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Comparing the efficacy of apple peels and a sodium-glucose cotransporter 2 inhibitor (ipragliflozin) on interstitial glucose levels: A pilot case study

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ABSTRACT

Background: Apple peels contain phlorizin, which can reduce plasma glucose levels in a manner similar to that of inhibitors for sodium-glucose cotransporters.
Objectives: In this study, we examined the influence of a peeled apple, a sodium-glucose cotransporter-2 inhibitor (ipragliflozin) in combination with a peeled apple, and an unpeeled apple on interstitial glucose in a healthy individual across 3 experiments.
Methods: For Experiments 1, 2, and 3, the healthy volunteer consumed 327 g peeled Sun Fuji apple, took 50 mg ipragliflozin, and then consumed 327 g peeled Sun Fuji apple, or consumed 370 g unpeeled Sun Fuji apple (peel weight was 43 g), respectively. In each condition, the apple was eaten within a 15-minute period and interstitial glucose levels were measured every 15 minutes for 11.5 hours using FreeStyle Libre (Abbott Laboratories, Abbott Park, Illinois).
Results: Results showed that neither consumption of the unpeeled apple nor ipragliflozin were able to suppress the rapid or transient increases in postprandial glucose; however, the 2 were found to comparably suppress interstitial glucose during the late phase.
Conclusions: On the whole, these findings demonstrate that eating unpeeled apples may be beneficial for plasma glucose management, but ipragliflozin is a superior option because the apple peel's function did not last as long as ipragliflozin. (*Curr Ther Res Clin Exp*. 2020; 81:XXX–XXX)

Introduction

The contribution of apple peels to good health has been well recognized since the discovery of phlorizin.[1] For example, research reveals its extract is protective against lipid peroxidation and inflammation in diabetic rats,[2] and dried apples have been discovered to improve body composition, lipid profiles, and inflammatory markers in overweight and obese children.[3] Curiously, this food has not been found to be effective at correcting plasma glucose levels,[2] although it may be because its phlorizin has been inactivated upon exposure to heat.[1] Thus, we investigated whether intake of fresh apple peels, in particular, would decrease plasma glucose levels in a healthy adult.

Case Presentation

To explore this aim, a member in our laboratory volunteered to be studied and was provided informed consent. This healthy volunteer was a nonsmoking man aged 61 years, with a body mass index of 25.5, normal glucose tolerance of 75 g (per an oral glucose tolerance test), and essential (ie, primary or idiopathic) hypertension, which he had been treating with candesartan (4 mg/d) for the past 5 years. He ceased taking any medication, including candesartan 48 hours before beginning and until the end of the study, maintained his lifestyle and body weight throughout, and fasted approximately 12 hours before each experiment.

This study comprised 3 experiments, which were repeated 3 times each on different days across a 3-month timespan. For

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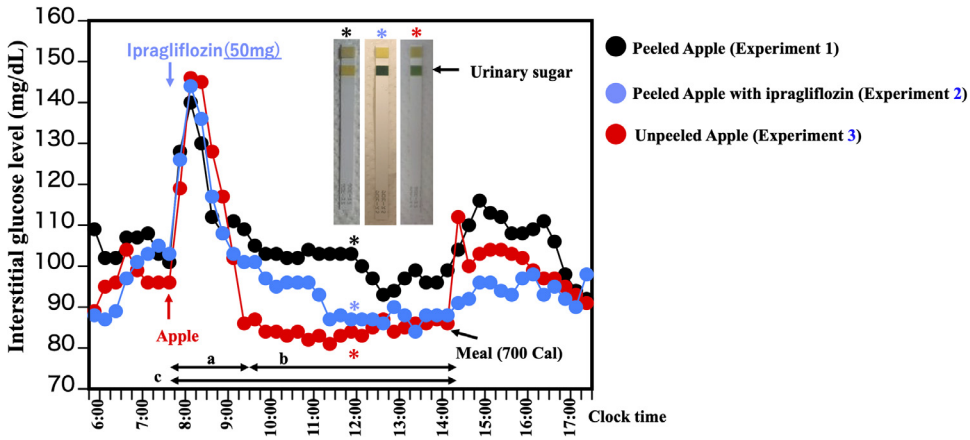

Fig. 1. The effect of apple peels and ipragliflozin on interstitial glucose levels. The black (Experiment 1), blue (Experiment 2), and red (Experiment 3) lines represent the glucose level after the patient ingested a peeled apple, a peeled apple with ipragliflozin, and an unpeeled apple, respectively. Three time periods were characterized as "a" (representing a rapid and transient elevation of postprandial interstitial glucose level), "b" (representing the late phase once glucose levels peaked), and "c" (representing the sum of the 2 phases, or rather, the time from the consumption of the apple to the 700-kcal meal). The short periods wherein the patient consumed the apple and took ipragliflozin are represented by the arrows. The 3 plots represent data from 1 of the 3 replicated experiments. The strips showcase the presence of urinary sugar (green squares). Each urine sample was collected at * timepoint; the black * represents Experiment 1, blue * represents Experiment 2, and red * represents Experiment 3.

Experiment 1, the volunteer consumed 327 g peeled Sun Fuji apple within 15 minutes, and then interstitial glucose levels were measured every 15 minutes for 11.5 hours using FreeStyle Libre (Abbott Laboratories, Abbott Park, Illinois).[4,5] For Experiment 2, the volunteer took 50 mg ipragliflozin and consumed 327 g peeled Sun Fuji apple within 15 minutes, and then interstitial glucose levels were measured. For experiment 3, the subject consumed 370 g unpeeled Sun Fuji apple (peel weight was 43 g) within 15 minutes, and then interstitial glucose levels were measured. Of note, the mean (SD) sugar content in each apple and phlorizin content in the peel were found to be 15.4% (0.5%) mg/100 g and 2.8 (0.45) mg/100 g, respectively, per measurements obtained by Japan Food Research Laboratories (Tokyo, Japan).[6,7] Therefore, it is estimated that the volunteer consumed 1.18 mg phlorizin in Experiment 3, which is sufficient to inhibit sodium-glucose co-transporter 2 (SGLT-2).[8]

Following comparisons of interstitial glucose levels between the experiments, results showed that neither the unpeeled apple nor ipragliflozin suppressed rapid or transient increases in postprandial interstitial glucose (indicated by period a). Consumption of the unpeeled apple and ipragliflozin comparably suppressed interstitial glucose levels during the late phase (indicated by period b); however, ipragliflozin was more effective than the unpeeled apple at suppressing interstitial glucose during the period of observation (Figs. 1 and **2**). In addition, when the volunteer ate a 700-kcal meal (lasagna) after the period of observation, his interstitial glucose level increased more following consumption of the peeled apple relative to the unpeeled apple, although again, the apple peel's function did not last as long as ipragliflozin because the interstitial glucose level did not change even after a 700-kcal meal ingestion in the case of ipragliflozin ingestion (Fig. 1).

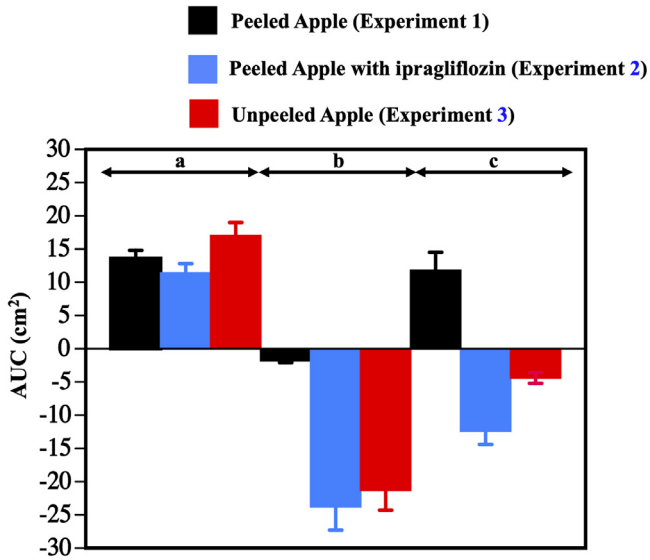

Fig. 2. The effect of apple peel and ipragliflozin on interstitial glucose levels are represented by the area under the curve. The bar values are expressed as means (SD). The black (Experiment 1), blue (Experiment 2), and red (Experiment 3) bars represent the interstitial glucose level when the patient consumed a peeled apple, a peeled apple with ipragliflozin, and an unpeeled apple, respectively. During periods b and c, the unpeeled apple and ipragliflozin decreased postprandial interstitial glucose level. During period c, ipragliflozin's effect was greater than that of the unpeeled apple.

Discussion

Apples are widely beneficial for metabolic health[9]; however, they contain fructose and glucose, which can be points of concern. In an earlier study, intake of an unpeeled apple by healthy subjects elevated their plasma glucose by approximately 30 mg/dL.[10] To our knowledge, this is the first investigation to report on the individual effects of apple peels and ipragliflozin on interstitial glucose levels. Here, we observed a rapid and transient increase in postprandial glucose (period a), followed by returning to the basal level during the late phase (period b) in the case of peeled apple consumption. Notably, we discovered that consumption of an unpeeled apple decreased glucose levels compared with the extent of a peeled apple consumption during the late phase (period b), which suggest that glucose reuptake by SGLT-2 was inhibited by either the apple peel or ipragliflozin. Based on our estimation, the concentration of phlorizin in the peel was sufficient to inhibit both SGLT-1 and SGLT-2. In fact, in experiments 2 and 3, glucose was detected in the healthy volunteer's urine, although the amount was greatest subsequent to taking ipragliflozin (Fig. 1). SGLT-1 controls absorption of glucose in the small intestine,[11] which might explain why eating the unpeeled apple suppressed interstitial glucose levels during the late phase. On the whole, our observations shed light on the advantages of eating unpeeled apples for enhanced plasma glucose

management. Future investigations are needed to determine which apple varieties and amounts of apple peels are the most effective.

This study has a few limitations that warrant discussion. First, our sample size was quite small (n = 1), so the generalizability of the results is restricted. Although the study only involved 1 volunteer, the data were considered indicative for the comparative effects of ingested apple peels and a sodium-glucose cotransporter inhibitor (ipragliflozin) on interstitial glucose levels. Therefore, repeating the same experimental condition was required to make the whole method highly reproducible. Thus, despite having a small sample number, we were able to compare and estimate the effects of ingested apple peel and sodium-glucose cotransporter inhibitor (ipragliflozin) on interstitial glucose levels. Nevertheless, these results should be verified in a larger cohort. Second, the study has a selection bias due to the ethnicity, age, sex, and weight of the participant and would benefit from the inclusion of a range of demographic characteristics. Third, there is the possibility that the patient's antihypertension medication, candesartan, may have influenced his clinical responses to the different experiments.[12]

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J. Okada and E. Yamada interpreted data. K. Okada prepared the figures. S. Okada and M. Yamada wrote and edited the manuscript. All authors approved the final version.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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