Women's Health Bull. 2015 January; 2(1): e23258. DOI: 10.17795/whb-23258

Published online 2014 December 15. **Research Article**

The Beneficial Effects of Calcium Supplementation Plus Low-Dose Aspirin on Metabolic Profiles in Pregnant Women at Risk for Pre-Eclampsia: Randomized, Double-Blind, Placebo-Controlled Trial

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Received: September 2, 2014; **Accepted:** September 8, 2014

Background: Increased metabolic profiles during pregnancy are associated with an increasing risk for maternal and fetal morbidity and remain a significant medical challenge. To our knowledge there are no reports on the favorable effects of calcium supplementation plus aspirin on metabolic profiles among pregnant women at risk for pre-eclampsia.

Objectives: This study was designed to determine the favorable effects of taking calcium supplement plus low-dose aspirin on metabolic profiles among Iranian pregnant women at risk for pre-eclampsia.

Patients and Methods: This randomized, double-blind, placebo-controlled trial was conducted on 54 primigravida pregnant women, aged from aged 18 to 40 years with gestational age of 27 weeks and positive roll-over test. The population under study was randomly divided into two groups each including 27 subjects. The case group received 500 mg calcium supplement plus 80 mg aspirin for 9 weeks, compared with untreated placebo control group. Fasting blood samples were taken at baseline and after intervention period to measure fasting plasma glucose (FPG) and serum lipid profiles.

Results: As compared to the placebo, consumption of calcium supplement plus low-dose aspirin resulted in a significant difference in serum triglycerides levels (8.8 *vs.* 51.7 mg/dL, P = 0.03). However, no significant differences were found between case and the placebo groups regarding fasting plasma glucose (FPG), and serum total, HDL, LDL cholesterol levels. As for the placebo group, significant increases were observed in serum total cholesterol (+ 12.4 mg/dL, P = 0.01) and triglycerides levels (+ 51.7 mg/dL, P < 0.0001).

Conclusions: The consumption of calcium supplement plus low-dose aspirin for 9 weeks in pregnant women at risk for pre-eclampsia resulted in significant reduction in serum triglycerides levels compared to the placebo group, but did not affect FPG and other lipid profiles.

*Keywords:*Calcium; Supplementation; Pre-Eclampsia; Pregnant Women

1. Background

Pre-eclampsia affects about 2-8% of pregnancies (1) and is a major cause of maternal and fetal morbidity and mortality worldwide (2). Several studies have shown that from the 12th week of gestation, phospholipids, total cholesterol (LDL, HDL), triglycerides and FPG increase in response to estrogen stimulation and insulin resistance (3, 4). Glycemic disorders, insulin resistance and dyslipidemia during pregnancy are associated with increased risk of pre-eclampsia and preterm birth (3, 5, 6), which could also result in fetal macrosomia, birth trauma, fetal death and respiratory distress syndrome in the offspring (7-11), increased risk in the future for cardiovascular diseases (CVD) in the mother (12, 13) and offspring (14).

Various strategies including, but not limited to, the use of oral hypoglycemic agents (OHA) (15), insulin injections (16) and using cholesterol-lowering agents (17) during pregnancy have been suggested to manage glycemic control and lipid profiles. Furthermore, nutritional therapy including low-cholesterol, low saturated fat diets (18, 19) and the use of antioxidants, vitamins E and A (20, 21) have also been indicated to lower circulating levels of FPG and lipid profiles during pregnancy. Recently, several studies have assessed the effects of calcium supplementation and low-dose aspirin on glycemic control and serum lipid profiles among non-pregnant women (22-26). However, there are conflicting data on the effects of calcium supplementation and low-dose aspirin on serum metabolic profiles. The beneficial effects of calcium supplementation on glycemic control and serum lipid profiles might be due to improving insulin sensitivity, decreased secretion of parathyroid hormone, lower production of inflammatory factors (27, 28) and stimulation of calcium influx into adipose tissue and increased lipolysis (29). In addition, the advantageous effects of low-dose aspirin on glycemic control and serum lipid profiles might be arising from improved insulin resistance by inhibiting

hepatic NF-κB activation and TNF-α (30) and reduced lipoprotein production by hepatocytes via the reduction of apolipoprotein (a) (apo (a)) gene transcription (26). To our knowledge, no reports are available indicating the advantageous effects of calcium supplementation plus low-dose aspirin on metabolic profiles in pregnant women at risk for pre-eclampsia.

2. Objectives

The aim of the current study was, therefore, to investigate the favorable effects of calcium supplement plus low-dose aspirin treatment on FPG and lipid profiles among pregnant women at risk for pre-eclampsia.

3. Patients and Methods

3.1. Participants

This randomized, double-blind, placebo-controlled trial was carried out in Kashan, Iran, between July 2013 to November 2013. For estimating sample size, we considered type one (α) and type two errors (β) of 0.05 and 0.20 (power = 80%), respectively, and LDL-cholesterol as a key variable. Based on a previous study (24), standard deviation (SD) of LDL-cholesterol was 0.66 mmol/L and the mean difference (d) of LDL-cholesterol was 0.50 mmol/L. The sample size of 27 subjects for each group was determined using the suggested formula for parallel clinical trials. The participants in the study comprised primigravida pregnant women in their third trimester, aged from 18 to 40 and at risk for pre-eclampsia who were selected from those that attended maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran. The gestational age was assessed from the date of last menstrual period and concurrent clinical assessment (31). The women excluded from the study were those who experienced maternal severe pre-eclampsia, intra uterine fetal death (IUFD), completed bed rest (CBR), placenta abruption, preterm delivery and gestational diabetes mellitus (GDM). The risk for pre-eclampsia was determined by roll-over test (32). The roll over test induces changes in systemic blood pressure, where turning from the left lateral to the supine position results in an increase of blood pressure in both healthy and pregnant women as well as women with pre-eclampsia (33), but the magnitude of blood pressure increase is higher in pre-eclamptic women (34). The population under study was randomly divided into two groups each including 27 subjects. The case group received 500 mg calcium supplement plus 80 mg aspirin for 9 weeks, compared with untreated placebo control group. All pregnant women were taking 400 μg/d folic acid supplements from the beginning of pregnancy and 30 mg/d ferrous sulfate from the second trimester. The study was conducted according to the Declaration of Helsinki guidelines. The ethical committee of Kashan University of Medical Sciences approved the study and informed written consent was obtained from all participants.

3.2. Study Design

At the baseline study (27 weeks of pregnancy), subjects were randomly assigned to receive calcium supplement plus low-dose aspirin or placebo for 9 weeks. Participants urged not to alter their routine physical activity or usual diets and avoid consuming any supplement other than the one provided to them by the investigators. Calcium supplement, aspirin and placebo were provided by Share Darou Co, Tehran, Iran. Compliance with the consumption of supplement was monitored once a week through phone calls. The compliance was also double-checked by recording three day dietary schedule throughout the study. The Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods, was used to obtain nutrient intakes of participants, based on these three-day food timetable.

3.3. Assessment of Anthropometric Measures

Anthropometric measurements were assessed at baseline at 27 weeks of gestation, and after 9 weeks of intervention at 36 weeks of gestation. Body weight was measured after an overnight fasting, with bare feet and minimal clothing, using digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretchable tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculated as weight in kg divided by height in meters squared.

3.4. Biochemical Assessment

Following 9 weeks intervention, 10 mL early morning fasting blood samples, to be considered as baseline, were taken at Kashan reference laboratory. Plasma glucose levels were quantified by the glucose oxidase/peroxidase (GOD-POD) method using commercial kits (Pars azmun Co, Tehran, Iran). Serum total cholesterol and triacylglycerol concentrations were assayed using comercial kits (Parsazmun Co, Tehran, Iran) by enzymatic colorimetric tests with cholesterol oxidase p-aminophenazone and glycerol phosphate oxidase, respectively (35). Serum HDL-cholesterol was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungistic acid (35). Serum LDL-cholesterol levels were also determined using available kits.

3.5. Randomization

Random assignment was done using computer-generated random numbers. Randomized allocation sequence, enrolment of participants and participants assigned to interventions were conducted by a trained midwife at maternity clinic. All participants in the study were blinded with respect to calcium supplement plus low-dose aspirin consumption or placebo.

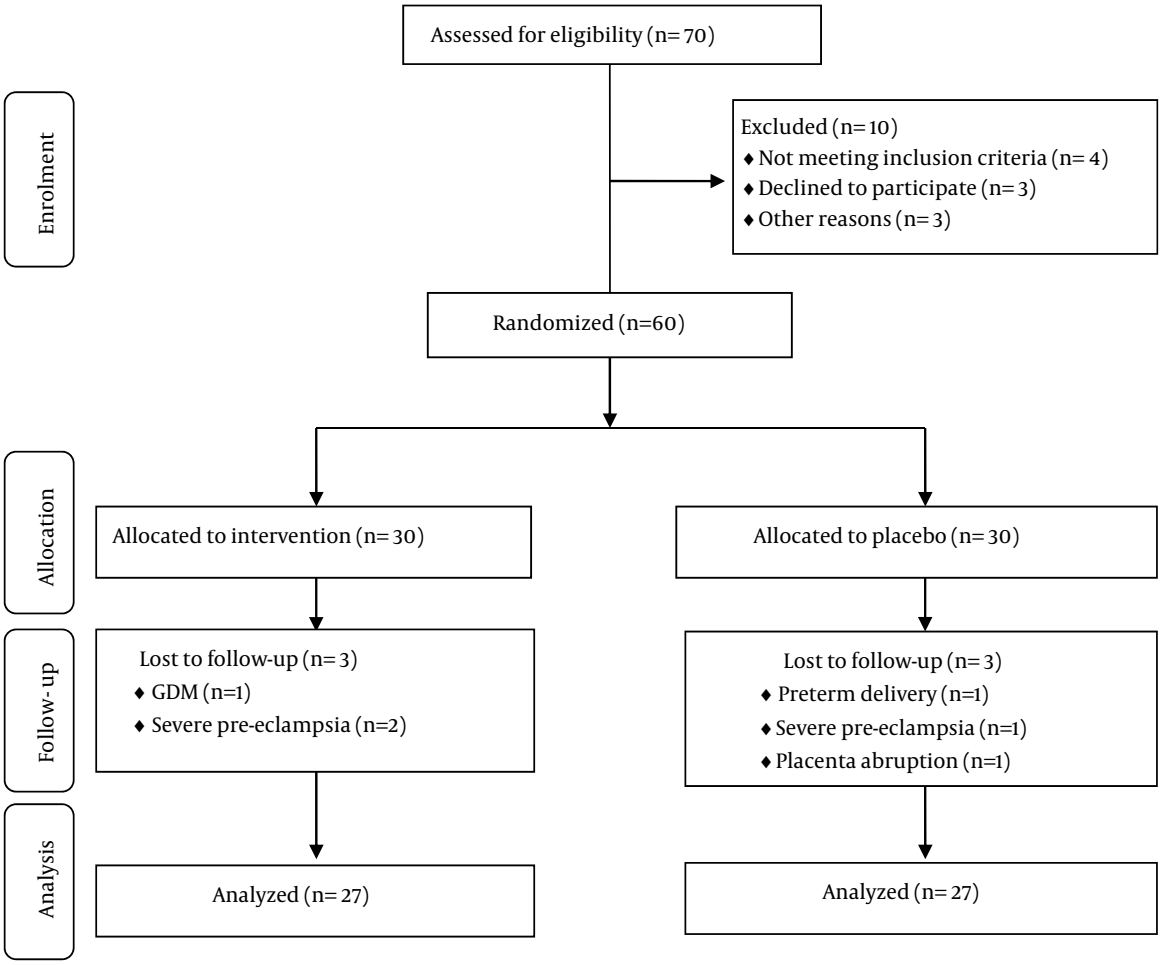

Figure 1. Summary of Patient Flow Diagram

3.6. Statistical Analysis

Histogram and Kolmogrov-Smirnov test were applied to ensure the normal distribution of variables to ensure the normal distribution of variables. The paired-samples t-tests were used to identify the differences and mean change for each variable in each group. Independent samples Student's t test was used to detect differences between groups, and $P < 0.05$ was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Illinois, USA) (Figure 1).

4. Results

Among individuals in the placebo group, 3 women of whom one had GDM and 2 had severe pre-eclampsia were excluded from the study. As for calcium supplement plus low-dose aspirin-treated group 3 women were excluded, of whom one had preterm delivery, one exhibited severe pre-eclampsia, and one suffered placenta abruption. Finally, all 54 participants including the case and placebo groups completed the trial.

There were no significant differences between the two groups regarding mean age, pre-pregnancy weight and BMI (Table 1). Similarly no significant difference was observed between the two groups with respect to the baseline weight, BMI and their means after intervention. Based on the three-day dietary records, no significant difference was shown between the two groups in terms of dietary intakes of energy, fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), cholesterol and dietary fiber (Table 2).

As shown in Table 3, consumption of calcium supplement plus low-dose aspirin resulted in a significant difference in serum triglyceride levels as compared to the placebo (8.8 *vs.* 51.7 mg/dL, $P = 0.03$). However, no significant differences were found between the case and the placebo groups in terms of FPG, serum total HDL and LDL-cholesterol levels. Moreover, there was a significant increase in serum total cholesterol and triglycerides levels (+ 12.4 mg/dL; $P = 0.01$, + 51.7 mg/dL; in the placebo group $P < 0.0001$.

Table 1. General Characteristics of the Study Participants (n = 27) [a]

Variable	Placebo Group	Calcium Plus Aspirin Group	P Value [b]
Maternal age, y	25.1 ± 3.6	26.6 ± 4.9	0.21
Height, cm	159.3 ± 6.2	161.0 ± 5.0	0.25
Pre-pregnancy weight, kg	62.6 ± 9.9	67.7 ± 10.7	0.07
Weight at study baseline, kg	67.5 ± 10.8	73.5 ± 11.6	0.06
Weight at end of trial, kg	70.7 ± 10.3	76.1 ± 10.7	0.06
Pre-pregnancy BMI, kg/m^2	24.6 ± 3.2	26.0 ± 3.6	0.13
BMI at study baseline, kg/m^2	26.6 ± 3.8	28.3 ± 3.8	0.10
BMI at end-of-trial, kg/m^2	27.8 ± 3.5	29.3 ± 3.5	0.12

[a] Data are expressed as Mean ± SD.
[b] Obtained from independent t-test.

Table 2. Dietary Intakes of Study Participants at Baseline Period and Throughout the Study (n = 27) [a, b]

Variables	Baseline Period			Throughout the Study		
	Placebo Group	Calcium Plus Aspirin Group	P Value [b]	Placebo Group	Calcium Plus Aspirin Group	P Value [c]
Energy, kcal/d	2331 ± 318	2398 ± 271	0.37	2359 ± 217	2438 ± 181	0.13
Fat, g/d	81.3 ± 15.5	84.9 ± 12.6	0.32	82.4 ± 19.2	87.2 ± 13.5	0.26
SFA, g/d	25.3 ± 5.6	24.7 ± 5.5	0.70	23.7 ± 6.9	24.8 ± 5.2	0.50
PUFA, g/d	25.2 ± 6.4	26.3 ± 6.2	0.49	27.2 ± 6.4	29.0 ± 7.7	0.32
MUFA, g/d	23.0 ± 6.4	23.8 ± 7.3	0.67	22.6 ± 8.2	22.9 ± 4.8	0.86
Cholesterol, mg/d	196.8 ± 106.5	191.6 ± 105.2	0.85	193.8 ± 135.6	217.2 ± 118.8	0.48
Dietary fiber, g/d	19.9 ± 4.6	20.8 ± 4.3	0.43	18.0 ± 5.0	19.0 ± 4.2	0.39

[a] Abbreviations: MUFA, monounsaturated fatty acid, PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.
[b] Data are expressed as mean ± SD.
[c] Obtained from independent t-test.

Table 3. Mean ± SD of FPG and Serum Lipid Profiles at Baseline and After the Intervention (n = 27) [a, b]

Variables	Placebo Group				Calcium Plus Aspirin Group				P Value [c]
	Wk0	Wk9	Change	P Value [d]	Wk0	Wk9	Change	P Value [d]	
FPG, mg/dL	74.7 ± 8.2	75.2 ± 13.5	0.5 ± 15.3	0.88	78.1 ± 18.0	74.9 ± 18.0	-3.2 ± 19.4	0.39	0.44
Total cholesterol, mg/dL	237.0 ± 46.1	249.4 ± 42.4	12.4 ± 25.6	0.01	253.7 ± 78.6	242.0 ± 47.2	-11.7 ± 83.4	0.47	0.15
Triglycerides, mg/dL	192.3 ± 52.9	244.0 ± 57.8	51.7 ± 35.0	< 0.0001	244.5 ± 100.7	253.3 ± 72.5	8.8 ± 98.4	0.64	0.03
HDL cholesterol, mg/dL	69.1 ± 19.4	69.7 ± 16.8	0.6 ± 11.7	0.80	65.9 ± 12.9	68.3 ± 16.9	2.4 ± 11.7	0.30	0.57
LDL cholesterol, mg/dL	129.4 ± 43.4	131.4 ± 43	2.0 ± 23.7	0.66	139.0 ± 66.0	125.3 ± 45.7	-13.7 ± 67.7	0.30	0.26
Total: HDL cholesterol ratio	3.6 ± 1.1	3.7 ± 0.9	0.1 ± 0.7	0.53	3.9 ± 1.2	3.7 ± 0.9	-0.2 ± 1.3	0.34	0.26

[a] Abbreviations: FPG, fasting plasma glucose; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein-cholesterol.
[b] Data are expressed as mean ± SD.
[c] Indicating group differences (independent samples t-test).
[d] Indicating group differences (paired samples t-test).

5. Discussion

Our study revealed that taking calcium supplement plus low-dose aspirin for 9 weeks among pregnant women at risk for pre-eclampsia resulted in a significant difference in serum triglycerides levels. There were no significant effect of calcium supplementation plus low-dose aspirin on FPG, serum total HDL, LDL cholesterol levels as compared to the placebo. Pregnant women are very susceptible to increased levels of lipid profiles and insulin resistance especially in the third trimester. Elevated lipid profiles and glycemic disorders during pregnancy would

result in the development of several complications including pre-eclampsia and preterm birth (5), fetal macrosomia, birth trauma and fetal death (7-11).

We did not find any significant effect of calcium supplementation plus low-dose aspirin on FPG for 9 weeks during pregnancy. In a study by Pittas et al. (36) the use of combined calcium-vitamin D supplements resulted in lower rise on FPG among participants with impaired fasting glucose compared with placebo group after 3 years. Consumption of a low-calcium (500 mg/d)/low-dairy (one serving/d) or a high-dairy (1200 mg calcium/d diet including three servings of dairy) diet did not affect fasting glucose among obese African-American adults after 24 weeks (37). There was no significant effect of calcium supplementation on fasting glucose among healthy subjects (38). The same results were obtained with consumption of whole milk and fermented milk, with the comparable fat and lactose content, on fasting glucose and insulin response (39). However, calcium supplementation showed a marked increase in serum glucose levels in animals treated with higher calcium doses after 5 weeks (40). In relation to aspirin effect on fasting glucose, Sun et al. (30) showed that administration of aspirin caused no significant reduction in fasting glucose level, but improved insulin resistance compared to the diabetic group in streptozotocin-induced type 2 diabetic rats. However, consumption of high-dose aspirin reversed hyperglycemia and hyperinsulinemia in obese rodents by sensitizing the insulin signaling (41). Different findings might be explained by the different study designs, discrepancy in subjects, different dosages of calcium supplement plus low-dose aspirin as well as duration of the study.

The current study showed that consumption of calcium supplement plus low-dose aspirin for 9 weeks during pregnancy resulted in a significant reduction in serum triglyceride, but had no effect on serum HDL and LDL cholesterol levels. In a study by Li et al. (23) consumption of calcium supplement led to a significant increase in serum HDL-cholesterol and decreased serum LDL-cholesterol levels compared with the placebo group among obese Chinese women after 26 weeks. Calcium-vitamin D supplementation including 600 mg elemental calcium and 200 IU vitamin D/tablet in healthy, overweight or obese women also showed a significant decrease in serum triglycerides and LDL-cholesterol levels after 15 weeks (24). Furthermore, a significant decrease by 16% in serum triglycerides concentrations, and an increase by 8% in serum LDL-cholesterol levels were found with consumption of vitamin D supplement compared to the placebo group (42). However, Karandish et al. (43) observed increased serum triglycerides and VLDL-cholesterol concentrations following 1000 mg/d calcium supplement intake among overweight or obese women after 30 days. The effect of an energy-restricted diet providing either 400-500 mg calcium/d from dairy products in placebo group or 1200-1300 mg calcium/d from an additional 800 mg calcium carbonate in high calcium group or from an extra 3 servings of dairy products in high dairy group in obese adults also did not affect serum LDL, HDL cholesterol and triglycerides levels after 24 weeks (44). Furthermore, consumption of aspirin has resulted in a significant decrease of serum triglycerides levels in streptozotocin-induced type 2 diabetic rats compared to the control group, but did not affect serum total LDL and HDL cholesterol concentrations (30). Administration of high-dose aspirin was also reversed dyslipidemia in obese rodents by sensitizing insulin signaling (41). Several mechanisms can explain the effects of calcium supplementation plus low-dose aspirin on decreased serum triglycerides levels. In this context, higher calcium intake may result in a decrease in fatty acid absorption and an increase in fecal fatty acid content, resulting from production of insoluble calcium-fatty soaps in the gut (45). This reduced absorption of fatty acid, especially saturated fatty acid, could result in decreased levels of serum triglycerides, and total and LDL cholesterol (46). Furthermore, increasing dietary calcium may lead to an increase in intracellular calcium in liver that stimulates microsomal triglycerides transfer protein (MTP) (47). Probably, MTP lowers the formation, secretion of VLDL and decreases the concentrations of serum triglycerides. In addition, the use of aspirin may help improve the insulin resistance (30). Increased hepatic insulin sensitivity may lead to decreased hepatic gluconeogenesis, postprandial hypoinsulinemia and decreased formation of triglycerides in the liver cells.

Several limitations must be considered in the interpretation of our findings. First of all, calcium dosage of our study was low; thus, a higher dose of calcium supplement could have resulted in greater change on serum total, LDL, HDL cholesterol levels. Secondly, we could not assess the effects of calcium supplementation plus low-dose aspirin on birth outcome. In addition, we did consider all dependent variables such as serum triglycerides, total cholesterol and HDL cholesterol as primary outcomes in the current study. Therefore, the sample size based on LDL cholesterol presented the required sample size for all other variables. Our study power was 80%, which requires further investigations including trials with larger sample size to confirm our findings.

In conclusion, consumption of calcium supplement plus low-dose aspirin for 9 weeks in pregnant women at risk for pre-eclampsia resulted in a significant change on serum triglycerides concentrations as compared to the placebo group, but could not affect FPG and serum total, HDL, LDL cholesterol levels.

Acknowledgements

The authors would like to thank Naghavi Clinic (Kashan, Iran) for their assistance in this project.

Authors' Contributions

Maryam Karamali drafted the manuscript; Zatollah Asemi carried out the statistical analysis, prepared the

manuscript and interpreted the findings. Both authors approved the final version of the manuscript.

Funding/Support

The present study was supported by a grant from the Vice-chancellor for Research, Kashan University of Medical Sciences, Kashan, Iran. The authors would like to thank Naghavi Clinic (Kashan, Iran) for their assistance throughout this study.

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