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ORIGINAL RESEARCH

Analysis of the Endocrine Responses to Anti-Diabetes Drugs: An Issue of Elevated Plasma Renin Concentration in Sodium-Glucose Co-Transporter 2 Inhibitor

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Purpose: Glucose metabolism is associated with several endocrine disorders. Anti-diabetes drugs are crucial in controlling diabetes and its complications; nevertheless, few studies have been carried out involving endocrine function. This study aimed to investigate the association between anti-diabetes drugs and endocrine parameters.

Patients and Methods: We performed a study of 180 consecutive patients with type 2 diabetes who attended a medical center. Laboratory measurements of metabolic values and endocrine parameters were assessed after a stable treatment regimen of more than 12 weeks. The differences in various endocrine parameters were compared between subjects with or without certain anti-diabetes drugs, with the administrated anti-diabetes drugs being analyzed to find independent risks associated with elevated endocrine parameters.

Results: After maintaining stable treatment, acceptable glycemic control was noted with an average HbA1c of 7.55% in females and 7.43% in males. Participants taking sulfonylurea (55.8 vs 26.34 ng/L, P=0.043), dipeptidyl peptidase-4 inhibitor (DPP4i) (47.14 vs 32.26 ng/L, P=0.096), or sodium-glucose co-transporter 2 inhibitor (SGLT2i) (64.58 vs 28.11 ng/L, P=0.117) had higher plasma renin concentrations compared to those without this drug but the aldosterone levels did not differ, as well as for other adrenal tests and thyroid function. Under linear regression modeling, SGLT2i was found to be independently associated with a risk of high renin level (beta coefficient: 30.186, 95% confidence interval: 1.71─58.662, P=0.038), whereas sulfonylurea only had borderline associations (B: 21.143, 95% CI: −2.729─45.014, P=0.082). Additionally, renin-angiotensin-aldosterone system (RAAS) blockade (B: 36.728, 95% CI: 12.16─61.295, P=0.004) or diuretics (B: 47.847, 95% CI: 2.039─93.655, P=0.041) was also independently associated with increased renin levels.

Conclusion: SGLT2i was the only class of anti-diabetes drugs independently associated with elevated renin levels, with results similar to RAAS blockade and diuretics. Although SGLT2i appears to protect reno- and cardio-function, the clinical impact of increased renin warrants further precise study for verification.

Keywords: type 2 diabetes, renin-angiotensin-aldosterone system, plasma renin concentration, sodium-glucose co-transporter 2 inhibitor, endocrine

Introduction

Type 2 diabetes, despite its complex pathophysiology, is essentially an endocrine disease leading to metabolic disorders caused by insulin dysfunction. Beyond insulin hormone, glucose intolerance was associated with several other endocrine disorders.[1,2] It has been shown that elevated thyroid hormones, particularly free T4, as well as low levels of free T3 or free T4 were positively associated with the occurrence of diabetes.[3,4] The effects of hyperthyroidism on glucose metabolism involve enhanced hepatic gluconeogenesis together with increased glycogenolysis; the subsequent

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hyperglycemia and hyperinsulinemia also lead to insulin resistance,[5] yet, hypothyroidism-induced low metabolic rates would lead to weight gain and increased risk of diabetes.[4] Excess cortisol impairs glucose metabolism primarily through an overall increase in free fatty acid turnover and decreasing phosphorylation of the insulin receptor, resulting in a decrease in insulin action and a reduction in glucose disposal.[6] A positive association was found between renin and prevalent diabetes, prediabetes, and glucose metabolism markers.[7] Aldosterone is considered to impair glucose metabolism by decreasing insulin secretion via reactive oxygen species and decreasing insulin sensitivity by impairing normal adipocyte differentiation or function and translocation of membrane glucose transporter in skeletal muscle.[8] Moreover, the renin-angiotensin-aldosterone system (RAAS) has been closely linked to diabetic complications, particularly cardiovascular disease, and nephropathy.

Anti-diabetes drugs play a crucial role in controlling the disease and its complications, but their impact on other endocrine parameters such as aldosterone, renin, adrenal function, and thyroid function is not fully understood. In the past decade, emerging studies regarding the impact of anti-diabetes drugs on cardiovascular outcome and renal prognosis have been reported,[9] but only limited investigation has been carried out involving their effect on endocrine function. Metformin has been reported to decrease adrenocorticotropic hormone (ACTH) and cortisol by activating adenosine monophosphate-activated protein kinase (AMPK),[10] while other studies imply that sulfonylureas, metformin, and thiazolidinediones are associated with thyroid dysfunction.[11] Furthermore, sodium-glucose co-transporter 2 inhibitor (SGLT2i) has been studied for interference with the plasma aldosterone-to-renin ratio in primary aldosteronism diagnosis because its diuresis might activate the RAAS.[12]

As type 2 diabetes has a high prevalence worldwide across ethnic groups, it is imperative to clarify the possible extra-effects of treatment drugs for clinicians. Given the close relationship between diabetes and endocrine disorder and limited evidence for the association between anti-diabetes drugs and endocrine parameters, we began investigating the effects of anti-diabetes drugs on endocrine function. Identification of potential alterations in aldosterone, renin, adrenal function, and thyroid function associated with anti-diabetes drugs would help clinicians make informed decisions regarding treatment strategies and optimize patient care.

Materials and Methods

Participants

This retrospective observational study was conducted in the Endocrinology Outpatient Department of Chang Gung Memorial Hospital to examine the association between endocrine parameters and the use of anti-diabetes drugs in patients with type 2 diabetes who were on stable treatment regimens. Adult patients aged 18 years or older, diagnosed with type 2 diabetes and receiving stable anti-diabetes, antihypertensive, and lipid-lowering medications for at least 12 weeks before enrollment were included in the study. Eligible participants were required to have regular clinic visits and complete medical records, including laboratory results and medication adherence data. Patients were excluded if they experienced hyperglycemic crises, severe illness, surgery, or abnormal fasting behavior during the study period, as well as those who were pregnant or undergoing dialysis. The study was conducted from May 2022 to April 2023, enrolling consecutive eligible participants. Given the exploratory nature of this analysis and the absence of prior studies systematically addressing this relationship, a formal sample size calculation was not conducted. Instead, the sample size was determined based on practical considerations, including the availability of eligible participants and resource limitations. The Institutional Review Board of Chang Gung Memorial Hospital approved this retrospective study (No. 202400336B0), while the reporting of this study conformed to STROBE guidelines.[13]

Clinical Characteristics and Data

The clinical characteristics of patients, including age, gender, diabetes duration, body mass index, and smoking or alcohol-drinking habits as well as comorbidities including retinopathy, proteinuria, hypertension, coronary heart disease, and cerebrovascular accident were recorded at their clinic visits. A series of laboratory tests were conducted on the enrollment day to assess glycemic control (pre-meal blood sugar and HbA1c), circulating lipid profile, circulating liver enzyme activity, and estimated glomerular filtration rates (eGFRs) as well as endocrine parameters including plasma

renin concentration (PRC), plasma aldosterone concentration, ACTH, cortisol, and thyroid function. The anti-diabetes drugs for these patients during this treatment period included sulfonylurea, metformin, acarbose, glinide, pioglitazone, dipeptidyl peptidase-4 inhibitor (DPP4i), sodium-glucose co-transporter 2 inhibitor (SGLT2i), glucagon-like peptide 1 (GLP-1) analog and insulin. Additionally, the class of antihypertensive drugs and lipid medications was also recorded.

Statistical Analysis

We listed the variables according to gender with comparisons performed using Pearson's chi-square test for categorical variables. The Mann–Whitney *U*-test was used to analyze continuous variables because not all exhibit a normal distribution. We also used the Mann–Whitney *U*-test to compare the differences in various endocrine parameters between subjects taking or not taking certain anti-diabetes drugs. Radar plots were used to visualize average endocrine values. In light of the finding that there was a significant association between renin levels and the use of anti-diabetes drugs, we further evaluated risk factors for high levels of renin using linear regression models to identify the anti-diabetes drug independently associated with renin. Beyond the medications, the confounders for regression adjustment included clinical characteristics of age, gender, body mass index, HbA1c, eGFR, and potassium level. The beta coefficient (B) values and 95% confidence interval of anti-diabetes drugs and other diabetes-related medications correlated with elevated renin levels are presented by the forest plot. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). software.

Results

Characteristics of Patients

One hundred and eighty consecutive patients with type 2 diabetes were recruited, among whom, 84 subjects were female and 96 were male. The comparison of clinical characteristics of the participants between genders is shown in Table 1. The mean ages of participants did not differ and were 60.9 years in females and 60.87 in males (P=0.881) with a similar diabetes duration of 10.14 and 9.68 years in females and males respectively (P=0.372). Obvious higher alcohol drinking (23.96%) and smoking (20.83%) habits were noted in male subjects. The proportions of diabetic complications were similar for retinopathy (22.62% in females and 13.54% in males, P=0.112) and proteinuria (33.33% and 34.38%, P=0.883). The proportions of associated comorbidities were highest in hypertension both of females and males, being 71.43% and 68.75% (P=0.696) followed by coronary heart disease being significantly higher in males (3.57% and 15.63%, P=0.007) and cerebrovascular accident (7.14% and 6.25%, P=0.811).

Medications

The dosage regimens of anti-diabetes drugs, antihypertensive drugs, and lipid medications throughout the study period were not changed and are displayed in Table 1. The proportions of anti-diabetes drugs were similar between females and males except for the GLP-1 analog. Among these, around 37.5~39.29% of patients took sulfonylurea, 88.54~90.48% took metformin, 35.42~36.9% took DPP4i, 20.24~31.25% took SGLT2i, and 16.67~21.43% underwent insulin injection therapy. GLP-1 analog was used by 14.29% of female patients but only 2.08% of males (P=0.002). The other anti-diabetes drugs including acarbose, glinide, and pioglitazone were used by ≤ 10% of all patients without significant difference. The use proportion of antihypertensive drugs was also similar in all patients with 53.13~54.76% RAAS blockade, 28.13~30.95% calcium channel blocker, 22.92~28.57% β-blocker, and 4.17~11.9 diuretics. Additionally, around 70% of patients were taking statin, and 13% taking fibrate as a treatment for hyperlipidemia.

Biochemistry Measurements

Table 2 expresses the serum biochemistry data. After maintaining stable dosage regimens for at least 90 days, most participants achieved acceptable glycemic control. The average pre-meal blood sugar (AC) was around 135.16 mg/dL for females and 136.11 mg/dL for males, while the average HbA1c reached 7.55% in females and 7.43% in males. Both genders exhibited similar eGFR values, averaging 90.89 mL/min/1.73m^2 and 85.91 mL/min/1.73m^2, respectively, indicating normal renal function. The liver enzyme activity of alanine aminotransferase (ALT) was within the normal

Table 1 Clinical Characteristics and Diabetes-Related Medications of Participants

Characteristic	Mean (Standard Deviation) or No. (%)				
	Female (n=84)		Male (n=96)		*P* value
Age (years)	60.90	(11.99)	60.87	(12.43)	0.881
Diabetes duration (years)	10.14	(5.51)	9.68	(6.28)	0.372
Body mass index	26.75	(4.90)	27.27	(4.52)	0.256
Alcohol	2	(2.38%)	23	(23.96%)	<0.001*
Smoker	0	(0%)	42	(20.83%)	<0.001*
Retinopathy	19	(22.62%)	13	(13.54%)	0.112
Proteinuria	28	(33.33%)	33	(34.38%)	0.883
Hypertension	60	(71.43%)	66	(68.75%)	0.696
Coronary heart disease[a]	3	(3.57%)	15	(15.63%)	0.007*
Cerebrovascular accident[b]	6	(7.14%)	6	(6.25%)	0.811
Anti-Diabetes drugs					
Sulfonylurea	33	(39.29%)	36	(37.50%)	0.806
Metformin	76	(90.48%)	85	(88.54%)	0.673
Acarbose	2	(2.38%)	4	(4.17%)	0.686
Glinide	6	(7.14%)	1	(1.04%)	0.051
Pioglitazone	1	(1.19%)	1	(1.04%)	1.000
DPP4i[c]	31	(36.90%)	34	(35.42%)	0.836
SGLT2i[d]	17	(20.24%)	30	(31.25%)	0.093
Insulin	18	(21.43%)	16	(16.67%)	0.415
GLP-1[e] analog	12	(14.29%)	2	(2.08%)	0.002*
Hypertension agents					
RAAS blockade[f]	46	(54.76%)	51	(53.13%)	0.826
Calcium channel blocker	26	(30.95%)	27	(28.13%)	0.678
β-blocker	24	(28.57%)	22	(22.92%)	0.386
Diuretics[g]	10	(11.90%)	4	(4.17%)	0.053
Statin	61	(72.62%)	66	(68.75%)	0.570
Fibrate	11	(13.10%)	13	(13.54%)	0.930

Notes: *Significance: *P* value < 0.05[a] Coronary heart disease including history of ischemic heart disease or coronary artery disease [b]Cerebrovascular accident including history of embolic, ischemic, or hemorrhagic stroke [c]DPP4i = dipeptidyl peptidase 4 inhibitor [d]SGLT2i=sodium-glucose co-transporter 2 inhibitor [e]GLP-1 = glucagon-like peptide 1 [f] Renin-angiotensin-aldosterone system blockade including angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or spironolactone. [g]Diuretics including loop diuretics or thiazide.

Table 2 Metabolic and Endocrine Biochemistry Parameters of Participants

	Female (n=84)		Male (n=96)		*P* value
AC sugar (mg/dL)	135.16	(33.04)	136.11	(46.34)	0.315
HbA1c (%)	7.55	(1.39)	7.43	(1.36)	0.561
eGFR (mL/min/1.73m^2)	90.89	(36.80)	85.91	(27.55)	0.360
ALT (U/L)	27.29	(23.06)	38.68	(70.75)	0.017*
Cholesterol (mg/dL)	171.14	(24.22)	161.07	(29.61)	0.008*
Triglyceride (mg/dL)	153.89	(88.65)	175.25	(157.12)	0.602
HDL (mg/dL)	49.60	(11.44)	44.04	(11.40)	<0.001*
LDL (mg/dL)	93.93	(24.81)	90.86	(24.70)	0.436

(*Continued*)

Table 2 (Continued).

	Female (n=84)		Male (n=96)		*P* value
Na (mEq/L)	141.04	(2.06)	140.76	(2.43)	0.367
K (mEq/L)	4.37	(0.42)	4.43	(0.40)	0.212
Renin (ng/L)	26.93	(37.00)	46.99	(87.75)	0.122
Aldosterone (ng/dL)	13.56	(7.88)	10.90	(6.90)	0.011*
ACTH (pg/mL)	22.64	(14.96)	31.25	(18.25)	<0.001*
Cortisol (ug/dL)	10.92	(4.00)	12.12	(4.10)	0.052
TSH (uIU/mL)	1.78	(1.23)	1.62	(0.97)	0.518
Free T4 (pmol/L)	13.26	(2.82)	13.37	(4.00)	0.940

Note: *Significance: *P* value < 0.05.

Abbreviations: AC, pre-meal; HbA1c, glycated hemoglobin; ALT, Alanine aminotransferase; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

range in females (27.29 U/L) and slightly elevated in males (38.68 U/L) (*P*=0.017). Females exhibited slightly higher cholesterol levels than males (171.14 vs 161.07 mg/dL, respectively, *P*=0.008) but fell within the normal range. Triglycerides were also similar in both genders, although males displayed average levels slightly exceeding the normal range (175.25 mg/dL). Additionally, females demonstrated higher HDL levels than males (49.6 vs 44.04 mg/dL, respectively, *P*<0.001), as well as LDL levels (93.93 vs 90.86 mg/dL, respectively, *P*=0.436) though were not significant. The electrolytes including sodium and potassium levels displayed no significant differences between genders and remained within the normal range.

Regarding the endocrine parameters, females exhibited lower renin levels (PRC) compared to males (26.93 vs 46.99 ng/L, *P*=0.122), with the latter group showing values slightly exceeding the normal range (reference: 5.41–34.53 ng/dL in an upright position). Conversely, females had higher aldosterone levels (13.56 vs 10.9 ng/dL, *P*=0.011), yet these remained within the normal range (reference: 3.47–27.5 ng/dL in an upright position). Either ACTH (22.64 vs 31.25 pg/mL, *P*<0.001) or cortisol levels (10.92 vs 12.12 ug/dL, *P*=0.052) were lower in females than males, but both groups were within the normal range. The average thyroid function was within the normal range in both genders.

Anti-Diabetes Drugs and Endocrine Parameters

The radar pictures in Figure 1 illustrate the difference in each endocrine parameter between subjects taking each indicated anti-diabetes drug or not. Considering the low utility percentages of acarbose, glinide, and pioglitazone, these drugs were not analyzed. Patients taking sulfonylurea (SU) had higher average renin levels compared to those without this drug (55.8 vs 26.34 ng/L, *P*=0.043) but the aldosterone levels did not differ (12.81 vs 11.72 ng/dL, *P*=0.443), as well as for other adrenal tests and thyroid function. As for metformin, it was found that subjects taking it had slightly higher renin levels (38.59 vs 29.53 ng/L, *P*=0.298), lower levels of aldosterone (11.92 vs 14.04 ng/dL, *P*=0.328), and slightly higher levels of ACTH (27.66 vs 23.59 pg/mL, *P*=0.374) and cortisol (11.63 vs 10.88 ug/dL, *P*=0.888); however, the level of free-T4 remained unchanged. With DPP4i, the renin levels of subjects were higher than those without the drugs (47.14 vs 32.26 ng/L, *P*=0.096), as well as slightly higher ACTH (30.25 vs 25.68 pg/mL, *P*=0.117), and cortisol levels (12.06 vs 11.3 ug/dL, *P*=0.201), but aldosterone and thyroid function were not affected. As with DPP4i, subjects with SGLT2i had higher average levels of renin concentration (64.58 vs 28.11 ng/L, *P*=0.117), with other endocrine parameters including aldosterone (11.76 vs 12.28 ng/dL, *P*=0.729) remaining similar. Regarding the injected drugs, including insulin and GLP-1 analogs, the analysis of all endocrine parameters revealed no difference.

Impacts on the Plasma Renin Concentration Level

Figure 2 shows the forest plot of the impact of each anti-diabetes drug and antihypertensive drug on PRC level under adjusted co-variables including age, gender, body mass index, HbA1c, eGFR, and potassium level, established using the linear regression model. The Fisher-Snedecor test (*F*-test) in the linear regression model showed an F-statistic of 2.38 and

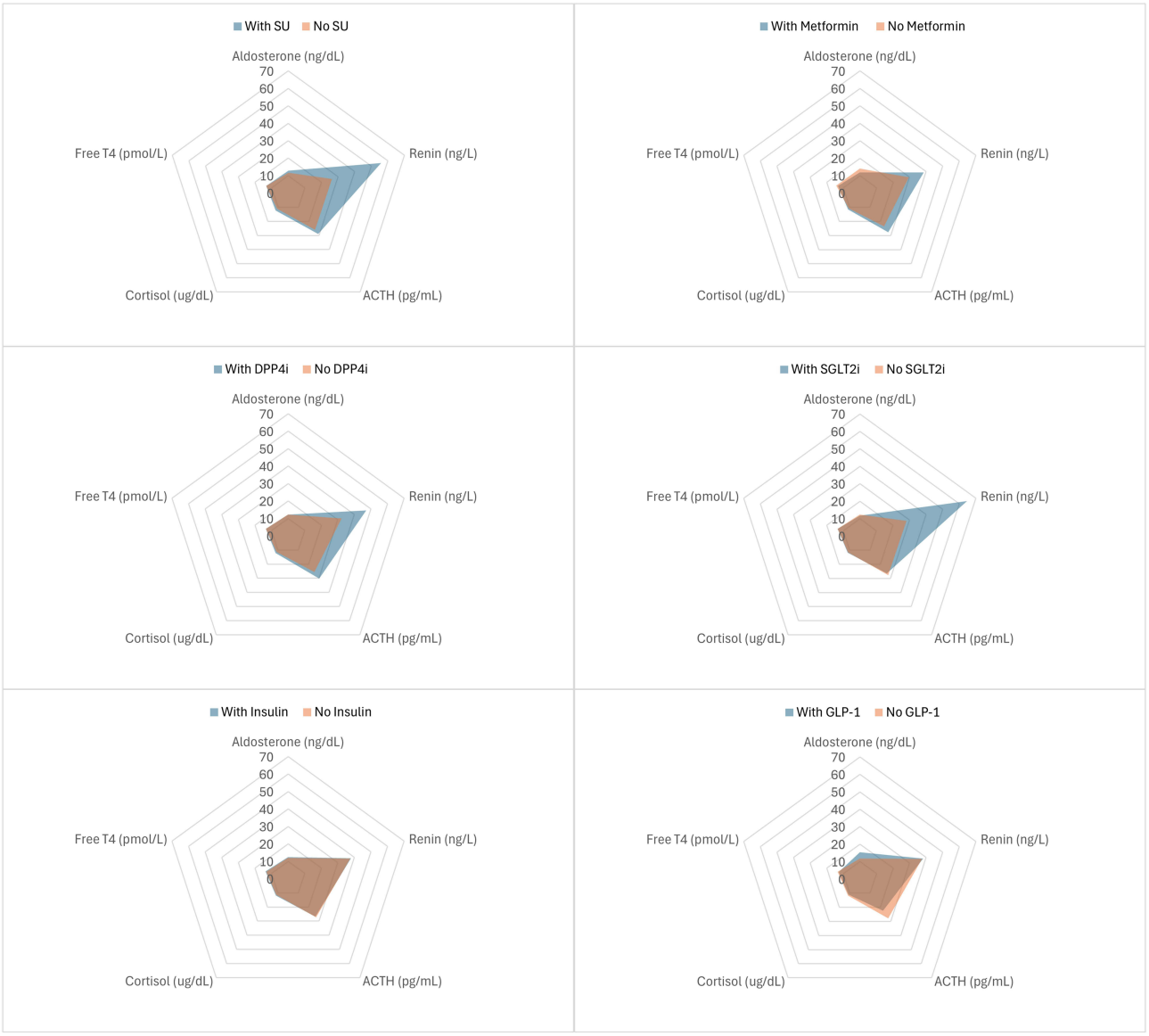

Figure 1 Compare the endocrine parameters of subjects taking or not taking a certain anti-diabetes drug.
Notes: Participants taking sulfonylurea (SU) (55.8 vs 26.34 ng/L, *P*=0.043), DPP4i (47.14 vs 32.26 ng/L, *P*=0.096), or SGLT2i (64.58 vs 28.11 ng/L, *P*=0.117) had higher average plasma renin concentrations compared to those otherwise. Subjects taking metformin had slightly higher renin levels (38.59 vs 29.53 ng/L, *P*=0.298), lower levels of aldosterone (11.92 vs 14.04 ng/dL, *P*=0.328), and slightly higher levels of ACTH (27.66 vs 23.59 pg/mL, *P*=0.374) and cortisol (11.63 vs 10.88 ug/dL, *P*=0.888).

the corresponding *P* value of 0.002, which indicated that the model is statistically significant. After adjustment, SGLT2i was found to be the only class of anti-diabetes drug with an independently positive impact on renin level with a B value of 30.186 and a 95% confidence interval of 1.71 to 58.662 (*P*=0.038), while no other anti-diabetes drug had a significant impact and sulfonylurea was only borderline associated with renin level but did not reach statistical significance (B value: 21.143, 95% CI: −2.729–45.014, *P*=0.082). Beyond the anti-diabetes drug, the utility of RAAS blockade (B value: 36.728, 95% CI: 12.16–61.295, *P*=0.004) or diuretics (B value: 47.847, 95% CI: 2.039–93.655, *P*=0.041) was also independently associated with increased renin levels in patients with diabetes.

Discussion

In our study population, male participants demonstrated higher rates of unhealthy behaviors, including alcohol consumption and smoking, as well as lower HDL levels, which may account for their higher prevalence of coronary heart disease. An interesting gender difference was observed in endocrine parameters, with females exhibiting lower renin

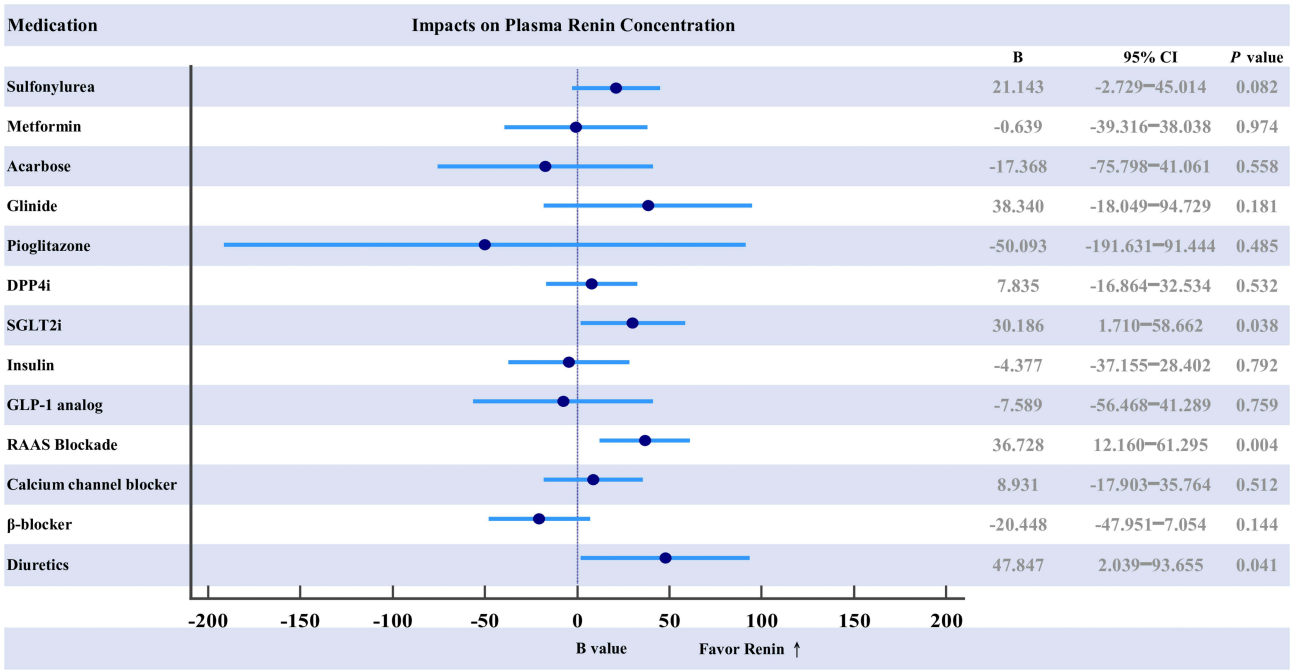

Figure 2 Forest plot of the impact of each diabetes-related drug on the plasma renin concentration levels among participants, determined using the linear regression model.
Notes: SGLT2i was independently associated with elevation of renin levels (B: 30.186, 95% CI: 1.71—58.662, *P*=0.038). RAAS blockade (B: 36.728, 95% CI: 12.16—61.295, *P*=0.004) or diuretics (B: 47.847, 95% CI: 2.039—93.655, *P*=0.041) was also independently associated with increased renin levels.

levels and higher aldosterone levels than males. The difference between genders is believed to be attributed to the influence of sex hormones. In males, testosterone downregulates aldosterone synthase mRNA, resulting in decreased aldosterone production.[14] Conversely, in females, estrogen suppresses key components of the RAAS, including renin, angiotensin-converting enzyme, and the angiotensin II type 1 receptor.[15] The findings of our study are consistent with established hormonal theories and demonstrate the clinical relevance of our study population.

As far as we are aware, this is the first study to examine the relationship between anti-diabetes drugs and endocrine parameters in individuals with diabetes, wherein we report that increased renin was noted in subjects treated with certain anti-diabetes drugs, particularly sulfonylureas, DPP4i, and SGLT2i. After adjusting for each drug and other clinical variables, SGLT2i was the only anti-diabetes drug to show a significant association with renin elevation.

Interestingly, SGLT2i was closely correlated with renal hemodynamic stability. Two regulation mechanisms respond to maintain renal hemodynamic stability; one is the RAAS, and the other is the tubuloglomerular feedback (TGF) via the juxtaglomerular apparatus initiating a reduction of glomerular filtration rate when sodium (Na+) concentration at the sensor site is increased.[16,17] SGLT2 is expressed in the proximal tubule which mediates the reabsorption of approximately 90% of the filtered glucose accompanied with less than 5% of sodium.[18,19] For diabetes, to respond to elevated glomerular-filtered loads of glucose, SGLT2 expression increased in diabetic kidneys.[20] The high glucose concentration in the tubule also enhances Na+ reabsorption by SGLT2s with subsequent decreased solute concentration of fluid reaching the macula densa, resulting in deactivation of TGF and following the dilatation of afferent arterioles and glomerular hyperfiltration.[19,20] The action of SGLT2 inhibitors then commenced with the reabsorption of sodium and glucose being attenuated which led to the re-establishment of the TGF and consequent improvement of hyperfiltration.[18]

Despite that, there was a paradox involving the SGLT2i effect on RAAS. During the restoration of TGF via an increase in macula densa salt transport by SGLT2i action, adenosine triphosphate (ATP) was broken down into adenosine diphosphate plus adenosine, which acts as a vasoconstrictor on adjacent afferent arteriole to attenuate glomerular hyperfiltration.[21] Notably, the adenosine not only mediates vasoconstriction but also provides contemporary inhibition of renin release through a calcium channel-mediated pathway.[22] Based on the theory above, the renin release should be suppressed undergoing the action of SGLT2i.

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However, the RAAS plays a crucial role in regulating blood pressure, fluid balance, and electrolyte homeostasis. Beyond the salt reduction sensed by macula densa, the reduced renal perfusion pressure following low fluid volume also activates the RAAS.[16] It has been demonstrated that SGLT2i has a diuretic effect by presenting increased urine volume.[23–25] A plasma volume reduction (around 7%) was also observed in subjects treated with dapagliflozin[26] supposedly induced through aquaresis caused by SGLT2i via inhibiting aquaporin-2 (AQP2), a water channel protein mediating the water reabsorption in the collecting duct.[27] SGLT2i would induce AQP2 downregulation, and the stimulated adenosine during restored TGF by SGLT2i could also inhibit AQP2 via the adenosine A1 receptor.[19] Accordingly, SGLT2i-induced diuresis and the associated volume depletion were supposed to stimulate the renin release to activate the RAAS.[28]

Clinical investigations of SGLT2i on renin release also exhibited contradictions, akin to the aforementioned theoretical paradox, where after treatment with SGLT2i, plasma renin activity increased in two clinical studies[26,29] but remained stable in another.[30] According to our study, although having an unremarkable impact on aldosterone, SGLT2i was positively associated with plasma renin concentration versus other anti-diabetes drugs regardless of antihypertensive drug use or glycemic control status. While current evidence indicates cardioprotection and renoprotection,[9] SGLT2i-related renin elevation should be concerning due to either the potential activation of the RAAS or the adverse effects of renin itself. Renin has been demonstrated to be a profibrotic factor independent of the angiotensin pathway[31] and is associated with kidney damage independently of aldosterone.[32] Furthermore, renin has been speculated to be involved in the pathogenesis of various diseases, including cancer via activation of MAPK/ERK and PI3K/AKT/mTOR pathways,[33] complement-mediated kidney diseases,[34] hypertension, pre-eclampsia, diabetic microangiopathy, cardiovascular disease, and obesity.[35]

Aside from the SGLT2i, only sulfonylureas had a borderline positive association with renin levels among anti-diabetes drugs. An animal study indicated that sulfonylureas may activate the RAAS due to acting on the vascular smooth muscle potassium channel and changes in renal arterial resistance.[36] However, the limited evidence and our present statistical result do not support this claim. Contrary to this, RAAS blockade and diuretics are believed to stimulate renin secretion and are compatible with our results. Blockade of the RAAS at any point in the cascade can result in a compensatory increase in plasma renin concentration through the suppression of the negative feedback inhibition of renin release.[37,38] Diuretics, similar to or even more than SGLT2i, cause sodium and volume depletion in the body, thereby activating compensatory systems and releasing renin.[39]

The present study carries some limitations because of its retrospective design. Retrospective studies inherently rely on existing data, which might introduce biases and limitations. In the present study, no comparison of endocrine parameter change was made between pre- and post-treatment with the indicated drug, requiring further prospective studies for verification. The regression analysis was a post-hoc analysis; therefore, the findings suggest a potential association rather than causality and should be interpreted with caution. Another limitation of our study is related to the measurement of renin levels according to plasma renin concentration rather than plasma renin activity. Caution should therefore be exercised when interpreting or applying these results; despite this, we consider accession to and analysis of these endocrine parameters among patients with different anti-diabetes drugs to be valuable.

Conclusion

In summary, we observed an increase in renin levels among subjects taking certain anti-diabetes drugs, while other endocrine functions, apart from renin, showed no significant changes. Additionally, SGLT2i was the only class of anti-diabetes drugs independently associated with increased renin, as were RAAS blockade and diuretics. Further prospective precise studies are warranted to verify the clinical impact of elevated renin; nevertheless, the current evidence still clearly indicates the benefit of SGLT2i on reno- and cardio-protection for diabetics.

Abbreviations

RAAS, renin-angiotensin-aldosterone system; ACTH, adrenocorticotropic hormone; AMPK, adenosine monophosphate-activated protein kinase; PRC, plasma renin concentration; SU, sulfonylurea; SGLT2i, sodium-glucose co-transporter 2 inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide 1; AC, pre-meal, HbA1c, glycated hemoglobin, ALT, alanine aminotransferase, eGFR, estimated glomerular filtration rate, HDL, high density lipoprotein, LDL: low density lipoprotein; TGF, tubuloglomerular feedback; AQP2, aquaporin-2; CI, confidence interval.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to IRB regulation but are available from the corresponding author upon reasonable request.

Ethics Statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (No. 202400336B0). The IRB allowed for the exemption of the informed consent of subjects since the study was retrospectively analyzed on anonymized data (National Department of Health Medical Affairs No.1010265083).

The study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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