


# Effects of tofogliflozin on adrenocorticotrophic hormone, renin and aldosterone, and cortisol levels in elderly patients with diabetes mellitus

## A retrospective study of a patient cohort

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### Abstract

Adrenocorticotrophic hormone (ACTH) and cortisol reportedly play a role in glycemic control in patients with type 2 diabetes mellitus (T2DM); however, the underlying mechanism remains controversial. We retrospectively investigated the effect of tofogliflozin on serum ACTH and cortisol levels in elderly patients with T2DM.

Patients received 20 mg tofogliflozin daily for 3 months. Serum ACTH and cortisol levels were measured at baseline, as well as after 1 month and 3 months of tofogliflozin therapy.

Serum ACTH levels were significantly reduced 3 months after tofogliflozin treatment ( $P < .01$ ). Additionally, serum cortisol levels were reduced 3 months after tofogliflozin treatment, demonstrating borderline significance ( $P = .05$ ). The higher body mass index (BMI;  $\geq 25 \text{ kg/m}^2$ ) group showed higher ACTH and cortisol levels than the lower BMI ( $< 25 \text{ kg/m}^2$ ) group, with borderline significance ( $P = .05$ ). Renin levels were significantly increased 1 month after treatment ( $P < .05$ ), maintaining serum aldosterone levels in parallel with the extracellular fluid.

Our findings suggested that tofogliflozin decreased both serum ACTH and cortisol levels, with higher levels observed in the high BMI group. Tofogliflozin increased serum renin levels while maintaining serum aldosterone and extracellular fluid levels. Collectively, tofogliflozin could affect the hypothalamic-pituitary-adrenal pathway in patients with T2DM, especially in the low BMI group.

**Abbreviations:** ACTH = adrenocorticotropine hormone, BMI = body mass index, T2DM = type 2 diabetes mellitus.

**Keywords:** adrenocorticotrophic hormone, aldosterone, body mass index, cortisol, elderly, extracellular fluid, renin, SGLT2 inhibitor, tofogliflozin, type 2 diabetes mellitus

## 1. Introduction

Regulation of the hypothalamic-pituitary-adrenal (HPA) axis system plays a vital role in biological mechanisms, including stress, depression, and type 2 diabetes mellitus (T2DM).<sup>[1]</sup> Obesity is known to influence cortisol secretion and metabo-

lism,<sup>[2]</sup> and cortisol reportedly affects glucose metabolism.<sup>[3]</sup> It has been suggested that sodium and glucose transport functionally interact with insulin signaling via mineralocorticoids.<sup>[4]</sup> Six sodium-glucose co-transporter 2 (SGLT2) inhibitors, ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin,

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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and luseogliflozin, are commercially available in Japan.<sup>[5]</sup> In addition to the glucose-lowering effect, SGLT2 inhibitors can reportedly influence the renin-angiotensin-aldosterone system.<sup>[6]</sup> Patients with diabetes present impaired cortisol and/or growth hormone in response to severe hypoglycemia, with age, shorter DM duration, and higher body mass index (BMI) independently associated with an abnormal growth hormone response.<sup>[7]</sup> 11 $\beta$ -Hydroxysteroid dehydrogenase type 1 (HSD1), a cortisol-regenerating enzyme, was found to be effective in obese patients with diabetes.<sup>[8]</sup> HSD1-mediated regulation of intracellular cortisol is indicated to play a fundamental role in mechanisms contributing to the pathogenesis of metabolic syndrome.<sup>[9]</sup> In contrast, there were no significant changes in cortisol levels over 6 years based on the T2DM status.<sup>[10]</sup> These mechanisms suggest the regulation of glucose metabolism via the HPA; however, the underlying mechanisms of action remain unclear. The objective of the present study was to investigate the effect of tofogliflozin on the HPA axis.

## 2. Patients and methods

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was approved by the Clinical Research Ethics Committee of the Kanazawa Medical University Himi Municipal Hospital.

Herein, we performed a retrospective study to investigate the effect of tofogliflozin, an SGLT2 inhibitor, on the HPA system in elderly patients with T2DM. This study included elderly patients diagnosed with T2DM at the Kanazawa Medical University Himi Municipal Hospital from April 2017 to March 2019, as described previously.<sup>[11–13]</sup> Briefly, elderly patients aged  $\geq 65$  years received a single 20mg dose of tofogliflozin daily for 3 months. Patients with significant comorbidities were excluded. Demographic and baseline characteristics were collected from the patients' medical records. HbA1c, serum glucose level, body fluid, body fat, muscle mass, eGFR, BUN, and serum electrolytes were measured throughout the study period. Cortisol levels were measured in blood samples collected before breakfast. In addition, the body fluid composition was measured. Aldosterone levels were measured 30 minute after awakening from nighttime sleep. Data regarding patient characteristics were collected, including sex (men/women), age (years), BMI, serum levels of adrenocorticotropic hormone (ACTH), and cortisol measured at baseline, as well as 1 month and 3 months after tofogliflozin treatment.

Data values obtained after 1 and 3 months of tofogliflozin administration were compared with baseline levels using a paired *t* test. A mixed-effect model was applied to evaluate the effects of time, BMI, and their interaction on both ACTH and cortisol levels. All statistical analyses were 2-tailed, and statistical significance was set at  $P < .05$ . Data were analyzed using the freely available EZR (Easy R) software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).<sup>[14]</sup>

## 3. Results

The number of patient included in the present study was 56. The mean patient age was  $82.0 \pm 6.5$  years at baseline levels, including both male ( $n=24$ ) and female ( $n=32$ ) patients. The mean BMI was  $23.2 \text{ kg/m}^2$ . Co-administered drugs included dipeptidyl peptidase-4 ( $n=37$ ), biguanides ( $n=18$ ), sulfonylureas ( $n=8$ ), angiotensin receptor blockers ( $n=12$ ), calcium channel blockers

**Table 1**

**Time-wise comparison of endocrinological variables (n = 56).**

Administration of tofogliflozin	Baseline	1 mo
HbA1c (%)	7.4 $\pm$ 1.3	7.0 $\pm$ 1.0
Glucose (mg/dL)	172.1 $\pm$ 63.2	161.2 $\pm$ 78.9
Body fluid (%)	26.4 $\pm$ 5.7	25.8 $\pm$ 5.6
Intracellular fluid (%)	15.7 $\pm$ 3.6	15.3 $\pm$ 3.5
Extracellular fluid (%)	10.7 $\pm$ 2.1	10.4 $\pm$ 2.3
Body fat (% of baseline)	100.0	93.7
Muscle mass (% of baseline)	100.0	97.9
ACTH (pg/mL)	33.7 $\pm$ 23.3	26.1 $\pm$ 16.4
Cortisol ( $\mu\text{g/mL}$ )	13.4 $\pm$ 5.4	11.8 $\pm$ 3.9
Renin ( $\mu\text{g/mL}$ )	3.9 $\pm$ 6.1	6.7 $\pm$ 8.8*
Aldosterone ( $\mu\text{g/mL}$ )	88.0 $\pm$ 42.5	97.4 $\pm$ 56.0
eGFR (mL/min/1.73 m <sup>2</sup> )	60.5 $\pm$ 23.2	58.2 $\pm$ 24.3
BUN ( $\mu\text{g/mL}$ )	19.9 $\pm$ 9.9	19.7 $\pm$ 7.2
Serum Na <sup>+</sup> (mEq/L)	138.8 $\pm$ 3.5	139.5 $\pm$ 3.0
Serum K <sup>+</sup> (mEq/L)	4.2 $\pm$ 0.6	4.2 $\pm$ 0.5
Serum Cl <sup>-</sup> (mEq/L)	102.5 $\pm$ 12.2	104.4 $\pm$ 5.0

ACTH = adrenocorticotropic hormone, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate.

\*  $P < .05$ .

By paired *t* test compared to baseline.

( $n=27$ ), and diuretics ( $n=16$ ). Following tofogliflozin administration for 1 month, HbA1c levels decreased, as shown in Table 1. The decrease was statistically significant at 3 months, as shown in Table 2. Serum glucose level also showed trend of decrease throughout the study period, although not statistically significant. Intracellular and extracellular fluid and muscle mass were maintained, whereas body fat tended to decrease. Regarding hormonal levels, ACTH levels significantly decreased at 3 months, whereas renin significantly increased at 1 month. Cortisol tended to decrease and aldosterone levels were maintained. The estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) levels, known to reflect renal function, were maintained throughout the study period. Serum electrolytes, sodium, potassium, and chloride were also maintained.

**Table 2**

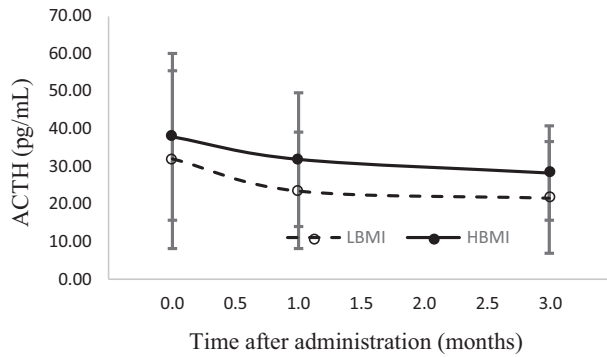
**Time-wise comparison of endocrinological variables (n = 56).**

Administration of tofogliflozin	Baseline	3 mo
HbA1c (%)	7.4 $\pm$ 1.3	6.7 $\pm$ 0.8**
Glucose (mg/dL)	172.1 $\pm$ 63.2	159.4 $\pm$ 53.4
Body fluid (%)	26.4 $\pm$ 5.7	26.6 $\pm$ 6.1
Intracellular fluid (%)	15.7 $\pm$ 3.6	15.9 $\pm$ 3.5
Extracellular fluid (%)	10.7 $\pm$ 2.1	10.9 $\pm$ 2.2
Body fat (% of baseline)	100.0	87.4
Muscle mass (% of baseline)	100.0	100.6
ACTH (pg/mL)	33.7 $\pm$ 23.3	23.5 $\pm$ 14.2**
Cortisol ( $\mu\text{g/mL}$ )	13.4 $\pm$ 5.4	11.5 $\pm$ 4.4
Renin ( $\mu\text{g/mL}$ )	3.9 $\pm$ 6.1	7.3 $\pm$ 12.6
Aldosterone ( $\mu\text{g/mL}$ )	88.0 $\pm$ 42.5	87.5 $\pm$ 37.6
eGFR (mL/min/1.73 m <sup>2</sup> )	60.5 $\pm$ 23.2	59.3 $\pm$ 28.4
BUN ( $\mu\text{g/mL}$ )	19.9 $\pm$ 9.9	19.5 $\pm$ 7.8
Serum Na <sup>+</sup> (mEq/L)	138.8 $\pm$ 3.5	140.5 $\pm$ 3.3**
Serum K <sup>+</sup> (mEq/L)	4.2 $\pm$ 0.6	4.2 $\pm$ 0.5
Serum Cl <sup>-</sup> (mEq/L)	102.5 $\pm$ 12.2	106.0 $\pm$ 3.3*

ACTH = adrenocorticotropic hormone, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate.

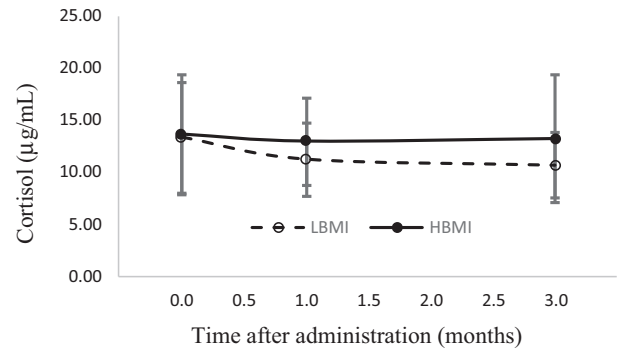
\*  $P < .05$ .

\*\*  $P < .01$  by paired *t* test compared to baseline.



p = 0.05 between low and high BMI by mixed effect model

**Figure 1.** Serum ACTH concentration after administration of tofogliflozin. ACTH = adrenocorticotropine hormone, BMI = body mass index, LBMI = low body mass index, HBMI = high body mass index.

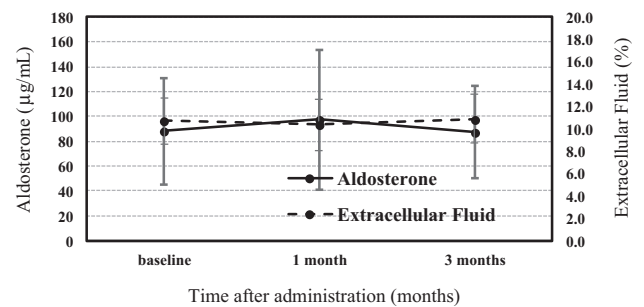


p = 0.05 between low and high BMI by mixed effect model

**Figure 2.** Serum cortisol concentration after administration of tofogliflozin. BMI = body mass index, LBMI = low body mass index, HBMI = high body mass index.

Figure 1 shows that ACTH levels were significantly lower in low-BMI group over the course of the study period, demonstrating borderline significance ( $P = .05$ ). Figure 2 also reveals that cortisol levels were decreased in low-BMI group, demonstrating borderline significance ( $P = .05$ ). The results of the mixed-effect model analyses are summarized in Tables 3 and 4, revealing a BMI and time-dependent decrease in ACTH ( $P < .05$ ) and BMI-dependent change in cortisol levels with borderline significance ( $P = .05$ ). The interaction between BMI and time was not statistically significant.

Figure 3 demonstrates that both the aldosterone level and extracellular fluid were maintained during the 3-month tofogliflozin treatment.



**Figure 3.** Serum aldosterone concentration and extracellular fluid after administration of tofogliflozin.

**Table 3**

Results of 2-factor mixed effect model to evaluate effects and interaction of ACTH.

SOV	df	Sum sq.	Mean sq.	F	Prob>F	Significance
BMI	1	1425.2	1425.2	4.8	.030	*
Time	2	2489.8	1244.9	4.2	.017	*
Patients	35	12487.5	356.8	0.3	.958	
BMI × Time	2	29.2	14.6	0.0	.952	
Error	105	30969.2	294.9			
Total	162	47400.9				

Analysis of variance table for the mixed effects model.

ACTH = adrenocorticotropine hormone, BMI = body mass index, df = degree of freedom, F = F statistic, Mean sq. = mean squares, Prob = probability, SOV = source of variance, Sum sq. = sum of squares. \*  $P < .05$ .

**Table 4**

Results of 2-factor mixed effect model to evaluate effects and interaction of cortisol.

SOV	df	Sum sq.	Mean sq.	F	Prob>F	Significance
BMI	1	82.5	82.5	3.4	.050	*
Time	2	122.1	61.1	2.5	.087	
Patients	35	701.2	20.0	0.3	.742	
BMI × Time	2	30.4	15.2	0.6	.538	
Error	105	2561.5	24.4			
Total	162	3498.1				

Analysis of variance table for the mixed effects model.

BMI = body mass index, df = degree of freedom, F = F statistic, Mean sq. = mean squares, Prob = probability, SOV = source of variance, Sum sq. = sum of squares.

\*  $P < .05$ .

#### 4. Discussion

The present study confirmed that tofogliflozin decreased serum ACTH and cortisol levels, indicating that tofogliflozin influences the HPA pathway in patients with T2DM, especially in the low BMI group. Furthermore, our findings revealed the significant effects of BMI and time using a mixed-effect model. Tofogliflozin also increased serum renin while maintaining serum aldosterone and extracellular fluid levels.

The mechanism is still unclear, although SGLT2 inhibitor acts on proximal tubule of the kidney, reduce glucose reabsorption thereby lowering blood glucose levels. Among the SGLT2 inhibitors, tofogliflozin is the shortest acting drug, with half-life of 5.4 hours, which suggest that tofogliflozin may act on short loop inhibition of ACTH rather than long loop inhibition. During the study period, the serum sodium levels were almost maintained. Utsunomiya et al,<sup>[15]</sup> also demonstrated that serum sodium levels were almost stable throughout 24-month study period of tofogliflozin administration. Serum cortisol and aldosterone are considered equally potent independent predictors of all-cause mortality risk in patients with systolic and non-systolic chronic heart failure of any cause.<sup>[16]</sup>

Subclinical hypercortisolism reportedly plays a role in several metabolic disorders, including diabetes.<sup>[17]</sup> In women, cortisol and prolactin levels have been associated with diabetes<sup>[18]</sup> and BMI.<sup>[19]</sup> As shown in Tables 2 and 3, there was statistical differences in BMI using 2-factor mixed effect model with borderline of *P* value. Although the value is borderline, in the mixed effect model, other confounding variables such as time and patients were adjusted, thus the statistical robustness was guaranteed. In patients with obesity, the serum cortisol level after a low-dose dexamethasone suppression test may predict diabetes mellitus and hypertension.<sup>[20]</sup> A case study has been shown that ACTH and cortisol levels were inadequately increased in patients with T2DM.<sup>[21]</sup> Moreover, canagliflozin was found to improve obesity and insulin resistance in a diabetic patient with Cushing disease undergoing postoperative steroid therapy.<sup>[22]</sup>

Furthermore, cortisol serves, in part, as a mineralocorticoid despite its drawback.

If our results are generally accurate, it may be necessary to state that Na absorption is suppressed by decreasing cortisol, thus lowering blood pressure and impacting the electrolyte balance. Cortisol, via a non-Rac aldosterone-mediated pathway, is known to be involved in mineralocorticoid activity.<sup>[23]</sup> This evidence supports our results that reduced cortisol levels can be associated with suppressed mineralocorticoid activity, leading to lower blood pressure, stress, and sympathetic inhibition mediated by SGLT2 inhibitors.

The association between Alzheimer disease (AD) and DM is relevant to adrenal hyper-responsiveness to ACTH.<sup>[24]</sup> In addition, metabolic alkalosis caused by glucocorticoid excess, possibly via activation of the mineralocorticoid receptor, may act with diabetic ketoacidosis (DKA) to induce mixed acid-base disorder, which can potentially obscure SGLT-2i-associated DKA.<sup>[25]</sup>

The effect of tofogliflozin on body composition and glycemic control has also been examined by Kamei et al,<sup>[26]</sup> revealing that bioelectric impedance assessments are often used to characterize body composition owing to its simplicity and portability, which is based on the phenomenon that the conduction of electrical current through body fluids is substantially greater in fat-free

mass than in fat mass, as fat-free mass contains most of the body fluid and electrolytes.

This finding is consistent with the present study, indicating that extracellular fluid loss is temporary and then returns to normal, with an initial compensatory increase in aldosterone levels.<sup>[27]</sup>

Typically, older individuals are known to present less cellular water than younger individuals, placing them at risk of developing dehydration with SGLT2 inhibitors. In the present study, we observed no changes in renal function, cellular fluid, or muscular mass.

In addition, our previous data presented no change in IVCmax (inferior vena cava maximal diameter),<sup>[13]</sup> indicating that there is no change in the volume of the vessel, that is, no intravascular dehydration.<sup>[28]</sup> Furthermore, we observed no changes in intracellular and extracellular body fluids. SGLT2 inhibitors are known to affect the volume of extracellular fluid when compared with furosemide.<sup>[29]</sup>

In addition, sarcopenia should be considered when administering SGLT2 inhibitors in elderly patients.<sup>[30]</sup> Herein, we observed no change in muscle mass, suggesting that treatment with tofogliflozin could reduce the risk of sarcopenia or frailty during the short-term observation period.

The results of our study should be considered in the context of several potential limitations. First, owing to the observational nature of the study, and despite robust statistical techniques, the possibility of residual, unmeasured confounding factors cannot be excluded. Specifically, certain patient and physician factors may not be adequately captured. Second, the present study evaluated 3 months of drug treatment, which could be insufficient to detect changes in physiological parameters. Long-term follow-up is warranted to clarify the effects of tofogliflozin on cortisol and ACTH levels. Third, the present study lacked control groups; thus, the presence of underlying contributors (exercise, diet, restricting smoking, and alcohol consumption) could affect the study outcomes.

#### 5. Conclusions

Collectively, our findings indicated that tofogliflozin decreased both serum ACTH and cortisol levels, depending on BMI levels. Tofogliflozin increased serum renin levels while maintaining serum aldosterone and extracellular fluid levels. In particular, tofogliflozin has been suggested to affect the HPA pathway in patients with T2DM.

#### Author contributions

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**Validation:** Toshihiro Higashikawa.

**Visualization:** Toshihiro Higashikawa.

**Writing – original draft:** Toshihiro Higashikawa.

**Writing – review & editing:** Toshihiro Higashikawa.

## References

- [1] Joseph JJ, Golden SH. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. *Ann N Y Acad Sci* 2017;1391:20–34.
- [2] Andrew R, Phillips DI, Walker BR. Obesity and gender influence cortisol secretion and metabolism in man. *J Clin Endocrinol Metab* 1998;83:1806–9.
- [3] Barbot M, Ceccato F, Scaroni C. Diabetes mellitus secondary to Cushing's disease. *Front Endocrinol (Lausanne)* 2018;9:284.
- [4] Nizar JM, Shepard BD, Vo VT, et al. Renal tubule insulin receptor modestly promotes elevated blood pressure and markedly stimulates glucose reabsorption. *JCI Insight* 2018;3:e95107.
- [5] Tahara A, Takasu T, Yokono M, et al. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. *J Pharmacol Sci* 2016;130:159–69.
- [6] Miyaoka D, Tsuda A, Hayashi N, et al. Development of hyperkalemia following treatment with dapagliflozin(DAPA) in a patient with type 2 diabetes after bilateral adrenalectomy. *CEN Case Rep* 2018;7:29–33.
- [7] Rhyu YA, Jang JY, Park S, et al. Impaired cortisol and growth hormone counterregulatory responses among severe hypoglycemic patients with type 2 diabetes mellitus. *Endocrinol Metab (Seoul)* 2019;34:187–94.
- [8] Stimson RH, Andrew R, McAvoy NC, et al. Increased whole-body and sustained liver cortisol regeneration by 11beta-hydroxysteroid dehydrogenase type 1 in obese men with type 2 diabetes provides a target for enzyme inhibition. *Diabetes* 2011;60:720–5.
- [9] Whorwood CB, Donovan SJ, Flanagan D, et al. Increased glucocorticoid receptor expression in human skeletal muscle cells may contribute to the pathogenesis of the metabolic syndrome. *Diabetes* 2002;51:1066–75.
- [10] Spanakis EK, Wang X, Sanchez BN, et al. Lack of significant association between type 2 diabetes mellitus with longitudinal change in diurnal salivary cortisol: the multiethnic study of atherosclerosis. *Endocrine* 2016;53:227–39.
- [11] Higashikawa T, Ito T, Mizuno T, et al. The effects of 12-month administration of tofogliflozin on electrolytes and dehydration in mainly elderly Japanese patients with type 2 diabetes mellitus. *J Int Med Res* 2018;46:5117–26.
- [12] Higashikawa T, Ito T, Mizuno T, et al. Effects of tofogliflozin on cardiac function in elderly patients with diabetes mellitus. *J Clin Med Res* 2020;12:165–71.
- [13] Higashikawa T, Ito T, Mizuno T, et al. Gender differences in cardiac function following three-month administration of tofogliflozin in patients with diabetes mellitus. *J Clin Med Res* 2020;12:530–8.
- [14] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
- [15] Utsunomiya K, Kakiuchi S, Senda M, et al. Safety and effectiveness of tofogliflozin in Japanese patients with type 2 diabetes mellitus: results of 24-month interim analysis of a long-term post-marketing study(J-STEP/LT). *J Diabetes Investig* 2020;11:906–16.
- [16] Guder G, Bauersachs J, Frantz S, et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation* 2007;115:1754–61.
- [17] Chiodini I, Torlontano M, Scillitani A, et al. Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. *Eur J Endocrinol* 2005;153:837–44.
- [18] Dutka R, Chmyr N, Svitlyk H, et al. Prolactin, cortisol, free thyroxine and thyroid-stimulating hormone - markers of staging of metabolic syndrome as a risk factor of coronary artery disease and type 2 diabetes mellitus. *Georgian Med News* 2019;297:80–3.
- [19] Fukuda Y, Yamamoto S, Kameda M. Association between lifestyle characteristics and body mass index of mothers of children with allergic diseases. *J Clin Med Res* 2019;11:780–8.
- [20] Hepson S, Sencar E, Sakiz D, et al. Serum cortisol level after low dose dexamethasone suppression test may be predictive for diabetes mellitus and hypertension presence in obese patients: a retrospective study. *Diabetes Res Clin Pract* 2020;161:108081.
- [21] Kamiya Y, Murakami M. Type 2 diabetes mellitus accompanied by isolated adrenocorticotropic hormone deficiency and gastric cancer. *Intern Med* 2009;48:1031–5.
- [22] Nishihama K, Furuta N, Maki K, et al. Canagliflozin improves obesity and insulin resistance in a diabetic patient with Cushing's disease undergoing postoperative steroid therapy: a case report. *Biomed Rep* 2018;9:497–502.
- [23] Shibata S, Nagase M, Yoshida S, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. *Nat Med* 2008;14:1370–6.
- [24] Notarianni E. Cortisol: mediator of association between Alzheimer's disease and diabetes mellitus? *Psychoneuroendocrinology* 2017;81:129–37.
- [25] Sagalla N, Weaver A, Qamar A, et al. SAT-453 diabetic "Ketoalkalosis" due to SGLT2 inhibitor in the setting of Cushing's disease. *J Endocrine Soc* 2019;3(Suppl 1): SAT-453.
- [26] Kamei S, Iwamoto M, Kameyama M, et al. Effect of tofogliflozin on body composition and glycemic control in Japanese subjects with type 2 diabetes mellitus. *J Diabetes Res* 2018;2018:6470137.
- [27] Schork A, Saynisch J, Vosseler A, et al. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. *Cardiovasc Diabetol* 2019;18:46.
- [28] Al-Sofiani ME, Ganji SS, Kalyani RR. Body composition changes in diabetes and aging. *J Diabetes Complications* 2019;33:451–9.
- [29] Ohara K, Masuda T, Murakami T, et al. Effects of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on fluid distribution: a comparison study with furosemide and tolvaptan. *Nephrology (Carlton)* 2019;24:904–11.
- [30] Mesinovic J, Zengin A, De Courten B, et al. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. *Diabetes Metab Syndr Obes* 2019;12:1057–72.