Diabetes & Metabolism 45 (2019) 399–400

Available online at ScienceDirect www.sciencedirect.com

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Letter to the editor

# Decreased plasma aldosterone levels in patients with type 2 diabetes mellitus: A possible pitfall in diagnosis of primary aldosteronism

ARTICLE INFO

*Keywords:*
Plasma aldosterone levels
Primary aldosteronism
Type 2 diabetes mellitus

The number of patients with type 2 diabetes mellitus (T2DM) and/or hypertension has been markedly increasing, and is one of our most serious social issues at present. T2DM is mainly induced by overeating and/or a lack of exercise, and characterized by pancreatic β-cell dysfunction and/or insulin resistance in various insulin target tissues, such as the liver, fat and skeletal muscle. Hypertension is mostly induced by an unbalanced diet (consumption of excess amounts of salt) and/or several adrenal diseases, such as primary aldosteronism (PA) [1]. In fact, attention has been drawn to the fact that the frequency of PA is rather high in patients with secondary hypertension [2]. The main characteristics of PA are increased plasma aldosterone levels and decreased plasma renin activity. Hyperaldosteronism is, at least in part, associated with pathogenesis of the metabolic syndrome and T2DM [3,4]. It remains unknown, however, how the renin–aldosterone system (RAS) is influenced under diabetic conditions. In the present study, the RAS was evaluated in healthy and diabetic subjects.

At Kawasaki Medical School Hospital, plasma renin activity and aldosterone levels were examined in patients with T2DM, and also in healthy subjects who were visiting the hospital for a medical checkup. As it is well known that several antihypertensive drugs can influence the RAS, subjects who were taking angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEis) and/or diuretics (DUs) were excluded in our study. In addition, those who had severe renal dysfunction [estimated glomerular filtration rate (eGFR) $< 50$ mL/min/1.73 m$^2$) were also excluded. The study protocol was approved by the hospital ethics committee (No. 2797).

Baseline characteristics of our healthy ($n = 198$) and diabetic patients ($n = 197$) were as follows, respectively: age, $48.4 \pm 8.0$ years and $58.8 \pm 14.7$ years; males/females, 170/28 and 113/84; body mass index (BMI), $22.8 \pm 2.7$ kg/m$^2$ and $24.4 \pm 4.8$ kg/m$^2$; $HbA_{1c}$, $5.0 \pm 0.4\%$ and $9.0 \pm 2.4\%$; systolic blood pressure, $116.5 \pm 11.9$ mmHg and $125.8 \pm 14.7$ mmHg; diastolic blood pressure, $73.2 \pm 8.9$ mmHg and $69.6 \pm 9.7$ mmHg; and presence of hypertension 0% ($n = 0$) and 28.4% ($n = 56$). To examine how the RAS is influenced by diabetic conditions, plasma renin activity and aldosterone levels were measured (Fig. 1A).

The results showed no significant difference in plasma renin activity between healthy and T2DM patients ($1.47 \pm 0.93$ ng/mL/h vs. $1.47 \pm 1.11$ ng/mL/h; Fig. 1B). However, plasma aldosterone levels in those with T2DM were significantly lower compared with healthy subjects ($79.41 \pm 33.86$ pg/mL vs. $96.64 \pm 36.99$ pg/mL; $P = 0.001$; Fig. 1C). Thus, it may be that such a decrease of aldosterone levels in T2DM most likely leads to PA being overlooked in T2DM patients. When PA was diagnosed using Japanese diagnostic criteria (plasma aldosterone level $> 100$ pg/mL and plasma aldosterone level/renin activity $> 200$), only six were diagnosed as PA out of 197 patients

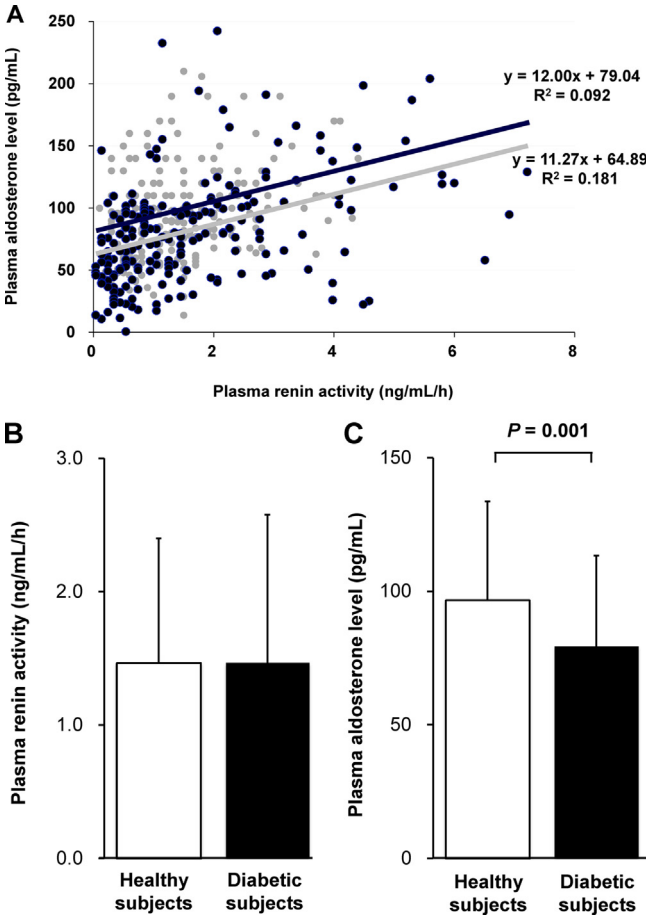


**Fig. 1.** A. Levels of plasma renin activity and plasma aldosterone in healthy subjects ($n = 198$, gray dots) and type 2 diabetes mellitus patients ($n = 197$, black dots); and comparisons of (B) plasma renin activity and (C) plasma aldosterone levels in healthy subjects and diabetic patients. Data are means ± SD; *P* value was determined by Student's *t* test.

https://doi.org/10.1016/j.diabet.2018.06.003

with T2DM. However, considering the phenomenon that plasma aldosterone levels are decreased in T2DM, it is possible that PA was overlooked in a substantial number of these patients.

The data in this study serve as a warning that it is easy to miss the presence of PA in patients with T2DM and, therefore, great care and caution are necessary in such a situation. In other words, this appears to be a possible pitfall in the diagnosis of PA in patients with T2DM. It may therefore be better to reexamine the diagnostic criteria of PA, at least in Asian patients with T2DM, as further evaluation is still necessary to demonstrate whether the present data are true for relatively obese Caucasians. In addition, while ARBs and/or ACEis are often used in those with T2DM, it is well known that ARBs, ACEis and/or DUs all decrease aldosterone levels. Thus, in principle, none of these drugs should be used before evaluation of the RAS, although it may sometimes be difficult to stop these drugs in clinical practice due to the presence of severe hypertension. Needless to say, as it is possible to overlook the presence of PA in such situations, it is also necessary to be very careful when diagnosing PA.

It is likely that hyperglycaemic conditions tend to bring out hyperosmotic diuresis, which could, at least in theory, increase plasma renin and aldosterone levels. Indeed, renin and aldosterone levels are known to increase following the use of DUs. Nonetheless, as shown in our present study, plasma aldosterone levels in patients with T2DM are significantly lower compared with healthy subjects. Therefore, we believe the data in this study are noteworthy. Although it remains unclear as to precisely why aldosterone levels are decreased under diabetic conditions, one possibility is that the response to angiotensin II is reduced under such conditions. It is also known that the transduction of various signals, such as after insulin binds to its receptor, is worsened in diabetes and, therefore, while speculative, signal transduction after angiotensin II binds to its receptor might be worsened in hyperglycaemic states. Further experimental evaluation is now necessary to clarify the mechanism by which aldosterone levels are decreased under conditions of diabetes.

It has also been reported that patients with diabetes have low renin states [5–7], but this is not necessarily true of all diabetes patients, as revealed by the present study. Therefore, it may be assumed that, when renin activity is not altered in spite of the presence of diabetes, decreased aldosterone levels under such conditions is accompanied by a decreased aldosterone/renin ratio, which can lead to the overlooking of PA in patients with diabetes. In addition, while it is known that aldosterone levels are decreased in those with diabetic nephropathy and/or autonomic neuropathy [8–10], our present study has shown that aldosterone was decreased even in those with near-normal renal function (eGFR $\geq$ 50 mL/min/1.73 $m^2$). Therefore, it appears that the presence of PA in patients with diabetes could easily be missed regardless of the presence or absence of diabetic nephropathy. Moreover, it is known that hyperkalaemia is often observed in people with hyperglycaemia and can exert adverse effects on the body. Therefore, a decrease in aldosterone levels is not only a pitfall in the diagnosis of hyperaldosteronism, but could also lead to a reduction of hyperkalaemia, which is often observed under diabetic conditions.

Thus, in general, aldosterone levels are decreased in patients with T2DM and, as this appears to be a pitfall in the diagnosis of PA in such patients, great care should be taken in clinical practice even when ARBs, ACEis and/or DUs are not being taken.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

## Authors' contributions

All authors have contributed significantly and in keeping with the latest guidelines of the International Committee of Medical Journal Editors. T.A. is the guarantor of this work and, as such, had full access to all data in the study, and takes responsibility for the integrity and accuracy of the data. T.A. also researched data and wrote the manuscript. M.T., F.K., T.K. and H.H. researched data and contributed to the discussion. T.M., N.O., K.K. and H.K. contributed to and reviewed the manuscript.

## Disclosure of interest

H.K. has received honoraria for lectures and received scholarship grants from Sanofi, Novo Nordisk, Lilly, Boehringer Ingelheim, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Kissei Pharma, AstraZeneca, Astellas, Novartis, Kowa, Chugai and Taisho Pharma.

K.K. has been an advisor to, and has received honoraria for lectures and scholarship grants from, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical Co., Ltd, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim Co., Ltd, Chugai, Daiichi Sankyo and Sanofi.

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T. Anno[a,*], T. Mune[b], M. Takai[a], T. Kimura[b], H. Hirukawa[b], F. Kawasaki[a], N. Okimoto[a], K. Kaku[a], H. Kaneto[b]
[a]*Department of General Internal Medicine 1, Kawasaki Medical School, 2-6-1 Nakasange, Kita-ku, 700-8505 Okayama, Japan*
[b]*Department of Diabetes, Endocrinology and Metabolism, Kawasaki Medical School, 701-0192 Kurashiki, Japan*

*Corresponding author
*E-mail address:* anno-t@umin.ac.jp (T. Anno).

Received 14 May 2018
Received in revised form 9 June 2018
Accepted 10 June 2018
Available online 19 June 2018