Korean Circ J. 2018 Mar;48(3):227-229
https://doi.org/10.4070/kcj.2018.0003
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Emerging Role of Aldosterone in Mediating the Vicious Cycle of Obesity, Insulin Resistance and Metabolic Syndrome

Sungha Park, MD, PhD

Division of Cardiology, Severance Cardiovascular Hospital and Cardiovascular Research Institute, Yonsei University College of Medicine, Seoul, Korea

▸ See the article "Independent Association of Serum Aldosterone Level with Metabolic Syndrome and Insulin Resistance in Korean Adults" in volume 48 on page 198.

Received: Jan 3, 2018
Revised: Feb 18, 2018
Accepted: Mar 2, 2018

Correspondence to
Sungha Park, MD, PhD
Division of Cardiology, Severance Cardiovascular Hospital and Cardiovascular Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: shpark0530@yuhs.ac

ORCID iDs
Sungha Park
https://orcid.org/0000-0001-5362-478X

Conflict of Interest
The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

Since Dr. Conn initially described the classical clinical presentation of hyperaldosteronism induced by aldosterone producing adenoma, the association between primary aldosteronism and diabetes has been well documented.[1)2)] Aldosterone excess may induce glucose intolerance and insulin resistance by; 1) impairment of glucose stimulated insulin secretion by increasing oxidative stress and inflammation in islet cells, 2) increase in hepatic gluconeogenesis and hepatic insulin resistance, 3) impairment of insulin sensitivity in adipose tissues and skeletal muscles, and 4) decreased adipokine secretion from the adipose tissues.[2)5)] The direct effect of aldosterone on skeletal muscles have particular importance as skeletal muscles are responsible for 85% of glucose disposal. In a study by Lastra et al.,[6)] aldosterone antagonism was associated with reduction in reactive oxygen species generation and improvement of insulin stimulated glucose transport in skeletal muscles of TG(mRen2)27 rats.

Obesity itself has been shown to be associated with increased serum level of aldosterone. In obese individuals, adipocytes produce excess amount of free fatty acids which is associated with increased production of epoxy-keto derivative of linoleic acids. The excess production of these epoxy-keto derivatives is known to be potent stimulator of aldosterone production by the adrenal gland. In short, obesity begets increase aldosterone secretion which begets increased insulin resistance.[2)7)]

In clinical studies, aldosterone excess has been shown to be associated with insulin resistance and glucose intolerance. In cross sectional analysis, plasma aldosterone level has been shown to be associated with increased the homeostasis model assessment for insulin resistance (HOMA-IR) and inversely associated with insulin resistance.[2)3)] Aldosterone producing adenomas have been shown to have impairment of glucose stimulated insulin secretion which is normalized after adrenalectomy.[8)] Also, aldosterone excess at baseline has been shown to be associated with increased risk of insulin resistance and non-insulin dependent diabetes at follow-up. In a nationwide cohort study of Taiwan, Wu et al.[9)] analyzed 754 aldosterone producing adenoma patients who were matched with 3,016 essential hypertension subjects as control. After a mean follow-up of 5.2 years, patients who underwent adrenalectomy had fewer incidence of new onset diabetes mellitus and total mortality compared to control.

Also, regardless of the presence of primary aldosteronism or not, the level of plasma aldosterone has been shown to be associated with future development of insulin resistance. In a prospective study of 564 subjects in a general population, Kumagai et al.,[10] demonstrated that plasma aldosterone level is associated with development of insulin resistance at 10 years of follow-up. However, this study was limited by the fact that they did not exclude subjects with primary aldosteronism and did not exclude subjects who were taking anti-hypertensive medications, such as beta blockers, renin-angiotensin-aldosterone (RAS) inhibitors and diuretics, that could significantly influence the level of plasma aldosterone.

Recently, a study was done in 892 Koreans aged ≥20 years who underwent evaluation for hypertension, diabetes or dyslipidemia at 6 tertiary hospitals between 2015–2016. Among these subjects, 829 who did not have primary aldosteronism and were not taking beta blockers, RAS inhibitors or diuretics were included in the analysis. The results showed that serum aldosterone, but not plasma renin activity or aldosterone/renin ratio, were significantly higher in subjects with metabolic syndrome and positively correlated with individual components of metabolic syndrome, HbA1c and HOMA-IR. The study has significant merit in that; 1) subjects who were taking medications that could influence the level of serum aldosterone were excluded from analysis and 2) the study demonstrates the possibility of significant influence of aldosterone on insulin resistance and metabolic syndrome in subjects who does not have primary aldosteronism.[11] However, the limitation of the study, as stated by the authors, is the cross-sectional design of the study. As such, we cannot determine if the aldosterone itself is associated with increasing insulin resistance or the increasing level of serum aldosterone with increase in visceral obesity was the reason for the significant association. Therefore, future studies to determine whether or not baseline aldosterone level and prospective changes in the level of aldosterone are associated with future development of metabolic syndrome and non-insulin dependent diabetes mellitus.

REFERENCES

1. Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med* 1965;273:1135-43.
PUBMED | CROSSREF
2. Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 2009;150:776-83.
PUBMED | CROSSREF
3. Luther JM. Effects of aldosterone on insulin sensitivity and secretion. *Steroids* 2014;91:54-60.
PUBMED | CROSSREF
4. Selvaraj J, Sathish S, Mayilvanan C, Balasubramanian K. Excess aldosterone-induced changes in insulin signaling molecules and glucose oxidation in gastrocnemius muscle of adult male rat. *Mol Cell Biochem* 2013;372:113-26.
PUBMED | CROSSREF
5. Yamashita R, Kikuchi T, Mori Y, et al. Aldosterone stimulates gene expression of hepatic gluconeogenic enzymes through the glucocorticoid receptor in a manner independent of the protein kinase B cascade. *Endocr J* 2004;51:243-51.
PUBMED | CROSSREF
6. Lastra G, Whaley-Connell A, Manrique C, et al. Low-dose spironolactone reduces reactive oxygen species generation and improves insulin-stimulated glucose transport in skeletal muscle in the TG(mRen2)27 rat. *Am J Physiol Endocrinol Metab* 2008;295:E110-6.
PUBMED | CROSSREF
7. Goodfriend TL, Ball DL, Egan BM, Campbell WB, Nithipatikom K. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. *Hypertension* 2004;43:358-63.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2018.0003

8. Catena C, Lapenna R, Baroselli S, et al. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. *J Clin Endocrinol Metab* 2006;91:3457-63.
PUBMED | CROSSREF
9. Wu VC, Chueh SJ, Chen L, et al. Risk of new-onset diabetes mellitus in primary aldosteronism: a population study over 5 years. *J Hypertens* 2017;35:1698-708.
PUBMED | CROSSREF
10. Kumagai E, Adachi H, Jacobs DR Jr, et al. Plasma aldosterone levels and development of insulin resistance: prospective study in a general population. *Hypertension* 2011;58:1043-8.
PUBMED | CROSSREF
11. Min SH, Kim SH, Jeong IK, et al. Independent association of serum aldosterone level with metabolic syndrome and insulin resistance in Korean adults. *Korean Circ J* 2018;48:198-208.
CROSSREF

https://doi.org/10.4070/kcj.2018.0003