contributing to the increased CV morbidity and mortality observed in this condition.

Laboratory abnormalities

GHD is known to adversely affect lipid metabolism [46, 68–70]. However, literature data remain variable, as patients with GHD represent a heterogeneous group differing in age of onset, etiology, and the presence of additional pituitary hormone deficiencies—ranging from isolated GHD to panhypopituitarism. These factors may influence the degree and pattern of lipid profile derangement in GHD patients.

Furthermore, the impact of GHD on lipid profiles varies across life stages—childhood, transition, and adulthood—and should be interpreted in this context [46, 68–70].

In children with GHD, data on dyslipidemia are conflicting. Some studies report hypercholesterolemia [71–73], while others observe no significant lipid abnormalities [74–76]. Nonetheless, children with GHD frequently display an atherogenic lipid profile characterized by elevated TC, LDL-C, and TG, along with reduced HDL-C [77–80]. This pattern resembles the dyslipidemia of metabolic syndrome, often seen in GHD children with obesity, such as those with hypothalamic obesity following craniopharyngioma [79].

Studies investigating lipid changes during the transition phase have also yielded inconsistent results, partly due to variability in GH treatment washout duration. While some report no changes in lipid levels after therapy cessation [81], others have demonstrated increases in total cholesterol, LDL-C, and TG, along with decreases in HDL-C [74, 82–84]. Notably, longer therapy interruptions and more severe GHD are associated with more pronounced dyslipidemia during this period [85–87].

Lp(a) levels in adolescents with untreated GHD show conflicting results [88, 89], likely due to strong genetic determinants and small sample sizes, which limit interpretability [89].

In adults, GHD is commonly associated with dyslipidemia, typically presenting as elevated TC and LDL-C, with variable effects on TG and HDL-C [46, 68, 90–92]. Increased sd-LDL particles—considered more atherogenic—have been reported, along with elevated postprandial remnant lipoproteins, both of which improve with GH replacement therapy. However, levels of ApoB, ApoA-I, and Lp(a) are generally unaffected [46, 68, 90–92].

Some earlier studies suggested a correlation between GHD severity (based on GH stimulation tests) and lipid abnormalities [93], but these findings have not been consistently confirmed, particularly when BMI-adjusted diagnostic criteria are applied [58, 94–96]. Moreover, interpretation of lipid abnormalities in adult GHD is complicated by the frequent coexistence of other pituitary hormone deficiencies (thyroid, adrenal, gonadal) and their respective replacement therapies, which themselves influence lipid metabolism [58, 94–96].

The multinational KIMS database has provided valuable insights into demographic and clinical factors influencing lipid profiles in 2,589 adults with GHD [58]. Analyses revealed that females exhibited approximately 0.2 mmol/L higher total cholesterol, primarily due to higher HDL-C, with no significant differences between pre- and postmenopausal women. TC and LDL-C levels increased steadily with age, plateauing after 50 years, while HDL-C remained stable, and TG followed a similar trajectory to total cholesterol. Age at GHD onset, disease duration, severity, etiology, extent of hypopituitarism, BMI, waist-hip ratio, waist circumference, and prior radiotherapy did not significantly affect baseline cholesterol levels. Other factors, such as smoking and epilepsy, were associated with higher cholesterol, whereas diabetes mellitus correlated with lower cholesterol. LDL-C trends mirrored those of total cholesterol [58].

Table 2 Typical lipid in growth hormone deficiency

Parameter	Change	Mechanism
TC	↑	Reduced LDL-R expression and decreased cholesterol turnover
LDL-C	↑	Decreased receptor-mediated clearance and bile acid conversion
HDL-C	↔ or ↓	Altered hepatic lipase and CETP activity impair reverse transport
TG	↔ or ↑	Decreased LPL activity and fatty acid oxidation
LDL particle quality	↔ or ↑ sd-LDL	Shift toward smaller, denser particles linked to insulin resistance
ApoB	↔ or ↑	Reduced clearance prolongs plasma residence
ApoA-I	↔ or ↓	Decreased synthesis due to hormonal deficiency
Lp(a)	↔ or ↑	Strong genetic influence; variable response to GH replacement

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; CETP, cholesteryl ester transfer protein; GH, growth hormone.

Beyond quantitative lipid alterations, the quality of LDL particles plays a crucial role in CV risk [97, 98]. Smaller dense LDL particles are considered more atherogenic [97, 98]. Current evidence suggests that patients with GHD do not exhibit increased levels of sd-LDL, and that short-term GH replacement therapy does not significantly modify LDL subfraction distribution [99, 100] Table 2.

Medical treatment

Recent guidelines analyzed the effect of GH replacement therapy on lipid metabolism, but there are no clear indications regarding cholesterol lowering treatment in GHD patients affected by dyslipidemia [101].

Considering standard medical treatment, few studies analyzed the effect of statin in GHD patients [102]. A treatment with simvastatin ranging from 20 to 40 mg/day was able to improve lipid levels without the need to titrated more the dose in patients with GHD compared to controls [102].

No studies analyzed the effect of ezetimibe, bempedoic acid, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors or inclisiran in GHD patients.

On the contrary, the effect of GH replacement therapy on serum lipid levels has been investigated in numerous studies. GH exert beneficial effects on serum total and LDL-C by increasing numbers of LDL-Rs on hepatocytes both at protein and mRNA level, independently by IGF-1 release [103].

The meta-analysis by Maison et al. of 37 blinded, randomized placebo-controlled trials (up to 2003) and the subsequent meta-analysis by Newman et al. (2015) involving over 1000 subjects demonstrated the effect of GH treatment in reducing total and LDL-Clevels, without significant effect on HDL-C or TG levels [67, 104].

The effect of GH replacement therapy on lowering cholesterol levels was observed also in patients in statin treatment [105, 106].

In addition to the effect of GH on LDL-Rs on liver cells, GH decreases circulating PCSK9 levels, with increase of hepatic LDL-Rs [45]. Consequently, the clearance of LDL-C is enhanced by GH treatment, thus opening an interest point in GH untreated patients for PCSK9 inhibitors [107].

Nutritional intervention

Consistent evidences demonstrated that high intake of fruit, non-starchy vegetables, nuts, legumes, fish, vegetable oils, yoghurt, and wholegrains, along with a low consumption

of red and processed meats, refined carbohydrates, and salt, is associated with a lower incidence of CV events [108]. Thus, dietary patterns as DASH diet and the Mediterranean diet have been demonstrated to reduce CV risk [109]. In particular, the PREDIMED trial indicated that participants following a Mediterranean diet, supplemented with extra-virgin olive oil or nuts, had a significantly lower incidence of major CV events compared with a low-fat diet [110].

GH and IGF-1 secretion are potentiated by many nutrients [111]. Considering visceral adiposity and metabolic diseases characterizing GHD patients, a Mediterranean diet could be appropriate in this setting, as it has been demonstrated to be able to favor GH secretion [112]. In a high adherent Mediterranean diet, the intake of several nutrients should be encouraged, as proteins of vegetable origin or from dairy products, extravirgin olive oil, and seeds, rich in alfa-linoleic acid, because these nutrients are able to stimulate IGF-1 secretion. Sugars and fats consumption should be discouraged for the effect on serum lipid and to avoid a blunting of residual GH and IGF-1 secretion [112]. Foods rich in vitamin D and rich in Zn, iodine, Ca2+, and Mg should be encouraged to take advantage in GH and IGF-1 secretion [111].

Hypothyroidism

Pathophysiological mechanisms

Hypothyroidism represents one of the most prevalent causes of secondary dyslipidemia [113]. Thyroid hormones exert broad regulatory effects on lipid metabolism through their nuclear receptors, thyroid hormone receptor isoforms α and β (THRα, THRβ), which mediate tissue-specific actions. THRβ predominates in the liver, promoting fatty acid oxidation, while THRα is more expressed in the heart and bone, mediating lipogenic and metabolic effects [113]. The liver is also directly responsive to thyroid-stimulating hormone (TSH) through specific receptors, and elevated TSH levels may independently impair lipid metabolism and contribute to hepatic steatosis [114]. Moreover, the liver plays a central role in thyroid hormone homeostasis, being responsible for the peripheral conversion of thyroxine (T4) to the active triiodothyronine (T3) via deiodinases, and for the synthesis of thyroid hormone–binding proteins such as thyroxine-binding globulin, transthyretin, and albumin [115].

Thyroid hormones stimulate basal metabolic rate, protein synthesis, and both hepatic lipogenesis and lipolysis [114]. They regulate cholesterol synthesis, clearance, and turnover, in part by promoting bile acid formation and fecal cholesterol excretion [116]. These actions deplete hepatic cholesterol pools and upregulate cholesterol biosynthesis and receptor-mediated uptake from circulation, maintaining lipid balance [116]. In hypothyroidism, impairment of these mechanisms leads to decreased cholesterol clearance, resulting in hypercholesterolemia characterized by increased total and LDL-C levels, and frequently elevated TG [117]. Reduced LDL-R expression, diminished bile acid synthesis, and decreased fatty acid oxidation collectively promote atherogenesis [117].

Both overt and subclinical hypothyroidism significantly alter lipid metabolism and increase CV risk [114]. A central mechanism involves reduced T3-mediated activation of Sterol Regulatory Element-Binding Protein 2 (SREBP2), a transcription factor essential for LDL-R synthesis, leading to impaired LDL clearance and elevated circulating LDL-C [114]. Additionally, hypothyroidism enhances intestinal and hepatic cholesterol absorption via upregulation of Niemann–Pick C1-like 1 (NPC1L1) protein, decreases plasma CETP activity, and increases circulating ApoB lipoproteins [118, 119]. These alterations shift cholesterol from HDL toward LDL and VLDL fractions, suppress reverse cholesterol transport, and diminish bile acid–mediated cholesterol elimination. Decreased microRNA-181 expression further enhances sterol O-acyltransferase 2 (SOAT2) activity, leading to excess cholesterol ester formation within lipoproteins [118, 119].

Hypertriglyceridemia in hypothyroidism arises primarily from reduced LPL activity and impaired TG clearance, coupled with increased hepatic VLDL synthesis. These abnormalities stem from decreased autophagic degradation of lipid droplets (lipophagy) and reduced carnitine palmitoyltransferase-1a (CPT1a) expression, the rate-limiting enzyme of fatty acid β-oxidation [118, 119]. Consequently, hepatic lipid accumulation ensues, promoting insulin resistance, oxidative stress, and inflammation—key drivers of metabolic dysfunction–associated steatotic liver disease (MASLD) [116]. Thyroid hormones normally stimulate lipophagy, mitochondrial biogenesis, and β-oxidation via autophagy-related proteins and acyl-CoA dehydrogenases, thus reducing reactive oxygen species (ROS) generation. Impairment of these pathways in hypothyroidism results in hepatocellular lipid accumulation and oxidative injury [120].

With disease progression, excessive deposition of long-chain saturated fatty acids and their toxic metabolites induces hepatocellular lipotoxicity, inflammation, and fibrogenesis [121–123]. Activated hepatic stellate cells transform into fibroblasts, contributing to fibrosis and progression toward metabolic dysfunction-associated steatohepatitis (MASH) [121–123]. These mechanisms explain the therapeutic rationale for thyroid hormone analogs and thyromimetic agents in treating MASH [123, 124].

Beyond hepatic manifestations, hypothyroidism contributes to the broader cluster of metabolic abnormalities defining metabolic syndrome (MetS), characterized by visceral obesity, hypertriglyceridemia, low HDL-C, hypertension, and insulin resistance [125, 126]. Metabolic dysfunction-associated steatotic liver disease (MASLD), often considered the hepatic expression of MetS, is strongly associated with hypothyroidism and its metabolic sequelae [125, 126]. Thyroid dysfunction has been reported in up to 32% of individuals with MetS [127, 128], and patients with hypothyroidism show a higher prevalence of type 2 diabetes compared with euthyroid individuals [129, 130]. Notably, even thyroid hormone levels in the low-normal range have been linked to increased diabetes risk, independent of sex and thyroid autoimmunity [131]. Collectively, these data underscore the central role of thyroid hormones in integrating lipid metabolism, hepatic function, and systemic cardiometabolic health.

Laboratory abnormalities

Hypothyroidism, including both subclinical hypothyroidism and overt hypothyroidism, is frequently associated with alterations in serum lipid profiles, which contribute to increased CV risk and may exacerbate other metabolic derangements [132–134]. The severity of lipid abnormalities is generally proportional to the degree of thyroid-stimulating hormone elevation, with changes observable even when TSH is in the upper part of the reference range [133, 135]. In particular, elevated TC and LDL-C are the most consistently reported laboratory abnormalities in both subclinical and overt hypothyroidism, whereas TG and high-density lipoprotein cholesterol show more variable changes across studies [136, 137].

In subclinical hypothyroidism, total cholesterol and LDL-C are often increased, reflecting impaired LDL-Rmediated clearance and reduced hepatic cholesterol catabolism [133]. TG levels may be normal or modestly elevated, whereas HDL-C can be normal or slightly reduced, depending on study populations and comorbidities such as insulin resistance, obesity, or metabolic syndrome [136, 137]. Several meta-analyses confirm that LDL-C is the lipid parameter most affected by subclinical hypothyroidism, with higher elevations observed in subjects with TSH above 10 mIU/L [138]. Sd-LDL particles, which are highly atherogenic, may also be increased, although data remain limited [139]. ApoA-I, ApoB, and VLDL concentrations are generally not significantly altered in mild subclinical hypothyroidism [140].

Overt hypothyroidism is typically associated with more pronounced lipid alterations. TC, LDL-C, and TG are frequently elevated, and HDL-C is usually normal or reduced [133, 135, 141]. Cross-sectional studies have shown that 34–57% of patients with newly diagnosed overt hypothyroidism exhibit elevated TC or LDL-C, whereas 62–69% display low HDL-C or hypertriglyceridemia [142]. Post-thyroidectomy studies indicate that even short-term thyroid hormone deficiency can rapidly increase TC, LDL-C, TG, and the TC/HDL-C ratio [143, 144]. In overt hypothyroidism, LDL-C elevation often favors the formation of oxidized LDL, enhancing foam cell formation and atherogenesis [145, 146], Elevated Lp(a) levels have also been reported [147].

The pathophysiology underlying these laboratory findings involves multiple mechanisms. Reduced thyroid hormone action decreases LDL-R expression and impairs hepatic clearance of ApoB-containing lipoproteins, while diminished stimulation of lipoprotein lipase and impaired reverse cholesterol transport compromise TG metabolism and HDL functionality [143, 144]. Altered bile acid synthesis and excretion further reduce hepatic cholesterol catabolism, contributing to the accumulation of circulating TC and LDL-C [133]. Insulin resistance and MeTs components often coexist, exacerbating hypertriglyceridemia and promoting the formation of sd-LDL particles [132–134].

Hypothyroidism may also interact with other dyslipidemias, including familial disorders such as familial dysbetalipoproteinemia, which can present with markedly elevated TC and TG, xanthomas, and accelerated atherosclerosis [39, 148]. Therefore, comprehensive assessment of lipid abnormalities in hypothyroid patients is essential, particularly when severe or persistent derangements are observed despite normalization of thyroid-stimulating hormone with replacement therapy Table 3.

Medical treatment

Thyroid hormone replacement based on synthetic levothyroxine (LT4) monotherapy represents the standard of care for hypothyroidism [149, 150]. Patients with OH require treatment with doses of LT4 that are sufficient to normalize serum TSH levels, in order to abrogate or reduce the adverse health effects of thyroid hormone deficiency (including the detrimental cardiometabolic consequences) [150], while minimizing the risk of overtreatment [133]. LT4 monotherapy is effective in reversing or improving serum lipid abnormalities in both SCH and OH [150, 151]. In patients with hypothyroidism and dyslipidemia, mode of LT4 administration, LT4 dose adjustments and periodic serum TSH measurements should be in line with the international guidelines for the management of hypothyroidism [152].

Adults with hypothyroidism and markedly elevated serum TSH levels usually require 1.6 µg/kg of actual body weight as the starting daily LT4 dose to achieve the appropriate

Table 3 Typical lipid panel in hypothyroidism

Parameter	Subclinical Hypothyroidism	Overt Hypothyroidism	Main Mechanism
TC	↑	↑	Reduced hepatic LDL-R expression and impaired cholesterol clearance
LDL-C	↑	↑	Decreased LDL-R-mediated catabolism leading to accumulation of ApoB-containing lipoproteins
HDL-C	↔ or ↓	↔ or ↓	Altered lipoprotein metabolism; variable impact on reverse cholesterol transport
TG	↔ or slightly ↑	↑	Reduced LPL activity and impaired clearance of TG-rich lipoproteins
LDL particle quality	↔ or ↑ sd-LDL	↑ sd-LDL	Shift toward a more atherogenic profile
ApoB	↔	↔ or slightly ↑	Accumulation of ApoB-containing lipoproteins secondary to reduced clearance
ApoA-I	↔	↔	No consistent changes reported
Lp(a)	↔	↑	Impaired clearance of ApoB-containing lipoproteins; effect more evident in overt disease

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase.

serum TSH goal [150]. Nonetheless, the daily LT4 dose should be individualized based on factors other than actual or ideal body weight, such as age, lean body mass, etiology of hypothyroidism, pregnancy status, degree of TSH elevation, underlying comorbidities, and overall clinical context. The initial daily LT4 dose requirements are generally lower (e.g., 25–50 µg/day) in the presence of milder degrees of hypothyroidism (e.g., SCH or serum TSH ≤ 10 mIU/L), in older patients (such as those over 65 years), and/or in the presence of coexisting comorbidities (such as ASCVD). In patients with ASCVD and in the elderly, LT4 treatment of hypothyroidism should be started at low doses, with doses being titrated slowly based on serum TSH measurements [150].

In patients with primary hypothyroidism, serum TSH is the parameter used to adjust the LT4 dose, with target serum TSH levels typically ranging from 0.5 to 4 mIU/L [150]. Yet, target serum TSH levels can vary based on different factors, such as age, pregnancy and underlying comorbidities. In patients with hypothyroidism who are affected by dyslipidemia, it is not recommended to adjust LT4 doses to attain low-normal TSH values or high-normal triiodothyronine (T3) values. In general, LT4 therapy for the treatment of hypothyroidism-related dyslipidemia should aim to achieve serum TSH levels within the normal range [150]. Intervention studies found that achievement of serum TSH levels between 1.5 and 3.1 mIU/L after the initiation of LT4 therapy was associated with improvement of serum lipid profile in patients with hypothyroidism-related dyslipidemia [153, 154]. However, a systematic review and meta-analysis of 99 studies conducted on patients with overt primary hypothyroidism found that LT4-treated subjects with normal serum TSH levels, as compared to healthy controls, exhibited significantly higher serum LDL-C and TC levels [155]. In studies that had not assessed healthy controls, serum total cholesterol levels were 209.6 ± 3.4 mg/dL, while serum LDL-C levels were 138.2 ± 4.6 mg/dL. These findings suggest that LT4 monotherapy at doses that normalize serum TSH values may not always reverse hypothyroidism-related dyslipidemia [155].

In a systematic review and meta-analysis including 166 studies (n = 12,855 patients) and investigating the impact of treatment for hypothyroidism on serum lipids, L4 therapy in patients with OH was associated with a statistically significant reduction in total cholesterol (by -58.4 mg/dL), LDL-C (by -41.11 mg/dL), HDL-C (by -4.14 mg/dL), TG (by -27.25 mg/dL), ApoA (by -12.59 mg/dL), ApoB (by -33.96 mg/dL), and Lp(a) (by -5.6 mg/dL) [151]. The magnitude of change in serum lipids was similar for studies with more than 6 months of follow-up and for those with less than 3 months of follow-up. L4 therapy in patients with SCH was associated with similar changes, although with a smaller magnitude [significant reductions in TC (by -12.04 mg/dL), LDL-C (by -11.06 mg/dL), TG (by -4.52 mg/dL), ApoB (by -6.6 mg/dL), and Lp(a) (by -1.99 mg/dL)] [151].

Even though short-term data suggest that a preprandial thrice-daily regimen of synthetic liothyronine (LT3)-only therapy is superior to LT4 monotherapy in reducing TC, LDL-C, non-HDL-C and ApoB levels in adults with primary hypothyroidism [156], large-scale, long-term studies

are needed to establish the safety and efficacy profile of this treatment modality as compared to the standard LT4 monotherapy, particularly with respect to the risk of overdosing or underdosing, skeletal and cardiac toxicity, the need for strict compliance to the therapeutic regimen and the inconvenience of multiple daily dosing of LT3 (as compared to the single daily dosing of LT4) [150].Therefore, the use of LT3 monotherapy is currently not recommended for the treatment of patients with hypothyroidism, including those with hypothyroidism-related dyslipidemia. Similarly, it is not recommended to use combination synthetic LT4 and LT3 therapy for the management of hypothyroidism and related dyslipidemia [150].

If hypothyroidism-related dyslipidemia remains inadequately treated despite normalization of serum TSH levels under LT4 therapy, clinicians may consider titrating the LT4 dose to achieve the lower half of normal TSH range (0.5–2.5 mIU/L), while balancing the potential benefits against the risk of LT4 overtreatment (especially in older adults and in patients with CV disease) [39]. In patients with hypothyroidism and serum lipid abnormalities, concomitant residual CV risk and/or persistent dyslipidemia despite serum TSH normalization after initiation of thyroid hormone replacement therapy should be managed according to the international guidelines for the management of dyslipidemias, which include healthy lifestyle changes (such as healthy diet, regular physical exercise, smoking cessation, avoidance or restriction of alcohol consumption), appropriate weight management, and use of lipid-lowering drugs [39].

In patients with dyslipidemia related to central hypothyroidism, TSH is not a reliable measure of thyroid function status, while serum FT4 levels should be assessed to monitor the adequacy of the LT4 dose [149]. Higher FT4 values within the normal range seem to be associated with a better serum lipid profile in patients with central hypothyroidism [150]. In patients with central hypothyroidism, the primary biochemical therapeutic goal should be to maintain the serum FT4 values within the upper half of the reference range, although the target FT4 levels may be reduced in older patients or in patients with coexisting comorbidities in order to decrease the risk of overtreatment [150].

It is worth highlighting that the importance of treating dyslipidemia in the context of hypothyroidism also relies on the fact that hypothyroidism represents a modifiable risk factor for statin- and fibrate-related myotoxicity [157]. Among lipid-lowering drugs, bile acid sequestrants (cholestyramine, colestipol and colesevelam) should be avoided in patients with hypothyroidism-related dyslipidemia, since these drugs promote fecal excretion of thyroid hormones (by binding to them and reducing their enterohepatic recycling) [149] and interfere with the intestinal absorption of LT4 when taken simultaneously [158]. If a bile acid sequestrant is prescribed in LT4-treated subjects, the bile acid sequestrant and LT4 should be taken orally at least 4 h apart, in order to minimize LT4 malabsorption [133]. Among statins, the use of lovastatin should be avoided in LT4-treated patients with hypothyroidism [152], as previous reports have described interactions between these two drugs resulting in either exacerbation of hypothyroidism or development of thyrotoxicosis via mechanisms that are not fully elucidated [159].

With regard to children with SCH and OH, they should be treated in accordance with the international guidelines for the treatment of hypothyroidism in this population [150]. While most children with SCH do not progress to OH and remain asymptomatic without requiring thyroid hormone replacement therapy [149] the presence of dyslipidemia generally requires LT4 treatment of SCH in children over 3 years of age (at doses varying by age), especially when serum TSH levels are greater than 10 mIU/L in the setting of thyroid peroxidase antibody (TPOAb) positivity [149]. In fact, it has been shown that TC, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio and carotid intima-media thickness are significantly higher in children with SCH as compared to healthy euthyroid children [160].

Nutritional intervention

In this context, nutrition plays a relevant and complementary role as an adjunct to replacement pharmacological therapy, which remains the first-line treatment.

Iodine is essential for thyroid hormone synthesis, and its deficiency leads to goitre and hypothyroidism. This deficiency has also been associated with a more atherogenic lipid profile, particularly in women, while adequate supplementation may reduce the prevalence of hypercholesterolemia [161, 162]. Ensuring a daily intake that meets physiological requirements (150 µg/day in adults, according to WHO/UNICEF/ICCIDD) represents an important step in preventing thyroid and lipid disorders. Conversely, excessive intake (>1 mg/day) may impair thyroid function through the Wolff–Chaikoff effect [163].

Selenium plays an important role as an essential cofactor of deiodinases, the enzymes involved in the peripheral conversion of T4 to T3. In individuals with chronic autoimmune thyroiditis, a diet rich in selenium-containing foods, such as nuts, seeds, fish, meat, and whole grains, or selenium supplementation, may improve thyroid function and reduce serum levels of anti-thyroid antibodies [164]. The antioxidant and immunomodulatory properties of selenium may also contribute to improvements in the lipid profile and in the prevention of atherosclerosis. In this regard, selenium has been suggested to reduce oxidative stress, limit lipid peroxidation, and modulate endothelial dysfunction [165].

Zinc, another essential micronutrient, is involved in multiple metabolic processes [166]. Foods such as oysters, meats, seeds, legumes and whole grains are rich sources of it. Zinc may improve insulin sensitivity and enhance insulin secretion, thereby reducing the FFAs release to the liver and VLDL synthesis, potentially leading to decreased TG and LDL-C levels [166]. Clinical and preclinical studies suggest that zinc supplementation may also have beneficial effects on thyroid function, highlighting a potential interaction between micronutrients, thyroid metabolism, and lipid homeostasis [167].

Among the various dietary patterns, the Mediterranean diet is the most recommended, as it provides metabolic and CV benefits while potentially favourably impacting thyroid health [168, 169]. This diet is primarily plant-based, with high intakes of whole grains, fruits, vegetables, extra-virgin olive oil, and moderate alcohol consumption with meals. In particular, the use of extra-virgin olive oil appears to be associated with improvements in thyroid function in individuals with hypothyroidism [170]. The intake of polyunsaturated ω-3 fatty acids, such as those found in fish oil, not only reduces TG and cholesterol levels but may also enhance the lipid-lowering effects of thyroid hormones. Omega-3 fatty acids may modulate certain hepatic hormonal signaling pathways, including mitochondrial glycerol-3-phosphate dehydrogenase activity, thereby contributing to the regulation of lipid metabolism [171].

Phytosterols, present in nuts, vegetable oils, legumes, and whole grains, compete with cholesterol for intestinal absorption, thereby lowering total and LDL-C levels [172]. Preclinical studies also suggest that phytosterol intake may enhance thyroid activity, particularly when combined with probiotics [173].

Cruciferous vegetables (or Brassicaceae), such as broccoli, cauliflower, and Brussels sprouts, have been described as goitrogenic when consumed in large amounts, due to their high content of goitrin, which interferes with thyroid function by inhibiting thyroid peroxidase activity [168, 174]. However, a recent meta-analysis has highlighted that including cruciferous vegetables in the daily diet, particularly with adequate iodine intake, does not appear to negatively affect thyroid function [175]. Moreover, dietary intake of Brassicaceae has been reported to favorably influence the lipid profile, with significant reductions in TC, LDL-C, and oxidized LDL levels [176].

Soy is a debated component of the diet: its consumption is associated with improvements in the lipid profile [177], but due to its isoflavone content, it may reduce the absorption of thyroid hormones in individuals with hypothyroidism undergoing replacement therapy, potentially necessitating an increase in dosage [178].

Therefore, in individuals with dyslipidemia associated with hypothyroidism, a recommended nutritional approach includes reducing saturated and trans fats in favour of mono- and polyunsaturated fats, ensuring regular fiber intake, and limiting simple sugars and alcohol. These strategies, combined with adequate intake of iodine, selenium, and zinc, as well as mindful consumption of cruciferous vegetables and soy, may support thyroid function, improve the lipid profile, and reduce CV risk, complementing pharmacological therapy.

Hyperthyroidism

Pathophysiological mechanisms

Hyperthyroidism is a condition that profoundly accelerates energy metabolism [179]. Among its systemic effects, alterations in the lipid profile are particularly relevant, establishing a bidirectional relationship between thyroid function and lipoprotein metabolism. Specifically, hyperthyroidism leads to a decrease in TC, LDL-C, HDL-C, Lp(a), and ApoA-I and ApoB, whereas TG tend to remain unchanged, with slight variations depending on the clinical picture and the rate of thyroidal transition. The underlying pathophysiological mechanisms are multifactorial [179].

The liver represents the main organ through which thyroid hormones regulate cholesterol homeostasis [180]. T3 exerts a direct effect on the transcription of the LDL-Rs by promoting its hepatic expression through the SREBP-2 pathway. The increased number of LDL-Rs enhances LDL clearance and reduces plasma cholesterol levels. In parallel, T3 induces HMG-CoA reductase, the key enzyme of endogenous cholesterol synthesis; however, the augmented hepatic uptake exceeds the increase in intracellular synthesis, resulting in a net reduction of circulating LDL-C [180].

A key post-transcriptional regulator of cholesterol metabolism is PCSK9, which promotes lysosomal degradation of LDL-Rs [181]. It has been demonstrated that T3 suppresses hepatic PCSK9 expression; consequently, this mechanism preserves LDL-Rs density on the hepatocyte surface and enhances LDL clearance [181].

Another crucial mechanism concerns biliary excretion regulation [179]. T3 stimulates cholesterol-7α-hydroxylase (CYP7A1), the rate-limiting enzyme of bile acid synthesis, favouring the conversion of cholesterol into bile salts and their faecal elimination, thereby further contributing to plasma cholesterol reduction [179].

Thyroid hormones increase lipid turnover through combined activation of key enzymes [180]. In adipose tissue, T_3 stimulates lipolysis via activation of adipose TG lipase and enhancement of mitochondrial fatty acid oxidation. In the

liver and circulation, hyperthyroidism increases the activity of LPL and hepatic lipase (HL), facilitating TG hydrolysis and VLDL catabolism. The overall result is often a reduction in plasma TG, although normal or even elevated levels can occur, depending on diet, the degree of hypermetabolism, and the increase in hepatic lipogenesis indirectly induced by excessive FFAs flux [180].

HDL particles also undergo qualitative modifications during hyperthyroidism [180]. T_3 enhances the activity of LCAT and CETP, accelerating the lipid exchange and maturation cycle. This process may reduce plasma HDL-C concentrations while sometimes improving HDL functionality in reverse cholesterol transport. However, the response is heterogeneous: in some patients, HDL-C levels decrease; in others, they remain unchanged or show alterations in HDL2/HDL3 subfractions [180].

Beyond the direct action of thyroid hormones, TSH can also influence lipid metabolism through independent mechanisms [179]. TSH receptors have been identified in hepatocytes and adipocytes, where TSH can modulate HMG-CoA reductase activity and VLDL secretion. In subclinical hyperthyroidism, these lipid effects are attenuated and often not clinically significant [179].

The complex interplay between TSH, thyroid hormones, and peripheral tissues accounts for the interindividual variability observed in lipid profiles [179]. The lipid alterations associated with hyperthyroidism have relevant clinical implications in the evaluation of CV risk [151, 179]. Generally, hyperthyroid dyslipidaemia is less atherogenic than that associated with hypothyroidism, as it is characterised by reduced LDL-C and Lp(a) levels. Nevertheless, the restoration of euthyroidism may lead to a deterioration of the lipid profile, occasionally accompanied by an increase in BMI and a potential rise in CV risk [151, 179].

Laboratory abnormalities

Hyperthyroidism is associated with a distinct lipid profile compared with euthyroid or hypothyroid states, reflecting the profound effects of thyroid hormones on lipid synthesis, mobilization, degradation, and clearance [124, 182]. Patients with overt hyperthyroidism typically present with reduced TC and LDL-C, variable HDL-C levels, and normal to slightly decreased TG concentrations. ApoB levels are also usually decreased, consistent with a lower burden of atherogenic lipoproteins [124, 182].

The pathophysiology underlying these laboratory abnormalities involves upregulation of hepatic LDL-Rs, increased activity of hepatic and lipoprotein lipases, enhanced CETP activity, and decreased PCSK9 [183]. Thyroid hormones additionally promote cholesterol catabolism via increased bile acid synthesis and excretion, thereby accelerating lipid turnover and clearance. These mechanisms collectively result in reduced circulating TC and LDL-C, while HDL-C responses are more variable and may be slightly decreased or preserved [183]. TG concentrations are generally normal or slightly reduced, due to enhanced lipolysis and more rapid clearance of VLDLD and chylomicron remnants mediated by lipoprotein lipase [184]. In subclinical hyperthyroidism, lipid changes are less pronounced but may include modest reductions in VLDL secretion and plasma concentrations [185].

These lipid alterations are reversible with restoration of euthyroidism. Endocrine Society guidelines recommend re-evaluation of the lipid profile after achieving euthyroid status, as cholesterol concentrations may rise, potentially unmasking or worsening underlying dyslipidemia [179]. Meta-analytic data indicate that treatment of overt hyperthyroidism is associated with significant increases in TC (44.5 mg/dL), LDL-C (31.1 mg/dL), HDL-C (5.5 mg/dL), ApoA (15.6 mg/dL), ApoB (26.1 mg/dL), and Lp(a) (4.2 mg/dL), whereas TG changes are typically modest and non-significant (7.3 mg/dL) [151, 153]. These effects occur independently of the treatment modality and generally manifest within three months of achieving euthyroidism [151, 153].

Clinically, unexplained reductions in TC and LDL-C, in the absence of lipid-lowering therapy, may suggest underlying hyperthyroidism. Although thyroid hormone excess generally lowers atherogenic lipids, CV risk may remain elevated due to other systemic effects, including tachycardia, arrhythmias, and increased cardiac output. Accordingly, monitoring lipid profiles both before and after therapy is critical to detect changes that may require intervention.

In summary, overt hyperthyroidism is characterized by decreased TC and LDL-C, variable HDL-C levels, and normal-to-slightly decreased TG, reflecting enhanced lipid turnover and clearance. These laboratory abnormalities are reversible upon achievement of euthyroidism, emphasizing the importance of dynamic lipid monitoring in this population Table 4.

Medical treatment

The pharmacological management of dyslipidaemia in the context of hyperthyroidism requires a dynamic approach, as the lipid profile of these patients is strongly influenced by the thyroidal state and by the metabolic modifications induced by antithyroid therapy. The clinical priority is the restoration of euthyroidism, which itself leads to a substantial remodelling of lipid metabolism and may result in an apparent worsening of cholesterol parameters compared with the thyrotoxic phase. This phenomenon reflects a

Table 4 Typical lipid panel in hyperthyroidism

Parameter	Change	Mechanism
TC	↓	Increased LDL-R activity and bile acid conversion
LDL-C	↓	Enhanced LDL clearance
HDL-C	↔or ↓	Increased HL and CETP activity
TG	↔or ↓	Increased LPL activity; enhanced VLDL clearance
LDL particle quality	no data available	—
ApoB	↓	Reduced production and enhanced clearance
ApoA-I	↔or ↓	Slightly decreased synthesis
Lp(a)	↔	Minor or inconsistent changes

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; HL, hepatic lipase; CETP, cholesteryl ester transfer protein; VLDL, very-low-density lipoprotein; VLDL, very-low-density lipoprotein.

return to normal metabolic regulation rather than a true lipid disorder [180].

Therapeutic options for hyperthyroidism include synthetic antithyroid agents—mainly methimazole and propylthiouracil—radioiodine therapy with iodine-131, and thyroidectomy. Among these, methimazole represents the first-line treatment in most cases because of its efficacy and safety profile. It is administered at initial doses of 2.5–10 mg/day, with progressive titration based on clinical and biochemical response [186]. Propylthiouracil, used primarily during pregnancy or in cases of methimazole intolerance, acts similarly by inhibiting thyroid peroxidase and the peripheral conversion of T4 to T3 [186].

Although the main goal of antithyroid therapy is the normalisation of thyroid function, it has direct implications for lipid metabolism. Several studies have shown that the transition to euthyroidism is associated with a significant increase in TC, LDL-C, and, to a lesser extent, HDL-C, while TG levels tend to remain stable [179]. These variations derive both from the loss of the hypocholesterolaemic effect exerted by thyroid hormones and from drug-induced hepatic gene expression changes [187].

The magnitude of TC and LDL-C increase varies across studies but averages 30–45 mg/dL and 25–35 mg/dL, respectively, compared with baseline thyrotoxic values [179]. Although this rise reflects a return to normal metabolic function, it may carry residual CV risk in predisposed individuals, thereby warranting careful monitoring of the lipid profile during and after thyroid normalisation [188].

The initiation or modification of lipid-lowering therapy should be carefully evaluated in relation to the thyroidal status [151, 179]. Since the lipid profile is profoundly influenced by thyroid hormone concentrations, the treatment of dyslipidaemia should not be initiated or adjusted during the thyrotoxic phase, when cholesterol levels are artificially reduced. The lipid profile should be reassessed 3–6 months after antithyroid therapy, once stable euthyroidism has been achieved. Only then, if elevated LDL-C or TC values persist beyond individual targets, is the introduction of lipid-lowering treatment indicated according to the patient's CV risk profile [151, 179].

Statins represent the first-line class of agents for managing persistent dyslipidaemia following thyroid normalisation, owing to their well-established efficacy in reducing CV risk [189]. However, in hyperthyroid patients or those receiving antithyroid therapy, caution is advised with high-dose statins, since the risk of myopathy may be increased in the presence of hepatic dysfunction or altered muscular energy metabolism [190].

The choice of statin—such as atorvastatin or rosuvastatin—and its dosage should be based on a careful evaluation of hepatic function and the overall pharmacological profile, with periodic monitoring of liver enzymes and creatine kinase [191]. In cases where dyslipidaemia is resistant to treatment or statin intolerance/contraindications exist, intestinal cholesterol absorption inhibitors such as ezetimibe, or, in high CV risk patients, PCSK9 inhibitors (Alirocumab or Evolocumab), may be considered. These agents enhance hepatic LDL clearance [192].

Particular attention should be paid to patients treated with radioiodine or undergoing thyroidectomy, in whom iatrogenic hypothyroidism may constitute an additional risk factor for dyslipidaemia. Insufficient levothyroxine replacement therapy can further elevate TC and LDL-C levels, making close monitoring of both thyroid and lipid parameters essential [179]. In these cases, dose adjustment of levothyroxine is the first therapeutic step, as it alone can substantially improve the lipid profile [179].

Thus, the pharmacological management of dyslipidaemia associated with hyperthyroidism must be individualised and grounded on close integration between endocrine control and metabolic assessment. Achieving and maintaining euthyroidism are prerequisites for an accurate interpretation of the lipid profile and for determining the need for lipid-lowering therapy. Only after thyroid function has stabilised can the targeted use of statins or other lipid-lowering agents ensure effective CV risk reduction while preserving treatment safety.

Nutritional intervention

Nutritional therapy represents a key component in the clinical management of hyperthyroidism, aimed at stabilising energy homeostasis, preserving lean body mass, and

modulating associated dyslipidaemias, thereby contributing to an overall reduction in CV risk.

Thyroid hormone overproduction induces a marked increase in basal metabolic rate, an acceleration of protein catabolism, and significant alterations in lipid metabolism. In this context, dietary intervention should be individualised to counteract catabolic effects, optimise the lipid profile, and mitigate systemic oxidative stress.

The goal of nutritional therapy is twofold: to maintain an adequate energy balance and to modulate the lipid profile, reducing residual atherogenicity. Excessive dietary restriction should be avoided, as it may exacerbate protein catabolism and sarcopenia; conversely, an excessive caloric surplus may worsen dyslipidaemia. The ideal energy intake should be neutral or slightly positive, tailored to individual energy expenditure, preferably determined by indirect calorimetry or predictive equations corrected for thyroidal status [193, 194].

Adequate protein intake is crucial to preserve lean mass, support hepatic function, and sustain the synthesis of HDL-C. Evidence suggests a requirement of 1.2–1.6 g/kg/day, increasing up to 2.0 g/kg/day under metabolic stress or in cases of significant weight loss [195]. Intakes below 0.8 g/kg/day are associated with a risk of muscular atrophy and functional impairment [196].

Lean, high-quality protein sources — such as fish, poultry, legumes, soy, and low-fat dairy products — should be prioritised, while red and processed meats should be limited to reduce saturated fat intake and CV risk [197].

Plant-based proteins additionally provide dietary fibre and bioactive phytocompounds beneficial to lipid metabolism; however, vegetarian diets require attention to adequate intake of iron, zinc, calcium, vitamin B12, and iodine [196, 197].

Total fat intake should represent 25–35% of total daily calories, with a predominance of monounsaturated and polyunsaturated fatty acids derived from extra virgin olive oil, oily fish, nuts, and seeds. Reduction of saturated fats and elimination of trans fats are well-established recommendations, as these compounds aggravate dyslipidaemia and increase CV risk [196, 197].

Regular consumption of omega-3 fatty acids (EPA and DHA) is recommended, since they reduce plasma TG, improve HDL functionality, and modulate inflammatory activity [198].

From a carbohydrate perspective, hyperthyroidism profoundly alters glucose homeostasis, increasing gluconeogenesis, reducing glycogen synthesis, and inducing insulin resistance with consequent glycaemic fluctuations [199].

It is therefore essential to favour low-glycaemic-index complex carbohydrates from whole grains, legumes, fruits, and vegetables. These fibre- and micronutrient-rich foods ensure gradual glucose release, attenuate postprandial glycaemic peaks, and improve insulin sensitivity, with beneficial effects on TG control [197, 200].

Among proposed dietary models, the Mediterranean diet shows the strongest scientific evidence for improving lipid profiles and preventing CV disease. Characterised by high consumption of plant-based foods, predominant use of olive oil, regular fish intake, moderate dairy consumption, and limited red meat, the Mediterranean diet has been shown to significantly reduce LDL-C, increase HDL-C, lower TG, and decrease blood pressure [201].

These benefits derive from its high content of unsaturated fatty acids, fibre, polyphenols, and natural antioxidants [201]. From an inflammatory standpoint, this dietary pattern reduces levels of C-reactive protein, interleukin-6, and TNF-α, improving endothelial function and reducing oxidative stress, which is particularly pronounced in hyperthyroid patients [201].

Long-term adherence to the Mediterranean diet is associated with a significant reduction in CV events and overall mortality, establishing it as the reference model for secondary prevention [202].

Hyperthyroidism also increases the production of ROS and reduces total antioxidant capacity, promoting endothelial damage and atherosclerotic progression [203]. Therefore, a high intake of colourful fruits and vegetables, berries, green tea, dark chocolate, and high-phenolic-content extra virgin olive oil is recommended. These foods are rich in polyphenols, flavonoids, and vitamins C and E, which synergistically limit LDL oxidation and improve vascular reactivity [203].

Finally, meal distribution plays a complementary role in metabolic stabilisation [203, 204]. Dividing food intake into four or five regular meals per day promotes glycaemic stability, reduces excessive lipolysis, and attenuates lipid variability. Fractional meal patterns help prevent postprandial glycaemic and insulin spikes, enabling faster suppression of postprandial lipolysis and reducing the release of free fatty acids — which are elevated during fasting in hyperthyroidism and rapidly normalised after meals. This approach enhances energy efficiency and improves substrate metabolism control [203, 204].

After achieving euthyroidism, dietary strategies can be adjusted to prevent compensatory increases in plasma lipid levels.

Addison's disease

Pathophysiological mechanisms

Cortisol exerts complex and multifaceted effects on lipid metabolism at both systemic and tissue-specific levels [205]. The number of genes involved in lipid metabolism regulated by glucocorticoids (GCs) varies according to tissue type and experimental model, ranging from at least 274 in murine adipocytes to 585 transcripts across nine major metabolic tissues in mice [206]. In hepatic tissue, GC receptor activation regulates hundreds of genes coordinating lipid synthesis, oxidation, and transport [207].

Key GC-regulated genes with clinical relevance include: in adipose tissue, stearoyl-CoA desaturase 1/2/3 (SCD1/2/3), glycerol-3-phosphate acyltransferase 3/4 (GPAT3/4), 1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2), lipin-1 (LPIN1), hormone-sensitive lipase (LIPE), monoacylglycerol lipase (MGLL), cluster of differentiation 36 (CD36), low-density lipoprotein receptor-related protein 1 (LRP1), very low-density lipoprotein receptor (VLDLR), and solute carrier family 27 member 2 (SLC27A2); in hepatic tissue, angiopoietin-like 4 (ANGPTL4), sterol regulatory element-binding protein 1c (SREBP1c), fatty acid synthase (FASN), carbohydrate response element-binding protein (ChREBP), hes family bHLH transcription factor 1 (Hes-1), and sphingosine-1-phosphate receptor 2 (S1PR2) [208]. The number and identity of regulated genes are highly context-dependent, with individual genetic variation further modulating the transcriptomic response and metabolic complication risk [208].

Acutely, cortisol stimulates lipolysis, enhancing free fatty acid and glycerol mobilization from both subcutaneous and visceral adipose tissue, as demonstrated in vivo and in vitro [209, 210]. In chronic excess states, cortisol promotes characteristic adipose tissue redistribution, increasing visceral fat deposition while reducing peripheral fat stores, thereby contributing to central obesity [209, 210].

Conversely, in Addison's disease, clinically characterized by weight loss, anorexia, postural hypotension, profound fatigue, muscular and abdominal pain, and hyponatremia, the lipid profile is typically normal or reduced, and dyslipidemia is not characteristic of untreated adrenal insufficiency [211]. Addison's disease is associated with reduced lipolysis, impaired gluconeogenesis, and decreased fatty acid mobilization, resulting in diminished total cholesterol and HDL-C levels, particularly without GC replacement therapy [211]. Patients with secondary adrenal insufficiency exhibit lower HDL-C and adiponectin concentrations compared to controls, with these parameters increasing dose-dependently following GC replacement [212].

Cortisol deficiency profoundly disrupts lipid metabolism through multiple interconnected mechanisms affecting hepatic, adipose, and vascular tissues [213]. At the hepatic level, cortisol normally stimulates apolipoprotein B100 (ApoB100) and microsomal TG transfer protein gene expression, essential for VLDL assembly and secretion. In its absence, VLDL production decreases, leading to reduced total cholesterol and LDL-C levels [214]. Additionally, cortisol deficiency diminishes HMG-CoA reductase activity, further reducing endogenous cholesterol biosynthesis, while impaired gluconeogenesis limits substrate availability for de novo lipogenesis. Hepatic LDL-R expression is also dysregulated, altering lipoprotein clearance, and decreased fatty acid β-oxidation promotes hepatic TG accumulation [214].

In adipose tissue, cortisol normally potentiates catecholamine-mediated lipolysis through hormone-sensitive lipase activation [214, 215]. Its deficiency impairs basal lipolysis and reduces adipose TG lipase activity, disrupting the balance between lipolysis and lipogenesis. Furthermore, cortisol modulates lipoprotein lipase activity in adipose tissue, and its absence leads to reduced circulating TG clearance and impaired chylomicron and VLDL particle hydrolysis [214, 215].

Cortisol deficiency paradoxically increases insulin sensitivity while simultaneously impairing gluconeogenesis, creating hypoglycemic episodes that further limit substrate availability for lipid synthesis. Cortisol also regulates key gluconeogenic enzymes including PEPCK and G6Pase, whose reduced expression disrupts interconnected glucose and lipid metabolism pathways.

Beyond direct metabolic effects, cortisol deficiency eliminates crucial anti-inflammatory actions, resulting in elevated pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β [216]. These cytokines directly inhibit lipoprotein lipase activity and alter HDL-C metabolism, while increased CRP reflects systemic inflammation. Enhanced oxidative stress increases ROS production, promoting LDL-C oxidation into highly atherogenic oxidized LDL particles and contributing to endothelial dysfunction. These mechanisms collectively explain the increased CV risk despite apparently favorable lipid profiles in untreated patients [216].

Based on studies identifying AMPK as a key mediator of metabolic alterations induced by chronic GC excess, cortisol deficiency would theoretically produce inverse effects on AMPK activity[217]. In Cushing's syndrome, AMPK activity is significantly inhibited in visceral adipose tissue and cardiac muscle. In adrenal insufficiency, removal of this inhibitory signal should stimulate AMPK in these tissues, activating catabolic pathways like fatty acid oxidation and preventing visceral fat deposition, consistent with observed weight loss. Conversely, since GC excess

stimulates hypothalamic AMPK (driving increased appetite) and hepatic AMPK activity (contributing to fatty liver), adrenal insufficiency should result in AMPK inhibition at these sites. Hypothalamic AMPK reduction would contribute to anorexia, while decreased hepatic AMPK would prevent GC-induced lipogenesis and hepatic steatosis [217].

Finally, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) plays a central role in lipid metabolism by locally regulating GC activity, converting inactive cortisone into active cortisol in metabolically relevant tissues such as liver and adipose tissue [218].

Laboratory abnormalities

At diagnosis, patients with Addison's disease typically exhibit normal lipid profiles, including TC, LDL-C, HDL-C, and TG [205]. This absence of dyslipidemia likely reflects the catabolic state induced by GC deficiency, which suppresses lipogenesis and lipid accumulation. However, conventional GC replacement therapy, particularly at supraphysiological doses, may adversely impact lipid metabolism, resulting in elevated TC and LDL-C, and in some cases, reduced HDL-C [219].

Giordano et al. reported that patients receiving standard GC replacement exhibited increased TC, LDL-C, and TG, with approximately 10% having LDL-C above 160 mg/dL [220]. Notably, these alterations did not correlate with serum hormone levels or disease duration, suggesting that non-physiological cortisol exposure, rather than cumulative disease burden, drives these changes. Non-physiologic GC delivery, which fails to replicate the natural circadian rhythm, likely contributes to intermittent cortisol overexposure and subsequent metabolic derangements [220].

Table 5 Typical lipid panel in Addison's Disease

Parameter	Change	Mechanism
TC	↔ or ↑	Non-physiological GC exposure; altered lipid metabolism
LDL-C	↔ or ↑	Cortisol overexposure; impaired circadian mimicry
HDL-C	↔ or ↓	Variable response to GC replacement
TG	↔ or ↑	Enhanced lipogenesis under supraphysiological GC doses
LDL particle quality	no data available	—
ApoB	↔ or ↑	Prolonged circulation under conventional GC therapy
ApoA-I	↔ or ↓	Altered synthesis secondary to hormone replacement
Lp(a)	↔	Largely unaffected

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); GC, glucocorticoids.

Modified-release hydrocortisone formulations have been developed to more closely mimic physiological cortisol secretion. Dual-release hydrocortisone therapy has demonstrated beneficial effects on lipid metabolism in both primary and secondary adrenal insufficiency. Johannsson et al. observed modest TG increases and reductions in HDL-C in most patients after 24 weeks, while TC decreased, suggesting potential long-term CV benefit [221]. Similarly, Quinkler et al. reported slight reductions in TC with dual-release hydrocortisone compared to conventional therapy, with minimal changes in LDL-C, HDL-C, or TG [222]. Italian cohorts confirmed reductions in TC and LDL-C, while effects on HDL-C were inconsistent [223–225]. In secondary adrenal insufficiency, divergent results have been observed, with some studies showing TG increases and others reporting decreased HDL-C or no significant changes in TC, LDL-C, or tTG [226, 227].

Genetic variability in the GC receptor further modulates individual lipid responses. Polymorphisms such as BclI and N363S, which increase GC sensitivity, are associated with adverse lipid profiles, whereas ER22/23EK, conferring reduced sensitivity, is linked to lower LDL-C and a more favorable metabolic profile [228]. Giordano et al. demonstrated that homozygosity for the BclI allele is associated with higher prevalence of hypercholesterolemia and hypertriglyceridemia, independent of disease duration or GC dose, highlighting the role of genetic predisposition [229].

In conclusion, untreated Addison's disease is generally not associated with dyslipidemia. Conventional GC replacement may induce lipid alterations, including elevated TC, LDL-C, and TG, and occasionally reduced HDL-C. Modified-release hydrocortisone partially mitigates these effects, and GC receptor polymorphisms further modulate individual susceptibility Table 5.

Medical treatment

Assessment of concomitant endocrine and autoimmune conditions is essential to guide clinicians in selecting the most appropriate lipid-lowering strategy in patients with autoimmune Addison's disease. Routine screening of thyroid function (see section on thyroid disorders) is recommended, along with assessment for other autoimmune conditions such as premature ovarian failure, celiac disease, and atrophic gastritis, as these disorders can significantly influence lipid metabolism and should be identified and managed before initiating lipid-lowering therapy. Similarly, patients with secondary adrenal insufficiency may present with concomitant pituitary deficiencies that impact lipid metabolism and require specific management approaches, including hypogonadotropic hypogonadism, growth hormone deficiency, central hypothyroidism, and hyperprolactinemia.

Optimization of GC replacement should be undertaken before or alongside lipid-lowering therapy, since both the total daily dose and circadian pattern of administration influence lipid metabolism and CV risk. Among immediate-release formulations, current evidence suggests that prednisolone is less favorable compared to short-acting formulations such as hydrocortisone or cortisone acetate, although this might be influenced by total daily dose and overall GC exposure [230]. Data on the impact of dual-release hydrocortisone on cholesterol and TG levels remain inconsistent; however, this formulation may still represent the preferred option, particularly given its beneficial effects on body weight, metabolism, and immune function, which may contribute to an overall more favorable CV risk profile [231]. Continuous subcutaneous hydrocortisone infusion provides improved cortisol exposure–time profiles and clinical outcomes, although evidence on its effects on lipid parameters remains limited [232]. Regardless of the formulation used, GC overtreatment should be avoided, with recommended target daily doses of 15–25 mg/day for hydrocortisone or 3–5 mg/day for prednisolone [233, 234].

In case of persistent dyslipidemia despite optimization of GC replacement, lipid-lowering therapy may be initiated. LDL-C targets should follow international CV risk–based guidelines [39, 235]. In patients younger than 40 years, current guidelines provide no clear pharmacological thresholds [39, 189, 235]. Lifestyle modification remains first-line for mildly elevated LDL-C (120–159 mg/dL), while drug therapy is usually reserved for LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL with additional risk enhancers such as family history of premature ASCVD, elevated Lp(a), or subclinical atherosclerosis [39, 189, 235]. The most recent ESC/EAS update acknowledges that algorithms based on 10-year risk estimation underestimate CV risk in younger adults, and increasing evidence highlights that lifetime exposure to elevated LDL-C is a major determinant of future ASCVD [236, 237]. This is particularly relevant for Addison's disease, which often presents in young adults who already face increased CV morbidity and mortality, partly due to chronic GC therapy [238]. Therefore, in a young adult with autoimmune Addison's disease who continues to show persistently elevated LDL-C (e.g., 140–150 mg/dL) despite an optimized GC replacement and lifestyle intervention, it may be reasonable to consider initiating lipid-lowering therapy. Such decisions should be individualized, accounting for other risk factors, family history, and disease duration, while recognizing that conventional risk scores likely underestimate long-term risk in this population.

Statins remain the first-line therapy to reduce LDL-C [39, 235]. Dose and formulation should be determined by baseline levels and desired target LDL-C. GC replacement at physiological doses was not found to limit statin efficacy in lowering cholesterol levels. Ezetimibe can be added in case of suboptimal LDL-C control. Bempedoic acid has demonstrated benefit in statin-intolerant patients and may be considered as an alternative, while PCSK9 inhibitors and inclisiran are indicated in patients at high or very high CV risk not reaching LDL-C goals. Hypertriglyceridemia should be managed with lifestyle optimization, treatment of secondary causes, and, in high-risk cases, pharmacotherapy [39, 235]. Statins are recommended as first drug of choice, whereas omega-3 fatty acids, particularly high-dose icosapent ethyl (EPA), have shown significant CV risk reduction in patients with persistent hypertriglyceridemia despite statin therapy. Fibrates are reserved for severe hypertriglyceridemia, with caution regarding potential drug interactions [39, 235].

Nutritional intervention

Patients with adrenal insufficiency should receive the same lifestyle and dietary counseling as the general population with dyslipidemia [39, 235]. A Mediterranean dietary pattern, reduction of saturated and trans fatty acids, increased intake of polyunsaturated fats and soluble fiber, regular physical activity (150–300 min/week of moderate intensity), and weight reduction (5–10% when overweight) are all associated with improvements in LDL-C and TG and should be systematically recommended [39, 235].

Congenital adrenal hyperplasia

Pathophysiological mechanisms

CAH is the most frequent cause of pediatric adrenal insufficiency and presents unique factors influencing lipid metabolism and cardiometabolic risk [239]. Patients with classic CAH are exposed to exogenous GCs from early childhood, contributing to a lifelong increased CV risk. Additionally, CAH is characterized by chronic overactivation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in persistent androgen excess [239]. Androgens exert multiple effects on lipid metabolism, including modulation of hepatic lipase activity, influence on apolipoprotein synthesis, and alterations in lipoprotein particle size and composition [240, 241]. To suppress androgen overproduction, supraphysiological doses of GCs are often required, frequently using long-acting formulations (e.g., dexamethasone) and reverse-circadian schedules to blunt early-morning HPA surges [242, 243]. The combination of chronic androgen excess and high-dose GC therapy further impairs gonadal function in both men and women, aggravating adverse metabolic outcomes [242, 243]. These hormonal perturbations,

together with treatment-related factors, predispose CAH patients to insulin resistance, weight gain, unfavorable body composition, hypertension, and endothelial dysfunction, thereby creating a milieu conducive to dyslipidemia and CV risk [244].

Laboratory abnormalities

Lipid profiles in CAH are heterogeneous across ages, sex, phenotypes, and treatment regimens, making a typical pattern difficult to define. In pediatric and adult populations, low HDL-C levels are frequently reported, particularly in patients with poorly controlled androgen excess [245, 246]. Elevated TG are recurrent in children, adolescents, and adult women, especially in the context of persistent androgen exposure [247]. Increases in LDL-C and TC have also been observed, though less consistently across cohorts [244, 248]. Meta-analytic data do not show pooled differences in TC, LDL-C, HDL-C, or TG between CAH patients and controls, highlighting the influence of genotype, GC regimen, and comorbidities on circulating lipid levels [239]. Despite the variability in standard lipid parameters, adults with CAH exhibit increased cardiometabolic risk, underscoring that conventional lipid panels may underestimate the complexity of lipid metabolism dysregulation in this population Table 6.

Medical treatment

In fully grown patients with CAH, latest guidelines recommend optimizing total daily GC dose in the range between 15–25 mg/day hydrocortisone equivalents [239]. Chronic use of long-acting, potent GCs (e.g. dexamethasone or prednisolone) administered in an anti-circadian fashion, is strongly disfavored, as these regimens undermine cardiometabolic health [239]. However, in severe cases of CAH, standard treatment with short acting GCs may be insufficient in providing an adequate disease control. In this scenario, modified release hydrocortisone, offers a more physiological alternative to long-acting GCs. This formulation provides a more shaped circadian cortisol profile, and allows dose reductions in daily GCs without worsening lipid parameters [239]. Indeed, biochemical control improved under modified release hydrocortisone [249], and recently published data from a 4-year longitudinal follow-up showed a minor increase in median HDL-C and unchanged TG levels in a cohort of patients shifting from conventional HC to modified release hydrocortisone and decreasing total daily dose from 30 to 20 mg/day [249, 250]. Thus, in patients with CAH, shifting to modified release hydrocortisone is recommended, especially in patients receiving chronic long-acting GC therapy.

In case of persistent dyslipidemia in patients with CAH despite optimal dietary and lifestyle interventions, optimized GC therapy and biochemical control, lipid-lowering interventions can be considered [39, 235]. Management targets for LDL-C should follow general CV risk stratification according to international guidelines [39, 235].

Table 6 Typical lipid panel in congenital adrenal hyperplasia

Parameter	Change	Mechanism
TC	↔ or ↑	Chronic androgen excess and GC exposure
LDL-C	↔ or ↑	Enhanced production and reduced clearance
HDL-C	↓	Androgen-induced increase in hepatic lipase activity
TG	↔ or ↑	GC therapy and androgen excess stimulate VLDL synthesis
LDL particle quality	no data available	—
ApoB	↔ or ↑	Increased atherogenic lipoprotein production
ApoA-I	↔ or ↓	Reduced synthesis due to androgen excess
Lp(a)	↔	No consistent changes reported

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); GC, glucocorticoids.

Nutritional intervention

Lifelong GC treatment starting from childhood increases the risk of obesity and overweight in patients with CAH [239, 251]. Furthermore, impaired dietary decision-making has been described in children and adolescents with CAH, underscoring the importance of structured nutritional education and behavioral support [252]. Accordingly, systematic dietary counseling and nutritional follow-up should ideally be implemented from pediatric age and reinforced during the transition to adulthood, to support healthy growth, optimize body composition, and mitigate long-term cardiometabolic risk [253].

Cushing's syndrome

Pathophysiological mechanisms

GCs play a central role in the pathogenesis of dyslipidemia in Cushing's syndrome through multifaceted mechanisms that influence lipid mobilization, adipose tissue distribution, and hepatic lipid metabolism [254, 255]. Chronic GC excess establishes a metabolic milieu characterized by concurrent activation of lipolytic and adipogenic pathways, leading to

the redistribution of adipose tissue and the emergence of an atherogenic lipid profile [254, 255].

GCs enhance plasma FFA concentrations primarily by stimulating key lipolytic enzymes such as adipose TG lipase and hormone-sensitive lipase (HSL) [256]. This stimulation occurs via activation of the cyclic AMP (cAMP)–protein kinase A (PKA) signaling cascade and inhibition of phosphodiesterase 3B (PDE3B), which prolongs intracellular cAMP activity [215, 256]. GCs further potentiate the lipolytic effects of catecholamines and growth hormone, thereby reinforcing lipid mobilization during sustained GC exposure [257, 258].

Despite their lipolytic action, chronic GC excess paradoxically promotes adipose tissue expansion. Persistent GC exposure increases the expression and activity of LPL, the enzyme responsible for hydrolyzing TG from circulating VLDL and chylomicrons, thus facilitating FFA uptake and TG re-esterification within adipocytes [259, 260]. The liver contributes to this process by augmenting VLDL synthesis and secretion, further driving lipid flux toward adipose depots [261, 262]. The resulting phenotype—characterized by visceral adiposity and subcutaneous fat depletion—is attributed to the heightened sensitivity of visceral adipocytes to GCs, potentially mediated by tissue-specific differences in GC receptor isoform expression and signaling [263].

Local amplification of GC action intensifies adipogenesis via increased expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and hexose-6-phosphate dehydrogenase (H6PDH), enzymes that regenerate active cortisol intracellularly [264]. GC-inducible factors such as LIM domain only 3 (LMO3) and Dexras1 (Rasd1) further promote adipocyte differentiation by enhancing peroxisome proliferator-activated receptor gamma (PPARγ) activation [264]. Moreover, GCs modulate MAPK signaling through FOXO1-mediated upregulation of MAPK phosphatase-3 (MKP-3), influencing both adipocyte proliferation and maturation [265].

The effects of GCs on lipolysis are context-dependent, varying with exposure duration and tissue specificity [257]. Acute GC elevations, as during physiological stress, transiently enhance lipolysis and FFA turnover [266]. Conversely, chronic GC exposure shifts the balance toward TG storage, particularly in visceral fat and hepatic tissue [266]. Persistent FFA excess promotes ectopic lipid accumulation in insulin-sensitive organs, activating stress kinases such as c-Jun N-terminal kinase (JNK) and IKK-β, which phosphorylate insulin receptor substrates and disrupt downstream insulin signaling, leading to systemic insulin resistance—a defining metabolic feature of Cushing's syndrome [266].

In the liver, GCs upregulate lipogenic enzymes, including acetyl-CoA carboxylase and fatty acid synthase, while concurrently stimulating gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) [262]. These alterations, together with increased VLDL secretion and reduced β-oxidation, foster hepatic TG accumulation and dyslipidemia [261]. The downregulation of acyl-CoA dehydrogenase further suppresses fatty acid oxidation, exacerbating steatosis. Coexistent insulin resistance amplifies these metabolic disturbances, creating a self-perpetuating cycle of lipid and glucose imbalance [261].

Central nervous system alterations further complicate the metabolic phenotype. Chronic GC excess disrupts hypothalamic homeostatic circuits, enhancing endocannabinoid tone and AMP-K signaling, which promote hyperphagia [267]. Behavioral components may also contribute, as sustained GC exposure increases preference for energy-dense, palatable foods, aggravating weight gain and worsening dyslipidemia [268].

Laboratory abnormalities

Overall, 37–71% of Cushing's syndrome patients exhibit lipid abnormalities [266]. Hypercholesterolemia occurs in 16–60%, whereas hypertriglyceridemia is reported in 7–36% of cases [269, 270]. No consistent differences are observed between pituitary- and adrenal-dependent Cushing's syndrome, and lipid alterations do not correlate reliably with hypercortisolism severity [271, 272].

HDL-C alterations are less consistent, with reductions in 14–36% of patients [273, 274] and up to 20% in some cohorts [275]. Conversely, some studies report no differences versus controls, suggesting that factors beyond GC excess—including diet, physical activity, and genetics—modulate HDL-C [276]. Two or more lipid abnormalities occur in ~ 30% of patients, and elevated TC/HDL-C ratio is reported in 24–56%, indicating that composite lipid indices better capture CV risk than isolated parameters [273, 275]. Lp(a) data are limited and discordant, with some studies reporting elevation and others no change [277, 278].

Dyslipidemia contributes to increased CV risk in Cushing's syndrome by accelerating atherosclerosis and promoting higher CV mortality, even after hypercortisolism is corrected [279, 280]. Coexisting metabolic derangements, including visceral obesity, insulin resistance, hypertension, and a prothrombotic state, further compound CV risk [281]. Arterial stiffness, measured via carotid intima-media thickness, is increased in Cushing's syndrome patients and may persist post-treatment [273, 277]. Improvements in lipid profile correlate with reductions in arterial stiffness and enhanced endothelial function, emphasizing the benefit of treating dyslipidemia alongside cortisol normalization [279].

Conventional CV risk scores, such as SCORE2, often underestimate true risk in Cushing's syndrome, as they fail to incorporate disease-specific factors, including hypercortisolism-induced hypercoagulability, venous thromboembolism risk, and persistent vascular dysfunction [282]. Consequently, risk assessment in Cushing's syndrome should employ a multidimensional, disease-tailored approach, incorporating advanced imaging, evaluation of subclinical atherosclerosis, and proactive management of multiple metabolic and vascular risk factors [282] Table 7.

Medical treatment

Both hypercortisolism and specific lipid-lowering treatments play a crucial role to best manage dyslipidemia in Cushing's syndrome.

The cornerstone of treatment for endogenous hypercortisolism is represented by surgical resection of the hormone-secreting pituitary, adrenal, or ectopic tumor, and surgical remission, or marked improvement of cortisol excess, generally produce favorable trends in lipid metabolism [283, 284].

In patients with Cushing's disease, transsphenoidal surgery for ACTH-secreting pituitary tumors is frequently associated with significant reductions in TC and LDL-C, particularly among women, along with decreases in total and truncal fat mass, while HDL-C and TG showed no substantial variation [285]. However, even after long-term follow-up, lipid parameters often remain above those observed in BMI-matched healthy controls, indicating residual vascular damage and possible persistence of atherosclerotic burden despite hypercortisolism resolution [273, 277]. These findings underscore the importance of early intervention to prevent irreversible CV changes [273, 277].

Conflicting evidence exists regarding adrenal Cushing's syndrome: a marked decline in LDL-C following laparoscopic adrenalectomy, with post-operative values approximating those of healthy controls, has been observed, even in patients addressed to adrenalectomy for mild autonomous cortisol secretion [286]. Conversely, other studies reported no meaningful lipid changes post-adrenalectomy, highlighting heterogeneity across patient populations and study designs [287].

An Indian cohort encompassing various forms of endogenous hypercortisolism, including pituitary, adrenal, ectopic, and occult etiologies, demonstrated significant reductions in TC, LDL-C, VLDL-C, and TG after surgical remission [275]. Improvements correlated with HbA1c levels, suggesting the strict interplay between glucose and lipid metabolism, though the overall prevalence of dyslipidemia remained unchanged [275].

Pharmacological hypercortisolism treatment can modify lipid metabolism both indirectly, through cortisol normalization, and directly via drug-specific mechanisms [274]. Cabergoline, a dopamine agonist drug primarily used for hyperprolactinemia and off-label for Cushing's disease, has limited evidence in Cushing's disease regarding lipid outcomes [288]. Data from hyperprolactinemic cohorts suggest reductions in TC, LDL-C, and TG, likely attributable to D2 receptor activation rather than weight or hormonal changes [42, 289]. Pasireotide, a multireceptor somatostatin analogue drug, predominantly targeting SSTR5, has been demonstrated able to significantly reduce TC and LDL-C in patients achieving urinary free cortisol control [290, 291]. Nevertheless, these benefits may be counterbalanced by the deterioration in glucose homeostasis [290]. Regarding adrenal steroidogenesis inhibitors, ketoconazole exerts cholesterol-lowering effects by inhibiting adrenal steroid synthesis and hepatic cholesterol production, historically serving as a therapeutic option for familial hypercholesterolemia before the advent of statins [292, 293]. Levoketoconazole, the 2S,4R enantiomer of ketoconazole, has demonstrated reductions in TC and LDL-C [294]. In contrast, metyrapone has shown negligible or inconsistent lipid effects in clinical settings [295]. Osilodrostat has shown decreases in TC, LDL-C, and TG, though concomitant HDL-C reduction has been reported [296]. Mitotane stands out for its paradoxical impact, significantly elevating TC and LDL-C, while concomitantly increasing HDL-C, likely through estrogen-like effects and CYP450 induction [297, 298]. Mifepristone, the GC receptor antagonist, tends to lower HDL-C and alter HDL functionality, with inconsistent effects on LDL-C and TG, although improves glycemia and blood pressure [299].

Table 7 Typical lipid profile in Cushing's syndrome

Parameter	Change	Mechanism
TC	↑	Increased VLDL synthesis; reduced LDL-R activity
LDL-C	↑	Reduced receptor-mediated clearance
HDL-C	↓	Reduced ApoA synthesis; altered HDL maturation
TG	↑	Increased VLDL secretion; decreased LPL activity
LDL particle quality	↑ sd-LDL	Increased remnants and insulin resistance promote atherogenic particles
ApoB	↑	Increased atherogenic lipoprotein burden
ApoA-I	↓	Reduced synthesis
Lp(a)	↔ or ↑	Limited and discordant data; potential GC and metabolic effects on synthesis/clearance

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a); LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; GC, glucocorticoids.

Evidence on relacorilant, the investigational GC receptor antagonist, remains insufficient [300].

Regarding lipid-lowering treatments, given the elevated CV risk in patients with Cushing's syndrome, an intensive approach is warranted, even after Cushing's syndrome remission [39, 179, 235]. LDL-C remains the primary therapeutic target, with recommended goal < 70 mg/dL [39, 179, 235]. Statins are first-line agents to be considered if LDL ≥ 70 mg/dl, but drug–drug interactions require attention: ketoconazole and metyrapone inhibit CYP3A4, increasing statin plasma concentrations, whereas mitotane accelerates cholesterol synthesis and is metabolized via CYP3A4, favouring pravastatin or rosuvastatin in these contexts [297, 301]. If LDL target still remains unmet, ezetimibe is a safe adjunct, and PCSK9 inhibitors can be considered, with successful use reported in patients on mitotane [302, 303].

Current understanding suggests that, besides the chronic GC excess, elements of metabolic syndrome, such as visceral obesity, insulin resistance, and type 2 diabetes, may independently contribute to the development of an atherogenic lipid profile in patients with Cushing's syndrome [271, 277]. This multifactorial origin complicates the management of dyslipidemia in Cushing's syndrome and emphasizes the importance of a comprehensive metabolic evaluation, and a long-term lipid management even after endocrine remission.

Nutritional intervention

Nutritional interventions play a crucial role in managing dyslipidemia and improving the overall metabolic health [304].

Low-carbohydrate and ketogenic diets have shown promise results in improving metabolic parameters in Cushing's syndrome [304]. These dietary patterns can lead to weight loss, reduced inflammation, and improvements in lipid profiles, including reductions in TC and TG levels [304]. Specifically, very low-energy ketogenic therapy (VLEKT) and low-carbohydrate ketogenic diets have been demonstrated to effectively improve metabolic disorders in Cushing's disease, suggesting that nutritional interventions can complement conventional therapies to enhance metabolic and CV health. Furthermore, a ketogenic diet may suppress ghrelin, a hormone that stimulates hunger, potentially aiding in appetite and weight control in patients with Cushing's syndrome. However, the long-term effects and safety of such diets in patients with Cushing's syndrome require further investigation [304].

In addition to carbohydrate restriction, managing the other macronutrients protein and fat intake is crucial [305]. Adequate protein consumption supports muscle mass, which can be compromised in Cushing's syndrome due to the catabolic effects of cortisol excess. Sources of lean protein, such as poultry, fish, tofu, and legumes, should be emphasized [305].

Regarding fats, incorporating healthy fats from sources like avocados, nuts, and olive oil can provide essential FFA and support the overall metabolic health [304, 305].

Concomitantly, micronutrients supplementation is recommended due to their deficiency commonly observed in patients with Cushing's syndrome, mainly related to altered metabolism and dietary restrictions [306]. Specifically, an adequate intake of calcium and vitamin D is particularly important, especially considering that patients with Cushing's syndrome are at increased risk for osteoporosis to mitigate bone loss. Notably, beyond the bone effect, vitamin D supplementation has been associated with improvements in lipid profiles in patients with Cushing's syndrome, highlighting its potential role also in managing dyslipidemia [306].

Reducing sodium intake, by limiting processed foods and avoiding added salt, is suggested to improve the blood pressure control, considering that the elevated sodium retention and fluid imbalance exacerbate arterial hypertension observed in Cushing's syndrome [304, 305]. Moreover, adequate hydration is also essential [304, 305].

Dietary strategies aimed at stabilizing blood glucose levels, consuming high-fibre foods with low glycemic indices, such as whole grains, legumes, and non-starchy vegetables, are crucial to improve insulin sensitivity and consequently lipid metabolism [304, 305].

Nutritional interventions are a vital component in managing dyslipidemia associated with Cushing's syndrome [304]. While dietary modifications alone may not be sufficient, they can significantly enhance the effects of pharmacological treatments and contribute to improved metabolic health and reduced CV risk [304]. Further research is needed to establish standardized dietary guidelines and long-term outcomes for patients with Cushing's syndrome [179, 304].

Regular monitoring of lipid profiles, glucose levels, and other metabolic parameters is essential to assess the effectiveness of nutritional interventions and make necessary adjustments [304]. Given the complexity of Cushing's syndrome and its metabolic effects, a multidisciplinary approach involving endocrinologists, dietitians, and other healthcare professionals is recommended to develop and implement personalized nutrition interventions [179, 304].

Beyond the nutritional interventions, incorporating regular physical activity is an integral component of managing dyslipidemia in Cushing's syndrome [304]. Exercise can improve lipid profiles, enhance insulin sensitivity, and support weight control. Patients should engage in a combination

of aerobic and resistance training exercises, tailored to their individual capabilities and health status [304].

Male hypogonadism

Pathophysiological mechanisms

Male hypogonadism is increasingly recognized as a condition associated with adverse metabolic consequences, among which dyslipidemia represents a major determinant of CV risk [307, 308]. The pathophysiological mechanisms underlying this association are multifactorial and closely linked to androgen deficiency. Testosterone deficiency is associated with reduced lipolysis, promotes visceral adipose tissue accumulation, and fosters insulin resistance [309, 310]. These alterations enhance hepatic VLDL synthesis and impair TG clearance, leading to an atherogenic lipid environment [311, 312]. Furthermore, reduced activity of lipoprotein lipase and hepatic lipase in hypogonadal men is associated with decreased HDL-C and inefficient lipid remodeling [240, 241]. The hormonal imbalance is also accompanied by a pro-inflammatory adipokine profile characterized by increased leptin (which promotes vascular inflammation and smooth muscle cell proliferation), elevated TNF-α and interleukin-6 (drivers of insulin resistance and endothelial dysfunction), and reduced adiponectin (normally vasculoprotective and anti-inflammatory), further worsening lipid abnormalities and fostering a chronic low-grade inflammatory state that aggravates cardiometabolic risk [313, 314]. Finally, sarcopenia, which frequently coexists with hypogonadism, aggravates insulin resistance and amplifies the dysmetabolic phenotype [315, 316].

Table 8 Typical lipid profile in male hypogonadism

Parameter	Change	Mechanism
TC	↔ or ↑	Influenced by VLDL synthesis and insulin resistance
LDL-C	↔ or ↑	Modest increase; qualitative changes
HDL-C	↓	Reduced LPL and HL activity
TG	↑	Increased VLDL synthesis; reduced clearance
LDL particle quality	↑ sd-LDL	Shift to small, dense particles
ApoB	↔ or ↑	Reflects increased atherogenic lipoproteins
ApoA-I	↓	Reduced HDL formation
Lp(a)	no data available	—

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I.

Laboratory abnormalities

From a laboratory perspective, dyslipidemia in male hypogonadism is typically characterized by a mixed pattern. TG are often mildly elevated, HDL-C levels are consistently reduced, while LDL-C and total cholesterol show variable changes, with some studies reporting modest elevations [314, 317]. Qualitative alterations in LDL particles have also been described, with a shift toward smaller and denser fractions that are more atherogenic, potentially explaining why some hypogonadal men exhibit apparently normal LDL-C yet remain at increased CV risk [312]. These small, dense LDL particles display reduced affinity for the LDL-R and an increased tendency to undergo oxidative modifications, both of which enhance their atherogenic potential [318]. As a result, hypogonadal men may accumulate dysfunctional lipoproteins that accelerate endothelial injury and plaque formation despite apparently normal lipid values [318] Table 8.

Medical treatment

Pharmacological treatment combines lipid-lowering agents and endocrine interventions. Statins are first-line to lower LDL-C, while fibrates and omega-3 fatty acids are options in hypertriglyceridemia [319, 320]. Testosterone replacement therapy, when appropriate, reduces visceral fat, increases lean mass, and may lower TG, increase HDL-C, and variably affect LDL-C [319, 320]. Restoration of normal testosterone through testosterone replacement therapy or weight loss improves both metabolic and gonadal function; however, lipid-lowering therapy is often still required to achieve guideline-recommended targets [321, 322]. The effects of testosterone replacement therapy on lipids appear partly mediated by improvements in body composition and partly by direct actions on hepatic lipase and lipoprotein lipase, though results remain heterogeneous and highlight the importance of individualized monitoring [321, 322].

It is important to note that hypogonadism frequently coexists with obesity and type 2 diabetes, conditions that represent a primum movens in the development of androgen deficiency [323–325]. Therapies that target these disorders may therefore provide dual benefits on testosterone and lipid metabolism. Indeed, recent data show that glucagon-like peptide-1 receptor agonists, dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonists, and sodium–glucose cotransporter-2 inhibitors can improve body weight, insulin sensitivity, and lipid profiles, with emerging evidence also of positive effects on testosterone [323–325]. Beyond glycemic and weight control, these agents also exert favorable effects on hepatic steatosis and

vascular inflammation, which may further modulate lipid metabolism [326].

Nutritional intervention

Given the multifaceted pathophysiology, therapeutic strategies must target both hormonal and metabolic derangements. Nutritional therapy remains a cornerstone, especially in the frequent coexistence of obesity and insulin resistance [327]. Weight reduction (through caloric restriction, physical activity, or even bariatric surgery) improves visceral adiposity, insulin sensitivity, and indirectly testosterone levels [327]. The Mediterranean diet has demonstrated consistent benefits on metabolic and hormonal parameters, particularly in individuals with obesity and insulin resistance. VLEKT have also shown promising short-term effects, including rapid increases in serum testosterone and improvements in lipid profiles [328]. However, current evidence is largely limited to short-to-medium-term studies, and the long-term safety, sustainability, and endocrine impact of VLEKT remain areas of ongoing investigation.

Female hypogonadism

Pathophysiological mechanisms

Female hypogonadism, defined by reduced or absent estrogen production, exerts systemic effects that extend well beyond reproductive health [329, 330]. One of its most clinically relevant metabolic consequences is dyslipidemia, a quantitative and qualitative alteration in plasma lipids that significantly increases CV disease risk—the leading cause of morbidity and mortality in women globally [329, 330]. The marked sex-related difference in coronary artery disease observed between men and premenopausal women diminishes shortly after menopause, when CV protection conferred by estrogens is progressively lost [331]. This increase in CV risk is largely driven by a shift toward an atherogenic lipid profile, characterized by elevated TC, LDL-C, TG, and Lp(a), coupled with reduced HDL-C levels [332].

The earlier hypoestrogenism occurs, the greater its metabolic and CV implications. It may develop physiologically during menopause due to age-related ovarian failure or prematurely in the context of primary ovarian insufficiency (POI), whether congenital, autoimmune, or iatrogenic [333]. Early estrogen deprivation is associated with reduced lifespan, whereas longer lifetime estrogen exposure has been linked to slower epigenetic aging [334, 335]. POI is now formally recognized as a CV risk factor, and statin therapy is recommended in women aged 40–75 years with a 10-year CV risk of 7.5–19.9% [189]. Moreover, pooled data from ten observational studies involving over 200,000 postmenopausal women demonstrated that surgical menopause before age 35 or between 35 and 39 years significantly increases CVD risk, while estrogen therapy before age 50 mitigates this risk [336]. Similarly, women with functional hypothalamic amenorrhea—a frequent cause of secondary amenorrhea associated with stress and hypoestrogenism—exhibit endothelial dysfunction, visceral adiposity, and increased CV risk [337].

Estrogens, particularly estradiol (E2), play a central role in lipid homeostasis. At the hepatic level, they upregulate LDL-R, enhance ApoA-I synthesis—the main structural component of HDL—and suppress hepatic production of ApoB100, necessary for VLDL assembly [338, 339]. Estrogen deficiency therefore decreases LDL-R activity, leading to elevated circulating LDL-C, while impairing HDL synthesis and remodeling, ultimately reducing reverse cholesterol transport and HDL's anti-atherogenic capacity [340].

Estrogen deficiency also affects body fat distribution and insulin sensitivity, promoting a shift toward visceral adiposity and metabolic syndrome [341]. Visceral fat accumulation enhances lipolysis, increasing hepatic free fatty acid flux and stimulating TG and VLDL synthesis. Concomitant hyperinsulinemia inhibits LPL, impairing VLDL and chylomicron clearance and favoring the formation of small, dense LDL particles—potent contributors to atherosclerosis [341].

At the cellular level, estrogen deficiency is associated with mitochondrial dysfunction and increased reactive oxygen species (ROS) generation [342]. ROS promote LDL oxidation, endothelial injury, and hepatic lipid dysregulation [343]. HDL particles from postmenopausal women display diminished antioxidant and anti-atherogenic properties compared with those of premenopausal women [344].

Estrogen receptors (ERα, ERβ) regulate the transcription of key metabolic genes, including SREBP-1c, PPARα, and LXRα [345]. In hypogonadism, disrupted estrogen signaling reduces β-oxidation and enhances de novo lipogenesis, predisposing to hepatic steatosis and atherogenic dyslipidemia. Furthermore, hypoestrogenism promotes chronic low-grade inflammation characterized by elevated TNF-α and IL-6 and reduced IL-10, which exacerbates endothelial dysfunction and impairs lipoprotein metabolism [346].

Laboratory abnormalities

Lipid profile alterations in female hypogonadism reflect the underlying pathophysiological mechanisms and vary according to etiology [347]. Laboratory evaluation is crucial for early detection of CV risk and for guiding targeted interventions. Initial assessment should include TC, LDL-C, HDL-C, TG, and Lp(a), integrated with global risk

estimation using tools such as SCORE2 and SCORE1-OP, according to ESC/EAS guidelines [39, 235, 348].

Isolated hypercholesterolemia is the most frequent pattern, especially in menopause or POI, characterized by elevated TC and LDL-C, with normal or slightly reduced HDL-C and normal TG. This profile mainly reflects reduced hepatic LDL-R activity and impaired LDL clearance (typical values: TC > 240 mg/dL; LDL-C > 160 mg/dL; HDL-C normal or slightly reduced; TG < 150 mg/dL).

Mixed (atherogenic) dyslipidemia occurs in hypogonadism complicated by visceral obesity or insulin resistance, showing increased LDL-C and TG with reduced HDL-C. LDL particles are often smaller and denser, enhancing atherogenicity (typical values: LDL-C > 160 mg/dL; TG > 150 mg/dL; HDL-C < 50 mg/dL).

Isoated hypertriglyceridemia is less common but may be associated with high-carbohydrate diets, physical inactivity, or reduced LPL activity, sometimes representing early MASLD (typical values: TG > 200 mg/dL; LDL-C normal or slightly increased; HDL-C normal or reduced).

Isolated reduction in HDL-C may occur alone or with other lipid abnormalities, mainly due to reduced ApoA-I synthesis and qualitative HDL changes, impairing reverse cholesterol transport (typical values: HDL-C < 40–50 mg/dL; LDL-C and TG normal).

Primary hypogonadism (e.g., Turner syndrome, POI) generally presents with isolated hypercholesterolemia, particularly in lean women. Studies show elevated TC and LDL-C, with TG often increased compared with premenopausal controls [349, 350]. Secondary hypogonadism (e.g., hypothalamic–pituitary disorders, anorexia nervosa) may present with mixed dyslipidemia or isolated low HDL-C. Physiological menopause typically involves progressive LDL-C elevation with mild TG increase [351]. Women with PCOS show high prevalence of dyslipidemia, with 28–58% displaying elevated TG or low HDL-C [351].

Regular monitoring every 6–12 months, combined with comprehensive CV risk assessment, is recommended. Early initiation of estrogen replacement therapy, particularly via transdermal routes, can significantly improve lipid profiles [352]. Understanding the predominant dyslipidemic patterns in each subgroup allows personalized management and timely CV risk reduction [352] Table 9.

Table 9 Typical lipid profile in female hypogonadism

Parameter	Change	Mechanism
TC	↑	Reduced LDL-R activity; impaired clearance
LDL-C	↑	Reduced receptor-mediated clearance
HDL-C	↔ or ↓	Reduced ApoA-I synthesis; qualitative HDL impairment
TG	↔ or ↑	Increased in mixed dyslipidemia and insulin resistance
LDL particle quality	↑ sd-LDL (in mixed dyslipidemia)	Increased atherogenicity
ApoB	no data available	—
ApoA-I	↓	Reduced synthesis post-menopause
Lp(a)	↔	Generally stable

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a).

Medical treatment

Hormone replacement therapy comprises a combination of synthetic hormones that may be identical to those secreted from the ovaries during the reproductive years (estradiol and progesterone) [353]. Progestogen supplementation is not needed in women with the absence of uterus who can receive unopposed estrogen. Tibolone is another Hormone replacement therapy option; it belongs to the group of normethyltestosterone progestogen derivatives and it exhibits estrogenic, progestogenic and androgenic effects. Hypoestrogenism in postmenopausal or POI women can lead to vasomotor symptoms or genito-urinary symptoms (like vaginal, dryness and lower urinary tract symptoms) as well as longer term problems such as osteoporosis. The evidence now strongly support that hormone replacement therapy can improve hot flushes, genito-urinary symptoms and keep bones healthy, reducing the chance of osteoporosis either in postmenopausal women and in women with POI [353].

In POI women hormone replacement therapy may also help to prevent heart disease, suggesting continuing the treatment till the time at which they would naturally go through the menopause, at around 50. In postmenopausal women, discussion about whether, or how long, to continue the treatment should be guided through some important considerations on CV risk, due to the publication of the initial Women's Health Initiative trial results [354]. According to the timing hypotesis, a window of opportunity for hormone replacement therapy in postmenopausal women has now been well-recognized. Women who initiate estrogen therapy younger than 60 years and/or within 10 years of menopause show a 30% reduction of all causes mortality, a 50% reduction in CV mortality and myocardial infarction[354]. By using oral estrogens administration, a significant increase of VTE was also observed, which was not observed by using transdermal formulations [355].

Concerning metabolic effects, important data were reported by a recent meta-analysis which includes 17 non-duplicate RCTs with a total of 29,287 postmenopausal women, consisting of 15,350 (mean age ranged from 47 to 75 years) who were randomized to hormone replacement therapy including E alone (n = 5,553) or E + P (n = 9,797),

and 13,937 randomized to placebo [356]. In healthy, non-diabetic postmenopausal women hormone replacement therapy significantly lowers insulin resistance, with E alone demonstrating a greater reduction as compared to combined E + P therapy [356]. A previous meta-analysis showed important metabolic improvement also hormone replacement therapy vs placebo in women with diabetes [357]. In particular, hormone replacement therapy reduced fasting glucose, HOMA-IR, mean blood pressure and LDL-C/HDL-C ratio [357]. A recent systematic review and meta-analysis was specifcally aimed at investigating the impact of the administration of medroxyprogesterone acetate plus conjugated equine oestrogens on the lipid profile in postmenopausal women [358]. Hormone replacement therapy significantly affects serum lipids' concentrations by inducing a notable increase of HDL-C and TG levels while reducing LDL-C and TC values. These data indicate that postmenopausal women might have beneficial effect from hormone replacement therapy [358]. A systematic review and meta-analysis reported that tibolone also decreased TC, HDL-C and TG levels, whilst LDL-C concentrations were significantly treatment duration ≤ 26 weeks [359].

Concerning breast cancer risk, consistent evidence shown an increase in breast cancer risk among postmenopausal women with estrogen-plus-progestin hormone replacement therapy whilst estrogen-alone hormone replacement therapy has little impact on breast cancer risk in naturally or surgically menopausal women. Collective evidence also suggests that estrogen hormone replacement therapy is likely to offer health benefits to perimenopausal or postmenopausal women, including breast cancer survivors, as well as young BRCA1/2 carriers with prophylactic oophorectomy for ovarian cancer prevention [360].

Neurokinin 3 receptor antagonists have been recently developed as new non-hormonal treatment for counteracting vasomotor symptoms in menopausal women. Fezolinetant is one of the first approved and entered in the market in many countries, including the US, Europe, and Australia, at a dose of 45 mg once daily. It showed a relevant effect in reducing vasomotor symptoms due to menopause [361]. The most common adverse effects in the fezolinetant treated women were reported to be covid-19 (13.3%), headache (8.8%), and fatigue (5.8%) [362].

Nutritional intervention

Menopause is often accompanied by vasomotor, psychological, metabolic, and urogenital symptoms that significantly affect quality of life [363]. While hormone replacement therapy remains the standard treatment, many women turn to dietary modifications and food supplements as complementary or alternative strategies. Vasomotor symptoms (VMS), including hot flushes and night sweats, are among the most common manifestations of menopause. Evidence suggests that adopting healthy dietary patterns, particularly those rich in fruits, vegetables, wholegrains, legumes, and unsaturated fats, may contribute to a reduction in VMS, particularly when coupled with weight loss [363]. Large trials, such as the Women's Health Initiative Dietary Modification Trial, demonstrated that weight reduction was strongly associated with the alleviation of symptoms [364], while observational studies linked Mediterranean-type diets to decreased prevalence of VMS [365, 366]. Furthermore, RCTs suggest potential benefits of plant-based or vegan diets incorporating soy, although the role of bodyweight reduction as a confounder cannot be excluded [367, 368]. Isoflavones, plant-derived phytoestrogens abundant in soy, have been extensively investigated due to their structural similarity to estradiol [369]. Meta-analyses show mixed results, with some reporting significant reductions in hot flush frequency and severity, while others found no effect, largely due to heterogeneity in dosage, population characteristics, and duration [369, 370]. Equol, a metabolite of the soy isoflavone daidzein produced by intestinal bacteria, has been suggested to modulate individual responsiveness, with studies indicating that equol producers may derive greater benefit [371]. However, supplementation with equol yielded inconsistent results, and more robust studies are warranted [371]. Evidence for other phytoestrogens, such as lignans from flaxseed, remains limited and inconclusive [372], while red clover supplementation shows some promise but is not consistently supported by high-quality trials [373]. Botanical agents, including black cohosh and St John's Wort, have been examined for their role in managing VMS and psychological symptoms, yet findings remain inconclusive and concerns regarding dosage, preparation variability, and safety preclude routine clinical recommendations [373, 374].

Menopause is also associated with adverse changes in bodyweight and composition, such as increased fat mass, particularly visceral adiposity, and decreased lean mass [375]. Dietary interventions focusing on energy restriction, low-fat or fiber-rich diets, and calorie-controlled Mediterranean dietary models have consistently demonstrated beneficial effects on bodyweight and fat mass [375]. However, lean mass reductions are common, highlighting the importance of dietary protein intake and possibly exercise as adjuncts [376]. Evidence for specific macronutrient manipulations, such as high-protein or low-carbohydrate approaches, remains mixed, and long-term sustainability is uncertain [377]. Supplementation with phytoestrogens for weight management has yielded inconsistent findings, with some reports of modest reductions in bodyweight among non-Asian women, while others show no effect

[378]. Similarly, supplementation with omega-3 fatty acids, conjugated linoleic acid, calcium, vitamin D, or protein has produced variable results, suggesting that calorie balance rather than single-nutrient strategies remains central in bodyweight management during menopause [377].

Beyond VMS and weight changes, other symptoms such as joint pain, skin alterations, sleep disturbances, and urogenital complaints may also be influenced by diet, although evidence is limited. Some studies suggest that dietary interventions combining phytoestrogens, vitamins, or collagen supplementation may improve skin elasticity, hydration, or wrinkle depth, while others report modest benefits in joint pain relief with omega-3 fatty acids or phytoestrogens [379]. Nonetheless, methodological limitations and heterogeneity hinder definitive conclusions [377]. Urogenital symptoms, grouped under the term genitourinary syndrome of menopause, appear less responsive to dietary modifications; most trials, including those investigating phytoestrogens or vitamin D, have not demonstrated significant improvements, with only small-scale studies reporting marginal effects of botanical supplements such as fenugreek [380, 381]. Psychological symptoms, particularly depression and anxiety, are also prevalent during the menopausal transition. Observational studies support associations between healthier dietary patterns and improved mood, while limited RCTs indicate that diets such as DASH or Mediterranean-type interventions may confer benefits [382].

Beyond dietary composition, recent findings highlight the role of chrononutrition for menopause [383–385]. In a cross-sectional study of 100 postmenopausal women with overweight or obesity, found that lipid intake timing significantly influenced symptom severity: lower morning intake was linked to greater heart discomfort, whereas higher evening intake worsened CV-related symptoms. These associations persisted after adjusting for confounders, suggesting that not only diet quality but also nutrient timing may modulate menopausal symptoms and cardiometabolic risk. Favoring earlier intake of energy and lipids may therefore represent a useful nutritional strategy to improve symptom management and overall health in this population [384].

Polycistic ovary syndrome

Pathophysiological mechanisms

Dyslipidemia is certainly the most prevalent and persistent among CV risk factors in women with PCOS [386]. Obesity, particularly abdominal obesity, that is frequently associated to PCOS, notely enters into the pathophysiology of dyslipidemia, probalbly through mechanisms not dissimilar from the general population [387]. Among the pathophysiological factors more specific to PCOS, hyperandrogenism plays a trigger role [388]. Testosterone, in particular, acts increasing catabolism of HDL, through upregulation of two genes, scavenger receptor B1 and hepatic lipase [388]. In addition, testosterone decreases catabolic removal of LDL by attenuating estrogen receptor-mediated induction of LDL-R activity [388], and produces or aggravates insulin resistance [388]. Accordingly, of those PCOS with insulin resistance, 81% demonstrated lipid abnormalities compared with 65% of those with normal insulin sensitivity. Hepatic overproduction of ApoB-containing VLDL seems to be the crucial mechanism linking insulin resistance and hypertriglyceridemia [389]. Low HDL levels are also frequently associated with hypertriglyceridemia in insulin-resistant states. Oxidative stress, that is higly associated to PCOS even in normal-weight condition, has also been recognized in the pathophysiology of dyslipidemia [390].

Laboratory abnormalities

Women with PCOS commonly present with a characteristic atherogenic lipid profile, influenced by obesity, particularly abdominal obesity, insulin resistance (IR), and hyperandrogenism [386, 387]. LDL-C elevation is frequently observed in both lean and obese patients, and even in cases of normal LDL-C, women with PCOS are more likely to display atherogenic sd-LDL particles, particularly when circulating levels of sex hormone-binding globulin (SHBG) are low, reflecting hyperandrogenism and IR [391]. Low HDL-C is also commonly reported, especially in the presence of obesity and IR, whereas TG elevations are consistent and often appear early in life. Hepatic overproduction of ApoB-containing VLDL, driven by insulin resistance, represents a key mechanism linking hypertriglyceridemia to metabolic disturbances [389]. Hyperandrogenism contributes by increasing HDL catabolism through upregulation of scavenger receptor B1 and hepatic lipase, and by attenuating LDL-R mediated LDL clearance [388]. Oxidative stress, highly prevalent in PCOS even among normal-weight women, further aggravates lipid abnormalities [390]. Moreover, elevated Lp(a) concentrations have been observed in approximately one-quarter of PCOS women, suggesting an additional pro-atherogenic factor [392]. Lipid disturbances are aggravated by a positive family history of menstrual abnormalities and type 2 diabetes [393]. Women with PCOS and with obesity frequently exhibit the “atherogenic type” of dyslipidemia, characterized by low HDL-C, sd-LDL particles, and elevated TG [394]. Overall, the lipid profile in PCOS is frequently mixed/atherogenic, with variability according to obesity, IR, hyperandrogenism, and genetic/familial predisposition, highlighting the importance

of early screening and longitudinal monitoring for CV risk [388] Table 10.

Medical treatment

Insulin-sensitizing drugs (metformin and pioglitazone) in women with PCOS did not demonstrate significant change in lipid levels. The effect of metformin or pioglitazone as monotherapy on lipids in women with PCOS remains modest with mainly significant positive effect on the decrease in TG [395].

The effects of combined oral contraceptive pills (OCPs) in lipid metabolism in PCOS are not dissimilar from the general population; they generally increase HDL-C levels, with more evidente effects of forth generation vs. third generation OCPs, but they frequently increase LDL-C and TG. Therefore, OCPs therapy cannot be considered for the treatment of dyslipidemia in women with PCOS, at least with the compounds available [396].

The studies with statins (simvastatin and atorvastatin) in normal weight and obese women with PCOS showed that the use of statins was safe and effective in lowering total cholesterol, LDL-C and TG but without significant effect on HDL-C [395, 397]. A hypothesis of the beneficial effect of statins on lipid profile in PCOS is also through a reduction of hyperandrogenemia [389]. In vitro studies have, in fact, shown an inhibition of ovarian steroidogenic enzymes by statins. Moreover, statins reduce cholesterol availability by reducing cholesterol synthesis, a necessary substrate for steroid hormone synthesis [389]. Furthermore, statins possess both direct and indirect antioxidant activity, and oxydative stress contributes to hyperandrogenism in PCOS [398].

Table 10 Typical lipid profile in PCOS

Parameter	Change	Mechanism
TC	↑	Impaired LDL clearance; hepatic VLDL overproduction
LDL-C	↑	sd-LDL more prevalent; hyperandrogenism-related
HDL-C	↓	Androgen-mediated HDL catabolism; worsened by insulin resistance
TG	↑	Increased VLDL synthesis due to insulin resistance
LDL particle quality	↑ sd-LDL	Increased atherogenic particles
ApoB	no data available	—
ApoA-I	no data available	—
Lp(a)	↑	Elevated in a subset

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(a), lipoprotein(a).

However, a recent Cochrane analysis of the clinical studies with statins versus placebo or of statins plus metformin versus metformin in PCOS did not demostrate the superiority of statins in reducing testosterone circulating levels [399]. This Cochrane analysis did not also found any ameliorating effect of statin use (alone or combined with oral contraceptives-OCPs or metformin) on serum fasting insulin concentration or insulin resistance measured by HOMA-IR [399]. However, the number of studies included in the Cochrane analysis was extremely limited and, therefore, the conclusions of very low certainty [399]. Therefore, further well-designed RCTs are needed to support and increase the current level of evidence and help to position the use of statins in PCOS management. In particular, further research is needed to establish clear recommendations for their use in PCOS managemens, including which patients would benefict most, when to start treatment, the optimal duration of therapy, the specific effectiveness of statins in PCOS and the potential beneficts of combining statins with other treatments.This is a priority, since dyslipidemia is the most prevalent CV risk factor in women with PCOS, that is a high risk disease for CV events for the high prevalence of other CV risk factors such as obesity, hypertension, and diabetes.

Nutritional intervention

Nutritional strategies are central to the management of PCOS, not only for weight control but also for the amelioration of lipid abnormalities and the improvement of overall metabolic and reproductive health [400]. Current international guidelines emphasize lifestyle interventions, including dietary modifications and structured physical activity, as first-line therapy for all women with PCOS, irrespective of weight status [400].

Among dietary patterns, the Mediterranean diet is one of the most extensively studied and recommended for PCOS management [401]. Its emphasis on fruits, vegetables, whole grains, legumes, fish, extra virgin olive oil, and nuts provides a nutrient-dense profile rich in monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), antioxidants, and fiber, which together contribute to improved insulin sensitivity, reduction of low-grade inflammation, and favorable effects on lipid profiles [401]. Observational and interventional studies suggest that adherence to the Mediterranean diet is associated with improved metabolic outcomes, decreased visceral adiposity, and better reproductive function in women with PCOS, while also lowering CV risk [402–404].

Another strategy with growing evidence in PCOS is the adoption of low-glycemic index (GI) and low-glycemic load (GL) diets [405]. These diets, by attenuating postprandial glucose and insulin excursions, directly target insulin

resistance, a key driver of dyslipidemia in PCOS [406]. Clinical trials indicate that low-GI/GL dietary approaches improve insulin sensitivity, reduce circulating TG, and favorably modulate sex hormone-binding globulin (SHBG) and androgen levels, leading to improved menstrual regularity and ovulatory function [407].

Ketogenic diets have also been investigated in PCOS [408, 409]. By markedly reducing carbohydrate intake and promoting ketone body production, Ketogenic diets can lead to significant weight loss, improved glycemic control, and reductions in TG. Evidence suggests potential benefits for hyperandrogenism and menstrual cyclicity. However, concerns regarding the long-term safety, sustainability, and potential impact on LDL-C remain, making these diets a possible short-term therapeutic option under medical supervision, particularly in women with severe insulin resistance or obesity [408, 409].

In addition, intermittent fasting (IF) and time-restricted feeding (TRF) have emerged as novel strategies with potential application in PCOS [410, 411]. By modulating circadian rhythms, reducing insulin secretion, and promoting metabolic flexibility, IF/TRF may improve insulin sensitivity, weight control, and lipid parameters. Although data in PCOS are still preliminary, early evidence suggests improvements in metabolic markers and reproductive hormones, warranting further investigation [410, 411].

The role of specific nutrients and supplementation is also relevant. Vitamin D deficiency is common in PCOS and correlates with insulin resistance and dyslipidemia [412]. Supplementation has been shown to improve insulin sensitivity and lipid profiles in some studies, although results are heterogeneous [413]. Omega-3 fatty acids, through their anti-inflammatory and TG-lowering properties, represent another adjunctive option, with evidence supporting their capacity to improve lipid abnormalities and reduce androgen levels in PCOS. Other widely used micronutrients include inositol isomers (myo-inositol, D-chiro-inositol), which modulate insulin signaling and have been shown to improve ovulatory function and lipid metabolism [414], as well as pro- and prebiotics, which may act through modulation of gut microbiota and systemic inflammation [415].

A unifying concept across dietary interventions in PCOS is the focus on anti-inflammatory, nutrient-dense, and sustainable dietary patterns rather than restrictive caloric approaches alone [416]. The heterogeneity of PCOS phenotypes requires tailored nutritional strategies: for women with PCOS and overweight or obesity, energy restriction may be necessary to induce weight loss and improve metabolic health; whereas in women with normal weight, dietary quality, macronutrient distribution, and micronutrient adequacy remain crucial to target dyslipidemia and reproductive dysfunction. Importantly, psychological well-being and long-term adherence should be prioritized to avoid the detrimental cycle of restrictive dieting and weight regain, which can exacerbate metabolic complications [416].

In conclusion, nutrition plays a pivotal role in the management of PCOS-related dyslipidemia, Evidence supports the Mediterranean diet, low-GI/GL diets, ketogenic and low-carbohydrate approaches, intermittent fasting, and targeted supplementation as potential strategies, with benefits extending beyond lipid metabolism to insulin sensitivity, hormonal balance, and reproductive outcomes. Given the variability of PCOS phenotypes and individual responses to dietary interventions, a personalized, patient-centered approach is warranted, ideally within a multidisciplinary framework involving endocrinologists, nutritionists, and allied healthcare professionals. Future research should further clarify the comparative and long-term efficacy of different dietary strategies, with a focus on CV outcomes and the prevention of type 2 diabetes in this high-risk population.

Conclusions

Endocrine-related dyslipidemias represent a clinically significant yet frequently underestimated contributor to overall CV risk. Hormonal disturbances affecting the hypothalamic–pituitary, thyroid, adrenal, gonadal, and GH/IGF-1 axes lead to distinct, disease-specific lipid profiles through complex mechanisms involving lipoprotein synthesis, transport, and clearance. These alterations substantially promote atherosclerosis and cardiometabolic complications, often beyond the impact of traditional CV risk factors.

Despite their high prevalence and well-documented clinical relevance, dyslipidemias secondary to endocrine disorders are commonly underdiagnosed and suboptimally managed in routine practice. Early recognition of characteristic lipid patterns, as summarized in Fig. 1, and their appropriate interpretation within the endocrine context are essential for accurate CV risk stratification. Moreover, effective treatment of the underlying endocrine disease, combined with targeted lipid-lowering interventions when indicated, may result in meaningful improvements in cardiometabolic outcomes.

This Position Statement highlights the need for an integrated, multidisciplinary approach involving endocrinologists, cardiologists, and primary care physicians to optimize the management of secondary dyslipidemias. Increased awareness of the underlying pathophysiological mechanisms and their clinical implications is crucial to translate current evidence into more effective preventive and therapeutic strategies, ultimately reducing the CV burden in patients with endocrine diseases.

		Lipid parameters							
		TC	LDL-C	HDL-C	TG	LDL particle quality	ApoB	ApoA-I	Lp(a)
Endocrine diseases	Acromegaly	↔ or slightly ↓	↔ or slightly ↓	↓	Mild–moderate ↑	↑ sd-LDL	↔ or slightly ↓	↔ or ↓	↑
	GH deficiency	↑	↑	↔ or ↓	↔ or ↑	↔ or ↑ sd-LDL	↔ or ↑	↔ or ↓	↔ or ↑
	Subclinical hypothyroidism	↑	↑	↔ or ↓	↔ or slightly ↑	↔ or ↑ sd-LDL	↔	↔	↔
	Overt hypothyroidism	↑	↑	↔ or ↓	↑	↑ sd-LDL	↔ or slightly ↑	↔	↑
	Hyperthyroidism	↓	↓	↔ or ↓	↔ or ↓	n/a	↓	↔ or ↓	↔
	Addison's disease	↔ or ↑	↔ or ↑	↔ or ↓	↔ or ↑	n/a	↔ or ↑	↔ or ↓	↔
	CAH	↔ or ↑	↔ or ↑	↓	↔ or ↑	n/a	↔ or ↑	↔ or ↓	↔
	Cushing's syndrome	↑	↑	↓	↑	↑ sd-LDL	↑	↓	↔ or ↑
	Male hypogonadism	↔ or ↑	↔ or ↑	↓	↑	↑ sd-LDL	↔ or ↑	↓	n/a
	Female hypogonadism	↑	↑	↔ or ↓	↔ or ↑	↑ sd-LDL	n/a	↓	↔
	PCOS	↑	↑	↓	↑	↑ sd-LDL	n/a	n/a	↑

Increase | Decrease | Mixed/ uncertain | No change | No data available

Fig. 1 Lipid profile alterations across endocrine disorders. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; sd-LDL, small dense low-density lipoprotein; ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; Lp(**a**), lipoprotein(**a**); GH, growth hormone; CAH, congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome

Author contributions All authors contributed to the study conception and design. The first draft of the manuscript was written by all authors and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors did not receive support from any organization for the submitted work.

Data Availability No primary data were generated or analyzed for this work. All information supporting this article is derived from previously published studies, which are cited within the manuscript.

Declarations

Conflicts of interest Flavia Prodram has served on advisory boards for Novartis.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

References

1. Gadelha MR, Kasuki L, Lim DST, Fleseriu M (2019) Systemic complications of acromegaly and the impact of the current treatment landscape: an update. Endocr Rev 40(1):268–332
2. Melmed S, di Filippo L, Fleseriu M, Mercado M, Karavitaki N, Gurnell M et al (2025) Consensus on acromegaly therapeutic outcomes: an update. Nat Rev Endocrinol 21(11):718–737
3. Pivonello R, Auriemma RS, Grasso LF, Pivonello C, Simeoli C, Patalano R et al (2017) Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. Pituitary 20(1):46–62
4. Moller N, Jorgensen JO (2009) Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 30(2):152–177
5. Rajpathak SN, Gunter MJ, Wylie-Rosett J, Ho GY, Kaplan RC, Muzumdar R et al (2009) The role of insulin-like growth factor-I and its binding proteins in glucose homeostasis and type 2 diabetes. Diabetes Metab Res Rev 25(1):3–12
6. Chaves VE, Junior FM, Bertolini GL (2013) The metabolic effects of growth hormone in adipose tissue. Endocrine 44(2):293–302

7. Szego CM, White A (1948) The influence of purified growth hormone on fasting metabolism. J Clin Endocrinol Metab 8(7):594
8. Hansen TK, Gravholt CH, H OR, Rasmussen MH, Christiansen JS, Jorgensen JO (2002) Dose dependency of the pharmacokinetics and acute lipolytic actions of growth hormone. J Clin Endocrinol Metab 87(10):4691–4698
9. Olivecrona G (2016) Role of lipoprotein lipase in lipid metabolism. Curr Opin Lipidol 27(3):233–241
10. Pratipanawatr T, Pratipanawatr W, Rosen C, Berria R, Bajaj M, Cusi K et al (2002) Effect of IGF-I on FFA and glucose metabolism in control and type 2 diabetic subjects. Am J Physiol Endocrinol Metab 282(6):E1360–E1368
11. Scavo LM, Karas M, Murray M, Leroith D (2004) Insulin-like growth factor-I stimulates both cell growth and lipogenesis during differentiation of human mesenchymal stem cells into adipocytes. J Clin Endocrinol Metab 89(7):3543–3553
12. Costanza F, Basile C, Chiloiro S, Hessman E, Chantzichristos D, Pontecorvi A et al (2025) Impact of pasireotide on lipid and glucose metabolism in patients with acromegaly: A systematic review and meta-analysis. J Endocrinol Invest. https://doi.org/10.1007/s40618-025-02642-0
13. Dal J, Rosendal C, Karmisholt J, Feldt-Rasmussen U, Andersen MS, Klose M et al (2023) Sex difference in patients with controlled acromegaly-A multicentre survey. Clin Endocrinol (Oxf) 98(1):74–81
14. Mercado M, Ramirez-Renteria C (2018) Metabolic complications of acromegaly. Front Horm Res 49:20–28
15. Beentjes JA, van Tol A, Sluiter WJ, Dullaart RP (2000) Low plasma lecithin:cholesterol acyltransferase and lipid transfer protein activities in growth hormone deficient and acromegalic men: role in altered high density lipoproteins. Atherosclerosis 153(2):491–498
16. Olarescu NC, Heck A, Godang K, Ueland T, Bollerslev J (2016) The metabolic risk in patients newly diagnosed with acromegaly is related to fat distribution and circulating adipokines and improves after treatment. Neuroendocrinology 103(3–4):197–206
17. Esposito D, Boguszewski CL, Colao A, Fleseriu M, Gatto F, Jorgensen JOL et al (2024) Diabetes mellitus in patients with acromegaly: pathophysiology, clinical challenges and management. Nat Rev Endocrinol 20(9):541–552
18. Giordano C, Ciresi A, Amato MC, Pivonello R, Auriemma RS, Grasso LF et al (2012) Clinical and metabolic effects of first-line treatment with somatostatin analogues or surgery in acromegaly: a retrospective and comparative study. Pituitary 15(4):539–551
19. Feingold KR. (2000) The Effect of Endocrine Disorders on Lipids and Lipoproteins. In: Feingold KR, Ahmed SF, Anawalt B, Blackman MR, Boyce A, Chrousos G, et al., editors. Endotext. South Dartmouth (MA).
20. Wildbrett J, Hanefeld M, Fucker K, Pinzer T, Bergmann S, Siegert G et al (1997) Anomalies of lipoprotein pattern and fibrinolysis in acromegalic patients: relation to growth hormone levels and insulin-like growth factor I. Exp Clin Endocrinol Diabetes 105(6):331–335
21. Romanisio M, Pitino R, Ferrero A, Pizzolitto F, Costelli S, Antoniotti V et al (2023) Discordant biochemical parameters of acromegaly remission do not influence the prevalence or aggressiveness of metabolic comorbidities: a single-center study. Front Endocrinol (Lausanne) 14:1256975
22. Boero L, Manavela M, Merono T, Maidana P, Gomez Rosso L, Brites F (2012) GH levels and insulin sensitivity are differently associated with biomarkers of cardiovascular disease in active acromegaly. Clin Endocrinol (Oxf) 77(4):579–585
23. Nikkila EA, Pelkonen R (1975) Serum lipids in acromegaly. Metabolism 24(7):829–838
24. Sumino H, Murakami M (2016) [Causes and abnormal lipid laboratory values of secondary hyperlipidemia: endocrine disease]. Rinsho Byori 64(5):513–517
25. Maldonado Castro GF, Escobar-Morreale HF, Ortega H, Gomez-Coronado D, Balsa Barro JA, Varela C et al (2000) Effects of normalization of GH hypersecretion on lipoprotein(a) and other lipoprotein serum levels in acromegaly. Clin Endocrinol (Oxf) 53(3):313–319
26. Arosio M, Sartore G, Rossi CM, Casati G, Faglia G, Manzato E (2000) LDL physical properties, lipoprotein and Lp(a) levels in acromegalic patients. Effects of octreotide therapy. Atherosclerosis 151(2):551–557 (**Italian Multicenter Octreotide Study Group**)
27. Tan KC, Shiu SW, Janus ED, Lam KS (1997) LDL subfractions in acromegaly: relation to growth hormone and insulin-like growth factor-I. Atherosclerosis 129(1):59–65
28. Maffei P, Sicolo N, Plebani M (1999) Lipoprotein(a) in acromegaly. Ann Intern Med 130(6):537–538
29. Vilar L, Naves LA, Costa SS, Abdalla LF, Coelho CE, Casulari LA (2007) Increase of classic and nonclassic cardiovascular risk factors in patients with acromegaly. Endocr Pract 13(4):363–372
30. Cohen R, Chanson P, Bruckert E, Timsit J, Legrand A, Harris AG et al (1992) Effects of octreotide on lipid metabolism in acromegaly. Horm Metab Res 24(8):397–400
31. Shao XQ, Chen ZY, Wang M, Yang YP, Yu YF, Liu WJ et al (2022) Effects of Long-Acting Somatostatin Analogues on Lipid Metabolism in Patients with Newly Diagnosed Acromegaly: A Retrospective Study of 120 Cases. Horm Metab Res 54(1):25–32
32. Wang M, Guo S, He M, Shao X, Feng L, Yu Y et al (2020) High-Performance Liquid Chromatography-Mass Spectrometry-Based Lipid Metabolite Profiling of Acromegaly. J Clin Endocrinol Metab 105(3):34
33. Bredella MA, Schorr M, Dichtel LE, Gerweck AV, Young BJ, Woodmansee WW et al (2017) Body composition and ectopic lipid changes with biochemical control of acromegaly. J Clin Endocrinol Metab 102(11):4218–4225
34. Fellinger P, Wolf P, Pfleger L, Krumpolec P, Krssak M, Klavins K et al (2020) Increased ATP synthesis might counteract hepatic lipid accumulation in acromegaly. JCI Insight. 5(5):34
35. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C et al (2020) A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update. J Clin Endocrinol Metab 105(4):45
36. Slagboom TNA, van Bunderen CC, De Vries R, Bisschop PH, Drent ML (2023) Prevalence of clinical signs, symptoms and comorbidities at diagnosis of acromegaly: a systematic review in accordance with PRISMA guidelines. Pituitary 26(4):319–332
37. Jawiarczyk-Przybylowska A, Kuliczkowska-Plaksej J, Kolackov K, Zembska A, Halupczok-Zyla J, Rolla M et al (2023) FTO Gene Polymorphisms and Their Roles in Acromegaly. Int J Mol Sci 24(13):44
38. Ramos-Levi AM, Marazuela M (2019) Bringing cardiovascular comorbidities in acromegaly to an update. How should we diagnose and manage them? Front Endocrinol (Lausanne) 10:120
39. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al (2020) 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 41(1):111–188
40. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M et al (2022) 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol 29(1):5–115
41. Caron PJ, Petersenn S, Houchard A, Sert C, Bevan JS, Group PS (2017) Glucose and lipid levels with lanreotide autogel 120 mg in treatment-naive patients with acromegaly: data from the PRIMARYS study. Clin Endocrinol (Oxf) 86(4):541–551

42. Ciresi A, Amato MC, Guarnotta V, Lo Castro F, Giordano C (2013) Higher doses of cabergoline further improve metabolic parameters in patients with prolactinoma regardless of the degree of reduction in prolactin levels. Clin Endocrinol (Oxf) 79(6):845–852
43. Sesmilo G, Fairfield WP, Katznelson L, Pulaski K, Freda PU, Bonert V et al (2002) Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. J Clin Endocrinol Metab 87(4):1692–1699
44. Mishra M, Durrington P, Mackness M, Siddals KW, Kaushal K, Davies R et al (2005) The effect of atorvastatin on serum lipoproteins in acromegaly. Clin Endocrinol (Oxf) 62(6):650–655
45. Persson L, Cao G, Stahle L, Sjoberg BG, Troutt JS, Konrad RJ et al (2010) Circulating proprotein convertase subtilisin kexin type 9 has a diurnal rhythm synchronous with cholesterol synthesis and is reduced by fasting in humans. Arterioscler Thromb Vasc Biol 30(12):2666–2672
46. Newman CB (2023) Effects of endocrine disorders on lipids and lipoproteins. Best Pract Res Clin Endocrinol Metab 37(3):101667
47. Hupalowski NN, Sanches Rocha CP, Castaldo VF, Boguszewski CL, Cochenski Borba VZ (2025) Impact of nutrient intake on bone mineral density and bone quality in patients with acromegaly. Clin Nutr ESPEN 67:398–403
48. American Diabetes Association Professional Practice C. (2025) 10. Cardiovascular disease and risk management: Standards of care in diabetes-2025. Diabetes Care 48(1 Suppl 1):S207–S238
49. Diabetes, Nutrition Study Group of the European Association for the Study of D (2023) Evidence-based European recommendations for the dietary management of diabetes. Diabetologia 66(6):965–985
50. Marx N, Federici M, Schutt K, Muller-Wieland D, Ajjan RA, Antunes MJ et al (2023) 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 44(39):4043–4140
51. Delgado-Lista J, Alcala-Diaz JF, Torres-Pena JD, Quintana-Navarro GM, Fuentes F, Garcia-Rios A et al (2022) Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 399(10338):1876–1885
52. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F et al (2018) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 378(25):e34
53. Muszalska A, Wiecanowska J, Michalowska J, Pastusiak-Zgolinska KM, Polok I, Lompies K et al (2025) The Role of the Planetary Diet in Managing Metabolic Syndrome and Cardiovascular Disease: A Narrative Review. Nutrients 17(5):344
54. Bensaaud A, Seery S, Gibson I, Jones J, Flaherty G, McEvoy JW et al (2025) Dietary Approaches to Stop Hypertension (DASH) for the primary and secondary prevention of cardiovascular diseases. Cochrane Database Syst Rev 5(5):34
55. Grottoli S, Gasco V, Mainolfi A, Beccuti G, Corneli G, Aimaretti G et al (2008) Growth hormone/insulin-like growth factor I axis, glucose metabolism, and lypolisis but not leptin show some degree of refractoriness to short-term fasting in acromegaly. J Endocrinol Invest 31(12):1103–1109
56. Ho PJ, Friberg RD, Barkan AL (1992) Regulation of pulsatile growth hormone secretion by fasting in normal subjects and patients with acromegaly. J Clin Endocrinol Metab 75(3):812–819
57. Coopmans EC, Berk KAC, El-Sayed N, Neggers S, van der Lely AJ (2020) Eucaloric very-low-carbohydrate ketogenic diet in acromegaly treatment. N Engl J Med 382(22):2161–2162
58. Abs R, Feldt-Rasmussen U, Mattsson AF, Monson JP, Bengtsson BA, Goth MI et al (2006) Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults - a KIMS database analysis. Eur J Endocrinol 155(1):79–90
59. Hepprich M, Ebrahimi F, Christ E (2023) Dyslipidaemia and growth hormone deficiency - A comprehensive review. Best Pract Res Clin Endocrinol Metab 37(6):101821
60. Vijayakumar A, Yakar S, Leroith D (2011) The intricate role of growth hormone in metabolism. Front Endocrinol (Lausanne) 2:32
61. Salomon F, Cuneo RC, Hesp R, Sonksen PH (1989) The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321(26):1797–1803
62. Zachmann M, Fernandez F, Tassinari D, Thakker R, Prader A (1980) Anthropometric measurements in patients with growth hormone deficiency before treatment with human growth hormone. Eur J Pediatr 133(3):277–282
63. Rudling M, Parini P, Angelin B (1997) Growth hormone and bile acid synthesis. Key role for the activity of hepatic microsomal cholesterol 7alpha-hydroxylase in the rat. J Clin Invest 99(9):2239–2245
64. Ciresi A, Pizzolanti G, Leotta M, Guarnotta V, Teresi G, Giordano C (2016) Resistin, visfatin, leptin and omentin are differently related to hormonal and metabolic parameters in growth hormone-deficient children. J Endocrinol Invest 39(9):1023–1030
65. Sesmilo G, Miller KK, Hayden D, Klibanski A (2001) Inflammatory cardiovascular risk markers in women with hypopituitarism. J Clin Endocrinol Metab 86(12):5774–5781
66. Barbosa EJ, Glad CA, Nilsson AG, Filipsson Nystrom H, Gotherstrom G, Svensson PA et al (2012) Genotypes associated with lipid metabolism contribute to differences in serum lipid profile of GH-deficient adults before and after GH replacement therapy. Eur J Endocrinol 167(3):353–362
67. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P et al (2004) Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized. Placebo-Controlled Trials J Clin Endocrinol Metab 89(5):2192–2199
68. Abdu TA, Neary R, Elhadd TA, Akber M, Clayton RN (2001) Coronary risk in growth hormone deficient hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. Clin Endocrinol (Oxf) 55(2):209–216
69. de Boer H, Blok GJ, Van der Veen EA (1995) Clinical aspects of growth hormone deficiency in adults. Endocr Rev 16(1):63–86
70. Di Somma C, Scarano E, Savastano S, Savanelli MC, Pivonello R, Colao A (2017) Cardiovascular alterations in adult GH deficiency. Best Pract Res Clin Endocrinol Metab 31(1):25–34
71. Gacs G, Romics L (1987) Effect of growth hormone on serum lipoproteins in growth hormone deficiency. Exp Clin Endocrinol 90(2):227–231
72. Schaefer GB, Greger NG, Fesmire JD, Blackett PR, Wilson DP, Frindik JP (1994) Lipids and apolipoproteins in growth hormone-deficient children during treatment. Metabolism 43(12):1457–1461
73. Winter RJ, Green OC (1984) Effect of thyroxine and growth hormone on the hypercholesterolemia of growth hormone deficiency. Metabolism 33(1):54–57
74. Kuromaru R, Kohno H, Ueyama N, Hassan HM, Honda S, Hara T (1998) Long-term prospective study of body composition and lipid profiles during and after growth hormone (GH) treatment in children with GH deficiency: gender-specific metabolic effects. J Clin Endocrinol Metab 83(11):3890–3896
75. Sas T, Mulder P, Hokken-Koelega A (2000) Body composition, blood pressure, and lipid metabolism before and during long-term growth hormone (GH) treatment in children with short stature born small for gestational age either with or without GH deficiency. J Clin Endocrinol Metab 85(10):3786–3792

76. Winter RJ, Thompson RG, Green OC (1979) Serum cholesterol and triglycerides in children with growth hormone deficiency. Metabolism 28(12):1244–1249
77. Binay C, Simsek E, Yildirim A, Kosger P, Demiral M, Kilic Z (2015) Growth hormone and the risk of atherosclerosis in growth hormone-deficient children. Growth Horm IGF Res 25(6):294–297
78. Capalbo D, Lo Vecchio A, Farina V, Spinelli L, Palladino A, Tiano C et al (2009) Subtle alterations of cardiac performance in children with growth hormone deficiency: results of a two-year prospective, case-control study. J Clin Endocrinol Metab 94(9):3347–3355
79. De Leonibus C, De Marco S, Stevens A, Clayton P, Chiarelli F, Mohn A (2016) Growth hormone deficiency in prepubertal children: predictive markers of cardiovascular disease. Horm Res Paediatr 85(6):363–371
80. Lanes R (2004) Metabolic abnormalities in growth hormone deficiency. Pediatr Endocrinol Rev 2(2):209–215
81. Vahl N, Juul A, Jorgensen JO, Orskov H, Skakkebaek NE, Christiansen JS (2000) Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. J Clin Endocrinol Metab 85(5):1874–1881
82. Carroll PV, Drake WM, Maher KT, Metcalfe K, Shaw NJ, Dunger DB et al (2004) Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. J Clin Endocrinol Metab 89(8):3890–3895
83. Johannsson G, Albertsson-Wikland K, Bengtsson BA (1999) Discontinuation of growth hormone (GH) treatment: metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. J Clin Endocrinol Metab 84(12):4516–4524
84. Tauber M, Jouret B, Cartault A, Lounis N, Gayrard M, Marcouyeux C et al (2003) Adolescents with partial growth hormone (GH) deficiency develop alterations of body composition after GH discontinuation and require follow-up. J Clin Endocrinol Metab 88(11):5101–5106
85. Koltowska-Haggstrom M, Geffner ME, Jonsson P, Monson JP, Abs R, Hana V et al (2010) Discontinuation of growth hormone (GH) treatment during the transition phase is an important factor determining the phenotype of young adults with nonidiopathic childhood-onset GH deficiency. J Clin Endocrinol Metab 95(6):2646–2654
86. Lee YJ, Choi Y, Yoo HW, Lee YA, Shin CH, Choi HS et al (2022) Metabolic Impacts of Discontinuation and Resumption of Recombinant Human Growth Hormone Treatment during the Transition Period in Patients with Childhood-Onset Growth Hormone Deficiency. Endocrinol Metab (Seoul) 37(2):359–368
87. Rothermel J, Lass N, Bosse C, Reinehr T (2017) Impact of discontinuation of growth hormone treatment on lipids and weight status in adolescents. J Pediatr Endocrinol Metab 30(7):749–757
88. Capaldo B, Patti L, Oliviero U, Longobardi S, Pardo F, Vitale F et al (1997) Increased arterial intima-media thickness in childhood-onset growth hormone deficiency. J Clin Endocrinol Metab 82(5):1378–1381
89. Lanes R, Gunczler P, Lopez E, Esaa S, Villaroel O, Revel-Chion R (2001) Cardiac mass and function, carotid artery intima-media thickness, and lipoprotein levels in growth hormone-deficient adolescents. J Clin Endocrinol Metab 86(3):1061–1065
90. Cuneo RC, Salomon F, Watts GF, Hesp R, Sonksen PH (1993) Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. Metabolism 42(12):1519–1523
91. Giovannini L, Tirabassi G, Muscogiuri G, Di Somma C, Colao A, Balercia G (2015) Impact of adult growth hormone deficiency on metabolic profile and cardiovascular risk [Review]. Endocr J 62(12):1037–1048
92. O'Neal D, Hew FL, Sikaris K, Ward G, Alford F, Best JD (1996) Low density lipoprotein particle size in hypopituitary adults receiving conventional hormone replacement therapy. J Clin Endocrinol Metab 81(7):2448–2454
93. Colao A, Cerbone G, Pivonello R, Aimaretti G, Loche S, Di Somma C et al (1999) The growth hormone (GH) response to the arginine plus GH-releasing hormone test is correlated to the severity of lipid profile abnormalities in adult patients with GH deficiency. J Clin Endocrinol Metab 84(4):1277–1282
94. Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, Croce CG et al (2005) The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur J Endocrinol 153(2):257–264
95. Gasco V, Cuboni D, Varaldo E, Bioletto F, Berton AM, Bona C et al (2023) GHRH + arginine test and body mass index: do we need to review diagnostic criteria for GH deficiency? J Endocrinol Invest 46(10):2175–2183
96. Gasco V, Roncoroni L, Zavattaro M, Bona C, Berton A, Ghigo E et al (2020) Untreated adult GH deficiency is not associated with the development of metabolic risk factors: a long-term observational study. J Endocrinol Invest 43(2):197–207
97. Packard CJ, Demant T, Stewart JP, Bedford D, Caslake MJ, Schwertfeger G et al (2000) Apolipoprotein B metabolism and the distribution of VLDL and LDL subfractions. J Lipid Res 41(2):305–318
98. Rizzo M, Berneis K (2006) Low-density lipoprotein size and cardiovascular prevention. Eur J Intern Med 17(2):77–80
99. Rizzo M, Trepp R, Berneis K, Christ ER (2007) Atherogenic lipoprotein phenotype and low-density lipoprotein size and subclasses in patients with growth hormone deficiency before and after short-term replacement therapy. Eur J Endocrinol 156(3):361–367
100. Rizzo M, Trepp R, Berneis K, Christ ER (2008) Post-prandial alterations in LDL size and subclasses in patients with growth hormone deficiency. Growth Horm IGF Res 18(3):264–266
101. Yuen KCJ, Biller BMK, Radovick S, Carmichael JD, Jasim S, Pantalone KM et al (2019) American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care. Endocr Pract 25(11):1191–1232
102. Rissetti G, Zeni D, Ongaratti BR, Pereira-Lima JFS, Rech C, da Costa Oliveira M (2021) Lipid profile and response to statin therapy in patients with hypopituitarism. Arch Endocrinol Metab 64(6):673–678
103. Parini P, Angelin B, Lobie PE, Norstedt G, Rudling M (1995) Growth hormone specifically stimulates the expression of low density lipoprotein receptors in human hepatoma cells. Endocrinology 136(9):3767–3773
104. Newman CB, Carmichael JD, Kleinberg DL (2015) Effects of low dose versus high dose human growth hormone on body composition and lipids in adults with GH deficiency: a meta-analysis of placebo-controlled randomized trials. Pituitary 18(3):297–305
105. Florakis D, Hung V, Kaltsas G, Coyte D, Jenkins PJ, Chew SL et al (2000) Sustained reduction in circulating cholesterol in adult hypopituitary patients given low dose titrated growth hormone replacement therapy: a two year study. Clin Endocrinol (Oxf) 53(4):453–459
106. Monson JP, Jonsson P, Koltowska-Haggstrom M, Kourides I (2007) Growth hormone (GH) replacement decreases serum total and LDL-cholesterol in hypopituitary patients on maintenance HMG CoA reductase inhibitor (statin) therapy. Clin Endocrinol (Oxf) 67(4):623–628

107. Lind S, Rudling M, Ericsson S, Olivecrona H, Eriksson M, Borgstrom B et al (2004) Growth hormone induces low-density lipoprotein clearance but not bile acid synthesis in humans. Arterioscler Thromb Vasc Biol 24(2):349–356
108. Mozaffarian D (2016) Natural trans fat, dairy fat, partially hydrogenated oils, and cardiometabolic health: the Ludwigshafen Risk and Cardiovascular Health Study. Eur Heart J 37(13):1079–1081
109. Moore TJ, Vollmer WM, Appel LJ, Sacks FM, Svetkey LP, Vogt TM et al (1999) Effect of dietary patterns on ambulatory blood pressure : results from the Dietary Approaches to Stop Hypertension (DASH) Trial. DASH Collaborative Research Group Hypertension 34(3):472–477
110. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F et al (2018) Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279-90. N Engl J Med 378(25):2441–2442
111. Caputo M, Pigni S, Agosti E, Daffara T, Ferrero A, Filigheddu N et al (2021) Regulation of GH and GH Signaling by Nutrients. Cells 10(6):34
112. Muscogiuri G, Barrea L, Laudisio D, Di Somma C, Pugliese G, Salzano C et al (2019) Somatotropic axis and obesity: is there any role for the Mediterranean diet? Nutrients. https://doi.org/10.3390/nu11092228
113. Sinha RA, Bruinstroop E, Yen PM (2025) Actions of thyroid hormones and thyromimetics on the liver. Nat Rev Gastroenterol Hepatol 22(1):9–22
114. Chng CL, Goh GBB, Yen PM (2025) Metabolic and functional cross talk between the thyroid and liver. Thyroid 35(6):607–623
115. Russo SC, Salas-Lucia F, Bianco AC (2021) Deiodinases and the Metabolic Code for Thyroid Hormone Action. Endocrinology 162(8):34
116. Damiano F, Rochira A, Gnoni A, Siculella L (2017) Action of thyroid hormones, T3 and T2, on hepatic fatty acids: differences in metabolic effects and molecular mechanisms. Int J Mol Sci. https://doi.org/10.3390/ijms18040744
117. Biondi B (2019) Persistent dyslipidemia in patients with hypothyroidism: a good marker for personalized replacement therapy? J Clin Endocrinol Metab 104(2):624–627
118. Liu H, Peng D (2022) Update on dyslipidemia in hypothyroidism: the mechanism of dyslipidemia in hypothyroidism. Endocr Connect 11(2):34
119. Yap CS, Sinha RA, Ota S, Katsuki M, Yen PM (2013) Thyroid hormone negatively regulates CDX2 and SOAT2 mRNA expression via induction of miRNA-181d in hepatic cells. Biochem Biophys Res Commun 440(4):635–639
120. Mavromati M, Jornayvaz FR (2021) Hypothyroidism-associated dyslipidemia: potential molecular mechanisms leading to NAFLD. Int J Mol Sci. https://doi.org/10.3390/ijms222312797
121. Do A, Zahrawi F, Mehal WZ (2025) Therapeutic landscape of metabolic dysfunction-associated steatohepatitis (MASH). Nat Rev Drug Discov 24(3):171–189
122. Pu S, Zhao B, Jiang Y, Cui X (2025) Hypothyroidism/subclinical hypothyroidism and metabolic dysfunction-associated steatotic liver disease: advances in mechanism and treatment. Lipids Health Dis 24(1):75
123. Vidal-Cevallos P, Murua-Beltran Gall S, Uribe M, Chavez-Tapia NC (2023) Understanding the relationship between nonalcoholic fatty liver disease and thyroid disease. Int J Mol Sci. https://doi.org/10.3390/ijms241914605
124. Duntas LH, Brenta G (2018) A renewed focus on the association between thyroid hormones and lipid metabolism. Front Endocrinol (Lausanne) 9:511
125. Basil B, Myke-Mbata BK, Eze OE, Akubue AU (2024) From adiposity to steatosis: metabolic dysfunction-associated steatotic liver disease, a hepatic expression of metabolic syndrome - current insights and future directions. Clin Diabetes Endocrinol 10(1):39
126. Gurun M, Brennan P, Handjiev S, Khatib A, Leith D, Dillon JF et al (2024) Increased risk of chronic kidney disease and mortality in a cohort of people diagnosed with metabolic dysfunction associated steatotic liver disease with hepatic fibrosis. PLoS ONE 19(4):e0299507
127. Khatiwada S, Sah SK, Kc R, Baral N, Lamsal M (2016) Thyroid dysfunction in metabolic syndrome patients and its relationship with components of metabolic syndrome. Clin Diabetes Endocrinol 2:3
128. Teixeira P, Dos Santos PB, Pazos-Moura CC (2020) The role of thyroid hormone in metabolism and metabolic syndrome. Ther Adv Endocrinol Metab 11:2042018820917869
129. Biondi B, Kahaly GJ, Robertson RP (2019) Thyroid dysfunction and Diabetes Mellitus: Two closely associated disorders. Endocr Rev 40(3):789–824
130. Perros P, McCrimmon RJ, Shaw G, Frier BM (1995) Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabet Med 12(7):622–627
131. Jun JE, Jee JH, Bae JC, Jin SM, Hur KY, Lee MK et al (2017) Association between changes in thyroid hormones and incident Type 2 Diabetes: A seven-year longitudinal study. Thyroid 27(1):29–38
132. Chaker L, Razvi S, Bensenor IM, Azizi F, Pearce EN, Peeters RP (2022) Hypothyroidism. Nat Rev Dis Primers 8(1):30
133. Jonklaas J (2024) Hypothyroidism, lipids, and lipidomics. Endocrine 84(2):293–300
134. Tiller D, Ittermann T, Greiser KH, Meisinger C, Agger C, Hofman A et al (2016) Association of serum thyrotropin with anthropometric markers of obesity in the general population. Thyroid 26(9):1205–1214
135. Teixeira Pde F, Reuters VS, Ferreira MM, Almeida CP, Reis FA, Buescu A et al (2008) Lipid profile in different degrees of hypothyroidism and effects of levothyroxine replacement in mild thyroid failure. Transl Res 151(4):224–231
136. Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM et al (2014) Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. Med Sci Monit 20:1432–1441
137. Pearce EN (2012) Update in lipid alterations in subclinical hypothyroidism. J Clin Endocrinol Metab 97(2):326–333
138. Liu J, Chen Y, Ren B, He Y, Li F, Wang L et al (2023) Alteration of lipid profile between subclinical hypothyroidism and well-matched controls: a meta-analysis. Horm Metab Res 55(7):479–486
139. Saric MS, Jurasic MJ, Sovic S, Kranjcec B, Glivetic T, Demarin V (2017) Dyslipidemia in subclinical hypothyroidism requires assessment of small dense low density lipoprotein cholesterol (sdLDL-C). Rom J Intern Med 55(3):159–166
140. Treister-Goltzman Y, Yarza S, Peleg R (2021) Lipid profile in mild subclinical hypothyroidism: systematic review and meta-analysis. Minerva Endocrinol (Torino) 46(4):428–440
141. Khatri P, Neupane A, Banjade A, Sapkota S, Kharel S, Chhetri A et al (2021) Lipid Profile Abnormalities in Newly Diagnosed Primary Hypothyroidism in a Tertiary Care Centre of Western Nepal: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc 59(240):783–786
142. Shao F, Li R, Guo Q, Qin R, Su W, Yin H et al (2022) Plasma Metabolomics Reveals Systemic Metabolic Alterations of Subclinical and Clinical Hypothyroidism. J Clin Endocrinol Metab 108(1):13–25
143. Jung KY, Ahn HY, Han SK, Park YJ, Cho BY, Moon MK (2017) Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function. J Clin Lipidol 11(6):1347–1353

144. Sigal GA, Tavoni TM, Silva BMO, Kalil Filho R, Brandao LG, Maranhao RC (2019) Effects of Short-Term Hypothyroidism on the Lipid Transfer to High-Density Lipoprotein and Other Parameters Related to Lipoprotein Metabolism in Patients Submitted to Thyroidectomy for Thyroid Cancer. Thyroid 29(1):53–58
145. Diekman T, Demacker PN, Kastelein JJ, Stalenhoef AF, Wiersinga WM (1998) Increased oxidizability of low-density lipoproteins in hypothyroidism. J Clin Endocrinol Metab 83(5):1752–1755
146. Duntas LH, Mantzou E, Koutras DA (2002) Circulating levels of oxidized low-density lipoprotein in overt and mild hypothyroidism. Thyroid 12(11):1003–1007
147. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M (2000) Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid 10(9):803–808
148. Kalwick M, Roth M (2025) A comprehensive review of the genetics of dyslipidemias and risk of atherosclerotic cardiovascular disease. Nutrients. https://doi.org/10.3390/nu17040659
149. Chaker L, Papaleontiou M (2025) Hypothyroidism: a review. JAMA. https://doi.org/10.1001/jama.2025.13559
150. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS et al (2014) Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 24(12):1670–1751
151. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, Newman CB et al (2020) Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis. J Clin Endocrinol Metab. https://doi.org/10.1210/clinem/dgaa672
152. Centanni M, Duntas L, Feldt-Rasmussen U, Koehrle J, Peeters RP, Razvi S et al (2025) ETA guidelines for the use of levothyroxine sodium preparations in monotherapy to optimize the treatment of hypothyroidism. Eur Thyroid J. 14(4):34
153. Iqbal A, Jorde R, Figenschau Y (2006) Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromso Study. J Intern Med 260(1):53–61
154. Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR et al (2001) TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 86(10):4860–4866
155. McAninch EA, Rajan KB, Miller CH, Bianco AC (2018) Systemic Thyroid Hormone Status During Levothyroxine Therapy In Hypothyroidism: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 103(12):4533–4542
156. Celi FS, Zemskova M, Linderman JD, Smith S, Drinkard B, Sachdev V et al (2011) Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. J Clin Endocrinol Metab 96(11):3466–3474
157. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Associations Muscle Safety Expert P (2014) An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol 8(3 Suppl):S58-71
158. Northcutt RC, Stiel JN, Hollifield JW, Stant EG Jr (1969) The influence of cholestyramine on thyroxine absorption. JAMA 208(10):1857–1861
159. Demke DM (1989) Drug interaction between thyroxine and lovastatin. N Engl J Med 321(19):1341–1342
160. Unal E, Akin A, Yildirim R, Demir V, Yildiz I, Haspolat YK (2017) Association of subclinical hypothyroidism with dyslipidemia and increased carotid intima-media thickness in children. J Clin Res Pediatr Endocrinol 9(2):144–149
161. Herter-Aeberli I, Cherkaoui M, El Ansari N, Rohner R, Stinca S, Chabaa L et al (2015) Iodine Supplementation Decreases Hypercholesterolemia in Iodine-Deficient, Overweight Women: A Randomized Controlled Trial. J Nutr 145(9):2067–2075
162. Lee KW, Shin D, Song WO (2016) Low urinary Iodine concentrations associated with dyslipidemia in US adults. Nutrients 8(3):171
163. Chung HR (2014) Iodine and thyroid function. Ann Pediatr Endocrinol Metab 19(1):8–12
164. Huwiler VV, Maissen-Abgottspon S, Stanga Z, Muhlebach S, Trepp R, Bally L et al (2024) Selenium Supplementation in Patients with Hashimoto Thyroiditis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Thyroid 34(3):295–313
165. Wang N, Tan HY, Li S, Xu Y, Guo W, Feng Y (2017) Supplementation of micronutrient Selenium in metabolic diseases: its role as an antioxidant. Oxid Med Cell Longev 2017:7478523
166. Ranasinghe P, Wathurapatha WS, Ishara MH, Jayawardana R, Galappatthy P, Katulanda P et al (2015) Effects of Zinc supplementation on serum lipids: a systematic review and meta-analysis. Nutr Metab (Lond) 12:26
167. Maxwell C, Volpe SL (2007) Effect of zinc supplementation on thyroid hormone function. A case study of two college females. Ann Nutr Metab 51(2):188–194
168. Bellastella G, Scappaticcio L, Caiazzo F, Tomasuolo M, Carotenuto R, Caputo M et al (2022) Mediterranean Diet and Thyroid: An Interesting Alliance. Nutrients 14(19):34
169. Juresko I, Pleic N, Gunjaca I, Torlak V, Brdar D, Punda A et al (2024) The Effect of Mediterranean Diet on Thyroid Gland Activity. Int J Mol Sci 25(11):34
170. Pang KL, Lumintang JN, Chin KY (2021) Thyroid-Modulating Activities of Olive and Its Polyphenols: A Systematic Review. Nutrients 13(2):34
171. Rasekh F, Atashi-Nodoshan Z, Zarei A, Minaeifar AA, Changizi-Ashtiyani S, Afrasyabi Z (2022) Comparison of the effects of alcoholic extract of aerial parts of *Anvillea garcinii* and atorvastatin on the lipid profile and thyroid hormones in hypercholesterolemic rats. Avicenna J Phytomed 12(2):101–108
172. Whittaker MH (2000) Effects of dietary phytosterols on cholesterol metabolism and atherosclerosis: clinical and experimental evidence. Am J Med 109(7):600–601
173. Awaisheh SS, Khalifeh MS, Al-Ruwaili MA, Khalil OM, Al-Ameri OH, Al-Groom R (2013) Effect of supplementation of probiotics and phytosterols alone or in combination on serum and hepatic lipid profiles and thyroid hormones of hypercholesterolemic rats. J Dairy Sci 96(1):9–15
174. Felker P, Bunch R, Leung AM (2016) Concentrations of thiocyanate and goitrin in human plasma, their precursor concentrations in brassica vegetables, and associated potential risk for hypothyroidism. Nutr Rev 74(4):248–258
175. Galanty A, Grudzinska M, Pazdziora W, Sluzaly P, Pasko P (2024) Do Brassica Vegetables Affect Thyroid Function?-A Comprehensive Systematic Review. Int J Mol Sci 25(7):23
176. Darand M, Alizadeh S, Mansourian M (2022) The effect of *Brassica* vegetables on blood glucose levels and lipid profiles in adults. A systematic review and meta-analysis. Phytother Res 36(5):1914–1929
177. Baranska A, Blaszczuk A, Kanadys W, Baczewska B, Jedrych M, Wawryk-Gawda E et al (2021) Effects of Soy Protein Containing of Isoflavones and Isoflavones Extract on Plasma Lipid Profile in Postmenopausal Women as a Potential Prevention Factor in Cardiovascular Diseases: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 13(8):34
178. Messina M, Redmond G (2006) Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 16(3):249–258
179. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A, Fein HG et al (2020) Lipid Management in Patients with Endocrine

Disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 105(12):34
180. Rizos CV, Elisaf MS, Liberopoulos EN (2011) Effects of thyroid dysfunction on lipid profile. Open Cardiovasc Med J 5:76–84
181. Bonde Y, Breuer O, Lutjohann D, Sjoberg S, Angelin B, Rudling M (2014) Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. J Lipid Res 55(11):2408–2415
182. Duntas LH, Brenta G (2012) The effect of thyroid disorders on lipid levels and metabolism. Med Clin North Am 96(2):269–281
183. de Bruin TW, van Barlingen H, van Linde-Sibenius Trip M, van Vuurst de Vries AR, Akveld MJ, Erkelens DW. (1993) Lipoprotein(a) and apolipoprotein B plasma concentrations in hypothyroid, euthyroid, and hyperthyroid subjects. J Clin Endocrinol Metab. 76(1):121-6
184. Nikkila EA, Kekki M (1972) Plasma triglyceride metabolism in thyroid disease. J Clin Invest 51(8):2103–2114
185. Fabbrini E, Magkos F, Patterson BW, Mittendorfer B, Klein S (2012) Subclinical hypothyroidism and hyperthyroidism have opposite effects on hepatic very-low-density lipoprotein-triglyceride kinetics. J Clin Endocrinol Metab 97(3):E414–E418
186. Chaker L, Cooper DS, Walsh JP, Peeters RP (2024) Hyperthyroidism. Lancet 403(10428):768–780
187. Wu TY, Wang CH, Tien N, Lin CL, Chu FY, Chang HY et al (2020) A population-based cohort study on the association of hyperthyroidism with the risk of hyperlipidemia and the effects of anti-thyroid drugs on hepatic gene expression. Front Med 7:228
188. Nagamine T, Tanimura-Inagaki K, Nagao M, Kobayashi S, Shuto Y, Tamura H et al (2025) Impact of Graves hyperthyroidism treatment on lipid profiles and cholesterol dynamics: a prospective observational study. Ther Adv Endocrinol Metab 16:20420188251372381
189. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 73(24):3168–3209
190. Berta E, Harangi M, Zsiros N, Nagy EV, Paragh G, Bodor M (2014) Effect of thyroid hormone status and concomitant medication on statin induced adverse effects in hyperlipidemic patients. Pharmazie 69(6):420–423
191. Azemawah V, Movahed MR, Centuori P, Penaflor R, Riel PL, Situ S et al (2019) State of the art comprehensive review of individual statins, their differences, pharmacology, and clinical implications. Cardiovasc Drugs Ther 33(5):625–639
192. Writing C, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM et al (2022) 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 80(14):1366–1418
193. Hayashi A, Takano K, Kawakami Y, Hitomi M, Ohata Y, Suzuki A et al (2020) Short-term Change in Resting Energy Expenditure and Body Compositions in Therapeutic Process for Graves' Disease. Intern Med 59(15):1827–1833
194. Riis AL, Jorgensen JO, Gjedde S, Norrelund H, Jurik AG, Nair KS et al (2005) Whole body and forearm substrate metabolism in hyperthyroidism: evidence of increased basal muscle protein breakdown. Am J Physiol Endocrinol Metab 288(6):E1067–E1073
195. McClave SA, DiBaise JK, Mullin GE, Martindale RG (2016) ACG Clinical Guideline: Nutrition Therapy in the Adult Hospitalized Patient. Am J Gastroenterol 111(3):315–334
196. Heymsfield SB, Shapses SA (2024) Guidance on energy and macronutrients across the life span. N Engl J Med 390(14):1299–1310
197. Gonzalez-Campoy JM, St Jeor ST, Castorino K, Ebrahim A, Hurley D, Jovanovic L et al (2013) Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. Endocr Pract 19(Suppl 3):1–82
198. Wang T, Zhang X, Zhou N, Shen Y, Li B, Chen BE et al (2023) Association between Omega-3 fatty acid intake and dyslipidemia: A continuous dose-response meta-analysis of randomized controlled trials. J Am Heart Assoc 12(11):e029512
199. Potenza M, Via MA, Yanagisawa RT (2009) Excess thyroid hormone and carbohydrate metabolism. Endocr Pract 15(3):254–262
200. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH et al (2012) Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 97(9):2969–2989
201. Scaglione S, Di Chiara T, Daidone M, Tuttolomondo A (2025) Effects of the Mediterranean diet on the components of metabolic syndrome concerning the cardiometabolic risk. Nutrients. https://doi.org/10.3390/nu17020358
202. Rosenzweig JL, Bakris GL, Berglund LF, Hivert MF, Horton ES, Kalyani RR et al (2019) Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 104(9):3939–3985
203. Macvanin MT, Gluvic Z, Zafirovic S, Gao X, Essack M, Isenovic ER (2022) The protective role of nutritional antioxidants against oxidative stress in thyroid disorders. Front Endocrinol (Lausanne) 13:1092837
204. Dimitriadis G, Mitrou P, Lambadiari V, Boutati E, Maratou E, Koukkou E et al (2006) Glucose and lipid fluxes in the adipose tissue after meal ingestion in hyperthyroidism. J Clin Endocrinol Metab 91(3):1112–1118
205. Mir N, Chin SA, Riddell MC, Beaudry JL (2021) Genomic and Non-Genomic Actions of Glucocorticoids on Adipose Tissue Lipid Metabolism. Int J Mol Sci 22(16):34
206. Piechota M, Zieba M, Borczyk M, Golda S, Hajto J, Skupio U et al (2025) A cross-tissue transcriptomic approach decodes glucocorticoid receptor-dependent links to human metabolic phenotypes. BMC Genomics 26(1):462
207. Quagliarini F, Makris K, Friano ME, Uhlenhaut NH (2023) EJE Prize 2023: genes on steroids-genomic control of hepatic metabolism by the glucocorticoid receptor. Eur J Endocrinol 188(5):R111–R130
208. Hu W, Jiang C, Kim M, Yang W, Zhu K, Guan D et al (2021) Individual-specific functional epigenomics reveals genetic determinants of adverse metabolic effects of glucocorticoids. Cell Metab 33(8):1592–1609
209. Djurhuus CB, Gravholt CH, Nielsen S, Mengel A, Christiansen JS, Schmitz OE et al (2002) Effects of cortisol on lipolysis and regional interstitial glycerol levels in humans. Am J Physiol Endocrinol Metab 283(1):E172–E177
210. Stimson RH, Anderson AJ, Ramage LE, Macfarlane DP, de Beaux AC, Mole DJ et al (2017) Acute physiological effects of glucocorticoids on fuel metabolism in humans are permissive but not direct. Diabetes Obes Metab 19(6):883–891
211. Vaidya A, Findling J, Bancos I (2025) Adrenal Insufficiency in Adults: A Review. JAMA 334(8):714–725
212. Hayashi R, Tamada D, Murata M, Kitamura T, Mukai K, Maeda N et al (2019) Glucocorticoid replacement affects serum adiponectin levels and HDL-C in patients with secondary adrenal insufficiency. J Clin Endocrinol Metab 104(12):5814–5822
213. Bavaresco A, Mazzeo P, Lazzara M, Barbot M (2024) Adipose tissue in cortisol excess: what Cushings syndrome can teach us? Biochem Pharmacol 223:116137

214. de Guia RM, Herzig S (2015) How do glucocorticoids regulate lipid metabolism? Adv Exp Med Biol 872:127–144
215. Peckett AJ, Wright DC, Riddell MC (2011) The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism 60(11):1500–1510
216. Tomasello L, Coppola A, Pizzolanti G, Giordano C, Arnaldi G, Guarnotta V (2025) Dual-release hydrocortisone treatment improves serum and peripheral blood mononuclear cell inflammatory and immune profiles in patients with autoimmune primary adrenal insufficiency. Front Immunol 16:1489254
217. Christ-Crain M, Kola B, Lolli F, Fekete C, Seboek D, Wittmann G et al (2008) AMP-activated protein kinase mediates glucocorticoid-induced metabolic changes: a novel mechanism in Cushing's syndrome. FASEB J 22(6):1672–1683
218. Dineen RA, Martin-Grace J, Ahmed KMS, Taylor AE, Shaheen F, Schiffer L et al (2023) Tissue Glucocorticoid metabolism in adrenal insufficiency: a prospective study of dual-release Hydrocortisone therapy. J Clin Endocrinol Metab 108(12):3178–3189
219. Crown A, Lightman S (2005) Why is the management of glucocorticoid deficiency still controversial: a review of the literature. Clin Endocrinol (Oxf) 63(5):483–492
220. Giordano R, Marzotti S, Balbo M, Romagnoli S, Marinazzo E, Berardelli R et al (2009) Metabolic and cardiovascular profile in patients with Addison's disease under conventional glucocorticoid replacement. J Endocrinol Invest 32(11):917–923
221. Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B et al (2012) Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab 97(2):473–481
222. Quinkler M, Miodini Nilsen R, Zopf K, Ventz M, Oksnes M (2015) Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. Eur J Endocrinol 172(5):619–626
223. Giordano R, Guaraldi F, Marinazzo E, Fumarola F, Rampino A, Berardelli R et al (2016) Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. Endocrine 51(2):360–368
224. Guarnotta V, Ciresi A, Pillitteri G, Giordano C (2018) Improved insulin sensitivity and secretion in prediabetic patients with adrenal insufficiency on dual-release hydrocortisone treatment: a 36-month retrospective analysis. Clin Endocrinol (Oxf) 88(5):665–672
225. Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V et al (2018) Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. Lancet Diabetes Endocrinol 6(3):173–185
226. Gasco V, Giannelli J, Campioni L, Arvat E, Ghigo E, Grottoli S et al (2023) Benefits of dual-release hydrocortisone treatment on central adiposity and health-related quality of life in secondary adrenal insufficiency. J Endocrinol Invest 46(3):587–597
227. Mongioi LM, Condorelli RA, La Vignera S, Calogero AE (2018) Dual-release hydrocortisone treatment: glycometabolic profile and health-related quality of life. Endocr Connect 7(1):211–219
228. Koper JW, van Rossum EF, van den Akker EL (2014) Glucocorticoid receptor polymorphisms and haplotypes and their expression in health and disease. Steroids 92:62–73
229. Giordano R, Marzotti S, Berardelli R, Karamouzis I, Brozzetti A, D'Angelo V et al (2012) BCII polymorphism of the glucocorticoid receptor gene is associated with increased obesity, impaired glucose metabolism and dyslipidaemia in patients with Addison's disease. Clin Endocrinol (Oxf) 77(6):863–870
230. Quinkler M, Ekman B, Marelli C, Uddin S, Zelissen P, Murray RD et al (2017) Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency. Endocr Connect 6(1):1–8
231. Steintorsdottir SD, Oksnes M, Jorgensen AP, Husebye ES (2025) Extended-release hydrocortisone formulations-is there a clinically meaningful benefit? J Clin Endocrinol Metab 110(3):e566–e573
232. Oksnes M, Bjornsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM et al (2014) Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial. J Clin Endocrinol Metab 99(5):1665–1674
233. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD et al (2016) Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 101(2):364–389
234. Filipsson H, Monson JP, Koltowska-Haggstrom M, Mattsson A, Johannsson G (2006) The impact of glucocorticoid replacement regimens on metabolic outcome and comorbidity in hypopituitary patients. J Clin Endocrinol Metab 91(10):3954–3961
235. Mach F, Koskinas KC, Roeters van Lennep JE, Tokgozoglu L, Badimon L, Baigent C et al (2025) Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Atherosclerosis 2025(409):120479
236. Domanski MJ, Wu CO, Tian X, Hasan AA, Ma X, Huang Y et al (2023) Association of Incident Cardiovascular Disease With Time Course and Cumulative Exposure to Multiple Risk Factors. J Am Coll Cardiol 81(12):1151–1161
237. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM (2012) Lifetime risk and years lived free of total cardiovascular disease. JAMA 308(17):1795–1801
238. Skov J, Sundstrom A, Ludvigsson JF, Kampe O, Bensing S (2019) Sex-specific risk of cardiovascular disease in autoimmune Addison disease-A population-based cohort study. J Clin Endocrinol Metab 104(6):2031–2040
239. Krysiak R, Claahsen-van der Grinten HL, Reisch N, Touraine P, Falhammar H (2025) Cardiometabolic Aspects of Congenital Adrenal Hyperplasia. Endocr Rev. 46(1):80-148
240. Allan CA, McLachlan RI (2010) Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 17(3):224–232
241. Lanfranco F, Zitzmann M, Simoni M, Nieschlag E (2004) Serum adiponectin levels in hypogonadal males: influence of testosterone replacement therapy. Clin Endocrinol (Oxf) 60(4):500–507
242. Finkielstain GP, Kim MS, Sinaii N, Nishitani M, Van Ryzin C, Hill SC et al (2012) Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. J Clin Endocrinol Metab 97(12):4429–4438
243. Prete A, Auchus RJ, Ross RJ (2021) Clinical advances in the pharmacotherapy of congenital adrenal hyperplasia. Eur J Endocrinol 186(1):R1–R14
244. Tamhane S, Rodriguez-Gutierrez R, Iqbal AM, Prokop LJ, Bancos I, Speiser PW et al (2018) Cardiovascular and Metabolic Outcomes in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 103(11):4097–4103
245. Delai A, Gomes PM, Foss-Freitas MC, Elias J, Antonini SR, Castro M et al (2022) Hyperinsulinemic-Euglycemic Clamp Strengthens the Insulin Resistance in Nonclassical Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab 107(3):e1106–e1116
246. Espinosa Reyes TM, Pesantez Velepucha AK, Cabrera Rego JO, Valdes Gomez W, Dominguez Alonso E, Falhammar H (2023) Cardiovascular risk in Cuban adolescents and young adults with congenital adrenal hyperplasia. BMC Endocr Disord 23(1):241
247. Botero D, Arango A, Danon M, Lifshitz F (2000) Lipid profile in congenital adrenal hyperplasia. Metabolism 49(6):790–793
248. Farghaly HS, Metwalley KA, Raafat DM, Algowhary M, Said GM (2019) Epicardial fat thickness in children with subclinical

hypothyroidism and its relationship to subclinical atherosclerosis: a pilot study. Horm Res Paediatr 92(2):99–105
249. Merke DP, Mallappa A, Arlt W, Brac de la Perriere A, Linden Hirschberg A, Juul A et al (2021) Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab 106(5):e2063–e2077
250. Arlt W, Brac de la Perriere A, Hirschberg AL, Merke DP, Newell-Price JDC, Prete A et al (2025) Long-term outcomes in patients with congenital adrenal hyperplasia treated with hydrocortisone modified-release hard capsules. Eur J Endocrinol 193(1):76–84
251. Nguyen TTH, Le KM, Tran TAT, Nguyen KN, Can TBN, Bui PT et al (2025) Growth Assessment and Nutritional Status in Children with Congenital Adrenal Hyperplasia-A Cross-Sectional Study from a Vietnamese Tertiary Pediatric Center. Diagnostics (Basel). 15(12):34
252. Overholtzer LN, Luo S, Lim SL, Pickering TA, Fraga NR, Kim E et al (2025) Impaired Dietary Decision-Making in Children and Adolescents with Congenital Adrenal Hyperplasia. Horm Res Paediatr 3:1–10
253. Dennis J, Pitts L, Matalka L, Mays LC (2024) Comprehensive adolescent healthcare transition program for congenital adrenal hyperplasia: a quality improvement initiative. Health Care Transitions 2:100057
254. Pivonello R, Faggiano A, Lombardi G, Colao A (2005) The metabolic syndrome and cardiovascular risk in Cushing's syndrome. Endocrinol Metab Clin North Am 34(2):327–339
255. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A (2016) Complications of Cushings syndrome: state of the art. Lancet Diabetes Endocrinol 4(7):611–629
256. Xu C, He J, Jiang H, Zu L, Zhai W, Pu S et al (2009) Direct effect of glucocorticoids on lipolysis in adipocytes. Mol Endocrinol 23(8):1161–1170
257. Macfarlane DP, Forbes S, Walker BR (2008) Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. J Endocrinol 197(2):189–204
258. Shen WJ, Patel S, Miyoshi H, Greenberg AS, Kraemer FB (2009) Functional interaction of hormone-sensitive lipase and perilipin in lipolysis. J Lipid Res 50(11):2306–2313
259. Fried SK, Russell CD, Grauso NL, Brolin RE (1993) Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. J Clin Invest 92(5):2191–2198
260. Ottosson M, Vikman-Adolfsson K, Enerback S, Olivecrona G, Bjorntorp P (1994) The effects of cortisol on the regulation of lipoprotein lipase activity in human adipose tissue. J Clin Endocrinol Metab 79(3):820–825
261. Campbell JE, Peckett AJ, D'Souza AM, Hawke TJ, Riddell MC (2011) Adipogenic and lipolytic effects of chronic glucocorticoid exposure. Am J Physiol Cell Physiol 300(1):C198-209
262. Tilg H, Moschen AR (2008) Insulin resistance, inflammation, and non-alcoholic fatty liver disease. Trends Endocrinol Metab 19(10):371–379
263. Lee MJ, Pramyothin P, Karastergiou K, Fried SK (2014) Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochim Biophys Acta 1842(3):473–481
264. Yan C, Yang H, Wang Y, Dong Y, Yu F, Wu Y et al (2016) Increased glycogen synthase kinase-3beta and hexose-6-phosphate dehydrogenase expression in adipose tissue may contribute to glucocorticoid-induced mouse visceral adiposity. Int J Obes (Lond) 40(8):1233–1241
265. Feng B, He Q, Xu H (2014) FOXO1-dependent up-regulation of MAP kinase phosphatase 3 (MKP-3) mediates glucocorticoid-induced hepatic lipid accumulation in mice. Mol Cell Endocrinol 393(1–2):46–55
266. Arnaldi G, Scandali VM, Trementino L, Cardinaletti M, Appolloni G, Boscaro M (2010) Pathophysiology of dyslipidemia in Cushings syndrome. Neuroendocrinology 92(Suppl 1):86–90
267. Kahn BB, Alquier T, Carling D, Hardie DG (2005) AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab 1(1):15–25
268. Kola B, Christ-Crain M, Lolli F, Arnaldi G, Giacchetti G, Boscaro M et al (2008) Changes in adenosine 5'-monophosphate-activated protein kinase as a mechanism of visceral obesity in Cushing's syndrome. J Clin Endocrinol Metab 93(12):4969–4973
269. Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G (2004) High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol (Oxf) 61(6):768–777
270. Tauchmanova L, Rossi R, Biondi B, Pulcrano M, Nuzzo V, Palmieri EA et al (2002) Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocrinol Metab 87(11):4872–4878
271. Feingold KR (2000) Dyslipidemia in Patients with Diabetes. In: Feingold KR, Ahmed SF, Anawalt B, Blackman MR, Boyce A, Chrousos G, et al., editors. Endotext. South Dartmouth (MA).
272. Li Z, Zhang C, Geng C, Song Y (2022) Metabolic profile differences in ACTH-dependent and ACTH-independent Cushing syndrome. Chronic Dis Transl Med 8(1):36–40
273. Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C et al (2003) Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88(6):2527–2533
274. Greenman Y (2010) Management of dyslipidemia in Cushings syndrome. Neuroendocrinology 92(Suppl 1):91–95
275. Dhingra A, Ganie MA, Dharmshaktu P, Chakraborty S, Jyotsna VP, Gupta N (2019) Pattern of lipid abnormalities among South Asian Indians with Cushings syndrome and the short term impact of surgical correction of hypercortisolism. Horm Metab Res 51(5):309–314
276. Giordano R, Picu A, Marinazzo E, D'Angelo V, Berardelli R, Karamouzis I et al (2011) Metabolic and cardiovascular outcomes in patients with Cushing's syndrome of different aetiologies during active disease and 1 year after remission. Clin Endocrinol (Oxf) 75(3):354–360
277. Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M et al (1999) Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 84(8):2664–2672
278. Friedman TC, Mastorakos G, Newman TD, Mullen NM, Horton EG, Costello R et al (1996) Carbohydrate and lipid metabolism in endogenous hypercortisolism: shared features with metabolic syndrome X and NIDDM. Endocr J 43(6):645–655
279. Orr JS, Dengo AL, Rivero JM, Davy KP (2009) Arterial destiffening with atorvastatin in overweight and obese middle-aged and older adults. Hypertension 54(4):763–768
280. van Haalen FM, Broersen LH, Jorgensen JO, Pereira AM, Dekkers OM (2015) Management of endocrine disease: mortality remains increased in Cushings disease despite biochemical remission: a systematic review and meta-analysis. Eur J Endocrinol 172(4):R143–R149
281. Sharma ST, Nieman LK, Feelders RA (2015) Comorbidities in Cushings disease. Pituitary 18(2):188–194
282. group Sw, collaboration ESCCr (2021) SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 42(25):2439–2454
283. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM et al (2008) The diagnosis of Cushings syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93(5):1526–1540

284. Pivonello R, De Martino MC, De Leo M, Simeoli C, Colao A (2017) Cushings disease: the burden of illness. Endocrine 56(1):10–18
285. Krsek M, Silha JV, Jezkova J, Hana V, Marek J, Weiss V et al (2004) Adipokine levels in Cushing's syndrome; elevated resistin levels in female patients with Cushing's syndrome. Clin Endocrinol (Oxf) 60(3):350–357
286. Perogamvros I, Vassiliadi DA, Karapanou O, Botoula E, Tzanela M, Tsagarakis S (2015) Biochemical and clinical benefits of unilateral adrenalectomy in patients with subclinical hypercortisolism and bilateral adrenal incidentalomas. Eur J Endocrinol 173(6):719–725
287. Miyazato M, Ishidoya S, Satoh F, Morimoto R, Kaiho Y, Yamada S et al (2011) Surgical outcomes of laparoscopic adrenalectomy for patients with Cushing's and subclinical Cushing's syndrome: a single center experience. Int Urol Nephrol 43(4):975–981
288. Pivonello R, Pivonello C, Simeoli C, De Martino MC, Colao A (2022) The dopaminergic control of Cushings syndrome. J Endocrinol Invest 45(7):1297–1315
289. Auriemma RS, Granieri L, Galdiero M, Simeoli C, Perone Y, Vitale P et al (2013) Effect of cabergoline on metabolism in prolactinomas. Neuroendocrinology 98(4):299–310
290. Albani A, Ferrau F, Ciresi A, Pivonello R, Scaroni C, Iacuaniello D et al (2018) Pasireotide treatment reduces cardiometabolic risk in Cushing's disease patients: an Italian, multicenter study. Endocrine 61(1):118–124
291. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M et al (2012) A 12-month phase 3 study of pasireotide in Cushings disease. N Engl J Med 366(10):914–924
292. Miettinen TA (1988) Cholesterol metabolism during ketoconazole treatment in man. J Lipid Res 29(1):43–51
293. Stalenhoef AF, Stuyt PM, de Graaf J (1997) Effects of ketoconazole on plasma lipids and lipoprotein(a) in familial hypercholesterolaemia, compared with simvastatin. Neth J Med 51(1):10–15
294. Fleseriu M, Auchus RJ, Greenman Y, Zacharieva S, Geer EB, Salvatori R et al (2022) Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical, and radiologic outcomes. Eur J Endocrinol 187(6):859–871
295. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K et al (2015) Effectiveness of Metyrapone in treating Cushings syndrome: a retrospective multicenter study in 195 patients. J Clin Endocrinol Metab 100(11):4146–4154
296. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A et al (2020) Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol 8(9):748–761
297. Kroiss M, Plonne D, Kendl S, Schirmer D, Ronchi CL, Schirbel A et al (2016) Association of mitotane with chylomicrons and serum lipoproteins: practical implications for treatment of adrenocortical carcinoma. Eur J Endocrinol 174(3):343–353
298. Shawa H, Deniz F, Bazerbashi H, Hernandez M, Vassilopoulou-Sellin R, Jimenez C et al (2013) Mitotane-induced hyperlipidemia: a retrospective cohort study. Int J Endocrinol 2013:624962
299. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C et al (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 97(6):2039–2049
300. Pivonello R, Ferrigno R, De Martino MC, Simeoli C, Di Paola N, Pivonello C et al (2020) Medical Treatment of Cushing's Disease: An Overview of the Current and Recent Clinical Trials. Front Endocrinol (Lausanne) 11:648
301. Minetto MA, Lanfranco F, Motta G, Allasia S, Arvat E, D'Antona G (2011) Steroid myopathy: some unresolved issues. J Endocrinol Invest 34(5):370–375
302. Savarese G, De Ferrari GM, Rosano GM, Perrone-Filardi P (2015) Safety and efficacy of ezetimibe: a meta-analysis. Int J Cardiol 201:247–252
303. Tsakiridou ED, Liberopoulos E, Giotaki Z, Tigas S (2018) Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor use in the management of resistant hypercholesterolemia induced by mitotane treatment for adrenocortical cancer. J Clin Lipidol 12(3):826–829
304. Guarnotta V, Amodei R, Di Gaudio F, Giordano C (2023) Nutritional intervention in Cushings disease: the ketogenic diets effects on metabolic comorbidities and adrenal steroids. Nutrients. https://doi.org/10.3390/nu15214647
305. Dugandzic MK, Pierre-Michel EC, Kalayjian T (2022) Ketogenic diet initially masks symptoms of hypercortisolism in Cushings disease. Metabolites. https://doi.org/10.3390/metabo12111033
306. Guarnotta V, Di Gaudio F, Giordano C (2022) Vitamin D deficiency in Cushings disease: before and after its supplementation. Nutrients. https://doi.org/10.3390/nu14050973
307. Corona G, Vignozzi L, Sforza A, Mannucci E, Maggi M (2015) Obesity and late-onset hypogonadism. Mol Cell Endocrinol 418(Pt 2):120–133
308. Kelly DM, Jones TH (2015) Testosterone and obesity. Obes Rev 16(7):581–606
309. Grossmann M (2018) Hypogonadism and male obesity: focus on unresolved questions. Clin Endocrinol (Oxf) 89(1):11–21
310. Saad F, Gooren L (2009) The role of testosterone in the metabolic syndrome: a review. J Steroid Biochem Mol Biol 114(1–2):40–43
311. Corona G, Monami M, Rastrelli G, Aversa A, Tishova Y, Saad F et al (2011) Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med 8(1):272–283
312. Jones TH, Saad F (2009) The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process. Atherosclerosis 207(2):318–327
313. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A et al (2011) Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 165(5):687–701
314. Kelly DM, Jones TH (2013) Testosterone: A metabolic hormone in health and disease. J Endocrinol 217(3):R25-45
315. Sanz-Canovas J, Lopez-Sampalo A, Cobos-Palacios L, Ricci M, Hernandez-Negrin H, Mancebo-Sevilla JJ et al (2022) Management of Type 2 Diabetes Mellitus in elderly patients with frailty and/or sarcopenia. Int J Environ Res Public Health. https://doi.org/10.3390/ijerph19148677
316. Schluessel S, Bidlingmaier M, Martini S, Reincke M, Reisch N, Schaupp A et al (2024) Hypogonadism is frequent in very old men with multimorbidity and is associated with anemia and sarcopenia. Z Gerontol Geriatr 57(1):43–49
317. Wu FC, von Eckardstein A (2003) Androgens and coronary artery disease. Endocr Rev 24(2):183–217
318. Berneis KK, Krauss RM (2002) Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 43(9):1363–1379
319. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M et al (2016) Testosterone supplementation and body composition: Results from a meta-analysis of observational studies. J Endocrinol Invest 39(9):967–981
320. Corona G, Vena W, Pizzocaro A, Vignozzi L, Sforza A, Maggi M (2023) Testosterone therapy in diabetes and pre-diabetes. Andrology 11(2):204–214
321. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM et al (2018) Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 103(5):1715–1744
322. Corona G, Rastrelli G, Sparano C, Vignozzi L, Sforza A, Maggi M (2024) Advances in the treatment of functional male hypogonadism. Expert Rev Endocrinol Metab 19(2):163–177

323. Caruso I, Cignarelli A, Sorice GP, Perrini S, Giorgino F (2024) Incretin-based therapies for the treatment of obesity-related diseases. NPJ Metab Health Dis 2(1):31
324. Caruso I, Di Gioia L, Di Molfetta S, Cignarelli A, Palmer SC, Natale P et al (2023) Glucometabolic outcomes of GLP-1 receptor agonist-based therapies in patients with type 2 diabetes: a systematic review and network meta-analysis. EClinicalMedicine 64:102181
325. Gregoric N, Sikonja J, Janez A, Jensterle M (2025) Semaglutide improved sperm morphology in obese men with type 2 diabetes mellitus and functional hypogonadism. Diabetes Obes Metab 27(2):519–528
326. Sanyal AJ, Newsome PN, Kliers I, Ostergaard LH, Long MT, Kjaer MS et al (2025) Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med 392(21):2089–2099
327. Genchi VA, Rossi E, Lauriola C, D'Oria R, Palma G, Borrelli A et al (2022) Adipose tissue dysfunction and obesity-related male hypogonadism. Int J Mol Sci. https://doi.org/10.3390/ijms23158194
328. Cignarelli A, Santi D, Genchi VA, Conte E, Giordano F, Di Leo S et al (2023) Very low-calorie ketogenic diet rapidly augments testosterone levels in non-diabetic obese subjects. Andrology 11(2):234–244
329. Maas AH, Appelman YE (2010) Gender differences in coronary heart disease. Neth Heart J 18(12):598–602
330. Torosyan N, Visrodia P, Torbati T, Minissian MB, Shufelt CL (2022) Dyslipidemia in midlife women: approach and considerations during the menopausal transition. Maturitas 166:14–20
331. Meyer MR, Haas E, Barton M (2006) Gender differences of cardiovascular disease: new perspectives for estrogen receptor signaling. Hypertension 47(6):1019–1026
332. Anagnostis P, Antza C, Trakatelli C, Lambrinoudaki I, Goulis DG, Kotsis V (2023) The effect of menopause on lipoprotein (a) concentrations: a systematic review and meta-analysis. Maturitas 167:39–45
333. Federici S, Rossetti R, Moleri S, Munari EV, Frixou M, Bonomi M et al (2024) Primary ovarian insufficiency: update on clinical and genetic findings. Front Endocrinol (Lausanne) 15:1464803
334. Levine ME, Lu AT, Chen BH, Hernandez DG, Singleton AB, Ferrucci L et al (2016) Menopause accelerates biological aging. Proc Natl Acad Sci U S A 113(33):9327–9332
335. Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass ML et al (2017) Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Womens Health Initiative. Menopause 24(1):35–44
336. Zhu D, Chung HF, Dobson AJ, Pandeya N, Brunner EJ, Kuh D et al (2020) Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. Hum Reprod 35(8):1933–1943
337. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M et al (2017) Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 102(5):1413–1439
338. Carr MC (2003) The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 88(6):2404–2411
339. Thurston RC, Karvonen-Gutierrez CA, Derby CA, El Khoudary SR, Kravitz HM, Manson JE (2018) Menopause versus chronologic aging: their roles in womens health. Menopause 25(8):849–854
340. El Khoudary SR, Hutchins PM, Matthews KA, Brooks MM, Orchard TJ, Ronsein GE et al (2016) Cholesterol Efflux Capacity and Subclasses of HDL Particles in Healthy Women Transitioning Through Menopause. J Clin Endocrinol Metab 101(9):3419–3428
341. De Paoli M, Zakharia A, Werstuck GH (2021) The role of estrogen in insulin resistance: a review of clinical and preclinical data. Am J Pathol 191(9):1490–1498
342. Yoh K, Ikeda K, Horie K, Inoue S (2023) Roles of Estrogen, Estrogen Receptors, and Estrogen-Related Receptors in skeletal muscle: regulation of mitochondrial function. Int J Mol Sci. https://doi.org/10.3390/ijms24031853
343. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL (2017) Oxidative stress in atherosclerosis. Curr Atheroscler Rep 19(11):42
344. El Khoudary SR, Wang L, Brooks MM, Thurston RC, Derby CA, Matthews KA (2016) Increase HDL-C level over the menopausal transition is associated with greater atherosclerotic progression. J Clin Lipidol 10(4):962–969
345. Seidemann L, Lippold CP, Rohm CM, Eckel JC, Schicht G, Matz-Soja M et al (2024) Sex hormones differently regulate lipid metabolism genes in primary human hepatocytes. BMC Endocr Disord 24(1):135
346. Kunicki M, Rzewuska N, Gross-Kepinska K (2024) Immunophenotypic profiles and inflammatory markers in Premature Ovarian Insufficiency. J Reprod Immunol 164:104253
347. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B et al (2009) Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 54(25):2366–2373
348. Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F et al (2020) Menopause symptom management in women with dyslipidemias: An EMAS clinical guide. Maturitas 135:82–88
349. Knauff EA, Westerveld HE, Goverde AJ, Eijkemans MJ, Valkenburg O, van Santbrink EJ et al (2008) Lipid profile of women with premature ovarian failure. Menopause 15(5):919–923
350. Magdalena P, Olga KJ, Anna P, Robert J (2024) Unfavorably altered lipid profile in women with primary ovarian insufficiency. J Clin Lipidol 18(4):e602–e609
351. Rocha MP, Marcondes JA, Barcellos CR, Hayashida SA, Curi DD, da Fonseca AM et al (2011) Dyslipidemia in women with polycystic ovary syndrome: incidence, pattern and predictors. Gynecol Endocrinol 27(10):814–819
352. Nappi RE, Chedraui P, Lambrinoudaki I, Simoncini T (2022) Menopause: a cardiometabolic transition. Lancet Diabetes Endocrinol 10(6):442–456
353. Jayasena CN, Devine K, Barber K, Comninos AN, Conway GS, Crown A et al (2024) Society for endocrinology guideline for understanding, diagnosing and treating female hypogonadism. Clin Endocrinol (Oxf) 101(5):409–442
354. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288(3):321–333
355. Miller VM, Naftolin F, Asthana S, Black DM, Brinton EA, Budoff MJ et al (2019) The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned? Menopause 26(9):1071–1084
356. Li T, Jiang NS, Kaskey J, Schnatz PF, Nudy M (2025) Hormone therapy and insulin resistance in non-diabetic postmenopausal women: a systematic review and meta-analysis. Climacteric 3:1–9
357. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE (2006) Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab 8(5):538–554
358. Zhang YL, Xie L, Wu FL, Ding X, Hernandez-Wolters B, Gaman MA et al (2024) Comprehensive meta-analysis of the effects of oral medroxyprogesterone acetate plus conjugated equine oestrogens on the lipid profile in women: Insights from randomized controlled trials. Eur J Clin Invest 54(8):e14211

359. Lv C, Zhang W, Tan X, Shang X, Gaman MA, Salem H et al (2021) The effect of tibolone treatment on lipid profile in women: A systematic review and dose-response meta-analysis of randomized controlled trials. Pharmacol Res 169:105612
360. Kim J, Munster PN (2025) Estrogens and breast cancer. Ann Oncol 36(2):134–148
361. Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P et al (2023) Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet 401(10382):1091–1102
362. Schaudig K, Wang X, Bouchard C, Hirschberg AL, Cano A, Shapiro CMM et al (2024) Efficacy and safety of fezolinetant for moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy: phase 3b randomised controlled trial. BMJ 387:e079525
363. Noll P, Campos CAS, Leone C, Zangirolami-Raimundo J, Noll M, Baracat EC et al (2021) Dietary intake and menopausal symptoms in postmenopausal women: a systematic review. Climacteric 24(2):128–138
364. Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC et al (2012) Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. Menopause 19(9):980–988
365. Cano A, Marshall S, Zolfaroli I, Bitzer J, Ceausu I, Chedraui P et al (2020) The Mediterranean diet and menopausal health: An EMAS position statement. Maturitas 139:90–97
366. Vetrani C, Barrea L, Rispoli R, Verde L, De Alteriis G, Docimo A et al (2022) Mediterranean Diet: What Are the Consequences for Menopause? Front Endocrinol (Lausanne) 13:886824
367. Barnard ND, Kahleova H, Holtz DN, Del Aguila F, Neola M, Crosby LM et al (2021) The Womens Study for the Alleviation of Vasomotor Symptoms (WAVS): a randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. Menopause 28(10):1150–1156
368. Barnard ND, Kahleova H, Holtz DN, Znayenko-Miller T, Sutton M, Holubkov R et al (2023) A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial. Menopause 30(1):80–87
369. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J (2013) Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev 2013(12):CD001395
370. Li J, Li H, Yan P, Guo L, Li J, Han J et al (2021) Efficacy and safety of phytoestrogens in the treatment of perimenopausal and postmenopausal depressive disorders: a systematic review and meta-analysis. Int J Clin Pract 75(10):e14360
371. Newton KM, Reed SD, Uchiyama S, Qu C, Ueno T, Iwashita S et al (2015) A cross-sectional study of equol producer status and self-reported vasomotor symptoms. Menopause 22(5):489–495
372. Simbalista RL, Sauerbronn AV, Aldrighi JM, Areas JA (2010) Consumption of a flaxseed-rich food is not more effective than a placebo in alleviating the climacteric symptoms of postmenopausal women. J Nutr 140(2):293–297
373. Kanadys W, Baranska A, Blaszczuk A, Polz-Dacewicz M, Drop B, Kanecki K, et al. (2021) Evaluation of Clinical Meaningfulness of Red Clover (Trifolium pratense L.) Extract to Relieve Hot Flushes and Menopausal Symptoms in Peri- and Post-Menopausal Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 13(4).
374. Liu YR, Jiang YL, Huang RQ, Yang JY, Xiao BK, Dong JX (2014) *Hypericum perforatum* L. preparations for menopause: a meta-analysis of efficacy and safety. Climacteric 17(4):325–335
375. Goncalves C, Moreira H, Santos R (2024) Systematic review of Mediterranean diet interventions in menopausal women. AIMS Public Health 11(1):110–129
376. Seimon RV, Wild-Taylor AL, Keating SE, McClintock S, Harper C, Gibson AA et al (2019) Effect of Weight Loss via Severe vs Moderate Energy Restriction on Lean Mass and Body Composition Among Postmenopausal Women With Obesity: The TEMPO Diet Randomized Clinical Trial. JAMA Netw Open 2(10):e1913733
377. Yelland S, Steenson S, Creedon A, Stanner S (2023) The role of diet in managing menopausal symptoms: a narrative review. Nutr Bull 48(1):43–65
378. Glisic M, Kastrati N, Musa J, Milic J, Asllanaj E, Portilla Fernandez E et al (2018) Phytoestrogen supplementation and body composition in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Maturitas 115:74–83
379. Na Takuathung M, Klinjan P, Sakuludomkan W, Dukaew N, Inpan R, Kongta R et al (2023) Efficacy and safety of the Genistein nutraceutical product containing Vitamin E, Vitamin B3, and Ceramide on skin health in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. J Clin Med. https://doi.org/10.3390/jcm12041326
380. Carmignani LO, Pedro AO, Montemor EB, Arias VA, Costa-Paiva LH, Pinto-Neto AM (2015) Effects of a soy-based dietary supplement compared with low-dose hormone therapy on the urogenital system: a randomized, double-blind, controlled clinical trial. Menopause 22(7):741–749
381. Khanna A, John F, Das S, Thomas J, Rao J, Maliakel B et al (2020) Efficacy of a novel extract of fenugreek seeds in alleviating vasomotor symptoms and depression in perimenopausal women: a randomized, double-blinded, placebo-controlled study. J Food Biochem 44(12):e13507
382. Grigolon RB, Ceolin G, Deng Y, Bambokian A, Koning E, Fabe J et al (2023) Effects of nutritional interventions on the severity of depressive and anxiety symptoms of women in the menopausal transition and menopause: a systematic review, meta-analysis, and meta-regression. Menopause 30(1):95–107
383. Barrea L, Vetrani C, Altieri B, Verde L, Savastano S, Colao A et al (2021) The importance of being a Lark in post-menopausal women with obesity: a ploy to prevent Type 2 diabetes mellitus? Nutrients. https://doi.org/10.3390/nu13113762
384. Verde L, Barrea L, Frias-Toral E, Zambrano-Villacres R, Simancas-Racines D, Memoli P et al (2025) Timing matters: lipid intake and its influence on menopausal-related symptoms. J Transl Med 23(1):934
385. Verde L, Barrea L, Vetrani C, Frias-Toral E, Chapela SP, Jayawardena R et al (2022) Chronotype and Sleep Quality in Obesity: How Do They Change After Menopause? Curr Obes Rep 11(4):254–262
386. Gambineri A, Rosa S, Pandurevic S, Cecchetti C, Rotolo L, Dionese P et al (2025) Evolution of cardiovascular risk factors and the risk for cardiovascular events in a Caucasian population with polycystic ovary syndrome. Eur J Endocrinol 192(3):210–219
387. Patel N, Mittal N, Wilkinson MJ, Taub PR (2024) Unique features of dyslipidemia in women across a lifetime and a tailored approach to management. Am J Prev Cardiol 18:100666
388. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP (2007) Pathophysiology and types of dyslipidemia in PCOS. Trends Endocrinol Metab 18(7):280–285
389. Kolnikaj TS, Herman R, Janez A, Jensterle M (2024) The current and emerging role of statins in the treatment of PCOS: the evidence to date. Medicina (Kaunas). https://doi.org/10.3390/medicina60020244
390. Macut D, Bjekic-Macut J, Savic-Radojevic A (2013) Dyslipidemia and oxidative stress in PCOS. Front Horm Res 40:51–63
391. Wild RA, Rizzo M, Clifton S, Carmina E (2011) Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 95(3):1073–9 e1-11

392. Berneis K, Rizzo M, Hersberger M, Rini GB, Di Fede G, Pepe I et al (2009) Atherogenic forms of dyslipidaemia in women with polycystic ovary syndrome. Int J Clin Pract 63(1):56–62
393. Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K et al (1998) Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. J Clin Epidemiol 51(5):415–422
394. Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH et al (2008) A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. J Clin Endocrinol Metab 93(2):470–476
395. Abdalla MA, Shah N, Deshmukh H, Sahebkar A, Ostlundh L, Al-Rifai RH et al (2022) Effect of pharmacological interventions on lipid profiles and C-reactive protein in polycystic ovary syndrome: A systematic review and meta-analysis. Clin Endocrinol (Oxf) 96(4):443–459
396. Forslund M, Melin J, Alesi S, Piltonen T, Romualdi D, Tay CT et al (2023) Different kinds of oral contraceptive pills in polycystic ovary syndrome: a systematic review and meta-analysis. Eur J Endocrinol 189(1):S1–S16
397. Raval AD, Hunter T, Stuckey B, Hart RJ (2011) Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev 10:CD008565
398. Kodaman PH, Duleba AJ (2008) Statins in the treatment of polycystic ovary syndrome. Semin Reprod Med 26(1):127–138
399. Xiong T, Fraison E, Kolibianaki E, Costello MF, Venetis C, Kostova EB (2023) Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev 7(7):CD008565
400. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT et al (2023) Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol 189(2):G43–G64
401. Barrea L, Verde L, Annunziata G, Camajani E, Caprio M, Sojat AS et al (2024) Role of Mediterranean diet in endocrine diseases: a joint overview by the endocrinologist and the nutritionist. J Endocrinol Invest 47(1):17–33
402. Barrea L, Arnone A, Annunziata G, Muscogiuri G, Laudisio D, Salzano C et al (2019) Adherence to the Mediterranean Diet, dietary patterns and body composition in women with polycystic ovary syndrome (PCOS). Nutrients. https://doi.org/10.3390/nu11102278
403. Barrea L, Muscogiuri G, Pugliese G, de Alteriis G, Colao A, Savastano S (2021) Metabolically healthy obesity (MHO) vs. metabolically unhealthy obesity (MUO) phenotypes in PCOS: association with endocrine-metabolic profile, adherence to the Mediterranean Diet, and body composition. Nutrients. https://doi.org/10.3390/nu13113925
404. Mei S, Ding J, Wang K, Ni Z, Yu J (2022) Mediterranean diet combined with a low-carbohydrate dietary pattern in the treatment of overweight polycystic ovary syndrome patients. Front Nutr 9:876620
405. Saadati N, Haidari F, Barati M, Nikbakht R, Mirmomeni G, Rahim F (2021) The effect of low glycemic index diet on the reproductive and clinical profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. Heliyon 7(11):e08338
406. Zhang L, Jin Y, Yang A, Yu X, Li Y, Wang X et al (2025) Optimizing carbohydrate quality: a path to better health for women with PCOS. Front Nutr 12:1578459
407. Sordia-Hernandez LH, Ancer Rodriguez P, Saldivar Rodriguez D, Trejo Guzman S, Servin Zenteno ES, Guerrero Gonzalez G et al (2016) Effect of a low glycemic diet in patients with polycystic ovary syndrome and anovulation - a randomized controlled trial. Clin Exp Obstet Gynecol 43(4):555–559
408. Camajani E, Feraco A, Verde L, Moriconi E, Marchetti M, Colao A et al (2023) Ketogenic Diet as a Possible Non-pharmacological Therapy in Main Endocrine Diseases of the Female Reproductive System: A Practical Guide for Nutritionists. Curr Obes Rep 12(3):231–249
409. Cannarella R, Rubulotta M, Leonardi A, Crafa A, Calvo A, Barbagallo F et al (2025) Effects of ketogenic diets on polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biol Endocrinol 23(1):74
410. Kalsekar AS, Abdelrahim DN, Faris ME (2024) Effect of calorie restriction and intermittent fasting on glucose homeostasis, lipid profile, inflammatory, and hormonal markers in patients with polycystic ovary syndrome: a systematic review. Front Nutr 11:1362226
411. Ranneh Y, Hamsho M, Shkorfu W, Terzi M, Fadel A (2025) Effect of intermittent fasting on anthropometric measurements, metabolic profile, and hormones in women with polycystic ovary syndrome: a systematic review and meta-analysis. Nutrients. https://doi.org/10.3390/nu17152436
412. van Tienhoven XA, de Ruiz Chavez Gascon J, Cano-Herrera G, Sarkis Nehme JA, Souroujon Torun AA, Bautista Gonzalez MF et al (2025) Vitamin D in reproductive health disorders: a narrative review focusing on infertility, endometriosis, and polycystic ovarian syndrome. Int J Mol Sci. https://doi.org/10.3390/ijms26052256
413. Yu M, Chen S, Liu X, Dong H, Wang DC (2025) The impact of vitamin D supplementation on glycemic control and lipid metabolism in polycystic ovary syndrome: a systematic review of randomized controlled trials. BMC Endocr Disord 25(1):110
414. Muscogiuri G, Palomba S, Lagana AS, Orio F (2016) Current insights into Inositol isoforms, Mediterranean and ketogenic diets for polycystic ovary syndrome: from bench to bedside. Curr Pharm Des 22(36):5554–5557
415. Martinez Guevara D, Vidal Canas S, Palacios I, Gomez A, Estrada M, Gallego J et al (2024) Effectiveness of probiotics, prebiotics, and synbiotics in managing insulin resistance and hormonal imbalance in women with polycystic ovary syndrome (PCOS): a systematic review of randomized clinical trials. Nutrients. https://doi.org/10.3390/nu16223916
416. Cowan S, Lim S, Alycia C, Pirotta S, Thomson R, Gibson-Helm M et al (2023) Lifestyle management in polycystic ovary syndrome - beyond diet and physical activity. BMC Endocr Disord 23(1):14

Authors and Affiliations

Giovanna Muscogiuri[1,2,3] · Manuela Albertelli[4,5] · Giorgio Arnaldi[6] · Luigi Barrea[10] · Giuseppe Bellastella[7] · Marco Bonomi[8,9] · Marina Caputo[11] · Massimiliano Caprio[12,13] · Angelo Cignarelli[14] · Ludovico Di Gioia[15,16] · Francesco Frasca[18] · Davide Ferrari[17] · Alessandra Gambineri[19,20] · Valentina Gasco[21] · Federico Gatto[22,23] · Annalisa Giandalia[24] · Roberta Giordano[25,26] · Marco Infante[27] · Andrea Isidori[17] · Pasqualino Malandrino[28] · Gianluca Occhi[29] · Rosario Pivonello[30,31] · Nunzia Prencipe[21] · Flavia Prodam[32] · Chiara Simeoli[33] · Ludovica Verde[3,34] · Linda Vignozzi[35,36] · Salvatore Cannavò[24,37] · Francesco Giorgino[14] · Annamaria Colao[1,2] · Gianluca Aimaretti[38] · Diego Ferone[4,5] · Sebastio Perrini[15,16]

✉ Giovanna Muscogiuri
giovanna.muscogiuri@unina.it

Manuela Albertelli
manuela.albertelli@unige.it

Giorgio Arnaldi
giorgio.arnaldi@unipa.it

Luigi Barrea
luigi.barrea@unipegaso.it

Giuseppe Bellastella
giuseppe.bellastella@unicampania.it

Marco Bonomi
marco.bonomi@unimi.it

Marina Caputo
marina.caputo@uniupo.it

Massimiliano Caprio
massimiliano.caprio@sanraffaele.it

Angelo Cignarelli
angelo.cignarelli@gmail.com

Ludovico Di Gioia
l.digioia@miulli.it

Francesco Frasca
f.frasca@unict.it

Davide Ferrari
davide.ferrari@uniroma1.it

Alessandra Gambineri
alessandra.gambiner3@unibo.it

Valentina Gasco
valentina.gasco@unito.it

Federico Gatto
federico.gatto@unige.it

Annalisa Giandalia
agiandalia@unime.it

Roberta Giordano
roberta.giordano@unito.it

Marco Infante
marco.infante@unicamillus.org

Andrea Isidori
andrea.Isidori@uniroma1.it

Pasqualino Malandrino
linomalandrino@gmail.com

Gianluca Occhi
gianluca.occhi@unipd.it

Rosario Pivonello
rosario.pivonello@unina.it

Nunzia Prencipe
nunzia.prencipe@gmail.com

Flavia Prodam
flavia.prodam@med.uniupo.it

Chiara Simeoli
chiara.simeoli@unina.it

Ludovica Verde
ludovica.verde@unina.it

Linda Vignozzi
linda.vignozzi@unifi.it

Salvatore Cannavò
salvo.cannavo@unime.it

Francesco Giorgino
francesco.giorgino@uniba.it

Annamaria Colao
acolao@unina.it

Gianluca Aimaretti
gianluca.aimaretti@unito.it

Diego Ferone
ferone@unige.it

Sebastio Perrini
s.perrini@lum.it

[1] Unità Di Endocrinologia, Diabetologia E Andrologia, Dipartimento Di Medicina Clinica E Chirurgia, Università Degli Studi Di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy

[2] Cattedra Unesco "Educazione Alla Salute E Allo Sviluppo Sostenibile", University Federico II, 80131 Naples, Italy

[3] Department of Medicine, Division of Endocrinology, University of Arizona, Tucson, AZ, USA

[4] Endocrinology Unit, Department of Internal Medicine and Medical Specialties, University of Genova, Genoa, Italy

[5] Endocrinology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[6] Promozione Della Salute, Materno-Infantile, Di Medicina Interna E Specialistica Di Eccellenza "G. D'Alessandro" (PROMISE), Università Degli Studi Di Palermo, Palermo, Italy

[7] Unit of Endocrinology and Metabolic Diseases, Department of Advanced Medical and Surgical Sciences, AOU University of Campania "Luigi Vanvitelli", University of Campania "Luigi Vanvitelli", Naples, Italy

[8] Department of Medical Biotechnologies and Translational Medicine, University of Milan, Milan, Italy

[9] Department of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy

[10] Dipartimento Di Psicologia E Scienze Della Salute, Centro Direzionale, Università Telematica Pegaso, Via Porzio, Isola F2, 80143 Naples, Italy

[11] Unit of Endocrinology, Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy

[12] Laboratory of Cardiovascular Endocrinology, IRCCS San Raffaele, Via Di Val Cannuta 247, 00166 Rome, Italy

[13] Department for the Promotion of Human Sciences and Quality of Life, San Raffaele Open University, Via Di Val Cannuta 247, 00166 Rome, Italy

[14] Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Disease, University of Bari Aldo Moro, Bari, Italy

[15] Endocrinology Unit, Ecclesiastical Entity Regional General Hospital F. Miulli, Acquaviva delle Fonti, BA, Italy

[16] Section of Endocrinology, Department of Medicine and Surgery, LUM University, Casamassima, BA, Italy

[17] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

[18] Endocrinology Section, Department of Clinical and Experimental Medicine, Garibaldi Nesima Hospital, University of Catania, 95124 Catania, Italy

[19] Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

[20] Division of Endocrinology and Diabetes Prevention and Care, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy

[21] Department of Medical Science, Division of Endocrinology, Diabetes and Metabolism, University of Turin, Turin, Italy

[22] Department of Internal Medicine and Medical Specialties, University of Genoa, Endocrinology, Italy

[23] Endocrinology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[24] Department of Human Pathology of Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy

[25] Dip. Scienze Cliniche Biologiche, Diabetologia E Metabolismo, Università Di Torino, SCDU Endocrinologia, AOU Città Della Salute E Della Scienza Di Torino, Turin, Italy

[26] Department of Biological Sciences, Department of Medical Science, Division of Endocrinology, Diabetes and Metabolism, University of Turin, Turin, Italy

[27] Faculty of Medicine and Surgery, UniCamillus - Saint Camillus International University of Health Sciences, Via Di Sant'Alessandro 8, 00131 Rome, Italy

[28] Dipartimento Di Medicina Clinica E Sperimentale, UOC Di Endocrinologia, Università Di Catania, PO Garibaldi-Nesima, Catania, Italy

[29] Department of Biology, University of Padova, Padua, Italy

[30] Dipartimento Di Medicina Clinica E Chirurgia, Sezione Di Endocrinologia, Diabetologia, Andrologia e Nutrizione, Università Federico II Di Napoli, Naples, Italy

[31] Unesco Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy

[32] Unit of Endocrinology, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

[33] Dipartimento Di Medicina Clinica E Chirurgia, Sezione Di Endocrinologia, Diabetologia, Andrologia e Nutrizione, Università Degli Studi Di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy

[34] Dipartimento Di Medicina Clinica E Chirurgia, Centro Italiano Per La Cura E Il Benessere del Paziente Con Obesità (C.I.B.O), Università Degli Studi Di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy

[35] Department of Experimental Clinical and Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

[36] Centro Regionale Di Coordinamento Salute E Medicina Di Genere (CISMEG), Careggi University Hospital, Florence, Italy

[37] Endocrine Unit, "G. Martino" University Hospital, Messina, Italy

[38] Department of Medical Science, University of Turin, Turin, Italy