Original article

Acute effect of low-dose sugar ingestion on forearm blood flow in healthy men

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Background: Hyperglycemia is a major risk factor for cardiovascular disease resulting in vascular damage in both diabetic and non-diabetic people.
Objective: To determine acute effect of elevated plasma glucose from a low-dose sugar ingestion on forearm blood flow (FBF) in healthy men.
Methods: Ten healthy men (aged 24.1 ± 4.1 years) participated in two experimental conditions: 1) drinking 200 mL of water (Control), and 2) drinking 15 grams of sugar solution (Sugar). The two conditions were scheduled in random order with a minimum of three days of washout period between conditions. FBF was determined by venous occlusion plethysmography. Peak forearm blood flow (FBF_{peak}) and area under the curve of forearm blood flow (FBF_{AUC}) during reactive hyperemia were obtained before and every 30 minutes after sugar ingestion for 2 hours. Plasma glucose and serum insulin levels were measured before and 30, 60, and 120 minutes after sugar/water ingestion.
Results: In the Sugar, FBF_{peak} at 30 minutes significantly decreased when compared to baseline, 90 and 120 minutes ($P < 0.05$ for all comparisons). Comparing to the Control, FBF_{peak} at 30 minutes also significantly decreased ($P < 0.0001$). FBF_{AUC} at 30 minutes slightly but insignificantly decreased from baseline after sugar ingestion. Plasma glucose and serum insulin levels significantly increased at 30 minutes after sucrose ingestion and returned toward baseline afterward.
Conclusion: In healthy persons, a low amount of sugar ingestion acutely impairs vasodilating function. Decreased FBF_{peak} parallels with the elevation of plasma glucose and insulin responses after sugar ingestion.

Keywords: Acute hyperglycemia, forearm blood flow, reactive hyperemia, sugar, vascular function.

Hyperglycemia is a common feature in individuals with metabolic syndrome, especially diabetic patients.[1] On the other hand, healthy people can develop hyperglycemia after a meal, which is known as postprandial hyperglycemia.[2, 3] It has been shown that a rapid rise in postprandial plasma glucose leads to vascular dysfunction.[2 - 4] Endothelial cells are more susceptible to harm caused by hyperglycemia than other cell types.[5] According to previous studies, oral or intravenous glucose loading caused vascular dysfunction in individuals with impaired glucose tolerance[6], diabetic patients[7], and even healthy people.[8, 9]

Vascular dysfunction is a key factor in the development of cardiovascular disease (CVD), and it can occur well before atherosclerotic vascular changes.[10] In normal vascular function, the endothelium and vascular smooth muscle cells actively interact to regulate vasodilation and vasoconstriction.[11] When the normal equilibrium between vasoactive stimuli is disrupted, endothelial dysfunction occurs, resulting in a reduced response to vasodilatory stimuli.[12] Vascular dysfunction can be assessed by venous occlusion plethysmography during reactive hyperemia.[13] Reactive hyperemia is an increase in blood flow that occurs after a temporary arterial occlusion and is widely used in vascular

studies for measurement of blood vessel vasodilation capability.[14]

Diet containing high amount of added sugar is considered unhealthy.[15] Consumption of added sugar causes acute hyperglycemia[16], which has been related to the development of non-communicable diseases, such as type 2 diabetes, cardiovascular disease, and obesity.[17] Previous studies showed that an oral glucose tolerance test (75 g glucose) resulted in a decrease in vasodilating function within 1 hour [6, 8, 9, 18] as determined by flow-mediated vasodilation (FMD) of the brachial artery and forearm blood flow using venous occlusion plethysmography.[19, 20]

Although numerous studies have shown that high sugar consumption can lead to vascular dysfunction, people may not always ingest such high amount of sugar. Lower amount of sugar intake may occur more frequently in daily life. The evidence of the impact of a low-sugar diet on vascular function has been limited. Therefore, the purpose of the present study was to determine the acute effects of low amount of sugar ingestion induced changes in blood glucose and on forearm blood flow in healthy men.

Materials and methods
Study design

In the present study, a cross-over randomized trial design was conducted. Two conditions (Control and Sugar) were scheduled in random order, with a minimum of three days between conditions for a washout period. In the Sugar, subjects ingested a sugar solution containing 15 grams of sucrose while in the Control, they ingested drinking water. The main outcomes were forearm blood flow and blood glucose and insulin concentrations measured before and after the ingestions. All subjects were informed of the benefits and risks of taking part in the study. A written consent was provided by each participant before enrollment. The protocol in the study has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (COA no. 454/2020).

Subjects

Ten healthy men aged 18 - 35 years old were recruited into the study. All subjects were healthy as determined by being normotensive (blood pressure < 130/85 mmHg)[21], non-diabetic with a fasting plasma glucose of less than 100 mg/dL, normolipidemic, non-obese (body mass index < 25 kg/m²), non-smokers, and free of a family history of diabetes. They were also physically inactive, defined as not participating in at least 30 minutes of moderate-intensity (jogging, cycling, or recreational sports) on at least 3 days per week for the previous 3 months.[22] Subjects were ruled out if they had any nerve or upper limb muscle abnormalities, open wounds or inflammation in the arm or forearm region. Those who were currently taking cardiovascular disease drugs or having antioxidants or vitamins supplements in the week leading up to the experiments were also excluded.

Experimental procedures

Before each experimental initiation, the subjects fasted for at least 8 hours and abstained from alcohol, caffeine, and exercise for 24 hours. After arrival to the laboratory in the morning, they rested in a supine position for 10 minutes. Following that, venous blood samples for glucose and insulin were taken, and baseline measurements of forearm blood flow and blood pressure were obtained. Within 5 minutes, the subjects drank either a sugar solution (15 g sucrose dissolved in 200 mL water) or an equal amount of drinking water. After sugar or water ingestion, measurements of forearm blood flow and blood pressure were taken again every 30 minutes for 2 hours. Blood samples were obtained at 30, 60, and 120 minutes after ingestion of the liquids (Figure 1). All measurements were taken in a quiet room at a steady room temperature of 25 - 26°C.

Examination of forearm blood flow

The forearm blood flow (FBF) was measured by automatic venous occlusion strain gauge plethysmography (EC6, D.E. Hokanson Inc., USA). NIVP3 software (D.E. Hokanson Inc., USA). Arterial occlusion cuffs were placed on the upper arm and wrist on the non-dominant arm. The widest part of the forearm was wrapped in a mercury-in-silastic strain gauge. At the beginning of the examination, a wrist arterial cuff was inflated to 30 mmHg above systolic blood pressure to exclude hand circulation. During each measurement of FBF the venous occlusion cuff was inflated above systemic venous pressure (approximately 50 mmHg) for 10 seconds before being released for 5 seconds to occlude venous return but not arterial inflow. After recording resting forearm blood flow (FBF_{rest}) for three minutes, the arterial upper arm cuff was inflated above systolic blood

pressure (systolic P + 60 mmHg) for five minutes to occlude arterial flow to the forearm and subsequently induce reactive hyperemia (Figure 2). During reactive hyperemia, FBF was measured for 5 minutes after the arterial upper arm occlusion cuff was released. Peak forearm blood flow (FBF_{peak}), which is defined as the maximum FBF observed during reactive hyperemia, was recorded. The area under curve of the FBF (FBF_{AUC}) during the reactive hyperemic period of 5 minutes was calculated using trapezoidal rule. FBF_{peak} and FBF_{AUC} were evaluated at baseline and every 30 minutes after sugar ingestion for a period of 2 hours.
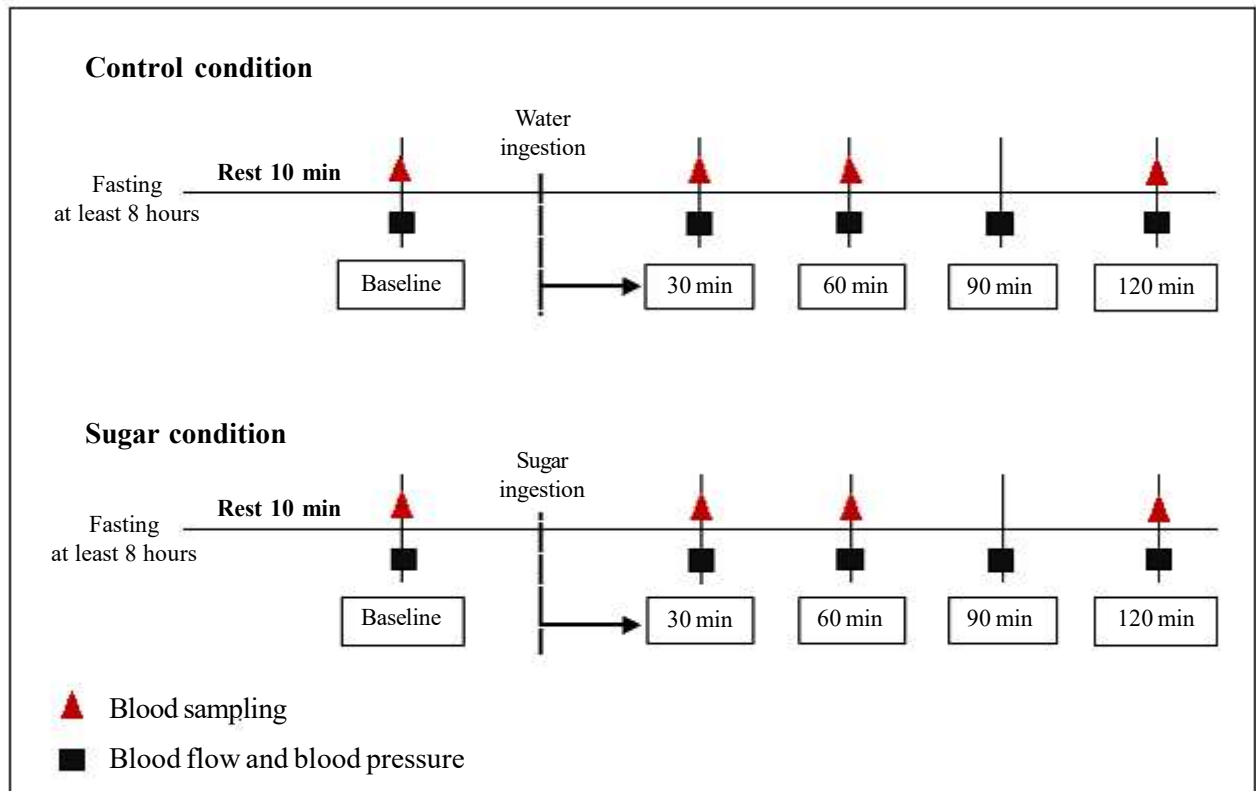

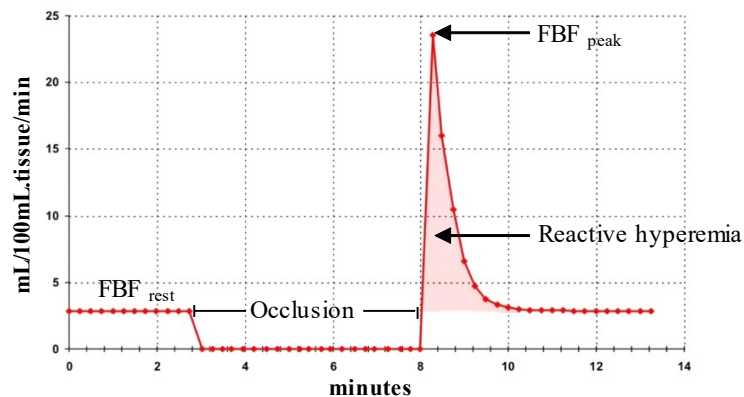**Figure 1.** Experimental protocol.

Figure 2. Reactive hyperemia.

Examination of blood pressure

Blood pressure was measured on the contralateral arm. The measurement was immediately obtained at the end of ischemia before and 30, 60, 90, and 120 minutes after sugar ingestion using an automated blood pressure measurement (BSM 6000 series, Nikon Kohden).

Blood collection and analyses

Blood samples for plasma glucose and serum insulin levels were serially drawn before and at 30, 60, and 120 minutes after ingesting sugar/water. Plasma glucose level was determined by enzymatic (Hexokinase/G-6-PDH) technique using the Alinity C (Abbott Laboratories, U.S.A.) in the accredited clinical laboratory of King Chulalongkorn Memorial Hospital. Serum insulin level was determined by Chemiluminescence immunoassay (CLIA) assay using the IMMULITE 2000 insulin (Siemens Healthcare, U.K.) in the approved center for medical diagnostic laboratories of the Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.0. All data were reported as mean ± standard deviation (SD) P - value < 0.05 was considered as statistically significant. A two-way (trial x time) analysis of variance (ANOVA) was used to assess the effects of sugar on the outcome parameters. Pairwise comparisons using the Bonferroni correction method was used to determine the differences between the two experiments and between the different times within each experiment.

Results

Baseline characteristics of 10 subjects are described in Table 1. Their baseline characteristics met the eligibility criteria.

Peak forearm blood flow

At baseline, there was no difference in FBF_{peak} between the two experimental conditions (25.2 ± 0.6 for Sugar vs 25.3 ± 0.5 mL/100 mL tissue/minute for Control, P-value > 0.99). In the Control, FBF_{peak} obtained at all time points did not change from baseline. In the Sugar, FBF_{peak} at 30 minutes (24.0 ± 0.7 mL/100 mL tissue/minute) after sugar ingestion was significantly lower when compared to baseline (25.2 ± 0.6 mL/100 mL tissue/minute, $P = 0.0002$), 90 minutes (24.8 ± 0.5 mL/100 mL tissue/minute, $P = 0.0069$), and 120 minutes (25.12 ± 0.51 mL/100 mL tissue/minute, $P = 0.0003$). FBF_{peak} at 30 minutes of Sugar showed a significant decrease when compared to Control ($P < 0.0001$) (Figure 3a).

AUC of forearm blood flow

FBF_{AUC} at baseline between the two experimental conditions was no different (Control 1703.3 ± 121.1 versus Sugar 1703.0 ± 121.8 mL/100 mL tissue/5 minutes, $P > 0.5$). FBF_{AUC} of the sugar condition at 30 minutes slightly decreased from baseline but was not significantly different (Figure 3b).

Table 1. Characteristics of the participants (n = 10).

Participant characteristics	Mean ± SD
Age (years)	25.5 ± 5.2
Weight (kg)	69.8 ± 7.1
Height (cm)	173.9 ± 6.2
BMI (kg/m²)	23.1 ± 1.7
SBP (mmHg)	115.7 ± 8.6
DBP (mmHg)	65.6 ± 6.8
Forearm circumference (cm)	25.5 ± 0.8
Fasting plasma glucose (mg/dL)	88.9 ± 3.5
Insulin (uIU/mL)	3.3 ± 1.3
Cholesterol (mg/dL)	174.8 ± 18.1
HDL-C (mg/dL)	50.3 ± 9.9
LDL-C (mg/dL)	109.4 ± 20.2
Triglyceride (mg/dL)	75.9 ± 22.3

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure,
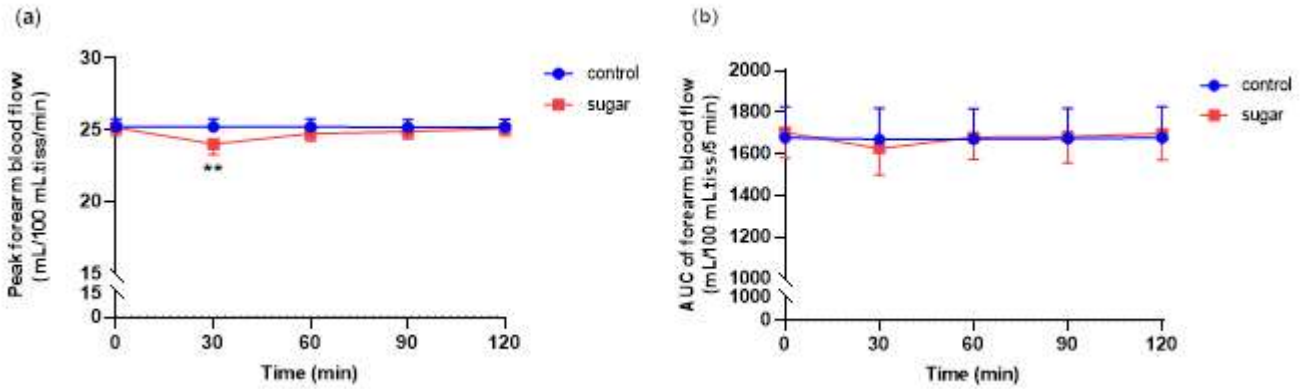HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

Figure 3. Peak forearm blood flow (FBF$_{peak}$) (a) and area under curve of FBF (FBF$_{AUC}$) (b) at baseline, 30, 60, 90 and 120 minutes after ingestion of water (control condition) or sugar solution (sugar condition). Values are means ± SD. (●) indicate control condition. (■) indicate sugar condition, **$P < 0.005$ compared to baseline, 90, and 120 minutes after sugar ingestion.

Plasma glucose level

There was no difference in the plasma glucose levels at baseline between the two experimental conditions (Control 78.8 ± 5.7 versus Sugar 80.2 ± 7.3 mg/dL, $P > 0.99$). The plasma glucose level of the Sugar at 30 minutes was significantly increased from the baseline (106.0 ± 11.2 vs. 81.3 ± 6.3 mg/dL, $P < 0.0001$) then returned to non-significantly different levels from the baseline at 60 minutes and 120 minutes (Figure 4a). In the Control, glucose levels were not significantly altered during the 2-hour course of experiment.

Serum insulin level

Between the two experimental conditions, there was no difference in serum insulin levels at baseline (Control 3.3 ± 1.3 versus Sugar 4.0 ± 1.9 uIU/mL, $P > 0.99$). In the sugar condition, serum insulin level at 30 minutes was significantly higher than the baseline (14.0 ± 7.1 vs. 4.0 ± 1.9 uIU/mL, $P < 0.0001$), whereas the levels at 60 and 120 minutes were not different from baseline (Figure 4b). In the Control, serum insulin levels did not change during the 2 hours of experiment.
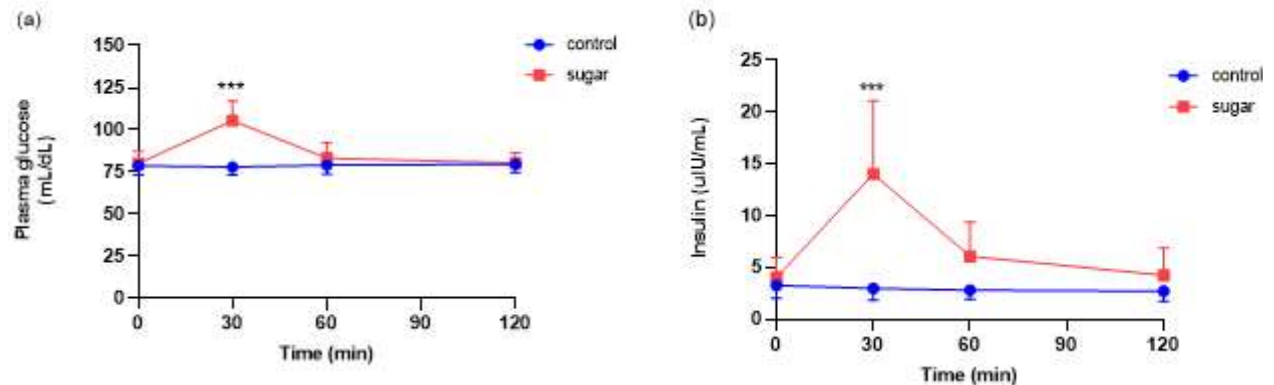

Figure 4. Plasma glucose (a) and serum insulin levels (b) at baseline and 30, 60, 90 and 120 min after sugar ingestion in control and sugar condition. Values are means ± SD. (●) indicate control condition. (■) indicate sugar condition, ***$P < 0.0001$ compere to baseline, 60, and 120 minutes.

Blood pressure

At baseline, there was no difference in systolic and diastolic blood pressure between the two experimental conditions. There was no difference between any time points within each condition.

Discussion

In the present study, the acute effect of low sugar ingestion on the forearm blood flow was investigated in healthy men. The main finding was that peak forearm reactive blood flow decreases within 30 minutes following ingestion of 15 grams of sugar. The impaired peak vasodilation corresponds with the increase of plasma glucose. Insulin levels also responds well to low amount of sugar ingestion. The present study highlighted the detrimental effect of low amount sugar and slight hyperglycemia on vascular function. Although the impairment transiently occurs, low amounts of sugar would normally be exposed by population in their daily lives. It is possible that repeatedly consumption of sugar even at low amounts may contribute to development of future vascular disorder in apparently healthy individuals.

Hyperglycemia has been reported to be involved in impaired vascular function and changes in blood vessel structure[23, 24], which lead to further CVD in the long term.[25, 26] In diabetic patients with chronic hyperglycemia, vascular endothelium is exposed to the long periods of high blood glucose levels or recurrent glycemic fluctuations.[27] Such events promoted metabolic and hemodynamic abnormalities including, the increased formation of advanced glycation end products (AGEs), increased reactive oxygen species (ROS) production, stimulation of protein kinase C (PKC) and the polyol pathway, and activation of the renin-angiotensin system (RAS).[28] Hyperglycemia has been suggested to play an important role in diabetes related artery damage and vascular complications.[29] In healthy people, vascular function impairment was induced by acute or postprandial hyperglycemia.[2, 3, 26] Many studies have suggested that acute hyperglycemia increases oxidative stress, which reduces nitric oxide (NO) production or bioavailability, a major contributing factor of vascular dysfunction.[4, 30] However, the clear mechanism of acute hyperglycemia induced vascular dysfunction is not completely understood.

Venous occlusion plethysmography is commonly used to assess limb blood flow in resting condition and at high rates of arterial inflow.[31] Reactive hyperemia induced by transient arterial occlusion was used as a vascular dilating capacity indicator in this study. According to a previous study [32], reactive hyperemia appears as a peak stimulus for FBF_{peak} and that quickly decays over time. Although the mechanism underlying reactive hyperemia has not been thoroughly revealed, evidence suggested that several factors may be involved. During reactive hyperemia, there is an increase in blood flow as a result of a combination of local myogenic response[33], shear stress[33, 34], and accumulation of endothelium-produced vasodilator chemicals such as nitric oxide, adenosine, prostaglandins, potassium, and endothelial hyperpolarizing factors.[34] Impaired vasodilating function induced by hyperglycemia has been subject to intense investigation.[35] Most studies have investigated high-dose glucose, and found that 75 grams of oral glucose successfully induced hyperglycemia and subsequently reduced FMD.[8, 9, 16] Furthermore, FBF_{AUC} during reactive hyperemia, another indicator of vasodilatory function, was impaired after 75 grams of oral glucose loading.[20] In this study, we reported that sugar ingestion even at low dose was able to decrease FBF_{peak} measured at 30 minutes after the ingestion. As plasma glucose has a relationship with blood viscosity[36], with an increased plasma glucose causing high viscosity and a decrease in shear rate on the arterial wall[37], this may explain elevated blood glucose induced by low sugar ingestion resulting in reduced FBF_{peak} after arterial occlusion in the present study. Although we demonstrated that FBF_{peak} was reduced, FBF_{AUC} remained unchanged with 15 grams of sugar ingestion. The discrepancy between the two outcome parameters was possibly due to the low dose of sugar utilized in the present study and the underlying biological function of the two measures. Generally, FBF_{peak} reflects the rate of peak arterial inflow of the forearm during the largest dilation of vascular wall while FBF_{AUC} reflects the total amount of blood flow regain over a 5-minute period of vasodilation in response to transient ischemia.

In a prior study, patients with the cardiovascular disease showed a lower forearm blood flow in response to intravenous acetylcholine infusion, indicating impaired endothelial mediated vasodilation associated with a reduction in nitric oxide release.[38] The long-term or repeated high-dose sugar consumption can impair vasodilation function and promote development of atherosclerosis.[39] The

present study employed a low-dose sugar ingestion inducing a transient impairment in vasodilating function, as determined by FBF_{peak}, which could be regarded as a physiologic response. A repetitive, low-dose sugar consumption during the day and long-term exposure to sugar may have a pathophysiologic contribution to atherosclerosis.

There were some limitations to the present study. First, only one amount of low sugar is determined, the effect of other amounts of sugar ingestion are not known. Second, the authors only investigated the effects of low sugar in the short term; thus, the long-term effects were not considered. Next, we only measured forearm blood flow at 30-minute intervals; thus, FBF_{peak} during reactive hyperemia were only obtained at the specified time points. Unassessed FBF_{peak} between the intervals were unknown. Finally, to eliminate the confounding effects of female hormones on vascular function, only male subjects were selected for this study.[40] Thus, the findings may be limited when applied to female and other populations.

Conclusion

In healthy subjects, low sugar consumption impaired vasodilating function by reduced peak forearm blood flow. This vascular impairment occurs simultaneously with elevated plasma glucose.

Acknowledgements

Conflict of interest

The authors, hereby, declare no conflict of interest.

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