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Effect of Calcium-vitamin D Supplementation on Metabolic Profiles in Pregnant Women at Risk for Pre-eclampsia: A Randomized Placebo-controlled Trial

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Abstract: Increased metabolic profiles during pregnancy are associated with an increased risk of maternal and neonatal morbidity and remain a significant medical challenge. To our knowledge, no reports are available indicating the effects of calcium-vitamin D supplementation on metabolic profiles among pregnant women at risk for pre-eclampsia. This study was designed to determine the effects of consumption calcium-vitamin D supplements on metabolic profiles among Iranian pregnant women at risk for pre-eclampsia. This randomized single-blind controlled clinical trial was performed among 49 pregnant women at risk for pre-eclampsia, primigravida, aged 18-35 year old who were carrying singleton pregnancy at their third trimester. Subjects were randomly assigned to consume the placebo (n = 25) or calcium-vitamin D supplements (n = 24) for 9 weeks. Calcium-vitamin D supplements were containing 500 mg carbonate calcium plus 200 IU vitamin D_3. Fasting blood samples were taken at baseline and after 9 week intervention to measures of Fasting Plasma Glucose (FPG) and serum lipid profiles. Consumption of calcium-vitamin D supplements resulted in decreased FPG and serum triglycerides levels as compared to the placebo (-9.1 vs. 0.5 mg dL^{-1}; p = 0.03, -11.7 vs. 49.9 mg dL^{-1}; p = 0.001, respectively). No significant differences were found comparing calcium-vitamin D supplements and the placebo in terms of their effect on serum total-, HDL-, LDL-cholesterol levels. Within-group differences in the placebo group revealed a significant increase in serum triglycerides levels (+49.9 mg dL^{-1}, p<0.0001). In conclusion, consumption of calcium-vitamin D supplements for 9 weeks during pregnancy among pregnant women at risk for pre-eclampsia resulted in decreased FPG and serum triglycerides levels as compared to the placebo group, but could not affect serum total-, HDL-, LDL-cholesterol levels.

Key words: Calcium-vitamin D supplementation, FPG, lipid profiles, pre-eclampsia, pregnant women

INTRODUCTION

Pre-eclampsia is a multisystem disorder that its incidence ranges from 3-7% for nulliparas and 1-3% for multiparas (Uzan *et al*., 2011). It constitutes a major cause of maternal morbidity and mortality worldwide (Carty *et al*., 2010). Overall, 10-15% of maternal deaths are directly associated with pre-eclampsia and eclampsia (Duley, 2009). Due to enhanced weight and fat storage primarily during the mid-pregnancy period (Rossner and Ohlin, 1995; Saleh *et al*., 2007; Mankuta *et al*., 2010), pregnancy is associated with elevated levels of metabolic profiles (Brizzi *et al*., 1999; Belo *et al*., 2002). Earlier studies indicated that in women suffering from hypertensive disease of pregnancy, increased plasma glucose and insulin resistance associated with metabolic disturbances including dyslipidemia and hyperinsulinemia (Solomon *et al*., 1999; Girouard *et al*., 2007). Changes to lipid metabolism may be result in the endothelial lesions observed in pre-eclampsia (Bayhan *et al*., 2005). Also, it has been reported that increased lipid profiles during pregnancy would result in increased risk of Cardiovascular Diseases (CVD) in later life of the mother (Winkler *et al*., 2000; Mankuta *et al*., 2010) and in its offspring's (Kusters *et al*., 2010).

Various strategies for the management of Fasting Plasma Glucose (FPG) and lipid profiles including, but not limited to, diet therapy such as the use of low-cholesterol, low saturated fat diets (Khoury *et al*., 2007; Torres *et al*., 2010), the use of Oral Hypoglycemic Agents (OHAs) (Khattab *et al*., 2011), insulin injections (Maymone *et al*., 2011) and the use of antioxidants, vitamins E and A

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(Mehendale *et al*., 2008; Valdes *et al*., 2009) during pregnancy have been suggested. Recently, several studies in non-pregnant women have been shown that calcium and vitamin D supplementation can decrease fasting glucose and serum lipid profiles (Major *et al*., 2007; Li *et al*., 2010; Eftekhari *et al*., 2011; Naharci *et al*., 2011). However, data on the effects of calcium and vitamin D supplementation on serum metabolic profiles are conflicting (Chung *et al*., 2009; Pittas *et al*., 2010; Wang *et al*., 2010). The beneficial effects of calcium and vitamin D supplementation on FPG and serum lipid profiles might be resulted from improvement insulin sensitivity, secretion decrease of parathyroid hormone, produced decrease of inflammatory factors (Zittermann *et al*., 2005; Wang *et al*., 2012) and stimulation of calcium influx into adipose tissue and increased lipolysis (Zemel *et al*., 2000).

To our knowledge, no reports are available indicating the effects of calcium-vitamin D supplementation on metabolic profiles among pregnant women at risk for pre-eclampsia. The aim of the current study was, therefore, to investigate the effects of calcium-vitamin D supplementation on FPG and lipid profiles among pregnant women at risk for pre-eclampsia.

MATERIALS AND METHODS

Participants: This randomized single-blinded controlled clinical trial was carried out in Kashan, Iran, during April 2011 to February 2012. Pregnant women at risk for pre-eclampsia, primigravida, aged 18-35 year old who were carrying singleton pregnancy at their third trimester were recruited in this study. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment (Gupta *et al*., 2004). Individuals with the above-mentioned inclusion criteria were called for participation in the study from among those that attended maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran. Women with maternal severe pre-eclampsia, Intra Uterine Fetal Death (IUFD), placenta abortion, preterm delivery and Gestational Diabetes Mellitus (GDM) were not included in the study. A total of 54 pregnant women were recruited in the study and were randomly assigned to consumed the placebo (n = 27) or calcium-vitamin D supplements (n = 27) for 9 weeks. Among individuals in the placebo group, 2 women [(gestational diabetes (n = 1) and severe pre-eclampsia (n = 1)] were excluded. The exclusions in calcium-vitamin D supplements group was 3 persons [preterm delivery (n = 1), severe pre-eclampsia (n = 1) and placenta abortion (n = 1)]. Finally, 49 participants [placebo (n = 25) and calcium-vitamin D supplements (n = 24)] completed the trial.

Study design: Pregnant women considered as high risk for pre-eclampsia which have the following status: nulliparous women, environmental, socioeconomic factors and obesity (Sibai *et al*., 2000; Lawlor *et al*., 2005). At the baseline study (25 weeks of pregnancy), subjects were randomly assigned to receive the placebo or calcium-vitamin D supplements (500 mg carbonate calcium plus 200 IU vitamin D_3/day) for 9 weeks. Participants were asked not to alter their routine physical activity or usual diets and not to consume any supplement other than the one provided to them by the investigators. The placebo and calcium-vitamin D supplements were provided by Share Darou Co., Tehran, Iran and Darou Pakhsh Co., Tehran, Iran, respectively. Calcium-vitamin D supplements and placebo provided to subjects monthly. Placebo, which consisted of lactose, was packed in identical coded tablets to guarantee blinding. We kept all supplements in a cool temperature before using. Compliance with the consumption of supplement was monitored once a week through phone interviews. The compliance was also double-checked by the use of three day dietary records completed throughout the study.

Assessment of anthropometric measures: Anthropometric measurements were assessed at baseline (25 weeks of pregnancy) and after 9 weeks of intervention (34 weeks of pregnancy). Body weight was measured in an overnight fasting status, without shoes and in a minimal clothing state by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculates as weight in kg divided by height in meters squared.

Biochemical assessment: Fasting blood samples (10 mL) were taken at baseline and after 9 week intervention at Kashan reference laboratory in an early morning after an overnight fast. Plasma glucose levels were quantified by the use of glucose oxidase/peroxidase (GOD-POD) method (Ndububa *et al*., 1999) with commercially available kits (Parsazmun Co., Iran). Serum total cholesterol and triacylglycerol concentrations were assayed using commercial kits (Parsazmoon Co., Iran) by enzymatic colorimetric tests with cholesterol oxidase p-aminophenazone and glycerol phosphate oxidase, respectively (Pietrzak *et al*., 2009). Serum HDL-cholesterol was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungstic acid. Serum LDL-cholesterol levels were also measured using available kits.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The ethical committee of Kashan University of Medical Sciences approved the study (No: 1384-90-5-18) and informed written consent was obtained from all participants.

Statistical analysis: To ensure the normal distribution of variables, Histogram and Kolmogorov-Smirnov test were applied. We used paired-samples t-tests to identify within group differences and the mean change for each variable in the two groups. Independent samples Student's t-test was used to detect differences between groups. To obtain nutrient intakes of participants based on these three-day food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods. $p<0.05$ was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

This study compared 49 pregnant women at risk for pre-eclampsia including 24 pregnant women in calcium-vitamin D supplements group with age average of 24.9±4.2 with 25 pregnant women in the control group with the age average of 24.9±3.7 years. We found no significant differences in the mean values of age as well as pre-pregnancy weight and BMI between the two groups. Baseline weight and BMI as well as their means after intervention were not significantly different between calcium-vitamin D supplements and the placebo groups (Table 1).

Based on the three-day dietary records, no statistically significant difference was shown between the two groups in terms of dietary intakes of energy, fat, Saturated Fatty Acids (SFA), Poly Unsaturated Fatty Acids (PUFA), Mono-Unsaturated Fatty Acids (MUFA), cholesterol and dietary fiber during the run-in period and throughout the study. Paired t-test showed that there were also no significant in dietary intakes (Table 2).

Consumption of calcium-vitamin D supplements resulted in significant decreased FPG (-9.1±16 vs. 0.5±15.9 mg dL^{-1}, p = 0.03) and serum triglycerides levels (-11.7±77 vs. 49.9±34.5 mg dL^{-1}, p = 0.001) as compared to the placebo. In other markers of lipid profiles (total-, HDL-, LDL-cholesterol) no statistically significant difference was observed among pregnant women who receiving calcium-vitamin D supplements and the placebo group. Within-group differences in the placebo group revealed a significant increase in serum triglycerides levels (49.9 mg dL^{-1}, p<0.0001). Also, received calcium-vitamin D supplements revealed a significant decrease in FPG levels (-9.1 mg dL^{-1}, p = 0.01) (Table 3).

Table 1: General characteristics of the study participants

Characteristics	Calcium-vitamin D group (n = 24)	Placebo group (n = 25)	p-value
Maternal age (y)	24.9±4.2	24.9±3.7	0.97
Height (cm)	160.8±8.1	159.3±6.3	0.46
Pre-pregnancy weight (kg)	68.8±11.3	63.0±10.2	0.06
Weight at study baseline (kg)	73.6±11.2	68.0±11.1	0.08
Weight at end-of-trial (kg)	76.4±11.1	71.0±10.7	0.09
Pre-pregnancy BMI (kg m^{-2})	26.6±3.4	24.8±3.3	0.07
BMI at study baseline (kg m^{-2})	28.5±3.7	26.7±3.9	0.11
BMI at end-of-trial (kg m^{-2})	29.5±3.7	28.0±3.6	0.13

Values are Mean±SD, p-values were determined by independent t-test

Table 2: Dietary intakes of study participants at run-in period and throughout the study

	Run-in period			Throughout the study		
	Calcium-vitamin D group (n = 24)	Placebo group (n = 25)	p-value	Calcium-vitamin D group (n = 24)	Placebo group (n = 25)	p-value
Energy (kcal day^{-1})	2450.0±231	2354.0±185	0.2	2425.0±185	2384.0±205	0.43
Fat (g day^{-1})	86.0±12.7	80.5±15.8	0.15	87.3±14.3	84.4±18.4	0.52
SFA (g day^{-1})	25.4±5.3	25.6±5.7	0.93	24.4±5.3	24.2±6.9	0.89
PUFA (g day^{-1})	26.3±6.5	24.7±6.3	0.35	29.3±8.0	27.6±6.4	0.39
MUFA (g day^{-1})	24.4±7.0	22.5±6.3	0.28	22.7±5.0	23.3±8.0	0.72
Cholesterol (mg day^{-1})	201.7±105.3	205.3±105.5	0.89	215.3±124.8	202.5±136.6	0.71
Dietary fiber (g day^{-1})	21.0±4.2	19.9±4.8	0.35	19.2±4.4	18.3±5.0	0.49

Values are Mean±SD, p-values were determined by independent t-test, SFA: Saturated fatty acid, PUFA: Poly unsaturated fatty acid, MUFA: Mono unsaturated fatty acid

Table 3: FPG and serum lipid profiles at baseline and after the intervention

	Calcium-vitamin D group (n = 24)				Placebo group (n = 25)				
	Week 0	Week 9	Change	^{a}p-value	Week 0	Week 9	change	^{a}p-value	^{b}p-value
FPG (mg dL^{-1})	78.0±13	68.9±14.3	-9.1±16	0.01*	74.7±8.5	75.2±14.0	0.5±15.9	0.86	0.03^{g}
Total cholesterol (mg dL^{-1})	230.0±53	226.7±45.5	-3.3±54.3	0.76	239.5±47.0	247.9±43.2	8.4±21.4	0.06	0.33
Triglycerides (mg dL^{-1})	216.4±79.8	204.7±49	-11.7±77	0.46	197.7±51.1	247.6±57.5	49.9±34.5	<0.0001*	0.001*
HDL-cholesterol (mg dL^{-1})	71.7±14.7	70.0±12.9	-1.7±14	0.54	67.9±19.4	68.2±16.5	0.3±11.7	0.88	0.57
LDL-cholesterol (mg dL^{-1})	115.0±44.7	114.0±45.8	-1.0±47.2	0.91	132.1±44.0	130.6±44.0	-1.5±20.4	0.7	0.95
Total HDL:cholesterol ratio	3.23±0.5	3.28±0.6	0.05±0.5	0.64	3.73±1.0	3.78±0.9	0.05±0.7	0.74	0.98

Values are Mean±SD, ^{a}p-values were determined by paired t-test, ^{b}p-values were determined by independent t-test, FPG: Fasting plasma glucose, HDL-cholesterol: High density lipoprotein-cholesterol, LDL-cholesterol: Low density lipoprotein-cholesterol, *p-value indicates a significant difference at p<0.05 between both groups

DISCUSSION

Our study revealed that consumption of calcium-vitamin D supplements for 9 weeks among pregnant women at risk for pre-eclampsia resulted in a significant decrease FPG and serum triglyceride levels. We did not find any significant effect of calcium-vitamin D supplements on serum total-, HDL-, LDL-cholesterol levels as compared to the placebo.

Pregnant women are very susceptible to increased levels of metabolic profiles especially in the third trimester. Elevated metabolic profiles during pregnancy would result in the development of several complications including pre-eclampsia and preterm birth (Ghio *et al*., 2011), vascular and metabolic diseases (Berends *et al*., 2008), small for gestational age and fetal growth restriction (Horgan *et al*., 2011).

Our data was not shown any statistically significant difference between the two groups in terms of dietary intakes of fat, SFA, PUFA, MUFA, cholesterol and dietary fiber. Consuming a low-fat diet and high amounts of non-hydrogenated vegetable oils might contribute to favorable effects on glucose tolerance and improved lipid profiles. Several studies have reached modulation of blood pressure, glycemic control and serum lipid profiles with consumption of low-fat diets and edible vegetable oils (Sankar *et al*., 2005; Sudhakar *et al*., 2011). Earlier studies have also shown that consuming a low-SFA and -cholesterol diet can result in decreased lipid profiles concentrations (Nakamura *et al*., 2010; Ploumidou *et al*., 2010). Furthermore, increasing dietary intakes of fiber especially soluble fiber has also been shown to reduce serum total cholesterol concentrations independent of dietary fat intake (Brown *et al*., 1999). Such findings have also been reported in hypercholesterolemic patients (Hermansen *et al*., 2005). Increasing intakes of a high-MUFA and -PUFA diet have been shown to reduce serum lipid profiles (Ros and Mataix, 2006). The beneficial effects of dietary intakes on glycemic control and the improved lipid profiles are highly result from food composition including fat, SFA, PUFA, MUFA, cholesterol and dietary fiber. In the current study, the absent effect of dietary composition on FPG and lipid profiles could be due to similar food pattern between two groups.

Our data showed that received calcium-vitamin D supplements for 9 weeks during pregnancy resulted in significant decrease FPG levels. Several epidemiological studies have demonstrated an inverse relationship between serum calcium and vitamin D levels with fasting plasma glucose (Sanchez *et al*., 1997; Devaraj *et al*., 2011; Gagnon *et al*., 2012). In a study by Eftekhari *et al*. (2011) vitamin D supplementation attenuated the increase in 3 glycemia and increased insulin secretion among type 2 diabetes mellitus patients after 12 weeks. Also, consumption of combined calcium-vitamin D supplements had a lower rise on FPG among participants with impaired fasting glucose compared with those on placebo after 3 years (p = 0.04) (Pittas *et al*., 2007). Furthermore, treatment with vitamin D supplement resulted in a significant decrease in homeostasis model assessment of Insulin Resistance (IR), serum insulin and glucose concentrations in elderly people with impaired fasting glucose after 4.7±2.5 months (Naharci *et al*., 2011). However, supplementation with 20000 or 40000 IU/week vitamin D_3 could not improve glucose metabolism among overweight or obese Caucasian subjects after 1-year (Jorde *et al*., 2010b). Improving fasting glucose or insulin sensitivity was not seen the following injection of two doses of 100000 IU vitamin D_3 among Caucasian adults with serum 25 (OH)D <50 nmol L^{-1} (Tai *et al*., 2008). Similar results were seen with consumption of 1000 mg calcium and 400 IU vitamin D_3 supplements on fasting glucose, insulin, HOMA-IR, or development of diabetes during 7 years of supplementation among health women (De Boer *et al*., 2008). Other minor studies, mainly without control groups, have shown conflicting results (Alvarez and Ashraf, 2010). Several mechanisms can explain the benefit effects of calcium-vitamin D supplementation on decreased FPG. Consumption of calcium-vitamin D supplements may be result in an increase in insulin sensitivity and then decreased FPG, suppression of chronic inflammation and increased expression of the insulin receptor and/or proteins of the insulin signaling cascade (Pikilidou *et al*., 2009; Von Hurst *et al*., 2010). Due to the increased adipose tissue and produced increase of pro-inflammatory factors by placenta (Kirwan *et al*., 2002; Jahromi *et al*., 2011a), pregnancy is associated with increased susceptibility to inflammatory factors (Asemi *et al*., 2011) and insulin resistance (Jahromi *et al*., 2011b). A mild inflammatory state is associated with insulin resistance. These cytokines, predominantly TNF-α and IL-6, are known to be released from adipose tissue (Weisberg *et al*., 2003) and result in induce insulin resistance and increased FPG (Von Hurst *et al*., 2010). Vitamin D has recognised anti-inflammatory actions and suppresses the release of TNF-α and IL-6 (Schleithoff *et al*., 2006).

Our findings showed that consumption of calcium-vitamin D supplements for 9 weeks during pregnancy resulted in significant decrease serum triglyceride levels, but could not affect serum total-, HDL-, LDL-cholesterol levels. Observational studies have shown an inverse relationship between serum calcium and vitamin D levels with lipid profiles (Reid and Bolland, 2008; Jorde and Grimnes, 2011). In a study by Jorde *et al*. (2010a) who included 8018 nonsmoking individuals in the cross-sectional study, there were highly significant positive associations between serum vitamin D levels with serum total-, HDL- and LDL-cholesterol and significant inverse associations between serum vitamin D levels with both LDL-/HDL-cholesterol ratio and serum triglycerides concentrations after adjustment for gender, age, BMI and month of blood sampling. So far merely a few intervention studies have been reported and the results provided by them are divergent. Furthermore, these studies are heterogeneous with respect to calcium and vitamin D dose, study duration and the characteristics of subjects. In a study by Li *et al*. (2010) the use of calcium supplement resulted in significant increased in serum HDL-cholesterol and decreased serum LDL-cholesterol levels compared with the placebo group in obese Chinese women after 26 weeks. Significant decreases in serum triglycerides and LDL-cholesterol levels was also seen with consumption of calcium-vitamin D supplements (600 mg elemental calcium and 200 IU vitamin D/tablet) among healthy, overweight or obese women after 15 weeks (Major *et al*., 2007). Significant decrease in serum triglycerides concentrations (16%) and increase in serum LDL-cholesterol levels (8%) were seen with received vitamin D supplement as compared to the placebo group (Jorde and Grimnes, 2011). However, the effect of an energy-restricted diet providing either 400-500 mg calcium dL^{-1} from dairy products (placebo group) or 1200-1300 mg calcium dL^{-1} from an additional 800 mg calcium carbonate (high calcium group) or from an additional 3 servings of dairy products (high dairy group) had no effect on serum LDL-, HDL-cholesterol and triglycerides concentrations among obese adults after 24 weeks (Zemel *et al*., 2004). Also, consumption of calcium supplement (1000 mg dL^{-1}) has been resulted in serum triglycerides and LDL-cholesterol concentrations in overweight or obese women after 30 days (Karandish *et al*., 2009).

Several mechanisms can explain the effects of calcium-vitamin D supplementation on decreased serum triglycerides levels. Higher calcium intake may be result in a reduction in fatty acid absorption and an increase in fecal fatty acid content, resulting from the formation of insoluble calcium-fatty soaps in the gut (Reid, 2004). Such a decreased in fat absorption, especially saturated fat, could reduce the serum triglycerides, total- and LDL-cholesterol levels (Vaskonen, 2003). Furthermore, an increase of intracellular calcium in liver was shown to stimulate Microsomal Triglycerides Transfer Protein (MTP) which is implicated in the formation and secretion of VLDL and then result in decreased serum triglycerides levels (Cho *et al*., 2005). In this regard, it has been shown that increasing dietary calcium inhibit the stimulation of calcium influx into adipose tissue result from calcitrophic hormones that occurs as a result of low calcium diets and that stimulates lipolysis (Zemel *et al*., 2000). Finally, the beneficial effects of calcium-vitamin D supplements on serum triglycerides concentrations observed in this study could be due to calcium as much as to vitamin D (Major *et al*., 2007). However, current studies tends toward the attribution of a larger contribution from calcium because the reported effects of vitamin D on apolipoprotein gene expression (Wehmeier *et al*., 2005) and serum triglycerides concentrations (Major *et al*., 2007; Wehmeier *et al*., 2005) are still controversial.

Several limitations must be considered in the interpretation of our findings. First of all, the study duration was short, only 9 weeks. A longer duration could have resulted in either greater changes or an accommodative effect on serum total-, LDL-, HDL-cholesterol levels, therefore it is recommended that similar studies conduct with a longer duration and higher dosage calcium-vitamin D supplements. Secondly, we couldn't assess the effects of calcium-vitamin D supplements on outcome birth. Thirdly, we could not assess the effects of receiving calcium-vitamin D supplements on the inflammatory markers including TNF-α and IL-6 related to dyslipidemia in pregnant women. This study concludes that consumption of calcium-vitamin D supplements for 9 weeks during pregnancy among pregnant women at risk for pre-eclampsia resulted in decreased FPG and serum triglycerides levels as compared to the placebo group, but could not affect serum total-, HDL-, LDL-cholesterol levels.

CONCLUSION

Pregnant women at risk for pre-eclampsia are very susceptible to increased levels of lipid profiles and glycemic disorders especially in the third trimester. It seems that calcium and vitamin D deficiency during pregnancy may be an important risk factor for hyperglycemia, insulin resistance, dyslipidemia and cardiovascular diseases. Considering the above cases, it is recommended that pregnant women at risk for pre-eclampsia receive routinely calcium-vitamin D supplementary treatment.

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