

EDITORIAL

Lipocrinology – the relationship between lipids and endocrine function

Sanjay Kalra¹, Gagan Priya²

¹Department of Endocrinology, Bharti Hospital, Karnal, India; ²Department of Endocrinology, Fortis Hospital, Mohali, India

Abstract

While lipids are an integral part of the endocrine clinic, the opposite is not necessarily true. The lipocrinology framework addresses this lacuna, by highlighting the similarities and multiple relationships between lipid and endocrine function. It reinforces the need to screen (clinically or biochemically) all dyslipidemic patients for endocrine disease and appropriate endocrine patients for dyslipidemia. Thus, it aims to improve clinical care for persons with lipid abnormalities as well as endocrine disease.

Keywords: adipose tissue, cholesterol, diabetes, HDL cholesterol, hormones, LDL cholesterol, lipotoxicity, triglycerides.

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Introduction

Lipocrinology is the study of the interrelationship between lipid metabolism and endocrine function in health and disease. Lipocrinology includes, in its ambit, the contribution of endocrine function to lipid health, occurrence of dyslipidemia in endocrine illness, and impact of lipids on the clinical course and prognosis of endocrine disease. The subject also covers the role of lipids in the diagnosis of endocrinopathies, influence of lipid-lowering drugs on endocrine function, and influence of endocrinotropic drugs on lipid levels. The role of the adipose tissue as an endocrine organ [1] is also included in the scope of lipocrinology. In Table 1, we highlight the vast scope of lipocrinology in the practice of medicine.

Dyslipidemia and endocrinopathy

Dyslipidemia is a common occurrence in the endocrine clinic. Dyslipidemia is known to coexist frequently with type 2 diabetes and obesity [2]. A unique lipophenotype, characterized by low high density lipoprotein-cholesterol (HDL-C), high triglycerides and small dense low density cholesterol (LDL-C), is well known in diabetes [3]. Similar lipid abnormalities characterize metabolic syndrome and polycystic ovary syndrome (PCOS) [4]. The polycystic ovary syndrome is associated with increases in LDL cholesterol, triglycerides, and lipoprotein a (Lp (a)) and decreases in HDL cholesterol. Obesity, metabolic syndrome and diabetes are associated with

significant alteration in fat distribution with increase in visceral and ectopic fat. This adiposopathy is a key driving factor that leads to deranged adipokine secretion, further contributing to chronic inflammation and lipotoxicity.

Lipodystrophies, both congenital and acquired, may be associated with significant insulin resistance and diabetes. Patients with generalized lipodystrophy have markedly reduced serum leptin levels and metreleptin replacement therapy has been used successfully in such patients to improve metabolic profile [5]. At times, lipodystrophy may be iatrogenic, as in insulin injection being associated with injection site lipodystrophy/lipoatrophy or lipohypertrophy [6].

Acromegaly is associated with hypertriglyceridemia (low HDL and high Lp (a)) [7], while Cushing's syndrome has hypercholesterolemia as a common manifestation [8]. Patients with endogenous Cushing's syndrome typically display an increase in total and LDL cholesterol and triglycerides. In hypothyroidism, LDL cholesterol and Lp (a) levels are raised [9]. Hyperthyroid patients exhibit low total cholesterol, LDL-C, HDL and Lp (a) levels, with variable reports regarding triglyceridemia [10]. Dyslipidemia is also common in hypogonadism and menopause. Men with low testosterone levels may have high LDL cholesterol and triglyceride, and decreased HDL cholesterol levels. Menopause in women is associated with a modest increase in LDL cholesterol with either no change or a small decrease in HDL cholesterol [10].

Table 1. The spectrum of lipocrinology.**Clinical approach**

- Management strategies may be common to endocrinology and dyslipidemia
 - Long term/chronic treatment for both
 - Motivation for injectable therapy (insulin, proprotein convertase subtilisin kinase 9 [PCSK9] inhibitors)
- Dyslipidemia increases atherosclerotic cardiovascular disease (ASCVD) risk in endocrinopathies
 - Prolactinoma
 - GH deficiency
 - Cushing's syndrome
 - Male hypogonadism
 - Polycystic ovary syndrome (PCOS)
- Endocrinopathy may unmask/mask lipid disorders
 - Genetic beta dyslipidemia (Type III) may be masked by hypothyroidism

Clinical presentation

- Lipid disorders and endocrinopathies coexist
 - Type 2 diabetes
 - Non-alcoholic steatohepatitis
 - PCOS
- Lipid disorders are a feature of many endocrinopathies
 - Acromegaly
 - Hypothyroidism
 - Hypogonadism
- Lipid levels influence the clinical course of endocrine disease
 - Premature ASCVD
 - Microvascular complications
 - Lipotoxicity and beta cell failure
- Gender and age influence lipid levels
 - Puberty: HDL-C falls and triglycerides increase in boys
 - Premenopausal women have higher HDL-C, lower LDL-C than men
 - Postmenopausal women have higher LDL, small dense LDL, Lp (a), especially after surgical menopause

Diagnosis

- Lipophenotype helps in differential diagnosis of endocrinopathies
 - Primary vs secondary hypothyroidism
 - Type 2 diabetes vs late onset autoimmune diabetes of adults (LADA)
- Lipids may be used to monitor endocrine therapy
 - Cholesterol levels were used to monitor thyroid replacement prior to advent of RIA
- Lipids may be used as an aid to clinical decision making
 - Subclinical hypothyroidism with higher LDL-C may benefit from L-thyroxine treatment
- Lipid sensitive imaging may be used to diagnose endocrine disease
 - Pheochromocytomas benign cortical adrenal adenoma

Management of endocrinopathy

- Lipid-lowering drugs may be used to treat endocrinopathy
 - Clofibrate for nephrogenic diabetes insipidus
 - Colesevelam for type 2 diabetes
 - Fenofibrate for diabetic retinopathy
 - Fenofibrate, statins for diabetic neuropathy
- Lipid-lowering drug may cause or worsen endocrinopathy
 - Statins and hyperglycemia
 - Clofibrate and syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Endocrine function may influence tolerance to lipid-lowering drugs
 - Vitamin D and statin intolerance

Management of dyslipidemia

- Hormone/peptide inhibitors are used to manage dyslipidemia
 - PCSK9i

Table 1. (Continued)

- Endocrine drugs may improve lipid health
 - Octreotide
 - L-thyroxin
 - Bromocriptine, cabergoline
 - Growth hormone
 - Ketoconazole
 - Incretin based therapies
 - Pioglitazone
- Endocrine drugs may worsen lipid health
 - Oral contraceptives
 - DMPA [depomedroxy progesterone acetate]
 - Androgen deprivation therapy
 - Mitotane
 - Anabolic steroid misuse

A unique endocrine disease, which is diagnosed through an error of lipid metabolism, is congenital lipid adrenal hyperplasia. Usually caused by recessive mutations in the gene encoding steroidogenic acute regulatory protein (StAR), it is characterized by lipid accumulation in the newborn's adrenal glands and leads to potentially fatal salt-wasting crisis [11].

Diagnosis

Occurrence of dyslipidemia in a person with other metabolic dysfunction (non-alcoholic steatohepatitis, PCOS, diabetes) contributes to a diagnosis of metabolic syndrome. In fact, current definitions of metabolic syndrome emphasize the importance of lipids by reserving two points for this condition, that is, low HDL and high triglycerides [12].

Lipid levels can be used to help inform the diagnosis of certain endocrine diseases. Dyslipidemia is more common in secondary hypothyroidism than in primary hypothyroidism, for example [10]. Both acromegaly and GH deficiency are characterized by hyper triglyceridemia and low HDL levels [10].

Lipid sensitive imaging or chemical shift MRI is used to differentiate between benign cortical adrenal adenoma and pheochromocytoma [13]. This modality is based upon measurement of the lipid content in the adrenal gland. Adrenal myelolipoma, a rare benign tumor of the adrenal gland, is composed of fatty and hematopoietic tissues. It appears as a well circumscribed lesion composed of predominantly fatty tissue with foci of myeloid tissue. On CT, the high lipid content gives a characteristic image with attenuation of –30 to –115 Hounsfield units.

Effect of hormone replacement on lipids

Growth hormone therapy decreases total cholesterol and LDL cholesterol but increases Lp (a) levels. However, the

administration of glucocorticoids frequently increases HDL cholesterol. Androgen deprivation therapy results in an increase in LDL cholesterol, triglycerides, and Lp (a) and a decrease in HDL cholesterol. The effect of testosterone replacement therapy on plasma lipids and lipoproteins is modest and variable, but high dose androgen therapy used by athletes can markedly decrease HDL cholesterol and also reduce Lp (a) levels. Estrogen administration decreases LDL cholesterol and Lp (a) levels, while increasing triglycerides and HDL cholesterol levels, but these effects are dependent on the dose and route of administration (transdermal has smaller effects than oral). Concurrent progesterone treatment has little or no effect on the decrease in LDL cholesterol induced by estrogen administration but may blunt the estrogen effect on HDL cholesterol and triglyceride levels depending on the androgenicity of the progesterone [10]. In general, less androgenic progestins are safer from a lipid perspective. Depomedroxy progesterone acetate (DMPA) may lead to reduction in HDL and increase in LDL levels. Estrogens may precipitate marked hypertriglyceridemia and the chylomicronemia syndrome in patients with triglyceride metabolism defects [10].

Effect on endocrine drugs on lipids

Various endocrine drugs influence lipid levels, too. The list of such drugs is long. Octreotide, GLP1RA, DPP4i and pioglitazone have a favorable impact on lipids. L-thyroxin supplementation in hypothyroid individuals also helps normalize the lipophenotype. Thyroid hormone analogues, which target lipids, without causing hyperthyroidism, are in development [9]. Glucocorticoids have variable effects on lipids. If prescribed to persons without inflammatory disease, they increase HDL. In high doses, they tend to increase LDL and triglycerides as well [10].

Endocrine peptide inhibitors, such as proprotein convertase subtilisin kinase 9 (PCSK9) inhibitors, are now approved for the management of familial hypercholesterolemia and in statin intolerance [14].

Use of lipid-lowering drugs in endocrinology

Various lipid-lowering drugs have found utility in the management of endocrinopathies. Clofibrate, for example, has been used for the management of nephrogenic diabetes insipidus [15], while colesevelam is approved for the treatment of type 2 diabetes [16]. Cholestyramine has been used in hyperthyroidism [17]. Fenofibrate is approved, in Australia, for the secondary prevention of diabetic retinopathy, and has a role in the management of diabetic neuropathy as well. These benefits are independent of its lipid lowering actions [18].

Lipid-lowering drugs have endocrine related adverse effects, too. Clofibrate is implicated as a cause of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Statin intolerance may be precipitated by endocrine dysfunction such as vitamin D deficiency [19].

Statins have been reported to impair insulin sensitivity, increase the risk of hyperglycemia and to lower aldosterone secretion in response to angiotensin II. A positive effect of statins on bone health is also noted in the form of increased BMD and reduced fracture risk. This effect seems to be dose dependent, and some newer drugs such as pitavastatin may improve insulin sensitivity [20]. This effect is mediated by an increase in adiponectin and reduction in oxidative stress [21]. Ezetimibe increased active glucagon-like peptide 1 (GLP-1) and improved glycemic control and pancreatic beta cell mass in rodent studies [22].

Effect of statins and other lipid-lowering drugs, such as ezetimibe and cholestyramine, on steroid hormonogenesis in adrenals and gonads needs further evaluation. While statins may reduce ovarian androgen production from

theca-interstitial cells and may have a beneficial response in PCOS, reports of reduction in LH secretion and testosterone production in males raise concerns. Impact on male fertility also needs evaluation [10].

Impact of lipid health on endocrine outcomes

Dyslipidemia is a major contributor to endocrine and metabolic health. The presence of lipid abnormalities is a risk factor for both macro and micro vascular complications in diabetes [23]. It contributes to premature atherosclerotic cardiovascular disease in endocrinopathies such as acromegaly, hypothyroidism and PCOS as well [10].

Lipotoxicity is a significant contributor to the pathogenesis of diabetes [24]. High free fatty acid (triglyceride) levels may impair beta cell function and lead to suboptimal therapeutic response of glucose-lowering drugs.

Summary

The discussion contained in the preceding paragraphs summarizes the extensive interrelationship between lipids and the endocrine system. The scope of this interaction is wide enough to merit the label 'lipocrinology.'

The novel concept of lipocrinology adds a new dimension to the fields of both lipidology and endocrinology. It stimulates the student, clinician and researcher to appreciate the multifaceted links between endocrinology and lipidology. The framework enhances our understanding of the pathophysiology, clinical features diagnosis and management of both lipid disorders and hormonal disease.

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Correspondence: Sanjay Kalra, Department of Endocrinology, Bharti Hospital, Karnal, India. brideknl@gmail.com

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