

Short-term renoprotective effect of SGLT-2 inhibitor for renal function and albuminuria in type 2 diabetes

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Original investigation

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Abstract

Background

Progression of diabetic nephropathy in type 2 diabetic patients is a factor that determines the prognosis of life. Empagliflozin and canagliflozin, two oral diabetic SGLT-2 inhibitors, have shown improved renal outcomes in type 2 diabetic patients with chronic kidney disease in a large clinical study. These results suggest that SGLT-2 inhibitors could be used not only for hypoglycemic effects, but also for renal protective effects in patients with type 2 diabetes. It is not fully understood in which contexts the use of SGLT-2 inhibitors is likely to exert its renal protective effects. The purpose of this study was to clarify the profiles of patients in whom SGLT-2 inhibitors are more likely to exert a renal protective effect in clinical practice. We examined renal function and urinary albumin changes in short-term use of SGLT-2 inhibitors by patient background.

Methods

We retrospectively analyzed the chart information of sixty-three type 2 diabetic patients (33 males, 30 females, average age 53.0 ± 13.0 years) who were given usual doses of a SGLT-2 inhibitor. We investigated changes in body weight, blood pressure, glucose metabolism index, lipid metabolism index, estimated glomerular filtration rate (eGFR) and albuminuria (urinary albumin-to-creatinine ratio, UACR) three months before and after administration of a SGLT-2 inhibitor.

Results

Three months after administration of an SGLT-2 inhibitor, there were improvements in glucose tolerance, weight loss, blood pressure, and lipid indices. In all cases, there was no significant change in eGFR, but UACR decreased significantly. UACR decreased regardless of Angiotensin II Receptor Blocker medication and significantly decreased in the nephropathy stage 2 and 3 groups. UACR decreased only in the group in which blood pressure, body weight, and HbA1c decreased before and after administration of the SGLT-2 inhibitor.

Conclusions

Our study shows that SGLT-2 inhibitors are independent of renin-angiotensin system (RAS) inhibitors, and in addition to direct renal protection, the comprehensive effects of SGLT-2 inhibitors, which lower body weight, blood pressure, and blood glucose, are also important for their renal protection effects.

Background

Type 2 diabetes is an increasing trend worldwide [1]. Although the long-term prognosis of patients with type 2 diabetes is improving, the mortality rate, especially mortality from cardiovascular disease, remains unsolved [2]. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are recently developed oral hypoglycemic drugs whose mechanism is mainly to inhibit glucose reabsorption from renal tubules via SGLT-2. It lowers blood glucose levels through urinary disposing. Unlike insulin or other oral hypoglycemic drugs that have effects such as insulin secretion, SGLT-2 inhibitors have been reported to have other beneficial effects, such as body weight loss and reduction of blood pressure, while maintaining a low risk of hypoglycemia [3]. In addition, SGLT-2 inhibitors are reported to have cardio-protective effects in patients with type 2 diabetes, not only in Western countries [4, 5], but in Asian countries as well [6]. Renal function and urinary albumin excretion rate are associated with cardiovascular death [7], and renal complications need to be considered when considering the risk of cardiovascular disease (CVD) for type 2 diabetes. Recently, a SGLT-2 inhibitor, canagliflozin, was reported to reduce the relative risk of primary endpoints by 30%, such as progression to end-stage renal failure, doubling of serum creatinine (Cre) levels, and death due to renal disease in patients with type 2 diabetes with chronic kidney disease (CKD) [8]. This is the first large-scale clinical trial with renal outcomes due to SGLT-2 inhibitors as the primary endpoint. This study addresses the growing need to focus on the renal protective effects of SGLT-2 inhibitors in diabetic patients.

Diabetic nephropathy is a diabetic microvascular complication. Nephropathy progresses to microalbuminuria, overt albuminuria, and decreased renal function, and is associated with increased mortality [9]. The prevalence of diabetic nephropathy in type 2 diabetes is reported as the proportion with microalbuminuria or overt albuminuria, which is 30–40% in Europe and the United States [10] and 7–20% in Asian countries [11]. In Japan, the prevalence of diabetic nephropathy in type 2 diabetic patients is reported as high as 42% [12]. Since renal replacement therapy such as hemodialysis or peritoneal dialysis impairs patient quality of life, the development of a therapy to prevent the development of chronic renal failure in type 2 diabetic patients is desired. At present, treatment of diabetic nephropathy mainly consists of treatment for glomerular hypertension by diet, glycemic control, treatment of hypertension, especially suppression of the renin-angiotensin system (RAS), and treatment for dyslipidemia [13]. Clinical studies examining the effectiveness of strict glycemic control, such as ACCORD [14], ADVANCE [15], and the Kumamoto study [16], showed that strict glycemic control could significantly suppress a new onset of microalbuminuria and progression to overt albuminuria. These results suggest that strict glycemic control may be effective for the early stage of nephropathy. At the same time, however, the effectiveness of strict glycemic control was not observed in kidney-related hard endpoints such as serum creatinine doubling, progression to end-stage renal failure, and kidney-related death [17]. In 2015, the SGLT-2 inhibitor empagliflozin reduced the deaths of diabetic patients at high risk of cardiovascular events by 40% [4], and also reduced the incidence and worsening rate of nephropathy by 38%, the doubling of serum creatinine by 44%, and the introduction of dialysis by 55% [18]. Of note, more than 80% of the study participants had already taken RAS inhibitors. RAS inhibitors had already been reported as improving renal-related hard endpoints, such as promoting resolution of urinary albumin in early nephropathy and suppressing renal function decline in cases of overt nephropathy [19–22]. Similar results indicate that the

CANVAS program, which administered canagliflozin to patients with type 2 diabetes at high risk for cardiovascular events, also reduced the development of albuminuria by 27%, and showed that the renal complex endpoint (decreased estimated glomerular filtration rate (GFR), initiation of renal replacement therapy, and death from renal disease) were significantly reduced by 40% [5]. These results suggest that SGLT-2 inhibitors may be an oral hypoglycemic drug with a different mechanism from that of RAS inhibitors in inhibiting the progression of diabetic nephropathy. Accordingly, it is important for clinicians to examine the background of patients in whom the renal protective effect of SGLT-2 inhibitors is likely to be exerted.

Previous large-scale clinical studies suggest that SGLT-2 inhibitors could be used as a drug with not only a hypoglycemic effect but also a renal protective effect in patients with type 2 diabetes. However, it is not fully understood in what background a SGLT-2 inhibitor is more likely to exert its effects. Therefore, we investigated changes in renal function and urinary albumin in the short-term use of SGLT-2 inhibitors, focusing on patient background before administration, especially changes in body weight, blood pressure, and blood glucose. The purpose of this study was to clarify in which patients the renal protective effect of SGLT-2 inhibitors at a usual dose in Japan is likely to be demonstrated in actual clinical settings.

Methods

Study group

Sixty-three type 2 diabetic patients, 33 males, 30 females, mean age 53.0 ± 13.0 years old, who visited the Kure Medical Center outpatient department who received a Japanese standard dose of SGLT-2 inhibitors were analyzed retrospectively for medical record information. The SGLT-2 inhibitors were: Empagliflozin 10 mg in 20 patients, Canagliflozin 100 mg in 20 patients, Dapagliflozin 10 mg in 11 patients, Tofogliflozin 20 mg in 9 patients, and Ipragliflozin 50 mg in 3 patients (Table 1). We examined changes in body weight, blood pressure, glucose metabolism indices, lipid metabolism indices, and indicators related to diabetic nephropathy, estimated glomerular filtration rate (eGFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [23]) and albuminuria (urinary albumin-to-creatinine ratio, UACR, with albumin measured in milligrams and creatinine in grams), as measured in a laboratory. No changes were made in diabetes or lipid treatment between the three months before and after administration of SGLT-2 inhibitors. Each participant was interviewed and provided informed consent. This study was approved by the Ethics Committee of National Hospital Organization of Kure Medical Center.

Table 1
–Baseline participant characteristics

N (Men/Women)	63 (33/30)
Age, <i>years</i>	53.0 ± 13.0
Height, <i>cm</i>	162.2 ± 1.3
Body weight, <i>kg</i>	78.1 ± 2.2
BMI, <i>kg/m²</i>	29.9 ± 7.9
Systolic BP, <i>mmHg</i>	139 ± 2
Diastolic BP, <i>mmHg</i>	81 ± 2
Fasting glucose, <i>mg/dl</i>	208.4 ± 11.0
HbA1c, %	9.4 ± 0.2
TC, <i>mg/dl</i>	197.5 ± 5.9
LDL-C, <i>mg/dl</i>	112.8 ± 4.7
HDL-C, <i>mg/dl</i>	49.0 ± 1.5
TG, <i>mg/dl</i>	213 ± 24
Non HDL-C, <i>mg/dl</i>	148.6 ± 5.7
Estimated GFR, <i>ml/min/1.73 m²</i>	85 (73–103)
Urinary albumin-to-creatinine ratio-mg/gCre	43 (13–252)
Urinary albumin-to-creatinine ratio-no.	
< 30/ 30 to 300/ >300	29/ 21/ 13
Concomitant medication- no.(%)	
Usual dose SGLT2 inhibitors	
Empagliflozin 10 mg	20 (31.7)
Canagliflozin 100 mg	20 (31.7)
Dapagliflozin 10 mg	11 (17.5)
Tofogliflozin 20 mg	9 (14.3)

BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; SGLT-2, Sodium-glucose cotransporter 2; GFR, glomerular filtration rate; DPP-4, dipeptidyl peptidase 4.

Data are presented as number, mean ± S.E. or median (25th –75th percentile levels).

N (Men/Women)	63 (33/30)
Ipragliflozin 50 mg	3 (4.8)
Angiotensin II receptor blocker	28 (44.4)
Statin	31 (49.2)
DPP-4 inhibitor	48 (76.2)
Metformin	27 (42.9)
Sulfonylurea	10 (15.9)
α-Glucosidase inhibitor	5 (7.9)
Pioglitazone	2 (3.2)
BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; SGLT-2, Sodium-glucose cotransporter 2; GFR, glomerular filtration rate; DPP-4, dipeptidyl peptidase 4.	
Data are presented as number, mean ± S.E. or median (25th –75th percentile levels).	

Biochemical analyses

After overnight fasting, each participant underwent a physical examination and venous blood collection. Body measurements were taken in the standing position. Body mass index (BMI) was calculated as weight (kg) / height (m)². Collected blood and urine samples were centrifuged and measured by each method. Plasma glucose levels were measured by the glucose oxidase method. HbA1c levels were measured by high-performance liquid chromatography (HPLC) with an HLC723-G9 instrument (Tosoh, Tokyo, Japan). Serum and urine creatinine levels were measured by the oxidase method (Mizuho Medy, Tokyo, Japan). eGFR (mL/min/1.73 m²) was calculated as: 194 x Serum creatinine (-1.094) x Age (-0.287) x 0.739 (if female) [23]. Serum total cholesterol (TC) and TG levels were assessed by an enzymatic method. High-density lipoprotein cholesterol (HDL-C) level was measured directly by homogenous assay. Low-density-lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation [24]. Urine albumin quantification was measured using the immunoturbidimetry method (Nittobo Medical, Tokyo, Japan).

Statistical Analysis

The data are expressed as the mean ± S.E or median (25th -75th percentile), depending on the data distribution. Because of the skewed distribution of data, TG, eGFR and UACR values were logarithmically transformed and analyzed. The differences in continuous variables were analyzed using Student's *t*-test. Categorical variables were analyzed using the χ^2 test. *P* values < 0.05 were considered statistically significant. All analyses were performed using the software package SPSS version 20 (IBM Co. Ltd., Armonk, NY, USA).

Results

Table 1 shows the patient background of each subject before SGLT-2 inhibitor administration. The average age was 53.0 ± 2.0 years old, BMI was 29.9 ± 7.9 kg/m², and overweight. Mean fasting blood glucose level was 208.4 ± 11.0 mg/dL and HbA1c was $9.4 \pm 0.2\%$, indicating poor blood glucose control. The eGFR of the baseline was 85 (73–103) mL/min/1.73 m² and UACR was 43(13–252) mg/gCr. From the view point of the classification of Diabetic Nephropathy 2014: A Report from Joint Committee on Diabetic Nephropathy Classification [25], the number of stage 1 (normoalbuminuria < 30 mg/gCr and eGFR ≥ 30 mL/min/1.73 m²) was 29, stage 2 (microalbuminuria 30 ~ 299 mg/gCr and eGFR ≥ 30 mL/min/1.73 m²) was 21, and stage 3 (macroalbuminuria ≥ 300 mg/gCr and eGFR ≥ 30 mL/min/1.73 m²) was 13. No patients were in stage 4 (e GFR < 30 mL/min/1.73 m²) and stage 5 (during dialysis therapy). Twenty-eight of 63 patients were under treatment with a usual dose of Angiotensin II Receptor Blocker (ARB).

There was improving glucose tolerance, such as fasting plasma glucose and HbA1c level, three months after new administration of SGLT-2 inhibitors as shown in Fig. 1a. Improvements in body weight (2.1 kg) and blood pressure (6 mmHg) are shown in Fig. 1b. Lipid parameters also improved (Total cholesterol 9.8 mg/dL, and nonHDL-C 10.2 mg/dL, Fig. 1c).

Data related to nephropathy are shown in Fig. 2. In all cases, eGFR did not change significantly from 85 (73–103) mL/min/1.73 m² to 83 (68–99) mL/min/1.73 m² after three months administration of the usual dose of SGLT-2 inhibitors ($P = 0.165$). However, UACR level decreased significantly from 43 (13–252) mg/gCr to 26 (11–143) mg/gCr ($P < 0.001$).

Next, to examine the effect of ARB administration at baseline on the renal protective effect of SGLT-2 inhibitors, changes in GFR and UCAR levels were analyzed according to the presence or absence of ARB oral administration. In the 28 patients with ARB oral administration, eGFR was significantly decreased 90 (76–110) mL/min/1.73 m² to 87 (76–111) mL/min/1.73 m² ($P = 0.044$), and the UACR level was also significantly decreased 26 (10–244) mg/gCr to 18 (8 -150) mg/gCr ($P < 0.001$) (Fig. 2.a). The other 35 patients without ARB oral administration, eGFR was similarly decreased from 84 (71–113) mL/min/1.73 m² to 82 (62–108) mL/min /1.73 m² ($P = 0.045$), UACR significantly decreased from 66 (13–429) mg /gCr to 29 (18–199) mg/gCr ($P = 0.002$) (Fig. 2.b).

Subsequently, the effects of SGLT-2 inhibitors were compared by diabetic nephropathy staging at baseline (Table 2). Body weight and glucose metabolism indices were significantly decreased in all groups from stage 1 to stage 3. Systolic blood pressure was significantly decreased only in the stage 1 group. GFR did not change significantly in all groups from stage 1 to stage 3. UACR levels were significantly reduced only in the stage 2 and stage 3 groups.

Finally, urinary albumin excretion is expected to be affected by changes in blood pressure, body weight, and glycemic control. Therefore, we analyzed changes in GFR and UACR according to subgroups with

decreased systolic blood pressure (n = 39) or without (n = 24), subgroups with decreased body weight (n = 49) or without (n = 14), and subgroups with improved HbA1c levels (n = 56) or not (n = 7), before and after administration of SGLT-2 inhibitors (Table 3). As a result, UACR level was significantly decreased only in the group in which systolic blood pressure, body weight, and HbA1c level were improved. eGFR did not change significantly in all groups.

Discussion

The new administration of SGLT-2 inhibitors improved glycemic control, and also reduced body weight, blood pressure, and urinary albumin in the short term. In this study, we found that a decrease in UACR levels was observed in patients with nephropathy in the second and third stages, especially in the group with decreased body weight, blood pressure, and blood glucose, regardless of oral administration of RAS inhibitors. This study shows that SGLT-2 inhibitors have a renal protective effect independent of RAS inhibitors, and in addition to the direct renal protective effects of SGLT-2 inhibitors, the comprehensive actions of SGLT-2 inhibitors, which improved body weight, blood pressure, and blood glucose, were also important for the renal protective effect.

SGLT-2 inhibitors are shown to have renal protective effects by directly lowering glomerular pressure, correcting glomerular hyperfiltration, and suppressing excessive glucose reabsorption by tubular cells [26–28]. In addition, inhibition of SGLT-2 reduces Glucose/Na⁺ reabsorption in proximal tubules and increases and regulates Na⁺ reaching tubule macrodensers, thereby correcting glomerular hyperfiltration, which has been reported to suppress nephropathy progression [29]. Meanwhile, it has been reported that hypertension increases proteinuria and albuminuria and causes a decrease in renal function due to glomerular load [30]. Obesity-related nephropathy has been also reported as an effect of obesity on the kidneys, resulting in increased glomerular filtration rate, increased renal blood flow, and renal swelling, and proteinuria [31]. In other words, the renal protective effects of SGLT-2 inhibitors may contribute not only to the direct effects on glomeruli, but also to comprehensive renal protective effects via weight loss, and a lowering of blood pressure and blood glucose. Increased urinary albumin is a predictor of the progression of diabetic nephropathy [9], and decreased urinary albumin has been reported to reduce the risk of end-stage renal failure and CVD [32].

Our study found a urinary albumin-improving effect from SGLT-2 inhibitors, especially in patients with relatively advanced stage 2 (microalbuminuria) and 3 (macroalbuminuria) nephropathy (Table 2), and these effects are independent of RAS inhibitors (Fig. 2a, b). There is a possibility that SGLT-2 inhibitors could be used in the future as an approved renoprotective medication in type 2 diabetes alongside ARB.

In this study, eGFR tended to decrease in the short term of 3 months after SGLT-2 inhibitor administration (Fig. 2). This is consistent with the fact that the canagliflozin group showed a greater decrease in eGFR in the early 12 months after the start of the study compared to the placebo group. In the CREDENCE trial, subsequent changes were slow, reversed from the placebo group after 12 months, and the long-term eGFR decline reduction effect was observed in the canagliflozin group [8]. SGLT-2 inhibitors have an effect

on improving glomerular hyperfiltration in diabetic nephropathy and this may be a possible mechanism for the short-term decline of GFR after administration of an SGLT-2 inhibitor.

Study limitations

There are some limitations in this research. First, this was an observational study. Indeed, prospective studies are needed to determine whether SGLT-2 inhibitors can improve renal function. Second, we targeted people who took multiple SGLT-2 inhibitors. The purpose of this study was to evaluate the usefulness of SGLT-2 inhibitors as a class effect, but we did not examine whether the effect differs depending on the type of single drug. Third, the subjects in this study had relatively good renal function (nephropathy stages 1 to 3). Further discussion is needed on renal protection in patients with more severe renal failure.

Conclusions

This study suggests that SGLT-2 inhibitors have a short-term effect on decreasing urinary albumin excretion, especially in patients with microalbuminuria and macroalbuminuria but not with normoalbuminuria, and especially in subjects with improved blood pressure, weight, and blood glucose levels. This is an important clinical finding that clarifies patients who are likely to exert the renal protective effects of SGLT-2 inhibitors.

Abbreviations

SGLT-2, Sodium-glucose cotransporter 2; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; RAS, renin-angiotensin system; CVD, cardiovascular disease; Cre, creatinine; CKD, chronic kidney disease; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ARB, Angiotensin II Receptor Blocker.

Declarations

Ethics approval and consent to participate

The study protocols were approved by the Ethics Committee of National Hospital Organization of Kure Medical Center, and informed consent was provided by all subjects.

Consent for publication

Not applicable

Availability of data and material

The datasets used/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no conflicts of interest.

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Authors' contributions

M.K. collected, analyzed and interpreted the data, and wrote the manuscript. R.S. reviewed the manuscript. K.T. collected the data and reviewed the manuscript. Y.Y. reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Tables 2 And 3

Due to technical limitations, tables 2 and 3 are only available as a download in the supplemental files section.

Figures

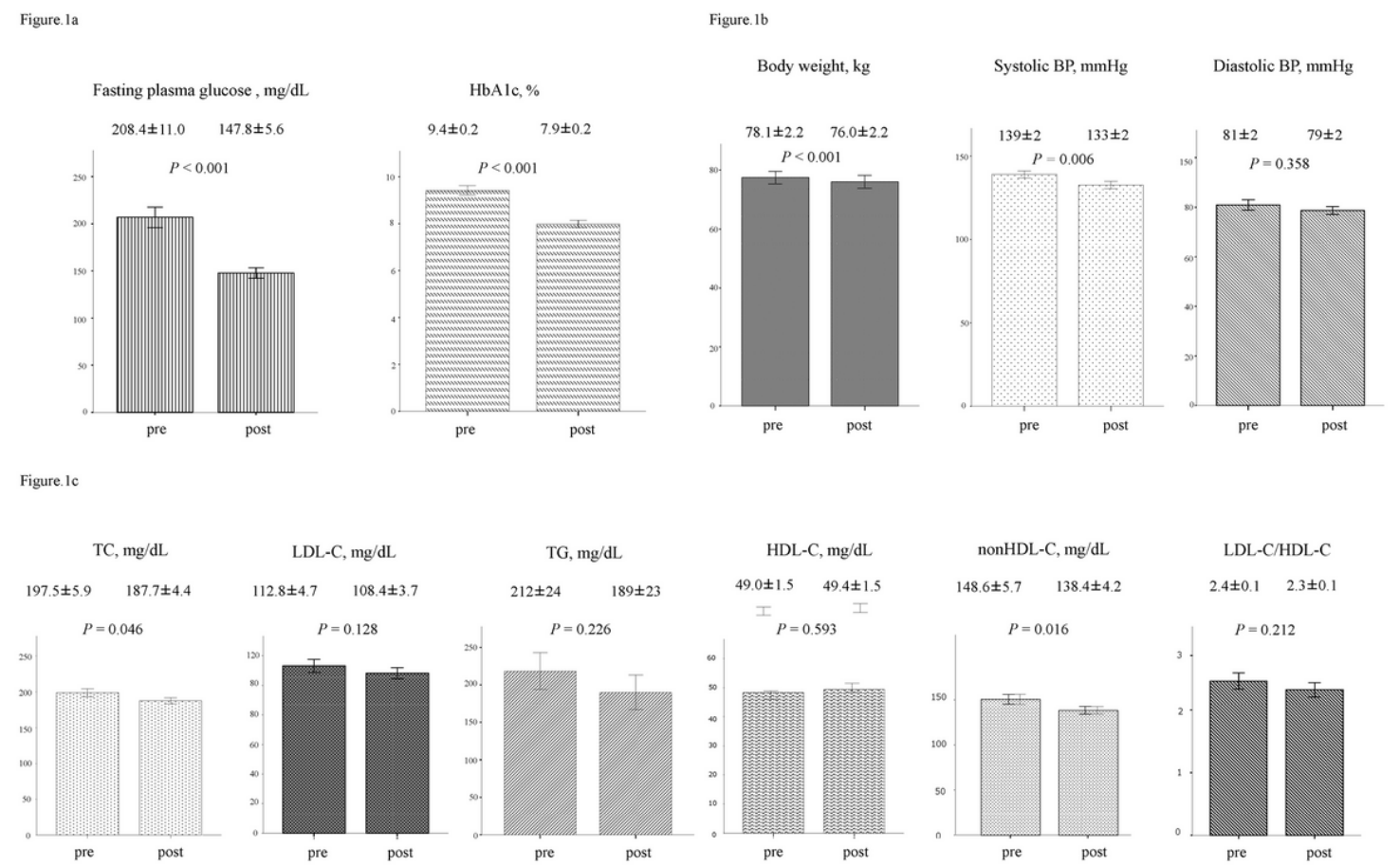


Figure 1

1a—Changes in glucose metabolism indices before and 3 months after administration of usual dose of SGLT-2 inhibitors. Values are shown as mean±S.E. HbA1c, Hemoglobin A1c. 1b—Changes in body weight

and blood pressures before and 3 months after administration of usual dose of SGLT-2 inhibitors. Values are shown as mean±S.E. BP, blood pressure. 1c–Changes in lipid metabolism indices before and 3 months after administration of usual dose of SGLT-2 inhibitors. Values are shown as mean±S.E. TC, total cholesterol, LDL-C, low density-lipoprotein cholesterol, TG, triglyceride, HDL-C, high density-lipoprotein cholesterol.

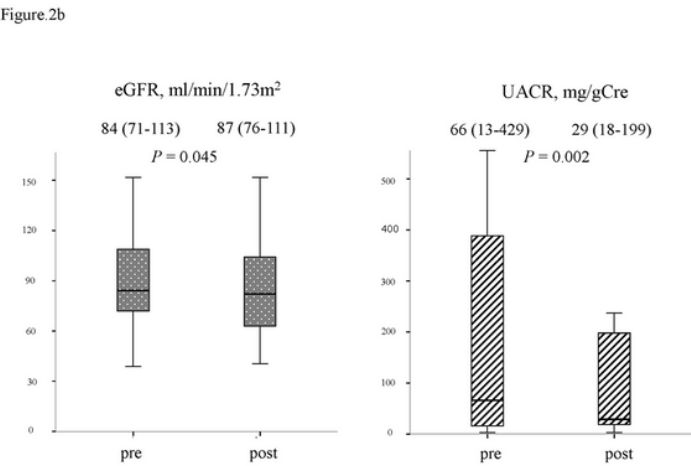
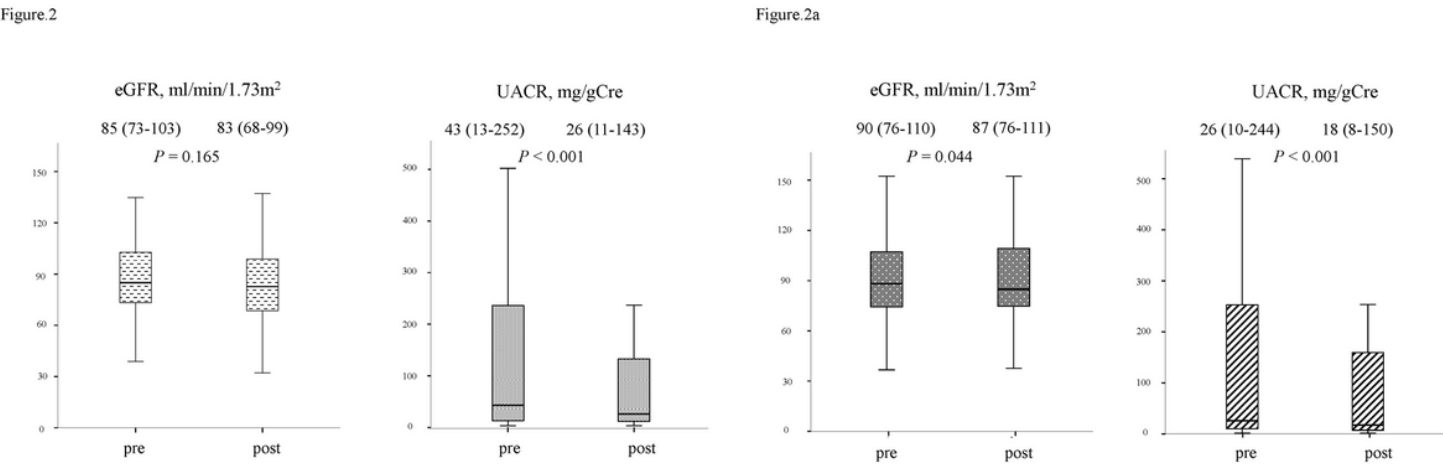


Figure 2

Changes in estimated GFR and UACR in all subjects before and 3 months after administration of usual dose of SGLT-2 inhibitors. Values are shown as median and the inter-quartile range. GFR, glomerular filtration rate , UACR, urinary albumin-to-creatinine ratio. 2a–Changes in estimated GFR and UACR in subjects with taking ARB internally before and 3 months after administration of usual dose of SGLT-2 inhibitors. The number of subjects taking ARB was 28. Values are shown as median and the inter-quartile range. ARB, Angiotensin II Receptor Blocker, GFR, glomerular filtration rate, UACR, urinary albumin-to-creatinine ratio. 2b–Changes in estimated GFR and UACR in subjects without taking ARB internally before and 3 months after administration of usual dose of SGLT-2 inhibitors. The number of subjects taking ARB was 35. Values are shown as median and the inter-quartile range. ARB, Angiotensin II Receptor Blocker, GFR, glomerular filtration rate, UACR, urinary albumin-to-creatinine ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables2and3.pdf](#)