Hypertension Research (2023) 46:803–805
https://doi.org/10.1038/s41440-022-01149-y

COMMENT

Autonomous cortisol secretion in patients with primary aldosteronism: A possible risk factor for new-onset diabetes mellitus

Kenichi Yokota[1] · Masakatsu Sone[1]

Keywords Aldosterone · Cortisol · New-onset diabetes mellitus · Primary aldosteronism

Received: 25 November 2022 / Revised: 8 December 2022 / Accepted: 12 December 2022 / Published online: 5 January 2023

Primary aldosteronism (PA), a typical form of secondary hypertension, is characterized by autonomous aldosterone hypersecretion. The risk of cardio-renal-vascular events, such as stroke, myocardial infarction, cardiomegaly, heart failure, atrial fibrillation, and renal impairments, is higher in patients with PA than in patients with essential hypertension. In addition, several clinical studies have shown abnormal glucose metabolism in patients with PA. Catena et al. conducted a prospective study in patients with PA. They showed that patients with aldosterone-producing adenoma (APA) and idiopathic hyperplasia (IHA) had insulin resistance, which was rapidly and persistently restored to normal conditions by surgery or aldosterone antagonist treatment [1]. In the German Conn's Registry, Reincke et al. reported that diabetes mellitus (DM) was more prevalent in patients with PA than in matched controls [2, 3]. In the Japan Primary Aldosteronism Study (JPAS), Akehi et al. also showed a higher DM prevalence in patients with PA than in the general population [4]. Furthermore, two meta-analyses assessing glucose metabolism in patients with PA showed a higher DM prevalence in patients with PA than in patients with essential hypertension (EHT) [5, 6].

Several hypotheses exist on the mechanisms that cause abnormal glucose metabolism in patients with PA (Fig. 1). In adipose tissue, excess aldosterone induces insulin resistance by producing oxidative stress [7] and increasing proinflammatory cytokines [8]. In the pancreas, aldosterone impairs pancreatic β-cells [9] and reduces insulin synthesis. In muscle, aldosterone decreases glucose uptake, glucose oxidation, and glycogen synthesis by inhibiting insulin signaling [8]. On the other hand, several clinical studies, including the German Conn's Registry and JPAS, have reported that the plasma aldosterone concentration (PAC) itself has no significant effect on DM prevalence [2, 4]. Therefore, the direct effects of aldosterone on glucose tolerance are still under debate.

The second mechanism that causes abnormal glucose metabolism in patients with PA is hypokalemia. Several studies have shown the relationship between thiazide-induced hypokalemia and impaired glucose metabolism [10, 11]. According to the German Conn's Registry, even in patients with PA, potassium levels are significantly and negatively correlated with 2-h glucose levels in an OGTT [3]. Watanabe et al. also reported a negative correlation between the serum potassium concentration and the insulin sensitivity index in patients with PA [12]. However, several studies have reported that serum potassium was not associated with a high DM prevalence in patients with PA [2, 13]. Therefore, the effect of hypokalemia on glucose metabolism in patients with PA is also under discussion.

The third mechanism of abnormal glucose metabolism in patients with PA is obesity. Obesity induces the production of adipocytokines, such as C1q/TNF-related protein 1, leptin, and resistin, which have been reported to elevate aldosterone via a renin-independent pathway [13–15]. In the JPAS, obesity prevalence was higher in patients with IHA than in patients with APA and EHT [16].

The fourth mechanism of abnormal glucose metabolism in patients with PA is cortisol hypersecretion comorbidity. For adrenal incidentaloma with mild autonomous cortisol excess (MACS), many reports have shown that complicated MACS increases DM prevalence [17–20]. Similarly, for PA, the prevalence of cortisol cosecretion is high, at 12.8–33.3% [4, 21–23], and is associated with impaired

✉ Masakatsu Sone
sonemasa@marianna-u.ac.jp

[1] Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

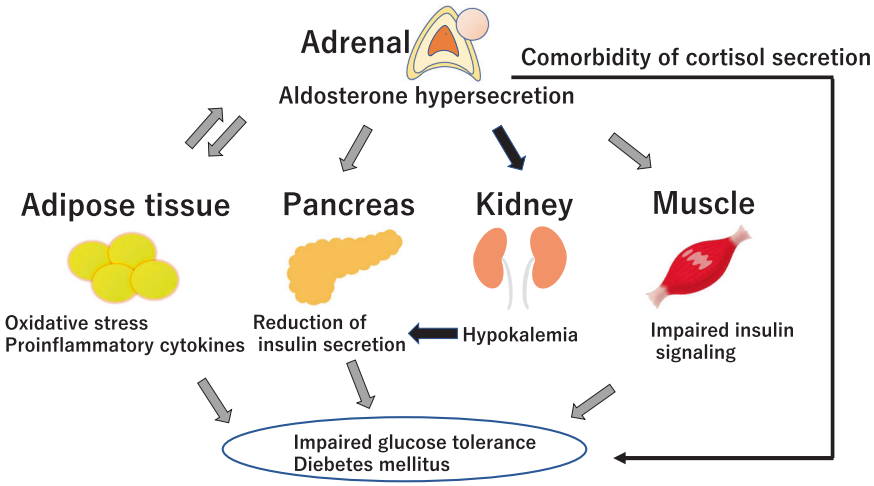

Fig. 1 Schematic presentation of mechanisms that cause abnormal glucose metabolism in patients with primary aldosteronism

glucose metabolism. Gerards et al. reported an association between autonomous cortisol secretion and DM in patients with PA [24]. In addition, Ohno et al. investigated the metabolic influences of a comorbid, apparently non-functioning adrenal tumor (AT) in patients with bilateral PA and showed that cortisol levels after a 1-mg dexamethasone suppression test and DM prevalence were higher in patients with AT than in those without AT [25].

Wu et al. previously reported that after a mean follow-up period of 5.2 years, patients with PA who underwent adrenalectomy had an attenuated new-onset DM (NODM) incidence, whereas those treated with mineralocorticoid receptor (MR) antagonists had an augmented NODM risk [26]. The present study evaluated the effect of autonomous cortisol secretion (ACS) on NODM in 387 patients with PA and clarified that PA patients with a concomitant cortisol level of ≧ 2.65 μg/dL after the 1-mg dexamethasone suppression test had a higher NODM incidence after a mean follow-up period of 4.31 years [27]. This result is consistent with those of previous studies and seems reasonable. However, the implication of accompanying MACS differed between APA and IHA. For APA, the presence of MACS generally suggests that an adenoma produces both aldosterone and cortisol. Therefore, when MACS accompanies APA, it can be generally cured by surgery after diagnosis. On the other hand, for IHA, MACS is generally thought not to be involved. However, if MACS accompanies IHA, MACS is considered to persist even after treatment with MR antagonists. Therefore, it is an important proposition whether IHA, which is probably caused by aldosterone-producing cell clusters, can be accompanied by MACS.

Overall, this study strengthened the findings of several previous reports showing that patients with PA have a higher DM prevalence and incidence. However, the molecular mechanisms and the difference between APA and IHA remain unclear and require further research.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G, Novello M, et al. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. J Clin Endocrinol Metab. 2006;91:3457–63.
2. Reincke M, Meisinger C, Holle R, Quinkler M, Hahner S, Beuschlein F, et al. Is primary aldosteronism associated with diabetes mellitus? Results of the German Conn's Registry. Horm Metab Res. 2010;42:435–9.
3. Hanslik G, Wallaschofski H, Dietz A, Riester A, Reincke M, Allolio B, et al. Increased prevalence of diabetes mellitus and the metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry. Eur J Endocrinol. 2015;173:665–75.
4. Akehi Y, Yanase T, Motonaga R, Umakoshi H, Tsuiki M, Takeda Y, et al. High prevalence of diabetes in patients With Primary Aldosteronism (PA) associated with subclinical hypercortisolism and prediabetes more prevalent in bilateral than unilateral PA: A large, multicenter cohort study in Japan. Diabetes Care. 2019;42:938–45.
5. Chen W, Li F, He C, Zhu Y, Tan W. Elevated prevalence of abnormal glucose metabolism in patients with primary aldosteronism: a meta-analysis. Ir J Med Sci. 2014;183:283–91.
6. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018;6:41–50.
7. Wada T, Ohshima S, Fujisawa E, Koya D, Tsuneki H, Sasaoka T. Aldosterone inhibits insulin-induced glucose uptake by degradation of insulin receptor substrate (IRS) 1 and IRS2 via a reactive oxygen species-mediated pathway in 3T3-L1 adipocytes. Endocrinology. 2009;150:1662–9.
8. Moustaki M, Paschou SA, Vakali EC, Vryonidou A. Secondary diabetes mellitus due to primary aldosteronism. Endocrine. 2022 Aug 24. https://doi.org/10.1007/s12020-022-03168-8. Epub ahead of print.

9. Chen F, Liu J, Wang Y, Wu T, Shan W, Zhu Y, et al. Aldosterone induces clonal β-cell failure through glucocorticoid receptor. Sci Rep. 2015;5:13215.
10. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. Hypertension. 2006;48:219–24.
11. Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shocken D, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes. 1983;32:106–11.
12. Watanabe D, Yatabe M, Ichihara A. Evaluation of insulin sensitivity and secretion in primary aldosteronism. Clin Exp Hypertens. 2016;38:613–7.
13. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, et al. Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci USA. 2003;100:14211–6.
14. Huby AC, Antonova G, Groenendyk J, Gomez-Sanchez CE, Bollag WB, Filosa JA, et al. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. Circulation. 2015;132:2134–45.
15. Iacobellis G, Petramala L, Cotesta D, Pergolini M, Zinnamosca L, Cianci R, et al. Adipokines and cardiometabolic profile in primary hyperaldosteronism. J Clin Endocrinol Metab. 2010;95:2391–8.
16. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, Takeda Y, et al. Obesity as a Key Factor Underlying Idiopathic Hyperaldosteronism. J Clin Endocrinol Metab. 2018;103:4456–64.
17. Elhassan YS, Alahdab F, Prete A, Delivanis DA, Khanna A, Prokop L, et al. Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess: a systematic review and meta-analysis. Ann Intern Med. 2019;171:107–16.
18. Prete A, Subramanian A, Bancos I, Chortis V, Tsagarakis S, Lang K, et al. Cardiometabolic disease burden and steroid excretion in benign adrenal tumors: a cross-sectional multicenter study. Ann Intern Med. 2022;175:325–34.
19. Li D, El Kawkgi OM, Henriquez AF, Bancos I. Cardiovascular risk and mortality in patients with active and treated hypercortisolism. Gland Surg. 2020;9:43–58.
20. Deutschbein T, Reimondo G, Di Dalmazi G, Bancos I, Patrova J, Vassiliadi DA, et al. Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study. Lancet Diabetes Endocrinol. 2022;10:499–508.
21. Späth M, Korovkin S, Antke C, Anlauf M, Willenberg HS. Aldosterone- and cortisol-co-secreting adrenal tumors: the lost subtype of primary aldosteronism. Eur J Endocrinol. 2011;164:447–55.
22. Nakajima Y, Yamada M, Taguchi R, Satoh T, Hashimoto K, Ozawa A, et al. Cardiovascular complications of patients with aldosteronism associated with autonomous cortisol secretion. J Clin Endocrinol Metab. 2011;96:2512–8.
23. Peng KY, Liao HW, Chan CK, Lin WC, Yang SY, Tsai YC, et al. Presence of subclinical hypercortisolism in clinical aldosterone-producing adenomas predicts lower clinical success. Hypertension. 2020;76:1537–44.
24. Gerards J, Heinrich DA, Adolf C, Meisinger C, Rathmann W, Sturm L, et al. Impaired glucose metabolism in primary aldosteronism is associated with cortisol cosecretion. J Clin Endocrinol Metab. 2019;104:3192–202.
25. Ohno Y, Sone M, Inagaki N, Takeda Y, Kurihara I, Tsuiki M, et al. Latent autonomous cortisol secretion from apparently nonfunctioning adrenal tumor in nonlateralized hyperaldosteronism. J Clin Endocrinol Metab. 2019;104:4382–9.
26. Wu VC, Chueh SJ, Chen L, Chang CH, Hu YH, Lin YH, et al. Risk of new-onset diabetes mellitus in primary aldosteronism: a population study over 5 years. J Hypertens. 2017;35:1698–708.
27. Wu VC, Chan CK, Peng KY, Chang YS, Chiang JY, Lee YJ, et al. New-onset diabetes mellitus risk associated with concurrent autonomous cortisol secretion in patients with primary aldosteronism. Hypertens Res. 2022. https://doi.org/10.1038/s41440-022-01086-w. Epub ahead of print.