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Original article

Capsaicin-containing chili improved postprandial hyperglycemia, hyperinsulinemia, and fasting lipid disorders in women with gestational diabetes mellitus and lowered the incidence of large-for-gestational-age newborns

Li-Jia Yuan [a, d], Yu Qin [a], Lin Wang [b], Yuan Zeng [a], Hui Chang [a], Jian Wang [c], Bin Wang [a], Jing Wan [a], Shi-Hui Chen [a], Qian-Yong Zhang [a], Jun-Dong Zhu [a], Yong Zhou [a, *], Man-Tian Mi [a, *]

[a] Chongqing Medical Nutrition Research Center, Chongqing Key Laboratory of Nutrition and Food Safety, Research Center for Nutrition and Food Safety, Institute of Military Preventive Medicine, Third Military Medical University, No. 30, Gaotanyan Street, Sha Pingba Distract, Chongqing 400038, China
[b] Department of Gynecology and Obstetrics, Southwest Hospital, Third Military Medical University, China
[c] Department of Nutrition, Xin Qiao Hospital, Third Military Medical University, China
[d] Department of Clinical Nutrition, No. 44 Hospital of the People's Liberation Army, China

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SUMMARY

Background & aims: Gestational diabetes mellitus (GDM) may increase the future health risks of women and their offspring. The aim of this study was to determine the effect of capsaicin supplementation on blood glucose, lipid metabolism and pregnancy outcomes in women with GDM.
Methods: Forty-four pregnant women with GDM at 22–33 gestational weeks were randomly assigned to the capsaicin group (5 mg/d of capsaicin) or to the placebo group (0 mg/d of capsaicin) for 4 weeks in a randomized, double-blind, placebo-controlled trial. The concentrations of fasting plasma glucose and serum insulin, 2-h postprandial plasma glucose (2-h PG) and serum insulin (2-h INS), and fasting serum lipids, liver and kidney function parameters, and calcitonin gene-related peptide (CGRP) were measured at 0 and 4 weeks. The maternal and neonatal outcomes were also recorded.
Results: Forty-two women completed the trial. Compared to the placebo group, 2-h PG and 2-h INS concentrations and 2-h postprandial HOMA-IR (2-h HOMA-IR) levels, and the fasting serum total cholesterol and triglycerides concentrations significantly decreased in the capsaicin group after treatment ($P < 0.05$). Moreover, the fasting serum apolipoprotein B and CGRP concentrations significantly increased in the capsaicin group ($P < 0.05$). The changes in the 2-h PG and 2-h INS concentrations and in the 2-h HOMA-IR were negatively correlated with the change in the serum CGRP concentration ($P < 0.05$). Furthermore, the incidence of large-for-gestational-age (LGA) newborns was significantly lower in the capsaicin group than in the placebo group ($P = 0.022$).
Conclusions: Capsaicin-containing chili supplementation regularly improved postprandial hyperglycemia and hyperinsulinemia as well as fasting lipid metabolic disorders in women with GDM, and it decreased the incidence of LGA newborns.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized in pregnancy. The expected GDM incidence has been 16%–18% of pregnancies worldwide [1]. GDM may increase future health risks for affected women and their offspring [2]. Excessive mother-to-fetus glucose transfer in pregnant women with GDM could cause adverse

Abbreviation: 2-h HOMA-IR, 2-hour postprandial HOMA-IR; 2-h INS, 2-hour postprandial serum insulin; 2-h PG, 2-hour postprandial plasma glucose; ADA, American Diabetes Association; CGRP, calcitonin gene-related peptide; GDM, gestational diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LGA, large for gestational age; SGA, small for gestational age.

* Corresponding authors. Tel.: +86 23 68752292; fax: +86 23 68752642.
E-mail addresses: zhouyongtmmu@outlook.com (Y. Zhou), mimantian@hotmail.com (M.-T. Mi).

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neonatal outcomes [3,4]. For example, compared to unaffected newborns, the incidence of large-for-gestational-age (LGA) newborns was higher if their mothers had GDM. Newborns with LGA who reach adulthood may be susceptible to diabetes and other diseases. Thus, the regulation of blood glucose concentrations in women with GDM is particularly important.

Because the use of oral hypoglycemic agents may lead to several adverse effects [5–7], most women with GDM have received insulin treatment [7]. Importantly, the adjustment of suboptimal diet and lifestyle habits has been the primary therapy for GDM and an important adjunctive treatment in insulin-dependent GDM [8].

Supplementation with certain phytochemicals such as polyphenols or natural plant foods rich in these phytochemicals may be effective in improving human glucose and lipid disorders. Capsaicin, which is primarily contained in chili, exerts multiple pharmacologic and physiologic effects, such as analgesia, and anticancer, anti-inflammation, antioxidant and anti-obesity activities [9]. Moreover, capsaicin contained in chili may also reduce postprandial blood glucose and improve insulin resistance, although it did not prove to alter fasting plasma glucose in healthy humans in 1 clinical trial [10,11]. Capsaicin may exert the above effects through the release of neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), and other neurokinins from sensory nerve terminals [12].

To our knowledge, GDM mainly manifests as glucose metabolism disorders caused by insulin resistance. The hypothesis presented in this study is that an intervention of capsaicin contained in chili would improve the insulin resistance as well as glucose and lipid metabolism profiles in women with GDM, in addition to maternal and neonatal outcomes. Thus, in the current study, we conducted a randomized clinical trial of recruited women with GDM to assess the effects of regular chili consumption for four weeks on metabolic and pregnancy outcomes.

2. Materials and methods

2.1. Subjects

Between April 1 and June 30, 2012, eighty pregnant women with GDM were screened at the Southwest Hospital of the Third Military Medical University, Chongqing, China. Ultimately, 44 eligible women with GDM were recruited into the study. According to the diagnostic criteria recommended by the American Diabetes Association (ADA) in 2011, GDM was diagnosed in pregnant women with fasting blood glucose concentrations higher than 5.1 mmol/L, or 1-h postprandial blood glucose concentrations higher than 10.0 mmol/L, or 2-h postprandial blood glucose concentrations higher than 8.5 mmol/L. Other inclusion criteria were pregnancy with a single fetus between 22 and 33 weeks of gestation; a BMI before pregnancy of between 18 and 30; and an unsuccessful prior lifestyle intervention including diet (without capsaicin) and exercise that lasted for 2 weeks. Pregnant women were excluded if they had one of the following conditions: women with a known or self-reported history of diabetes or heart, renal, or hepatic disease; a fetal anomaly; gestational hypertension; preeclampsia; fetal growth restriction; ruptured membranes, or the consumption of prescription medications for the treatment of GDM.

2.2. Study design

This study was a randomized, double-blind, placebo-controlled clinical trial. Eligible women were randomly assigned to the capsaicin ($n = 22$) or to the placebo group ($n = 22$). The randomization sequence was developed by an individual who was otherwise not involved in the trial using a computer-generated list, and was sealed until the study completion. All participants, care providers, and those who were assessing outcomes were blinded to the randomization sequence. The total duration of the trial was 4 weeks. This study was approved by the ethics committee of the Third Military Medical University, and each participant provided written informed consent. All procedures were conducted in accordance with the institutional guidelines and in compliance with the Helsinki Declaration. This trial was registered at the Chinese clinical trial registry as ChiCTR-TRC-12002193.

Before enrolling in the trial, all women accepted submission to a general physical examination and all provided health- and diet-related information. A food-frequency questionnaire including 118 food types was completed for each woman before the trial. At baseline and at the end of the trial, all of the women were asked to complete a 3-day record of their food intake, which was analyzed using the nutrition system of Chinese traditional medicine combined with Western medicine (2011) software (Dong Chen, Qingdao, China) to estimate daily energy and nutrient intake. After the 4-week intervention, all of the women attended our facility where the remaining chili powder and the related health information were collected.

2.3. Interventions

Every woman received medical nutrition therapy including an individualized recommended intake of daily energy according to the ADA and was encouraged to increase her daily physical activities. Additionally, women were instructed to consume 0.625 g of chili powder twice daily (total: 1.25 g per day) at lunch and dinner, respectively, for 4 weeks. In the capsaicin and the placebo groups, the chili powders were made from crushed *yanjiao 425* (one type of pop pepper; capsaicin content 4 mg/g) and *xingjiang sweet* (*Capsicum annuum* L, without capsaicin), respectively. The total capsaicin intake doses of women in the capsaicin and the placebo groups were 5 and 0 mg capsaicin per day, respectively. Both chili powders were packaged in unsealed aluminum foil bags. The dose of capsaicin used in the current trial was determined based on recent human and animal studies [10,13–15]. In a human study, a daily intake of 33 mg of capsaicin for 4 weeks was shown to be safe and effective in improving the attenuation of postprandial hyperinsulinemia and the inflammatory response in healthy humans [10,15]. Moreover, a single intake of 0.4 mg of capsaicin slightly increased glucose absorption and glucagon release in healthy humans [14]. In Mexico, the daily intake of capsaicin was 90–250 mg in high-capsaicin consumers who ate approximately 9–25 jalapeño peppers per day, and less than 30 mg in low consumers who ate less than 3 jalapeño peppers per day [16]. In Americans who consumed spicy foods more than 3 times every week, the mean daily intake of capsaicin was 3.6 mg [17]. Most of the Chongqing, China population consumed more than 3 dry red pod peppers (i.e., 3 g) daily. However, no clinical study has been conducted in pregnant women to our best knowledge. In an animal study, the gestating rats that consumed 7.5 mg of capsaicin per day (i.e., 30 mg/kg) for 55 days did not demonstrate a delayed thermonociceptive response of their offspring [18]. With respect to a safety factor set at 100, a dose of 18 mg capsaicin may be safe for pregnant women. However, in our previous pilot trial, 5 of 8 pregnant women were not tolerant of 2.5 g of dry red pepper powder that contained 10 mg capsaicin given daily for 2 weeks due to serious abdominal pain and diarrhea. Thus, a capsaicin dose of 5 mg was chosen for the current study.

2.4. Anthropometric measurements

Body weight was measured using electronic scales, with subjects wearing light clothing. Height was measured using a

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stadiometer. Fundal height and abdominal circumference were measured using a soft ruler. The fetal heart rate was measured using a fetal electrocardiograph monitor. Blood pressure was measured using an Omron digital sphygmomanometer (model T9P; Omron Healthcare Co., Ltd, IL, USA).

2.5. Maternal and neonatal outcome parameters

All maternal and neonatal outcome parameters were measured immediately after birth by the hospital midwives. Maternal outcomes included preeclampsia, postpartum hemorrhage, preterm birth, polyhydramnios and cesarean delivery. Preeclampsia was diagnosed when blood pressure was ≥140/90 mmHg, together with the presence of proteinuria (urinary protein ≥300 mg in a 24-h period or ≥ 1 ± by urine dipstick). Preterm birth was defined as occurring between 28 and 37 weeks of gestation in which the delivery was the result of the spontaneous onset of delivery. Neonatal outcome parameters included LGA or small-for-gestational-age (SGA) newborns, Apgar scores, hyperbilirubinemia, and hypoglycemia. LGA or SGA newborns were newborns whose birth weight was above the 90th percentile or below the 10th percentile adjusted for gestational age.

2.6. Blood variables

Plasma glucose, serum lipids, alanine aminotransferase, aspartate transaminase, urea nitrogen, creatinine and calcium were analyzed using a blood biochemical analyzer (AU2700; Olympus, Japan). Plasma glucose, serum total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations were measured using enzymatic reagents (BioSino Bio-Technology and Science Inc., China). Serum apolipoprotein AI and B, insulin, glycated albumin and C-peptide were measured by radioimmunoassay using commercially available kits (Chongqing Keyuan Medical Equipment Co., LTD, China). Serum uric acid concentrations were tested by a direct enzyme method (BioSino Bio-Technology and Science Inc., China) using the analyzer cited above. Serum lipoprotein $_{(a)}$ concentrations were assayed by a turbidimetric immunoassay (Ausbio Bio-Technology Inc., China) also using the stated analyzer. The serum C-peptide, glucagon, and CGRP concentrations were measured using enzymatic reagents (R&B, LTD, USA) according to the manufacturer's instructions. The inter- and intra-assay CVs for all of the above parameters were < 6%.

2.7. Data analysis

The primary outcomes of the current trial were the fasting plasma glucose and 2-h PG concentrations. The significance level was set at 0.05, statistical power was set as 0.80, and 2-tailed tests were used to estimate the sample size. This trial was designed to detect a 1.0 ± 0.5 mmol/L or 2.0 ± 1.5 mmol/L respective reduction in the fasting plasma glucose or 2-h PG concentrations after a 4-week intervention of capsaicin-containing chili, compared to a 0.2 ± 0.5 mmol/L or 0.5 ± 1.5 mmol/L respective reduction in the fasting plasma glucose or 2-h PG concentrations after a chili intervention that did not contain capsaicin. It was estimated that a sample size of 40 was sufficient to test the primary fasting plasma glucose and 42 to test for the 2-h PG hypotheses while allowing for a 20% dropout rate.

The data are presented as the means ± SD if they followed a normal distribution, or as medians (interquartile range) if they did not. Variables that deviated from normality were logarithmically transformed before statistical analyses. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as (fasting glucose concentrations × fasting insulin concentrations)/22.5. The change in each parameter equaled the difference of the values at 4 weeks from the values at baseline.

The differences in all variables between the two groups at baseline and at the end of the trial were tested using independent t-tests. The effects of the interventions were assessed by one-factor ANCOVA with the change at 4 weeks from baseline considered to be the dependent variable and the baseline value considered to be the covariate (Model 1). The effects of the interventions were also tested by one-factor ANCOVA after adjusting for age, gestational age, BMI and the corresponding parameter levels at baseline, and energy intake during the trial (Model 2). Pearson's correlation coefficients were calculated to evaluate the relationships between the changes in 2-h postprandial plasma glucose (2-h PG) and serum insulin (2-h INS), 2-h postprandial HOMA-IR (2-h HOMA-IR), total cholesterol, triglycerides, apolipoprotein B, and serum CGRP. Differences in the maternal and neonatal outcomes were tested by Chi-squared test or Fisher's exact test when needed. The P values reported were 2-sided and were considered to be significant when $P < 0.05$. All analyses were performed using IBM SPSS Statistics 19.0 (IBM, Japan).

3. Results

3.1. Baseline characteristics and mean daily nutrient intake of the women with GDM

Two participants in the capsaicin group withdrew from the study because they experienced mild diarrhea. Forty-two participants completed the study, including 20 and 22 women in the capsaicin and the placebo groups, respectively. The rates of the intervention power consummation were 98.6% and 97.9% in the capsaicin and placebo groups, respectively. The compliance of this trial was good. Except for the mild diarrhea that occurred in 2 women, other side effects in the capsaicin group included a heat sensation in the oral cavity (4 women), skin wheals that subsequently resolved (2 women) and increased frequency of defecation at the beginning of the trial, which then reverted to normal frequency after 2 or 3 days (6 women). No side effects were reported in the control group.

No differences were found for age, weight and BMI before pregnancy and at baseline, and the gestational age of the women with GDM between the two groups (Table 1). No differences were observed in the blood pressure, fundal height, and abdominal circumference of the women with GDM, as well as the fetal heart rate between the groups at baseline. After the 4-week trial, the above routine obstetric examination indicators were not significantly changed (Table 2).

Additionally, no differences in the mean daily energy and nutrient intake of the women with GDM were observed between the groups (Table 3).

3.2. Blood chemistry and metabolic outcomes of the women with GDM

At baseline, there were no significant differences in the blood glucose metabolism, serum lipids, and the liver and kidney functional parameters between the two groups (Table 1). Compared to the placebo group, the 2-h PG, 2-h INS and 2-h HOMA-IR of the GDM women were significantly reduced by 1.95 ± 1.64 mmol/L (mean ± SD), 13.96(5.54, 19.9) IU/L and 5.47 (1.95, 10.34) [median(interquartile range)], respectively in the capsaicin group after the 4-week intervention ($P < 0.05$). Additionally, the serum CGRP concentration in the GDM women were significantly increased to a greater degree in the capsaicin group than in the placebo group ($P < 0.05$).

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Table 1
General characteristics, obstetric conditions, glucose metabolism, liver and kidney function, and lipids of women with GDM at baseline.[a]

	Capsaicin (n = 20)	Placebo (n = 22)	*P*
Age (y)	31.1 ± 4.4	29.8 ± 4.5	0.36
Gestational age (weeks)	27.7 ± 3.3	27.7 ± 3.2	0.95
Height (cm)	158 ± 5	159 ± 3	0.59
Weight before pregnancy (kg)	58.4 ± 10.1	57.8 ± 9.8	0.85
BMI (kg/m^2) before pregnancy	23.2 ± 3.4	22.8 ± 3.8	0.73
Weight (kg) at trial entry	68.2 ± 9.5	68.4 ± 10.0	0.94
BMI (kg/m^2) at trial entry	27.1 ± 3.2	27.0 ± 3.8	0.91
Obstetric conditions			
Systolic blood pressure (mm Hg)	108 ± 12	113 ± 13	0.26
Diastolic blood pressure (mm Hg)	74 ± 8	71 ± 7	0.23
Fundal height (cm)	27.2 ± 2.9	27.9 ± 2.5	0.40
Abdominal circumference (cm)	99.0 ± 6.5	96.4 ± 5.7	0.18
Fetal heart rate (beats/min)	138 ± 9	142 ± 8	0.11
Glucose metabolism			
Fasting plasma glucose (mmol/L)	5.43 ± 0.65	5.25 ± 0.44	0.28
Fasting serum insulin (IU/L)	3.04(2.14, 6.61)	2.34(1.2, 4.43)	0.13
Fasting HOMA-IR	0.79(0.51, 1.59)	0.52(0.29, 1.03)	0.10
2-h PG (mmol/L)	7.83 ± 1.66	7.65 ± 1.58	0.72
2-h INS (IU/L)	23.25(12.6, 33.41)	18.02(9.38, 23.68)	0.24
2-h HOMA-IR	7.74(3.74, 12.94)	6.17(3.05, 9.34)	0.20
C-peptide (ng/mL)	2.10 ± 0.68	1.76 ± 0.49	0.08
Glucagon (pg/mL)	16.91 ± 8.15	15.92 ± 6.46	0.66
Glycated albumin (%)	10.31 ± 1.32	9.91 ± 1.02	0.29
CGRP (pg/mL)	7.19(4.12, 14.82)	7.64(4.95, 13.05)	0.98
Liver and kidney function			
Alanine aminotransferase (U/L)	22.0 ± 5.0	24.5 ± 7.8	0.23
Aspartate transaminase (U/L)	35.3 ± 11.3	39.9 ± 6.7	0.11
Uric acid (μmol/L)	247 ± 61	248 ± 40	0.97
Urea nitrogen (mmol/L)	3.05 ± 0.54	3.47 ± 0.87	0.07
Creatinine (μmol/L)	47.6 ± 7.1	44.5 ± 7.0	0.17
Ca++ (mmol/L)	1.75 ± 0.16	1.82 ± 0.23	0.27
Lipids			
Total cholesterol (mmol/L)	6.03 ± 1.03	5.78 ± 1.04	0.48
Triglycerides (mmol/L)	3.87 ± 1.10	3.36 ± 0.82	0.10
LDL-cholesterol (mmol/L)	2.75 ± 0.66	2.80 ± 0.68	0.81
HDL-cholesterol (mmol/L)	1.65 ± 0.29	1.63 ± 0.30	0.86
Apolipoprotein A-I (g/L)	2.00 ± 0.25	1.99 ± 0.26	0.92
Apolipoprotein B (g/L)	1.30 ± 0.10	1.30 ± 0.14	0.95
Lipoprotein $_{(a)}$ (g/L)	178 ± 26	164 ± 26	0.10

[a] Values are the means ± SD or medians (interquartile range). Abbreviations: 2-h HOMA-IR: 2-h postprandial HOMA-IR; 2-h INS: 2-h postprandial serum insulin; 2-h PG: 2-h postprandial plasma glucose; CGRP: calcitonin gene-related peptide; GDM: gestational diabetes mellitus; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

At the end of the trial, the serum total cholesterol and triglyceride concentrations of the GDM women were significantly decreased to a greater degree (1.21 ± 1.64 and 1.12 ± 1.20 mmol/L, respectively) in the capsaicin group than in the placebo group after being adjusted for several variables ($P < 0.05$, Model 2). Meanwhile, the serum apolipoprotein B concentration of the women with GDM was slightly increased in the capsaicin group after the 4-week intervention. No differences between the two groups were observed with respect to other blood chemistry results after 4 weeks.

Additionally, the change in the 2-h PG and 2-h INS concentrations, and the 2-h HOMA-IR levels were negatively correlated with the change in CGRP concentration ($r = -0.399$, -0.380 and -0.430, respectively, and $P = 0.009$, 0.013 and 0.005, respectively). Nevertheless, no correlation was noted between the changes in the serum lipids and the serum CGRP concentrations.

3.3. Maternal and neonatal outcomes of the trial

There were no significant differences in the maternal outcomes between the two groups (Table 4). Among the newborns, the proportion of LGA newborns was lower in the capsaicin group than in the placebo group (1 in 20 and 8 in 22, respectively, $P = 0.036$). No significant differences were observed between the groups with regard to the proportion of SGA newborns, Apgar scores, hyperbilirubinemia and newborn hypoglycemia.

4. Discussion

In the current study, the important findings were that capsaicin consumption for 4 weeks effectively improved postprandial blood glucose metabolism and fasting lipid metabolism in women with GDM, and interestingly lowered the incidence of LGA newborns.

Insulin resistance is the primary etiology for GDM [2]. In the current study, capsaicin supplementation improved the postprandial hyperglycemia and hyperinsulinemia, but did not influence the fasting plasma glucose and insulin concentrations, or insulin resistance in women with GDM. These findings were similar to many previous studies performed in healthy humans [10,11,13,14]. Ahuja KD and colleagues performed a clinical trial in 36 healthy persons and indicated that the consumption of chili-containing meals for 4 weeks may attenuate postprandial hyperinsulinemia [10], whereas it did not change the fasting glucose and insulin concentrations [11]. The mechanisms underlying the beneficial effects of capsaicin on postprandial blood glucose and insulin may be via increasing glucose absorption from the gastrointestinal tract and increasing glucagon release [14]. Importantly, this study was the first to report this healthful effect of capsaicin or chili on postprandial glucose regulation in women with GDM.

Furthermore, the present study confirmed the beneficial effects of regular consumption of capsaicin-containing chili on the lipid metabolism in women with GDM. However, another clinical study found that a capsaicin-containing chili intervention did not affect the lipid metabolism in healthy humans [11]. The major difference between the current study and that study was in the type of subjects who participated. Thus, capsaicin or chili consumption may be helpful for attenuating lipid disorders, but may not affect normal lipid metabolism.

Overt hyperglycemia during pregnancy is associated with significantly increased risks of adverse perinatal outcomes. In an observational hyperglycemia and adverse pregnancy outcomes study, elevated maternal blood glucose concentrations were associated with LGA newborns [2]. Moreover, treatment of mild GDM could reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders [19]. The present study demonstrated that women with GDM at between 22 and 33 weeks of gestation who were regularly supplemented with capsaicin-containing chili for 4 weeks demonstrated a significantly lower proportion of LGA newborns. Although the capsaicin-containing chili intervention did not affect other maternal and neonatal outcomes in the current study, the reduction in the incidence of LGA newborns still has important, practical significance.

Additionally, the current study demonstrated that capsaicin supplementation significantly increased serum CGRP concentrations in women with GDM, which was correlated with the effects of capsaicin on postprandial glucose regulation or insulin resistance. The serum CGRP levels are decreased in patients with diabetes mellitus and coronary artery disease [20]. CGRP has been shown to modulate glucose homeostasis by antagonizing insulin action in skeletal muscle and liver [21,22]. Thus, capsaicin perhaps improved postprandial glucose regulation or insulin resistance in women with GDM by increasing CGRP release followed by the stimulation of TRPV1. However, other studies have found a negative association between CGRP release and glucose homeostasis. Riera CE and co-workers demonstrated that the reduction of CGRP production promoted insulin secretion and metabolic health in long-lived

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Table 2
General characteristics, obstetric conditions, glucose metabolism, liver and kidney function, and lipids of women with GDM at the end of the trial.[a]

	Capsaicin (n = 20)		Placebo (n = 22)		*P*		
	4 week	Change	4 week	Change	4 week	Model 1[b]	Model 2[c]
Weight (kg)	69.0 ± 9.4	0.8 ± 0.7	69.6 ± 9.8	1.2 ± 1.0	0.83	0.15	–
BMI (kg/m^2)	27.4 ± 3.2	0.3 ± 0.3	27.5 ± 3.6	0.5 ± 0.4	0.98	0.18	–
Obstetric conditions							
Systolic blood pressure (mm Hg)	111 ± 12	2 ± 14	111 ± 13	−2 ± 14	0.89	0.79	0.71
Diastolic blood pressure (mm Hg)	71 ± 9	−2 ± 8	72 ± 6	1 ± 3	0.84	0.19	0.18
Fundal height (cm)	29.1 ± 2.1	1.9 ± 1.8	29.3 ± 2.5	1.4 ± 1.4	0.81	0.47	0.57
Abdominal circumference (cm)	103.0 ± 5.7	4.0 ± 6.0	99.4 ± 5.1	3.0 ± 4.7	0.038	0.12	0.10
Fetal heart rate (beats/min)	138 ± 9	0 ± 15	139 ± 10	−3 ± 13	0.62	0.41	0.36
Glucose metabolism							
Fasting plasma glucose (mmol/L)	5.16 ± 0.41	−0.28 ± 0.57	5.06 ± 0.39	−0.19 ± 0.43	0.45	0.79	0.85
Fasting serum insulin (IU/L)	1.95(0.81, 3.18)	−1.33(−3.48, 0.88)	2.15(1.53, 3.16)	−0.02(−2.16, 1.15)	0.81	0.60	0.59
Fasting HOMA-IR	0.44(0.16, 0.79)	−0.29(−1, 0.17)	0.52(0.33, 0.73)	−0.01(−0.6, 0.28)	0.71	0.63	0.62
2-h PG (mmol/L)	5.88 ± 0.62	−1.95 ± 1.64	7.07 ± 1.03	−0.58 ± 1.56	<0.001	<0.001	<0.001
2-h INS (IU/L)	8.04(5.34, 11.83)	−13.96(−19.9, −5.54)	17.13(14.36, 20.71)	0.23(−9.39, 5.55)	<0.001	<0.001	<0.001
2-h HOMA-IR	2.01(1.59, 2.97)	−5.47(−10.34, −1.95)	5.68(4.84, 6.44)	−0.16(−4.24, 1.4)	<0.001	<0.001	<0.001
C-peptide (ng/mL)	2.04 ± 0.79	−0.07 ± 0.6	1.99 ± 0.49	0.23 ± 0.4	0.83	0.20	0.18
Glucagon (pg/mL)	19.8 ± 9.18	2.88 ± 7.51	14.16 ± 6.66	−1.75 ± 7.53	0.027	0.19	0.31
Glycated albumin (%)	10.06 ± 1.62	−0.25 ± 1.57	10.48 ± 1.48	0.57 ± 2.13	0.38	0.36	0.54
CGRP (pg/mL)	18.08(8.9, 28.83)	8.20(5.46, 15.53)	8.75(4.94, 17.35)	2.23(−3.46, 9.79)	0.026	0.026	0.025
Liver and kidney function							
Alanine aminotransferase (U/L)	23.8 ± 7.2	1.8 ± 6.9	26.4 ± 10.0	2.1 ± 12.9	0.342	0.48	0.72
Aspartate transaminase (U/L)	40.0 ± 8.2	4.7 ± 15.8	44.3 ± 9.1	4.4 ± 10.8	0.11	0.09	0.10
Uric acid (μmol/L)	247 ± 74	0 ± 56	259 ± 63	11 ± 73	0.57	0.54	0.40
Urea nitrogen (mmol/L)	3.52 ± 0.72	0.47 ± 0.69	3.53 ± 0.92	0.06 ± 1.04	0.98	0.52	0.46
Creatinine (μmol/L)	49.7 ± 11.8	2.1 ± 9.9	44.1 ± 6.1	−0.4 ± 10.0	0.056	0.12	0.10
Ca (mmol/L)	1.77 ± 0.24	0.02 ± 0.27	1.65 ± 0.24	−0.17 ± 0.36	0.113	0.13	0.33
Lipids							
Total cholesterol (mmol/L)	4.82 ± 1.10	−1.21 ± 1.64	5.66 ± 0.94	−0.14 ± 1.23	0.011	0.012	0.011
Triglycerides (mmol/L)	2.75 ± 0.71	−1.12 ± 1.20	3.30 ± 1.03	−0.06 ± 1.41	0.052	0.063	0.039
LDL-cholesterol (mmol/L)	2.71 ± 0.53	−0.04 ± 0.43	2.76 ± 0.50	−0.04 ± 0.83	0.711	0.77	0.78
HDL-cholesterol (mmol/L)	1.62 ± 0.29	−0.03 ± 0.17	1.54 ± 0.25	−0.09 ± 0.38	0.323	0.32	0.27
Apolipoprotein A-I (g/L)	1.93 ± 0.21	−0.07 ± 0.19	1.87 ± 0.21	−0.12 ± 0.36	0.343	0.35	0.50
Apolipoprotein B (g/L)	1.35 ± 0.15	0.05 ± 0.16	1.23 ± 0.14	−0.07 ± 0.19	0.009	0.010	0.005
Lipoprotein $_{(a)}$ (g/L)	206 ± 59	28 ± 50	186 ± 50	22 ± 54	0.254	0.52	0.73

[a] Values are the means ± SD or medians (interquartile range). Abbreviations: 2-h HOMA-IR: 2-h postprandial HOMA-IR; 2-h INS: 2-h postprandial serum insulin; 2-h PG: 2-h postprandial plasma glucose; CGRP: calcitonin gene-related peptide; GDM: gestational diabetes mellitus; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
[b] Model 1: one-factor ANCOVA, with the change at 4 weeks from baseline considered to be the dependent variable and the baseline value considered to be the covariate.
[c] Model 2: Model 1 adjusted for age, gestational age, BMI and energy intake during the trial.

TRPV1 knockout mice [23]. Walker CS and colleagues reported that α-CGRP knockout mice had improved glucose homeostasis and were resistant to diet-induced obesity [24]. Gram DX et al. found that CGRP- and TRPV1-depletion in the islets of Langerhans that were induced by subcutaneously injected high-dose capsaicin improved glucose homeostasis via the increase of insulin secretion in Zucker diabetic rats [25]. These studies suggested that TRPV1 and/or CGRP might manifest dual roles in metabolic regulation [26]. Moreover, the oral intake of capsaicin also changed the gut microbial environment in high-fat-diet-fed mice [27]. In the current trial, gut and intestinal flora may also have been altered in the women with GDM. The gut microbial flora may play an important role in energy and glucose homeostasis, and in the pathogenesis of metabolic disorders such as obesity and diabetes [28]. Further studies are required to evaluate the possible mechanisms underlying the effects of capsaicin on glucose regulation in GDM, or in type 1 or 2 diabetes.

There were several limitations to the present study. First, the above beneficial effects of capsaicin-containing chili in women with GDM were observed in a small sample. More clinical trials with larger sample sizes should be conducted to support these conclusions. Second, this study was conducted in women in Chongqing, China, where much of the population generally favor chili but are not likely to consume chili during pregnancy. Thus, chili intake could be well accepted among most of the women with GDM. However, the strongly pungent and nociceptive activity of capsaicin

Table 3
Mean daily nutrient intake of the women with GDM at 0 and 4 weeks.[a]

	Capsaicin (n = 20)			Placebo (n = 22)			*P*		
	0 week	4 weeks	Change	0 week	4 weeks	Change	0 week	4 weeks	Model 1[b]
Energy (kcal/d)	2472 ± 475	2217 ± 321	−255 ± 306	2608 ± 668	2300 ± 398	−308 ± 360	0.45	0.46	0.86
Protein (g/d)	85.3 ± 19.0	94.7 ± 7.9	9.4 ± 14.3	88.2 ± 20.6	99.7 ± 11.1	11.5 ± 15.4	0.64	0.10	0.08
(% of energy)	13.9 ± 2.2	17.2 ± 1.2	3.3 ± 2.5	13.6 ± 1.8	17.5 ± 1.3	3.9 ± 2.2	0.70	0.48	0.48
Carbohydrate (g/d)	341 ± 82	275 ± 51	−66 ± 69	371 ± 106	283 ± 56	−88 ± 73	0.31	0.64	0.76
(% of energy)	55.0 ± 6.1	49.4 ± 2.6	−5.6 ± 7.0	56.7 ± 6.1	49.1 ± 1.6	−7.6 ± 6.6	0.39	0.57	0.67
Total fat (g/d)	85.2 ± 18.9	82.0 ± 11.5	−3.2 ± 14.1	85.7 ± 29.0	85.6 ± 16.0	−0.1 ± 22.4	0.94	0.41	0.32
(% of energy)	31.1 ± 4.7	33.3 ± 2.0	2.3 ± 5.4	29.7 ± 5.9	33.4 ± 1.6	3.7 ± 6.5	0.41	0.85	0.98

[a] Values are the means ± SD or medians (interquartile range). Abbreviations: GDM: gestational diabetes mellitus.
[b] Model 1: one-factor ANCOVA, with the change at 4 weeks from baseline considered to be the dependent variable and the baseline value considered to be the covariate.

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Table 4
Maternal and neonatal outcomes of the capsaicin and GDM trial.[a]

	Capsaicin (n = 20)	Placebo (n = 22)	P
Preeclampsia	2 (10.0)	4 (18.2)	0.665
Postpartum hemorrhage	1 (5.0)	2 (9.1)	1.000
Preterm birth	1 (5.0)	1 (4.5)	1.000
Polyhydramnios	1 (5.0)	0 (0.0)	0.476
Cesarean delivery	8 (40.0)	9 (40.9)	1.000
SGA	3 (15.0)	4 (18.2)	1.000
LGA	1 (5.0)	8 (36.4)	0.022
1-min Apgar score < 7	2 (10.0)	3 (13.6)	1.000
5-min Apgar score < 7	1 (5.0)	1 (4.5)	1.000
hyperbilirubinemia	4 (20.0)	3 (13.6)	0.691
hypoglycemia	2 (10.0)	2 (9.1)	1.000

[a] Data are presented as n (%). Abbreviations: GDM: gestational diabetes mellitus; LGA: large for gestational age; SGA: small for gestational age.

may limit its applications in food or medicine in other countries or districts. Capsiate, contained in nonpungent peppers, may demonstrate actions similar to capsaicin and may replace capsaicin in studying the beneficial effects in humans. Third, the women with GDM only consumed chili powder containing capsaicin for 4 weeks. Several women among those who found that their GDM had improved voluntarily bought chili containing capsaicin from markets and continued to take chili after the end of the trial. However, no information from these women including the fasting and 2-h postprandial glucose levels was recorded. Overall, a longer intervention of chili containing capsaicin may not lead to side effects, and may have beneficial effects for women with GDM and their offspring. Finally, women with GDM exhibited an improvement only in postprandial glucose homeostasis, though not in fasting glucose homeostasis in this trial. These findings may be due to the lower dose of capsaicin used, the shorter intervention duration, or the delayed onset of GDM intervention.

In conclusion, supplementation with capsaicin-containing chili for 4 weeks improved postprandial hyperglycemia and hyperinsulinemia, and fasting lipid metabolic disorders in women with GDM, and decreased the incidence of LGA newborns. The effects of capsaicin on postprandial glucose regulation were associated with increased release of CGRP. Our findings indicated that capsaicin-containing chili was beneficial in regulating the lipid metabolism and the postprandial glucose metabolism in women with GDM. All of our findings should be further confirmed in larger clinical trials.

Conflict of interest

None.

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LJY, MTM and LW designed the research; LJY, YQ, YZ, HC, J Wang, BW, J Wan, SHC, QYZ, and JDZ conducted the research; LJY, YQ and YZ analyzed the data; LJY, YQ and YZ performed statistical analyses and wrote the manuscript; YZ and MTM had primary responsibility for the final content. All authors read and approved the final manuscript. All authors declared no conflicts of interest.

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