A large body of evidence suggests that aldosterone excess is a common cause of hypertension with a prevalence of primary aldosteronism (PA) of \( \approx 10\% \) in patients with mild-to-moderate hypertension and \( \approx 20\% \) in patients with resistant hypertension.\(^1\) Experimental and clinical data also demonstrate that aldosterone excess contributes importantly to the development and progression of cardiorenal disease. This effect is attributed in part to aldosterone-induced target organ inflammation and fibrosis. Separately, a growing number of studies link aldosterone with the metabolic syndrome in general and with separate components of the syndrome, specifically, hypertension, insulin resistance, and dyslipidemia. If cause and effect is proven, that is, if aldosterone is confirmed to independently contribute to the development of the metabolic syndrome, it would further explain the increased cardiovascular risk of patients with PA.

In this issue of Hypertension, Matrozova et al\(^2\) compared glucose and lipid profiles in a large cohort of patients with PA to matched controls with primary hypertension. The prevalence of hyperglycemia (impaired fasting glucose or diabetes mellitus) and blood levels of glucose and lipids did not differ between PA and control subjects, whereas the prevalence of impaired fasting glucose was actually lower in PA patients. The authors further report that fasting plasma glucose and serum lipid levels did not differ within the subtypes of PA, ie, those with an aldosterone-producing adenoma versus idiopathic hyperaldosteronism. In addition, neither fasting plasma glucose nor serum lipids levels improved after adrenalectomy. The authors conclude that PA is not associated with carbohydrate and lipid abnormalities and that the prevalence of metabolic syndrome does not differ significantly between patients with PA and those with primary hypertension.

These results are in contrast to previous studies showing that aldosterone is associated with metabolic disturbances. In a cross-sectional study, Colussi et al\(^3\) related plasma aldosterone levels with insulin sensitivity in 356 white patients with primary hypertension. Plasma aldosterone concentration was positively associated with plasma glucose, plasma insulin, C-peptide levels, and insulin resistance as indexed by homeostasis model assessment (HOMA). In a separate study, Mosso et al\(^4\) compared glucose and insulin sensitivity in 30 hypertensive patients with confirmed PA and 60 matched controls. The former had higher levels of glucose and lower levels of HOMA for pancreatic \( \beta \)-cell function and C-peptide levels. A negative correlation between HOMA for pancreatic \( \beta \)-cell function and the aldosterone:renin ratio was interpreted to suggest that the decreases in insulin release were attributable to increasing aldosterone levels.

Other studies have related aldosterone levels to other components of the metabolic syndrome and to risk of having the metabolic syndrome in general. In a family based study of 356 African descendents, plasma aldosterone correlated positively with waist circumference in men and inversely with high-density lipoprotein cholesterol in both men and women.\(^5\) In this same analysis, higher plasma aldosterone levels predicted increased risk of having the metabolic syndrome. In a separate study, Fallo et al\(^6\) found that the prevalence of metabolic syndrome was significantly higher in hypertensive PA patients compared with controls with primary hypertension. The higher prevalence of metabolic syndrome was mainly because of differences in glucose metabolism.

Goodfriend et al\(^7\) have suggested that aldosterone-induced hypokalemia may underlie the observed associations between increasing aldosterone levels and risk of hypertension, insulin resistance, and dyslipidemia (specifically, low HDL). With regard to insulin sensitivity, this effect would be similar to that of thiazide diuretics in that thiazide-induced hypokalemia is thought to promote glucose impairment (Figure). Aldosterone-induced hypokalemia, likewise promoting glucose impairment, is supported by the observation that plasma potassium levels inversely relate to blood glucose levels.\(^8\) Experimental studies demonstrating that increases in plasma potassium levels stimulate pancreatic insulin secretion are also consistent with the theory that aldosterone-induced hypokalemia impairs glucose metabolism.\(^9\)

Animal studies have suggested that aldosterone regulates insulin receptors. Hitomi et al\(^10\) examined the effects of hyperaldosteronism on insulin receptor substrate expression and insulin signaling pathways, including Akt phosphorylation and glucose uptake in rat vascular smooth muscle cells. Aldosterone decreased insulin receptor substrate-1 protein expression in a dose-dependent fashion, and aldosterone-induced degradation of insulin receptor substrate-1 was markedly attenuated by treatment with the selective mineralocorticoid receptor antagonist eplerenone.

In addition to the above observational studies, a small number of interventional studies support aldosteronism as a cause of impaired glucose metabolism. For example, Giacchetti et al\(^11\)
compared 25 patients with an aldosterone-producing adenoma treated by adrenalectomy with 36 patients with idiopathic hyperaldosteronism treated medically with mineralocorticoid receptor antagonists. Before treatment, multiple regression analysis demonstrated a positive correlation between HOMA and HOMA for pancreatic β-cell function and serum aldosterone levels in all patients. During follow-up, adrenalectomy was associated with significant reduction of plasma glucose and insulin levels but not mineralocorticoid receptor blockade.

The multiple positive studies discussed above must now be reconciled with the negative results of Matrozova et al. The latter is impressive in the number of subjects studied, in having been able to relate metabolic risk factors to PA patients with and without an aldosterone-producing adenoma, and in having documented an absence of change in metabolic parameters after adrenalectomy. However, the study is limited by its retrospective design and in having not done suppression testing, such as saline infusion or dietary salt loading, to confirm the diagnosis of PA, as is suggested by current guidelines. We and others have shown that a high aldosterone:renin ratio alone has a poor specificity for confirming PA. To what extent these strengths and weakness contributed to the disparate results compared with studies reporting positive results is unknown.

Clearly, additional studies are needed to determine the role of aldosterone in causing metabolic dysfunction. Because PA is highly prevalent and metabolic dysfunction is strongly associated with increased cardiovascular risk, it is clinically important to know if the two are mechanistically related. If so, use of mineralocorticoid receptor antagonists would be expected to lower cardiovascular risk both by reducing blood pressure and by improving the metabolic profile. Such a benefit would clearly be relevant to PA patients, but such an effect might also be relevant to a much larger group of patients with lesser degrees of aldosterone excess.

**Disclosures**

None.

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