Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

Rapid Communication

A Sodium-Glucose Cotransporter-2 Inhibitor Modulates the Skin Hydration State in Type 2 Diabetes Patients: Post-Hoc Analysis of a Prospective, Open-Label Pilot Study

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Received: October 11, 2021; **Accepted:** November 02, 2021; **Published:** November 09, 2021

Abstract

We conducted a prospective open-label, short-term, and double-arm exploratory study to investigate changes in the skin hydration state in Japanese patients with type 2 diabetes mellitus (T2DM) treated with either 50 mg ipragliflozin (a sodium-glucose cotransporter-2 inhibitor: SGLT2i) (n=8) or 50mg sitagliptin (as a control) (n=6) 1×/day for 14 days. We performed a post-hoc analysis of reported clinical data to determine whether ipragliflozin's effects on skin hydration were dependent on the baseline skin water content. The skin hydration state was measured by three standard methods. SGLT2i significantly reduced both the skin water content and the transepidermal water loss in only the T2DM patients with the higher baseline values (not in the lower baseline group classified by the respective median values). No such relationship occurred in the sitagliptin-treated patients. These results indicate that the skin hydration state is well controlled depending on the skin hydration state during 14-day treatment with SGLT2i.

Keywords: Type 2 diabetes mellitus; Sodium-glucose cotransporter-2 inhibitor; Transepidermal water loss

Introduction

Clinical trials of a Sodium-Glucose Cotransporter-2 inhibitor (SGLT2i) conducted in Asia reported the development of various types of skin lesions with pruritus, with an incidence of approx. 2%-3% [1]. Such skin lesions are usually observed within 14 days after the start of SGLT2i treatment [2]. Volume depletion that occurs during SGLT2i treatment might induce dry skin, as diuretic therapy does [3]. We thus hypothesized that skin disorders might be associated at least in part with dehydration of the subcutaneous tissues [4].

We had investigated whether a diuretic effect of the use of an SGLT2i (ipragliflozin) modulated the skin hydration state in patients with type 2 diabetes mellitus (T2DM) by comparing the effect of a dipeptidyl peptidase-4 inhibitor (DPP4i, sitagliptin) as a control [4]. The results revealed no significant difference in the changes of electrical conductance, capacitance, or Transepidermal Water Loss (TEWL) between these two drug treatments. The skin water content after a 14-day treatment with either drug was linearly correlated with the pre-treatment values. We concluded that a 14-day SGLT2i treatment did not significantly affect the skin hydration status of T2DM patients [4].

However, in the present post-hoc analysis of that study [4], we observed a negative correlation between the baseline skin water content and the SGLT2i-induced reduction of the skin water content, suggesting that the patients with higher skin water content at the pre-treatment stage showed a significant reduction of the water content after a 14-day SGLT2i treatment depending on the patients' basal skin hydration condition. In this post-hoc analysis, we re-evaluated modification of the skin hydration state after the treatment of SGLT2i.

Methods

Study population and measurement protocol

The double-arm exploratory study had been conducted to investigate changes in skin hydration in Japanese patients with T2DM treated with either 50mg ipragliflozin (n=8) or 50mg sitagliptin (n=6), once a day for 14 days. The eligible subjects were 14 T2DM patients with the mean age 68.5 years, mean diabetes duration 2.8 years, good glycemic control with a mean HbA1c <7.0% and its fluctuation within 0.3% in the 2 months prior to enrollment, and being treated with or without oral glucose-lowering medicine (only metformin <500mg/day). The eligible patients' baseline characteristics were reported in detail and did not differ between the two-treatment groups [4]. After the treatment, the HbA1c levels were slightly but significantly reduced in the ipragliflozin treatment group, but the changes in HbA1c from basal to after-treatment values did not differ between the 2-treatment groups [4]. The serum 3-hydroxy butyrate levels were significantly increased in the ipragliflozin group compared to the sitagliptin group [4].

The biophysical characteristics of each patient's skin were measured at the anterior surface of the forearm and the extensor surface of the lower leg, using the following noninvasive biophysical methods in the morning at the fasting state [4]. The skin electrical capacitance and electrical conductance reflecting the water content of the stratum corneum were measured by both a Corneometer®

Citation: Tezuka Y, Sekine O, Hirano A, Hanada Y, Harada K, Azuma C, et al. A Sodium-Glucose Cotransporter-2 Inhibitor Modulates the Skin Hydration State in Type 2 Diabetes Patients: Post-Hoc Analysis of a Prospective, Open-Label Pilot Study. Austin J Endocrinol Diabetes. 2021; 8(3): 1090.

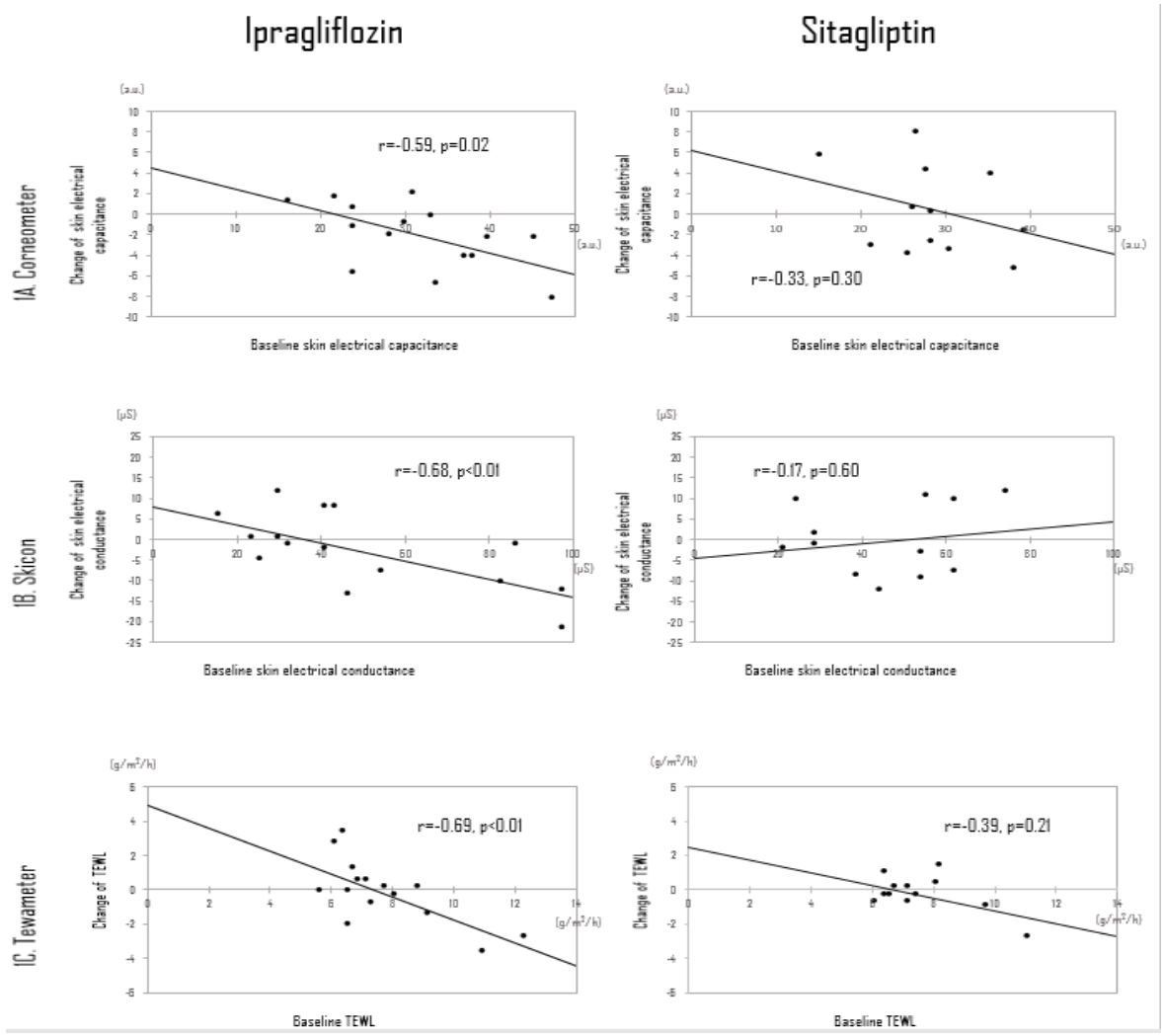

Figure 1: Correlation of the change in skin water contents (measured by a Corneometer and a Skicon) and transepidermal water loss (TEW; measured by a Tewameter) with each baseline value. Each patient had two baseline skin hydration measurement points, i.e., the forearm and lower-leg values. The changes in both the skin water content and the TEWL were significantly negatively correlated with each baseline value in only the patients treated with SGLT2i, not the patients treated with DPP4i. a.u.: arbitrary units, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: sodium-glucose cotransporter-2 inhibitor. WL: transepidermal water loss (g/m^2/h).

and a Skicon® (higher values indicate skin with more moisture), and the TEWL was measured by a Tewameter®. The water content and TEWL values were expressed as the mean of five and three serial measurements, respectively. The mean values of both sides of the forearm and lower leg were calculated. Before the measurements were taken, the patients were acclimated to a preadjusted temperature of 20±2°C and relative humidity of 50±5% for 20min in a private room.

Statistical analysis

The Shapiro-Wilk test was used to identify the distribution of a variable's values. We used Pearson's correlation coefficients to measure the association of the changes in hydration parameters after the drug treatment compared to the baseline parameters. The paired t-test was used to evaluate differences between the parameters pre-treatment and 14 days post-treatment. JMP ver. 11 (SAS Institute, Cary, NC, USA) was used for the statistical analyses. Two-sided p-values <0.05 were considered significant.

Results

In the post-hoc analysis of the prospective open-label study [4], a significant negative correlation was revealed between the baseline skin water content and the SGLT2i-induced reduction of the skin water content, which were measured by Corneometer®, Skicon®, and a Tewameter®, indicating that the T2DM patients with higher skin water content showed a significant reduction of each of these parameters after SGLT2i treatment depending on the patients' basal skin hydration condition compared to that of DPP-4i treatment (Figure 1A-1C). We therefore re-analyzed these previous data to investigate whether SGLT2i treatment could modulate the skin's water content and TEWL in T2DM patients depending on their skin hydration state by comparing the results of DPP4i treatment. We classified these continuous variables into two groups using the median value: the higher and lower groups in both the SGLT2i and DPP4i groups, respectively.

Table 1: Comparison of the changes in parameters of the skin hydration state from the baseline values between the SGLT2i and DPP4i treatment groups.

Skin measure*		SGLT2i (Ipragliflozin)			DPP4i (sitagliptin)		
		Day 0	Day 14	p-value†	Day 0	Day 14	p-value†
Corneometer®, a.u.	H‡	39.3±5.4	35.3±5.2	<0.01	33.7±5.0	32.3±5.8	0.35
	L‡	24.9±4.9	24.5±5.3	0.66	24.1±4.8	26.0±6.6	0.36
Skicon®, μS	H	72.5±23.8	63.8±20.4	<0.05	60.8±7.5	62.5±14.9	0.69
	L	29.9±8.6	31.7±10.4	0.41	31.8±8.8	29.1±5.5	0.45
Tewameter®, g/m²/h	H	9.2±1.8	7.9±1.1	<0.05	8.7±1.5	8.5±1.1	0.55
	L	6.5±0.5	7.1±1.8	0.34	6.7±0.3	6.7±1.2	0.92

Continuous data are presented as the mean and standard deviation.

*The Corneometer measures the skin's electrical capacitance to determine the water content of the stratum corneum; the Skicon measures the skin's electrical conductance as an additional index of water content. Transepidermal water loss was determined using the Tewameter TM300.

†By the paired-t test.

‡Groups classified the higher (H) and the lower (L) baseline groups based on the median values. Each point represents the combined data in skin hydration parameters from a forearm and a lower leg in each patient.

a.u: arbitrary unit; DPP4i: Dipeptidyl Peptidase-4 inhibitor; SGLT2i: Sodium-Glucose Cotransporter-2 inhibitor.

As shown in Table 1, there were significant reductions of not only skin electrical conductance and capacitance but also TEWL in only the SGLT2i-treated patients in the higher group of these three parameters. No such relationship was observed in the DPP4i-treated patients.

Discussion

Our findings indicate that the patients' skin hydration state was well preserved depending on the whole-body water balance under the diuretic effects of SGLT2i. The present findings were obtained in a short-term study in patients with well-controlled and recent-onset diabetes in both treatment groups.

It has been suggested that the volume depletion that occurs during the SGLT2i treatment is similar to the volume depletion due to classical diuretics. In patients with heart failure, treatment with SGLT2i reduced the plasma volume as well as extracellular volume [5]. However, SGLT2i treatment showed a greater reduction of extracellular water (ECW) volume in the higher ECW group compared with the lower pretreatment ECW group in patients with diabetic kidney disease [6]. Consistently, in healthy subjects, it has been suggested that treatment with SGLT2i reduced fluid volume to a greater extent than intravascular volume [7]. In diabetic rats with hyperglycemia, compensatory mechanisms to conserve solute and water even with persistent glycosuria induced by dapagliflozin treatment were described [8]. Thus, the present study's most important finding is that the patients' skin water content was well maintained under the diuretic effects of SGLT2i. Notably, the patients who had no obvious excess of extracellular volume showed a significant reduction of skin water content and transepidermal water loss, depending on the their water hydration state.

Although these observations of an SGLT2i-related modulation of the skin hydration state might not be directly related to skin disorders in SGLT2i-treated patients, it would be worthwhile to study the skin hydration state in T2DM patients with a higher risk of skin dehydration, in older patients with long diabetes durations, those with poor glycemic control, and those with an extensive use of diuretics.

We conclude that the skin water content as well as TEWL were well controlled under treatment with SGLT2i depending on the patients' pretreatment skin hydration state.

Declaration

Acknowledgements: We thank the participants of the study.

Disclosure: AK has acted as a medical consultant for Sunstar, Inc. and has received consulting fees. AH, YH and KH are employees of Sunstar Inc. The remaining authors have nothings to disclose.

Approval of the research protocol: The Institutional Review Board at the Kusatsu General Hospital approved the study protocol (approval date: 8 Sep 2017; Approval no. 2017-1011-02). Informed Consent: All participants provided written informed consent before participating in the study. Approval date of Registry and the Registration

Fundings: This study was in part supported by Sunstar Inc.

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