Aldosterone and Risk for Insulin Resistance

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There is increasing interest in exploring inappropriate activation of the renin-angiotensin-aldosterone system as a unifying mechanism between insulin resistance and other components of the metabolic syndrome.1,2 Recent data suggest that elevations in plasma aldosterone levels are associated with the insulin resistance independent of other components of angiotensin II. This relationship has been observed in studies exploring the association between primary aldosteronism, in which there are low levels of renin activity and angiotensin II, and insulin resistance.3 In this issue, Kumagai et al4 explored increases in aldosterone in the normal range at baseline as a predictor of development of insulin resistance in a prospective cohort of 10 years. Insulin resistance was ascertained by a homeostatic model assessment of insulin resistance.

The authors used a Japanese cohort of 1088 individuals without diabetes mellitus to explore the strength of the association between baseline aldosterone levels and development of insulin resistance. They then further excluded individuals with demonstrable insulin resistance at baseline and tracked the remaining 564 persons prospectively for 10 years. On univariate regression analysis at baseline, aldosterone levels correlated with age, measures of insulin resistance (fasting glucose and insulin), obesity (body mass index [BMI]/waist circumference), and dyslipidemia but not with the presence of hypertension or potassium level. Using a stepwise regression approach, age, dyslipidemia, and homeostatic model assessment-insulin resistance remained significantly correlated with aldosterone levels (Table 2 of Reference4).

Unique to this report is the prospective analysis of the relationship between plasma aldosterone levels and the development of insulin resistance. In the prospective cohort, 151 individuals developed insulin resistance. Those who developed insulin resistance were older and had higher levels of aldosterone, BMI/waist circumference, and triglycerides compared with those who did not develop insulin resistance. The authors created tertiles for increasing levels of aldosterone using a receiver operating characteristic with c-statistic approach and determined relative risk for the development of insulin resistance within each aldosterone tertile (Table 5). The authors report an increased risk on unadjusted analysis in the second and third tertiles that remained after adjustment for age, sex, and BMI (model 2) in the second tertile and after adjustment for measured clinical variables (through model 6) in the third tertile. Thus, these observations suggest that increasing levels of aldosterone in the normal range predict the development of insulin resistance.

Previous work in this area has evaluated the association between aldosterone and insulin resistance in cohorts mostly composed of individuals with primary aldosteronism, hypertension, and other components of the metabolic syndrome.1,4,5 Homeostatic model assessment-insulin resistance has been used to assess insulin resistance in those with primary aldosteronism and to explore this correlation.5,6 and a few studies have explored improvements in insulin resistance postresection of aldosterone-producing tumors.6,7 Results of the current investigation contrast with findings from a prospective analysis of Framingham data wherein increases in aldosterone in the normal range were similarly associated with insulin resistance at baseline; however, this relationship was lost in the longitudinal follow-up cohort. Disparate longitudinal results in these 2 studies may be attributed to differences in population characteristics (US versus Japanese) or analytic approach. In this Japanese cohort3 increases in BMI and waist circumference at 10 years, coupled with the strength of the association at baseline with determinants of dyslipidemia, suggest a strong relationship between aldosterone levels and metabolic risk. The exclusion of those insulin resistant at baseline and a nonsignificant relationship with hypertension suggest that dyslipidemia along with BMI/waist circumference and plasma aldosterone levels at baseline (Table 2 in Reference4) drove the risk for insulin resistance in this cohort. In this regard, in Japan obesity is defined as a BMI >258 and not a BMI >30 used by the World Health Organization. The difference in definitions are derived from data suggesting Japanese adults have a higher percentage of body fat compared with whites at any given level of BMI and that obesity-associated disorders begin in mild-to-moderate obesity adults in Japanese persons.9,10

That plasma aldosterone levels predicts the development of insulin resistance in this Japanese cohort translates recent basic science data showing that increased non-
genomic signaling through the mineralocorticoid receptor contributes to the development of insulin resistance.\textsuperscript{1,2} In this regard, activation of the mineralocorticoid receptor in muscle, liver, and fat tissue promotes a pro-oxidative/proinflammatory milieu that contributes to impairments in glucose use and disposal that result in reductions in insulin sensitivity (Figure). In skeletal muscle tissue, mineralocorticoid receptor activation reduces insulin-dependent metabolic signaling as a result of activation of redox sensitive serine/threonine kinases and associated serine/threonine phosphorylation of the insulin receptor substrate 1. This, in turn, leads to insulin receptor substrate 1 degradation and/or reduced engagement of phosphoinositide 3-kinase/downstream phosphorylation/activation of protein kinase B (Akt), which mediates a number of metabolic actions, including GLUT-4 translocation to the plasma membrane, as well as endothelial NO synthase phosphorylation/activation and increases in bioavailable NO.\textsuperscript{1} Thus, aldosterone can diminish insulin-stimulated glucose uptake in skeletal muscle directly (GLUT 4 translocation), as well as indirectly, by decreasing NO enhancement of insulin and glucose delivery to this tissue (Figure).

In summary, there are increasing basic science and clinical evidence that aldosterone adversely impacts insulin sensitivity. Indeed, the current longitudinal study\textsuperscript{3} indicates in a young Japanese population followed >10 years that high normal baseline levels of aldosterone predict risk for development of insulin resistance. However, the study included a relatively small Japanese cohort, and there is a need for investigation in more diverse populations.

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**Disclosures**

None.

**References**


**Figure.** The integrative relationship among aldosterone, visceral adipose tissue, and skeletal muscle. RAAS indicates renin-angiotensin-aldosterone system.


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