Hypertension and Dyslipidemia: Commonly Coexisting Risk Factors for Cardiovascular Disease

Hypertension and dyslipidemia are interrelated and share common pathophysiologic mechanisms, such as insulin resistance and endothelial dysfunction. Accumulating evidence shows that it is important to regulate hypertension and hyperlipidemia to reduce cardiovascular risk. However, medications such as β-blockers and thiazide diuretics, which are widely used for blood pressure regulation, are known to have several metabolic side effects. Despite deleterious effects on glucose metabolism and lipid metabolism, these medications have been proven to reduce cardiovascular risk. On the other hand, calcium channel blockers, angiotensin-converting enzyme inhibitors, and α-blockers have either no effect or favorable effects on the lipid profile. This review outlines the need to control hypertension, options for several antihypertensive medications, their differing effects on lipid metabolism, and the clinical implications of their effects on lipid parameters.

Introduction

Hypertension is a global public health dilemma reaching epidemic proportions. It is the most common primary diagnosis in the United States (35 million office visits as the primary diagnosis), and 30% of adults aged 20 years or older have a diagnosis of hypertension or are taking medications for its treatment [1]. Hypertension is an important modifiable risk factor for cardiovascular disease (CVD) and directly leads to major forms of atherosclerotic CVD including coronary artery disease, stroke, congestive heart failure, peripheral artery disease, and chronic kidney disease. Control of hypertension is a key strategy for primary and secondary prevention of CVD outcomes [2]. Longitudinal data from the Framingham Heart Study have shown that increases in systolic blood pressure (BP) by 20 mm Hg and diastolic BP by 10 mm Hg double the risk of a CVD event [3]. Similarly, evidence from several randomized controlled trials suggests that reduction of systolic BP by 5 to 10 mm Hg reduces the risk of stroke by nearly 35% to 40% and reduces the risk of coronary heart disease (CHD) by 15% to 25% [2,4,5]. Studies have shown that patients treated for hypertension, in spite of controlled BP, have an increased risk of CHD and myocardial infarction (MI) during the second decade of follow-up [6,7]. Further, a prospective cohort study over three decades demonstrated that despite substantial reductions in systolic and diastolic BP, treated hypertensive men had a much greater risk of stroke, MI, and mortality from CHD compared with normotensive men of same age. Authors have explained that these conflicting results, in part, could be due to the metabolic effects of antihypertensive medications such as β-blockers and thiazide diuretics, as well as to smoking and the association of hypertension with hypercholesterolemia [6].

Hypertension tends to cluster with other proatherogenic risk factors such as dyslipidemia, insulin resistance, obesity, and renal disease. Indeed, the association between hypertension and hyperlipidemia is extremely common; they share a common maladaptive cardiovascular response that contributes to insulin resistance and endothelial dysfunction, leading to artherosclerosis, CHD, and stroke [8]. The presence of dyslipidemia is thought to be a strong predictor of CHD and stroke and is commonly an adverse metabolic effect of antihypertensive medications. Therefore, addressing the effect of antihypertensive medications on conventional and nonconventional CVD risk factors is of utmost importance in further reducing such risk. This review outlines the metabolic effects of various classes of antihypertensive medications, with a particular emphasis on dyslipidemia, a potentially modifiable major CVD risk factor.
dyslipidemia [9–11]. Both are closely interrelated and this association is the imminent component of metabolic syndrome. Insulin resistance and endothelial dysfunction are additional factors.

**Insulin resistance**

Risk factors for CVD tend to cluster within individuals, and insulin resistance may be the link between hypertension and dyslipidemia. Depending on the population studied and the defining criteria used, about 25% to 40% of nonobese, nondiabetic patients with hypertension are insulin resistant [12]. A constellation of insulin resistance, reactive hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein cholesterol, and hypertension was initially designated as syndrome X by Reaven in 1988 [13]. Mechanisms for the development of hypertension in insulin resistance include renal sodium retention, activation of the sympathetic nervous system, altered membrane cation transport, growth-promoting effects on vascular smooth muscle cells, and enhanced vascular reactivity [14]. Insulin resistance is also associated with visceral fat’s resistance to the metabolic effects of insulin while retaining increased sensitivity to lipolytic hormones [14]. The result is increased release of free fatty acids into the portal system and the provision of excess substrate for hepatic synthesis of very low density lipoprotein (VLDL) and triglycerides [14]. As a result, the dyslipidemia associated with insulin resistance has elevated triglycerides and oxidized low density lipoprotein (LDL) with a low level of high density lipoproteins (HDL).

**Endothelial dysfunction**

It is well accepted that endothelial dysfunction plays an integral role in the pathogenesis of both hypertension and dyslipidemia. The vascular endothelium is an important regulatory organ for maintaining cardiovascular homeostasis and is involved in the release of various vasodilators (including nitric oxide [NO], prostacyclin, and endothelium-derived hyperpolarizing factor) and vasoconstrictors. The oxidatively modified form of LDL (ox-LDL) is recognized as a major cause of endothelial dysfunction via activation of lectin-like ox-LDL receptor-1 (LOX-1) [15,16,17•]. Products of oxidative stress and molecules that induce oxidative stress in settings of hyperlipidemia and hypertension are found to upregulate LOX-1. Activation of LOX-1 induces the generation of reactive oxygen species and decreases the release from endothelial cells of NO, which is a potent and antitrophic vasodilator [17•]. Recent evidence supports the idea that triglyceride-rich lipoproteins induce endothelial dysfunction by upregulating the expression of several pro-inflammatory genes, including vascular cell adhesion molecule-1 (VCAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), and intercellular adhesion molecule-1 (ICAM-1) [18].

**Antihypertensive Agents and Lipids**

Numerous studies have shown that antihypertensive medications—especially β-blockers and high-dose thiazide diuretics known to have an unfavorable lipid profile—have a significant influence on lipid metabolism [19–21]. Changes in the lipid profile induced by antihypertensive medications may be particularly noteworthy in the hypertensive population because many hypertensive patients already have underlying hyperlipidemia [22] and a slight increase in serum cholesterol levels can increase their risk of CVD [23]. A meta-analysis by Kasiske et al. [20] of 474 controlled and uncontrolled trials examining 85 antihypertensive agents in more than 65,000 subjects provided valuable insight into the effects of antihypertensive medications on lipid profile (Table 1).

**Diuretics**

The use of diuretics, especially thiazides, in the treatment of hypertension has been implicated in increased total cholesterol, LDL cholesterol, and triglyceride levels [20]. The effects on total and LDL cholesterol were greater among blacks. Higher doses of diuretics caused higher levels of LDL cholesterol, and the effects on triglycerides were more pronounced in men than women. Interestingly, there was no association between the type of thiazide diuretics used and their effects on triglycerides. Among thiazide diuretics, chlorthalidone led to a greater increase in LDL cholesterol levels, whereas indapamide did not alter triglyceride levels at all. The effects of diuretics on triglycerides were diminished over time, but the effects on other cholesterol levels were not associated with study duration [20].

In the ALLHAT trial, the chlorthalidone group had higher serum cholesterol levels at 2 years and 4 years than the lisinopril group. The total cholesterol levels were also higher in the chlorthalidone group than in the amlodipine group at 2 years but not at 4 years [21]. Further, in the SHEP study, low-dose chlorthalidone raised fasting triglyceride levels and had moderate or no progressive effect on total and HDL cholesterol levels [4]. Overall, these data suggest that thiazide diuretics have deleterious effects on the lipid profile, especially at higher doses. Despite this adverse effect on the lipid profile, however, thiazide diuretics have been shown to reduce major CVD events, including strokes and MI [21].

**β-Blockers**

Most β-blockers are not associated with any change in LDL and total cholesterol levels, but they have been implicated in increases in triglyceride levels and decreases in HDL levels. However, β-blockers with cardioselectivity and intrinsic sympathomimetic activity (ISA) decreased total and LDL cholesterol levels and increased HDL [19,20] (Table 1). For example, pindolol, a cardioselective β-1 blocker with ISA, lowered triglyceride and increased HDL cholesterol. However, atenolol, a cardioselective β-1 blocker without ISA, reduced HDL cholesterol levels and did not affect triglyceride, total cholesterol, and LDL cholesterol levels [19].