Management of Dyslipidemia in Cushing's Syndrome

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Key Words

Hyperlipidemia · Ketoconazole

Abstract

Cardiovascular risk factors such as hypertension, hyperlipidemia and glucose intolerance are highly prevalent in Cushing's syndrome. Lipid abnormalities have been reported in 40–70% of patients, including those with 'subclinical' disease. Surgical cure is associated with significant amelioration of lipid profile in the majority of patients. Treatment of persistent hyperlipidemia should be conducted according to the accepted general principles in use for other medical conditions. Nevertheless, patients requiring medical treatment for persistent hypercortisolism present specific challenges, according to the selected therapeutic agent. For example, treatment with the adrenolytic drug o,p'DDD is associated with a prominent increase in cholesterol levels that necessitates intensive use of lipid lowering agents. The use of ketoconazole, a potent inhibitor of cytochrome P450 3A4 (CYP3A4), may significantly increase plasma concentrations of certain statins (such as simvastatin and atorvastatin) that undergo metabolism by the same pathway, thus increasing the risk of complications and side effects. Therefore, preference should be given to HMG-CoA inhibitors that are me-

tabolized by different pathways, such as pravastatin. In summary, hyperlipidemia should be aggressively treated in patients with Cushing's syndrome in view of the increased cardiovascular morbidity and mortality associated with this disorder.

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Introduction

Cushing's syndrome is associated with increased morbidity and mortality. The 5-year survival rate was reported to be 50% when effective treatment was not available [1]. Despite the significant improvement in therapeutic modalities, the standardized mortality ratio remains elevated [2]. Chronic hypercortisolism is associated with several cardiovascular risk factors, including diabetes, hypertension, visceral obesity and dyslipidemia, leading to an increased incidence of cardiovascular disease [3]. The relative risk for cardiovascular events is increased not only in endogenous Cushing's syndrome, but also as a consequence of treatment with high-dose glucocorticoids [4]. Even subclinical hypercortisolism [5] as well as cortisol levels in the highest tertile of the normal range [6] were associated with increased cardiovascular risk.

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Table 1. Prevalence of hyperlipidemia in Cushing's syndrome in relation to the cut-offs used for establishing the diagnosis

Series	High total cholesterol, mg/dl		High triglycerides, mg/dl	
	patients (%)	cut-off	patients (%)	cut-off
Colao et al. [12]	4/15 (26.7)	>240	1/15 (6.7)	>250
Faggiano et al. [13]	13/25 (52)	>240	5/25 (20)	>250
Mancini et al. [14]	12/49 (25)	>250	6/49 (12.5)	>250
Tauchmanová et al. [5]*	10/28 (35)	>200	10/28 (35)	>160

* Patients with subclinical Cushing's syndrome.

Dyslipidemia in Cushing's Syndrome

The effects of glucocorticoids on lipid metabolism are complex. Cortisol increases whole body lipolysis, but chronic hypercortisolemia results in increased fat mass [7]. On the one hand, glucocorticoids induce hormone-sensitive lipase activity in adipose tissue, augmenting intra-adipocyte triglyceride hydrolysis. On the other hand, hypercortisolemia stimulates lipoprotein lipase activity, which is further potentiated by hyperinsulinemia, leading to intravascular lipolysis and increased uptake of nonesterified fatty acids and glycerol in adipose tissue [8]. It has recently been shown that glucocorticoids inhibit AMP-activated protein kinase activity in adipose tissue, suggesting an additional mechanism to explain the deposition of visceral adipose tissue and the consequent central obesity observed in patients with hypercortisolemia [9]. The dyslipidemia in Cushing's syndrome is characterized by increased plasma levels of total cholesterol, LDL and VLDL cholesterol, and triglycerides [10]. Interestingly, patients who developed characteristic steroid-induced fat deposition (dorsocervical, facial, supraclavicular) during prolonged high-dose glucocorticoid treatment had higher total- and lower HDL-cholesterol levels than those who did not develop these morphological changes [11].

It is difficult to state the true prevalence of hyperlipidemia in patients with Cushing's syndrome, as cut-offs used to establish the diagnosis vary among different studies. Furthermore, most published series used criteria recommended in older guidelines such as the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) [12, 13] or the World Health Organization-International Society

of Hypertension (WHO/ISH) 1999 guidelines [14]. Total cholesterol is reported to be elevated in 25–52% of patients, whereas high serum triglycerides were found in 7–35% of patients (table 1). Reduced HDL-cholesterol levels were reported in 14.2% [14] to 36% [13] of patients. If current criteria were used, the rates of hyperlipidemia would probably be higher.

Is this prevalence higher than that found in the general population? The answer to this question is not simple, with inconsistent reports in the literature. Several factors may contribute to the discrepant results. Cushing's patient series are usually small, thus decreasing the statistical power for comparisons. Another important factor is whether the reference population to which patients' parameters were compared has been matched for BMI. Faggiano et al. [13] found that total and LDL-cholesterol levels were higher and that HDL-cholesterol levels were lower in patients compared to a group of healthy subjects. Nevertheless, when the same group of patients was compared to a group of BMI-matched controls, the only remaining difference was that HDL-cholesterol levels were lower in the patients' population, resulting in a significant higher cholesterol/HDL-cholesterol ratio (table 2). There were no differences in triglyceride levels among all groups. In contrast, Terzolo et al. [15] found higher triglyceride levels in patients with Cushing's disease in comparison to healthy controls (not matched for BMI) but there were no differences in cholesterol levels. Finally, total cholesterol, LDL cholesterol and triglycerides were higher, and HDL cholesterol was lower in patients with subclinical Cushing's syndrome in comparison to BMI-matched controls [5].

Table 2. Lipid parameters in patients with Cushing's disease at diagnosis and 1 year after remission, compared to healthy controls (control group 1) and to BMI-matched controls (control group 2): adapted from Faggiano et al. [13]

	Patients		Control 1 (sex and age matched)	Control 2 (BMI matched)
	active disease	1 year remission		
Number	25	25	32	32
BMI	29.2 ± 1.8	26.8 ± 1.5	22.8 ± 1.6	28.4 ± 1.8
Triglycerides, mg/dl	172 ± 35	159 ± 26	134 ± 26	182 ± 35
Total cholesterol, mg/dl	240 ± 25 ^a	213 ± 23	174 ± 15	219 ± 19
LDL cholesterol, mg/dl	168 ± 23 ^{c, d}	145 ± 19 ^a	103 ± 11	149 ± 15
HDL cholesterol, mg/dl	38 ± 3 ^{b, c}	43 ± 3.5 ^c	55 ± 2.3	50 ± 2.7
Total/HDL-cholesterol ratio	6.1 ± 0.6 ^{b, c}	5.1 ± 0.5 ^c	3.1 ± 0.3	4.3 ± 0.4

^a p < 0.05 vs. control 1; ^b p < 0.05 vs. control 2; ^c p < 0.01 vs. control 1; ^d p < 0.05 vs. remission.

Does Correction of Hypercortisolism Improve Dyslipidemia?

Most series report an improvement in hyperlipidemia with correction of hypercortisolemia, although a complete normalization of lipid parameters is usually not achieved. In a longitudinal study, 25 patients were evaluated at baseline and 1 year following remission or medical control of Cushing's disease. A significant decrease in LDL-cholesterol levels was observed, but levels remained higher than in healthy controls [13] (table 2). Similarly, in a cross-sectional study performed 5 years after cure or control of pituitary Cushing's disease, levels of total and LDL cholesterol were similar to the levels found in BMI-matched controls but higher than in normal controls. HDL cholesterol remained significantly lower in comparison to both control groups [12]. Correction of Cushing's syndrome after excision of adrenal adenomas led to a decrease in total cholesterol levels and in the total/HDL-cholesterol ratio [16]. No changes in lipid parameters were observed in patients operated for subclinical Cushing's syndrome reported by the same investigators. In contrast, in a prospective randomized study, 37.5% of patients who underwent excision of adrenal adenoma causing subclinical hypercortisolism had an improvement in lipid levels, whereas no improvement was observed in the conservatively treated arm [17]. Finally, Danilowicz et al. [18] showed that correction of cortisol overreplacement in patients with hypopituitarism caused a significant reduction in body weight, as well as cholesterol and triglyceride concentrations.

Management of Dyslipidemia in Cushing's Syndrome

There are no studies or guidelines as to how hyperlipidemia in Cushing's syndrome should be managed. As has been already mentioned, hypercortisolism is often associated with several cardiovascular risk factors. Therefore, quantification of cardiovascular risk is important to guide the intensiveness of treatment in the individual patient. A carefully conducted study calculated the global cardiovascular risk in a series of 49 patients with Cushing's syndrome. The estimated risk was calculated considering the combined effect of hypertension, diabetes, hyperlipidemia, family history of cardiovascular disease at an early age, present or past history of ischemic heart disease, cerebrovascular and peripheral vascular disease, life style factors, such as smoking and physical activity, and evaluation of target organ damage such as left ventricular hypertrophy, retinopathy, atherosclerotic plaques and proteinuria. Eighty percent of this cohort was classified as having a high or very high cardiovascular risk, according to the 1999 WHO/ISH guidelines [14]. Based on this premise, aggressive treatment of cardiovascular risk factors according to standard practice should be recommended for the majority of these patients. This policy should be adopted not only during the phase of active disease, but also in the long term, as it has been shown that even five years after disease remission the high rates of cardiovascular risk factors persisted [12].

Special Considerations

Effects of Pharmacological Therapy of Hypercortisolism on Lipid Levels

Ketoconazole

Ketoconazole is the most widely used drug in the pharmacotherapy of Cushing's syndrome. It is an anti-fungal imidazole derivative that blocks several steps in cortisol biosynthesis, particularly through inhibition of C17,20 lyase and 17 α -hydroxylase activities [19]. Ketoconazole is also an inhibitor of cholesterol biosynthesis, acting directly by blocking the conversion of methyl sterols to cholesterol and indirectly by suppressing cholesterol synthesis via feedback inhibition of HMG-CoA reductase by sterol intermediates [20]. It has been used to treat patients with familial hypercholesterolemia before the widespread use of HMG-CoA reductase inhibitors, reducing total, intermediate density and LDL cholesterol, as well as apoB levels by approximately 25% [20, 21]. Hence, the use of ketoconazole for the control of hypercortisolism may have a beneficial effect on lipid control.

Mitotane

Mitotane or o,p'-DDD is a DDT derivative used mainly for the treatment of adrenal carcinoma or cases of intractable Cushing's disease [22, 23]. It induces mitochondrial degeneration resulting in adrenocortical atrophy and necrosis. Additionally, it inhibits steroidogenesis by reducing cholesterol side-chain cleavage and 11 β -hydroxylation [19]. However, mitotane uniformly raises circulating cholesterol levels by reducing hepatic production of oxysterols, thus leading to increased levels of HMG-CoA reductase [24]. Maximal changes in cholesterol levels occur 1–5 months after drug initiation. Mitotane increases total serum cholesterol levels by 68%, with significant elevations in LDL cholesterol and apoB, but no changes in triglycerides, HDL-cholesterol, apoA-1 or

Lp(a) levels [24]. This effect was successfully reversed by treatment with simvastatin [24]. The deleterious effect of mitotane on lipid levels should be recognized and promptly treated.

Drug Interactions between Lipid-Lowering Drugs and Steroid Biosynthesis Inhibitors

Ketoconazole interferes with the metabolism of many drugs via the inhibition of several hepatic P450 enzymes, e.g. CYP3A4, CYP2C9, CYP1A2. Simvastatin, lovastatin and atorvastatin are metabolized by cytochrome P450 CYP3A4, therefore their plasma concentrations and the risk of myotoxicity are greatly increased by the concomitant use of ketoconazole. In this clinical situation, pravastatin and rosuvastatin are preferable, as they are excreted mainly unchanged and their plasma concentrations are not significantly increased by CYP3A4 inhibitors [25].

Conclusions

In addition to the correction of hypercortisolism, strict control of cardiovascular risk factors is essential to reduce the high rates of cardiovascular morbidity and mortality associated with Cushing's syndrome. In this context, hyperlipidemia should be aggressively treated according to general clinical practice, but giving special consideration to the effects that pharmacotherapy used to lower cortisol levels may have on lipid levels, as well as to possible drug interactions between steroid biosynthesis inhibitors and statins.

Disclosure Statement

Dr. Greenman has received honoraria from Novartis for her role as Chair of the Steering Committee in relation to the OASIS trial. No conflict of interest exists.

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