Draft F2.0// 37 Pages

The HORMONAL BIOLOGY of CHOLESTEROL

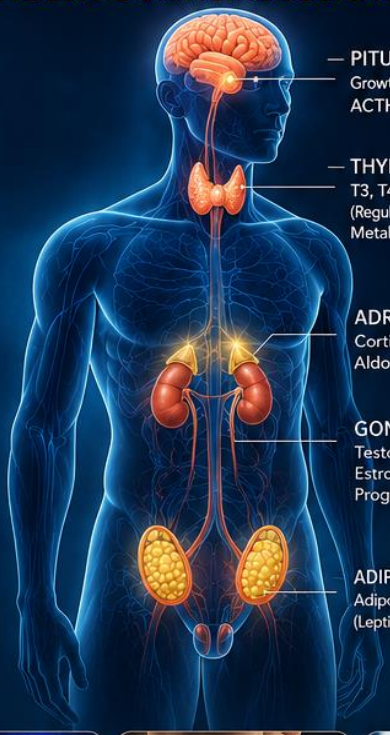
UNDERSTANDING THE ENDOCRINE REGULATION OF LIPID METABOLISM

CHOLESTEROL: THE ESSENTIAL MOLECULE

- Cell Membrane Integrity
- Vitamin D Synthesis
- Bile Acid Production
- Steroid Hormone Synthesis

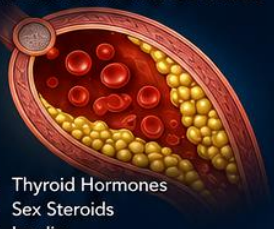
STEROID HORMONES DERIVED FROM CHOLESTEROL

Cholesterol
↓
Pregnenolone
↓
Cortisol | Testosterone
Aldosterone | Estrogen
Neurosteroids



- PITUITARY: Growth Hormone, ACTH
- THYROID: T3, T4 (Regulate Cholesterol Metabolism)
- ADRENALS: Cortisol, Aldosterone
- GONADS: Testosterone, Estrogen, Progesterone
- ADIPOSE TISSUE: Adipokines (Leptin, Adiponectin)

LIPID METABOLISM UNDER HORMONAL CONTROL



- Thyroid Hormones
- Sex Steroids
- Insulin
- Cortisol
- Growth Hormone

STATINS & CHOLESTEROL BALANCING BENEFITS AND PHYSIOLOGICAL NEEDS

- ↓ Cholesterol Synthesis
- ↓ CoQ10 Production
- Potential Effects on Hormone Synthesis

NEUROSTEROIDS
Mood, Sleep, Cognition, Stress Resilience

MITOCHONDRIAL HEALTH
Energy Production & CoQ10

VISERAL ADIPOSITY
An Endocrine Organ Driving Metabolic Risk

COMPREHENSIVE HORMONAL EVALUATION
Personalized Assessment for Better Outcomes

RESTORE HORMONE BALANCE
IMPROVE LIPIDS
ENHANCE HEALTH

CHOLESTEROL IS NOT THE ENEMY—HORMONAL DYSFUNCTION IS OFTEN THE ROOT CAUSE.

CARDIOVASCULAR HEALTH | HORMONAL BALANCE | METABOLIC OPTIMIZATION | NEUROENDOCRINE HEALTH | LONG-TERM WELLNESS

A CLINICAL HANDBOOK FOR PRACTITIONERS, STUDENTS, AND INFORMED PATIENTS

Mark L. Gordon, MD

Foreword

I would like to thank Veteran Pruitt for being the final inspiration that pushed me to complete this project, which was originally started during the COVID era. Over the years, cholesterol has acquired such a negative reputation throughout many sectors of medicine that individuals with "elevated" cholesterol who questioned the necessity of aggressive statin therapy were often viewed as uninformed, irresponsible, or even dangerous. During the COVID period, a similar social atmosphere emerged, where those who questioned prevailing medical narratives or declined vaccination were frequently marginalized or dismissed. The parallel is difficult to ignore.

What has slowly begun to emerge from years of suppression is a broader appreciation for cholesterol's essential role in human physiology, particularly in brain health. The importance of cholesterol in cerebral function has been documented repeatedly in the scientific literature for decades. More recently, these discussions have resurfaced in relation to dementia, cognitive decline, and neurodegenerative disease. Interestingly, many of these same discussions now include neurosteroids and brain hormones, which themselves are synthesized directly from cholesterol.

The consequences of excessively low cholesterol can be profound. In my own life, I witnessed the devastating loss of my mother, Beatrice, during a period where aggressive cholesterol reduction and statin therapy were heavily emphasized. While no single factor can fully explain cognitive decline, the relationship between cholesterol, neurosteroids, and brain function deserves thoughtful and unbiased consideration.

This paper explores what I describe as the "Causation Theory" of elevated cholesterol. From both my clinical observations and review of the scientific literature, it appears plausible that when hormones are insufficient, non-physiological, or not optimized for healthy human performance, the body, particularly the liver, may respond by increasing cholesterol production in an attempt to provide additional substrate for steroid hormone synthesis. In this context, elevated cholesterol may sometimes represent a compensatory physiological response rather than merely a pathological process.

As discussed in my recent paper, *The Fallacy of Laboratory Reference Ranges*, the numerical ranges commonly printed on laboratory reports are largely statistical population averages and do not necessarily define optimal health. True physiological optimization cannot be determined by laboratory values alone. Rather, it must also consider the individual's mental clarity, emotional stability, physical performance, resilience, and overall quality of life. The optimal range for any biomarker should therefore be determined collaboratively between the patient and a knowledgeable healthcare provider, with emphasis placed not only on the numbers themselves, but on how the individual is actually functioning and performing in daily life.

You can find more at www.TBIHELPNOW.org

With respect to all.

Mark L. Gordon, MD

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Section 1

Introduction

Hormones, Cholesterol, and the Misunderstood Biology of Lipid Disorders

For decades, elevated cholesterol and triglyceride levels have been viewed primarily through the lens of cardiovascular risk. Public health campaigns, pharmaceutical advertising, and conventional medical practice have largely framed cholesterol as a dangerous substance whose reduction should be a central goal of preventive medicine. While excessive lipid accumulation within vascular tissues can certainly contribute to atherosclerosis and cardiovascular disease, this simplified perspective frequently overlooks a critical biological reality: cholesterol is one of the most essential molecules in human physiology.

Cholesterol serves as the foundational substrate for the production of steroid hormones, neurosteroids, bile acids, cellular membranes, and vitamin D. Every steroid hormone in the human body originates from cholesterol through a carefully regulated sequence of enzymatic conversions occurring primarily within the adrenal glands, gonads, nervous system, and peripheral tissues. Testosterone, estrogen, progesterone, cortisol, DHEA, pregnenolone, and aldosterone all derive directly from cholesterol metabolism. Without adequate cholesterol availability, normal endocrine physiology becomes impossible.

Cholesterol → Pregnenolone → Steroid Hormones

This fundamental biological relationship creates an important paradox in clinical medicine. Hormonal insufficiencies and deficiencies themselves can significantly alter lipid metabolism, frequently resulting in elevations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and reductions in protective high-density lipoprotein cholesterol (HDL-C). In many individuals, dyslipidemia may not represent a primary lipid disorder at all, but rather a downstream manifestation of endocrine dysfunction.

Among the most well-established examples is hypothyroidism, where reductions in thyroid hormone activity impair hepatic LDL receptor function and reduce cholesterol clearance from circulation. Similarly, testosterone deficiency in men is strongly associated with elevated triglycerides, increased visceral adiposity, insulin resistance, and unfavorable HDL reductions. Menopause and declining estrogen levels in women frequently produce substantial increases in LDL cholesterol and cardiovascular risk. Growth hormone deficiency, cortisol dysregulation, insulin resistance, and neurosteroid depletion may also contribute to profound disturbances in lipid handling and energy metabolism.

Importantly, these endocrine influences extend beyond classical hormones alone. Neurosteroids and neuroactive steroids, including pregnenolone, progesterone, allopregnanolone, and DHEA, participate in

mitochondrial regulation, glucose utilization, inflammatory modulation, and hepatic lipid metabolism. Alterations in these compounds may indirectly influence lipid transport, adipose tissue biology, and metabolic efficiency.

The relationship between hormones and lipids is therefore bidirectional. Cholesterol supports hormone production, while hormones themselves regulate how cholesterol and triglycerides are synthesized, transported, stored, and utilized throughout the body. Disruption at any point within this network may contribute to abnormal laboratory findings frequently interpreted as isolated cardiovascular pathology.

This review examines how deficiencies and insufficiencies of classical endocrine hormones and neurosteroids influence cholesterol and lipid regulation. Particular emphasis will be placed on clinically relevant hormonal states that contribute to elevations in LDL cholesterol and triglycerides, while also exploring the broader physiological role of cholesterol as a critical building block for human survival and endocrine homeostasis.

Table 1. Cholesterol as the Precursor for Major Steroid Hormones

Cholesterol-Derived Product	Primary Physiological Role
Pregnenolone	Master precursor neurosteroid and steroid hormone substrate
Progesterone	Neuroprotection, reproduction, steroidogenesis intermediary
Testosterone	Muscle mass, metabolism, cognition, libido
Estrogen (Estradiol)	Cardiovascular protection, bone health, lipid regulation
Cortisol	Stress adaptation, glucose metabolism
DHEA	Neurosteroid support, metabolic regulation
Aldosterone	Fluid and electrolyte regulation
Vitamin D	Immune modulation, calcium regulation, metabolic signaling
Bile Acids	Fat digestion and lipid absorption

Table 2. Common Hormonal Deficiencies Associated with Dyslipidemia

Hormonal Deficiency	Common Lipid Findings
Hypothyroidism	↑ LDL-C, ↑ Total Cholesterol, ↑ Triglycerides
Testosterone Deficiency	↑ Triglycerides, ↓ HDL
Estrogen Deficiency	↑ LDL-C, ↓ HDL
Growth Hormone Deficiency	↑ LDL-C, ↑ Visceral Fat
Insulin Resistance	↑ Triglycerides, ↓ HDL, Small Dense LDL
DHEA Deficiency	Mild ↑ LDL and triglycerides
Cortisol Dysregulation	↑ Triglycerides and visceral adiposity

Section 2

Basic Physiology of Cholesterol and Lipid Regulation

Cholesterol and triglycerides are often discussed as if they are inherently harmful substances; however, both are indispensable to human survival. Lipids provide structural integrity to cellular membranes, serve as dense energy reservoirs, support neurological function, facilitate digestion, and act as the biochemical substrate for hormone production. The human body therefore maintains an extraordinarily complex regulatory system designed to balance lipid synthesis, transport, storage, and utilization.

Understanding how hormones influence lipid metabolism first requires an appreciation of the normal physiology of cholesterol and lipoprotein regulation.

Cholesterol: An Essential Biological Molecule

Cholesterol is a wax-like lipid molecule synthesized primarily within the liver, although nearly every cell in the body possesses the capacity to manufacture cholesterol when needed. Approximately 70–80% of circulating cholesterol is produced endogenously, while the remainder is obtained through dietary intake.

The liver synthesizes cholesterol through the mevalonate pathway, with the enzyme HMG-CoA reductase serving as the rate-limiting step.

$$\textit{HMG-CoA} \rightarrow \textit{Mevalonate} \rightarrow \textit{Cholesterol}$$

This pathway is clinically important because statin medications function by inhibiting HMG-CoA reductase, thereby reducing endogenous cholesterol synthesis.

Despite cholesterol's negative public reputation, it performs numerous vital physiological functions, including:

- Formation of cellular membranes
- Maintenance of membrane fluidity
- Production of steroid hormones (steroidogenesis)
- Synthesis of vitamin D
- Formation of bile acids necessary for fat absorption
- Support of neuronal structure and synaptic function
- Myelin formation within the nervous system

The brain itself contains nearly 20–25% of the body's total cholesterol despite representing only approximately 2% of total body weight, underscoring cholesterol's importance in neurological physiology.

Lipoproteins: The Transport System for Lipids

Because cholesterol and triglycerides are not water-soluble, they require specialized transport particles known as lipoproteins to move through circulation.

These lipoproteins differ according to density, lipid composition, and physiological function.

Table 3. Major Lipoproteins and Their Functions

Lipoprotein	Primary Function	Clinical Significance
Chylomicrons	Transport dietary triglycerides from intestine to blood	Elevated after meals
VLDL (Very Low-Density Lipoprotein)	Transports triglycerides from liver	Elevated in insulin resistance
IDL (Intermediate Density Lipoprotein)	Transitional lipoprotein	Precursor to LDL
LDL (Low-Density Lipoprotein)	Delivers cholesterol to tissues	Elevated levels linked to atherosclerosis
HDL (High-Density Lipoprotein)	Reverse cholesterol transport	Generally protective
Lipoprotein(a)	Genetically influenced LDL-like particle	Strong cardiovascular risk factor

Triglycerides and Energy Storage

Triglycerides are the primary storage form of fatty acids and serve as the body's major long-term energy reserve. Excess caloric intake, especially from carbohydrates and sugars, may be converted into triglycerides within the liver and adipose tissue.

Excess Glucose → Fatty Acids → Triglycerides

Elevated triglycerides frequently reflect:

- Insulin resistance (Type 2 Insulin Resistant Diabetes)
- Excess carbohydrate intake
- Metabolic syndrome
- Hormonal dysfunction
- Reduced mitochondrial fatty acid oxidation

Triglyceride metabolism is strongly regulated by hormones including insulin, thyroid hormones, testosterone, estrogen, cortisol, and growth hormone.

Hormonal Regulation of Lipid Metabolism

Hormones regulate nearly every aspect of lipid physiology, including:

- Hepatic cholesterol synthesis
- LDL receptor activity
- Lipoprotein lipase function
- Fatty acid oxidation
- Adipose tissue storage
- Reverse cholesterol transport
- Mitochondrial energy utilization

The endocrine system therefore acts as a master regulator of lipid balance.

When hormone levels decline, lipid handling frequently deteriorates.

Thyroid Hormones

Thyroid hormones are among the most important regulators of cholesterol metabolism. Triiodothyronine (T3) stimulates LDL receptor production within the liver, thereby enhancing clearance of circulating LDL cholesterol.

Thyroid hormones also:

- Increase mitochondrial fatty acid oxidation
- Enhance lipoprotein lipase activity
- Improve bile acid synthesis
- Promote metabolic energy expenditure

Reduced thyroid function commonly results in elevated LDL cholesterol and triglycerides due to impaired hepatic clearance.

Testosterone

Testosterone helps regulate:

- Visceral fat accumulation
- Insulin sensitivity
- Muscle mass
- Mitochondrial energy production
- Lipid oxidation
- Reduction of Pro-inflammatory Cytokines

Low testosterone states frequently promote increased triglycerides, reduced HDL cholesterol, and central adiposity.

Estrogen

Estrogen exerts several cardiometabolic protective effects, including:

- Increasing hepatic LDL receptor activity
- Supporting HDL production
- Improving endothelial function
- Reducing visceral fat deposition

This helps explain why cardiovascular risk often rises substantially after menopause when estrogen levels decline.

Insulin

Insulin plays a central role in triglyceride metabolism by suppressing lipolysis and regulating hepatic VLDL production.

When insulin resistance develops:

- Excess free fatty acids are released from adipose tissue
- The liver overproduces triglyceride-rich VLDL particles
- HDL cholesterol declines
- Small dense LDL particles increase

This characteristic lipid pattern is commonly referred to as diabetic dyslipidemia.

Neurosteroids and Neuroactive Steroids

Emerging evidence suggests that neurosteroids such as pregnenolone, progesterone, allopregnanolone, and DHEA may indirectly influence lipid metabolism through:

- Mitochondrial regulation
- Glucose utilization
- Insulin sensitivity
- Inflammatory modulation
- Stress adaptation

Although these relationships are still being investigated, neurosteroid insufficiency may contribute to broader metabolic dysfunction in aging and chronic illness.

Cholesterol as a Dynamic Physiological Resource

An important clinical concept often overlooked is that elevated cholesterol may represent a compensatory physiological response rather than solely a pathological abnormality.

Because cholesterol serves as the precursor for steroid hormones, the body may increase cholesterol synthesis when endocrine demand rises or hormonal production becomes inefficient.

For example:

- Hypogonadism may coexist with elevated cholesterol
- Menopause frequently increases LDL cholesterol
- Chronic stress may alter steroidogenic demand
- Low thyroid function impairs cholesterol utilization

Thus, elevated cholesterol levels should not always be interpreted in isolation without considering the broader endocrine environment.

Table 4. Hormonal Regulation of Key Lipid Functions

Hormone	Major Lipid Actions
Thyroid Hormones	Increase LDL clearance and fatty acid oxidation
Testosterone	Reduce visceral fat and triglycerides
Estrogen	Increase HDL and improve LDL clearance
Insulin	Regulates triglyceride storage and VLDL production
Growth Hormone	Stimulates lipolysis
Cortisol	Influences hepatic glucose and lipid metabolism
Pregnenolone/DHEA	Support mitochondrial and metabolic regulation

Section 3

Thyroid Hormones and Lipid Regulation

The Most Common Endocrine Cause of Elevated Cholesterol

Among all endocrine disorders associated with dyslipidemia, hypothyroidism is one of the most common and clinically significant causes of elevated cholesterol and triglycerides. Even mild reductions in thyroid hormone activity may substantially impair lipid metabolism, alter energy production, and increase cardiovascular risk.

Thyroid hormones regulate nearly every aspect of metabolic physiology. Through their influence on mitochondrial activity, hepatic metabolism, oxygen consumption, and enzymatic signaling, thyroid hormones act as central controllers of how the body produces, transports, and eliminates lipids.

When thyroid hormone levels decline, cholesterol metabolism slows, fatty acid utilization becomes impaired, and circulating lipids frequently accumulate within the bloodstream.

Overview of Thyroid Physiology

The thyroid gland primarily produces thyroxine (T4), which is converted within tissues into the biologically active hormone triiodothyronine (T3).

T3 binds to nuclear thyroid hormone receptors and influences the transcription of numerous genes involved in:

- Energy production
- Mitochondrial respiration
- Lipid oxidation
- Cholesterol transport
- Glucose metabolism
- Thermogenesis

$$T_4 \rightarrow T_3 \rightarrow \textit{Nuclear Receptor Activation}$$

Thyroid hormone activity is therefore essential for maintaining normal metabolic turnover and efficient lipid clearance.

Thyroid Hormones and LDL Cholesterol

One of the most important actions of T3 is stimulation of hepatic LDL receptor production.

LDL receptors located on hepatocytes remove LDL cholesterol particles from circulation and transport them into the liver for metabolism and elimination.

When thyroid hormone levels decline:

- LDL receptor density decreases
- Hepatic cholesterol clearance slows
- Circulating LDL cholesterol rises

$$\downarrow T_3 \rightarrow \downarrow \textit{LDL Receptors} \rightarrow \uparrow \textit{LDL Cholesterol}$$

This mechanism explains why hypothyroidism is strongly associated with:

- Elevated total cholesterol
- Increased LDL cholesterol
- Increased apolipoprotein B
- Increased triglycerides

In many patients, correction of hypothyroidism alone may substantially improve cholesterol levels without aggressive lipid-lowering therapy.

Thyroid Hormones and Triglycerides

Thyroid hormones also regulate triglyceride metabolism through their influence on:

- Lipoprotein lipase (LPL)
- Hepatic lipase
- Mitochondrial fatty acid oxidation
- Energy expenditure

Under normal conditions, lipoprotein lipase helps clear triglyceride-rich lipoproteins from circulation.

Hypothyroidism reduces this enzyme activity, leading to:

- Slower triglyceride clearance
- Increased VLDL accumulation
- Elevated serum triglycerides

Additionally, reduced thyroid hormone activity impairs mitochondrial β-oxidation of fatty acids, promoting increased fat storage and reduced metabolic efficiency.

Thyroid Hormones and HDL Cholesterol

The effects of hypothyroidism on HDL cholesterol are more variable than those seen with LDL cholesterol.

Some individuals may demonstrate:

- Mild HDL elevation due to reduced HDL catabolism
- Others may show reduced HDL function despite normal HDL quantity

Importantly, HDL quality and reverse cholesterol transport may become impaired even when HDL laboratory values appear acceptable.

Subclinical Hypothyroidism and Dyslipidemia

An important clinical concept is that even "subclinical" hypothyroidism may contribute to abnormal lipid findings.

Subclinical hypothyroidism typically refers to:

- Elevated thyroid-stimulating hormone (TSH)
- Normal circulating T4 levels

However, many individuals with subclinical disease experience:

- Reduced tissue thyroid activity
- Fatigue
- Weight gain
- Reduced metabolic efficiency
- Elevated LDL cholesterol

This has led some clinicians to question whether standard laboratory reference ranges adequately reflect optimal thyroid physiology.

Table 5. Common Lipid Changes in Hypothyroidism

Lipid Parameter	Typical Change
Total Cholesterol	↑↑
LDL Cholesterol	↑↑
Triglycerides	↑
VLDL	↑
ApoB	↑
HDL Cholesterol	**Variable**

Reverse T3 and Functional Thyroid Suppression

In some individuals, stress, inflammation, caloric restriction, illness, or chronic disease may increase production of reverse T3 (rT3), an inactive thyroid hormone metabolite.

Reverse T3 competes with T3 activity and may contribute to a state of "functional hypothyroidism" despite apparently normal thyroid laboratory values.

$$T_4 \rightarrow rT_3\ (inactive)$$

Final Clinical Perspective

Hormonal insufficiencies and deficiencies are frequently overlooked contributors to dyslipidemia. Recognition of the intimate relationship between cholesterol and endocrine physiology may provide clinicians and patients with a more balanced, biologically grounded understanding of metabolic disease.

In this context, cholesterol should not be viewed simply as a pathological substance to suppress, but rather as an essential physiological molecule whose regulation is deeply intertwined with human hormonal health, energy metabolism, and long-term systemic function.

About the Millennium

Since 2009, The Millennium Health Centers, Inc. has been committed to ensuring that financial limitations do not prevent veterans and active-duty service members from receiving care. Through our grant and subsidized funding programs, we have helped make advanced neuroendocrine and neuroinflammatory evaluations and treatment more accessible to those who have sacrificed for our country.

In 2020, thanks to the tremendous support generated through Dr. Mark Gordon's appearances on the Joe Rogan Experience, we expanded our assistance to include the spouses of veterans. Beginning in 2025, that commitment grew once again to include their children experiencing symptoms associated with traumatic brain injury and neuroinflammation. Every grant awarded is dependent upon available funding, allowing us to extend help wherever resources permit.

Unlike many charitable organizations, we do not actively seek outside fundraising. Instead, we have chosen to build a self-sustaining model in which proceeds from our educational programs and health products help fund veteran care. We also continue to support a number of veteran-owned and veteran-operated 501(c)(3) organizations whose missions align with our own.

Every purchase made through MillenniumHealthStore.com directly strengthens our ability to provide grants, expand educational initiatives, and extend care to more veterans and their families. It is a simple way to become part of a mission that has been changing lives for more than 15 years.

Thank you

Mark L. Gordon, MD

Mark L. Gordon, MD

CEO/Founder of the Millennium Health Centers, Inc.

The complete 37-paged report on The Hormonal Biology of Cholesterol may be purchased at www.MillenniumHealthStore.com under the Educational Products page. Your purchase will add to our ability to continue the work we do for our military. Thank you. Mark L. Gordon, MD