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# Hypocalcemia and Pregnancy-Associated Pre-eclampsia: A Dubitable Relationship

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**Abstract**
Pre-eclampsia is a multisystem disorder traditionally characterized by a combination of hypertension, a probable presence of urinary protein, along with other symptoms. It is defined as a blood pressure of >140 mmHg (systolic) and/or >90 mmHg (diastolic) on two occasions with an interval of at least 4-6 hours with or without proteinuria after twenty weeks of gestation. It is found to exclusively affect 3-5% of pregnant women worldwide, particularly those belonging to poor or developing countries and who seemingly possess a greater tendency to suffer from this disorder. Among the leading principal causes of maternofetal morbidity and mortality along with preterm delivery, untreated pre-eclampsia is recognized as one of them. Since no specific cure for pre-eclampsia has been discovered, preventive measures are followed which include administering low-dose aspirin, calcium, magnesium sulfate, along with changes in lifestyle and diet. There is certain evidence that shows various elements and minerals, such as calcium among many others, may play a crucial part in the prognosis of pre-eclampsia. This review describes the relationship between hypocalcemia and pregnancy-associated pre-eclampsia, according to the results reported worldwide.
**Keywords** Calcium, hypertension, pre-eclampsia, pregnant women, preterm delivery, supplementation.

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## Introduction

In 2014, new changes were made in the criteria required for diagnosing pre-eclampsia and were hence redefined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [1]. According to the ISSHP, pre-eclampsia is now defined as "de-novo hypertension present after twenty weeks of gestation combined with proteinuria (>300mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction and fetal growth restriction". Proteinuria is not considered a requirement in the current definition, therefore, pre-eclampsia is presently categorized as proteinuric pre-eclampsia and non-proteinuric pre-eclampsia, separately [2]. Low dietary calcium, as well as low concentrations of serum calcium, has been correlated with pre-eclampsia [3]. Anti-platelet therapy, magnesium sulfate, and calcium supplementation are the prophylactic measures which are used to control pre-eclampsia. Studies have been conducted in several different countries to understand the relation between pre-eclampsia and calcium imbalances. While the reported results have been rather conflicting, more studies seem to agree with the prospect of calcium supplementation having a beneficiary effect and consequence in the decline of incidences of pre-eclampsia among pregnant women, with some trials not demonstrating a much favorable effect. Several studies have shown that women who have a high-risk benefit from calcium supplementation the most.

## Calcium deficiency- a possible precursor of pre-eclampsia

There is a strong correlation between calcium imbalances and pre-eclampsia. Hypocalcemia can be seen in most cases of pre-eclampsia and could possibly be a strong etiological factor. In women who have a low dietary calcium intake, calcium supplementation in a high dose reduces pre-eclampsia (RR: 0·36, CI: 0·20–0·65) [4]. Even though calcium supplementation is not recommended in adult females with a normal intake of dietary calcium, the WHO recommends calcium supplementation (1·5–2 g daily) for adult females with low dietary calcium intake in the second half of their pregnancy [5]. This recommendation applies to most situations in which the primary origin of dietary calcium is grains, such as corn or wheat, and is therefore based on the systematic review of supplementing calcium in a high dose during pregnancy [6]. The theory of dietary calcium supplementation being effective in preventing pre-eclampsia when given in early pregnancy is being tried in a randomized trial in women previously affected by pre-eclampsia [7]. Generally, dietary Ca intake is inadequate in low-resource environments [8]. The finding that pre-

eclampsia was less usual in the Mayan Indians who held out in Guatemala, who had relatively high calcium-containing diets, led to the theory that dietary calcium deficiency might be one of the key links between poverty and pre-eclampsia [9]. Subsequent meta-analysis indicated that pre-eclampsia, in populations with low dietary calcium intake, was lowered by calcium supplementation in the second half of gestation [10].

## Outcomes of calcium supplementation

Some epidemiological studies, but not all, suggested that there is an inverse relation between the frequency of pre-eclampsia/eclampsia, and dietary calcium intake [11]. Steegers et al. [12] have stated that a review conducted based on the evidence had not found any relation between supplementation of calcium and a fall in risk of pre-eclampsia, but that a decline may be ascertained to some degree in calcium-deficient populations. The recap, that was cited, was an assessment by the Food and Drug Administration (FDA), of the available scientific proofs and evidence, to validate a current health claim for supplementing calcium, where trials in which all pregnant women receiving a lower baseline intake of calcium were excluded. The Cochrane meta-analytic thinking and taxonomic review of placebo-controlled double-blind trials had come at a dissimilar conclusion [13]. This review had found that supplementation of calcium, when compared with placebo, had brought down the risk of high blood pressure in a substantial way (RR: 0·65, CI: 0·53–0·81), with the overall total risk of preparing pre-eclampsia (RR: 0·45, CI: 0·31–0·65), and especially the danger of pre-eclampsia in women at a high risk (RR: 0·22, CI: 0·12–0·42) along with women with a lower baseline calcium intake (RR: 0·36, CI: 0·20–0·65). The danger linked with preterm birth was likewise significantly lowered with calcium (RR: 0·76, CI: 0·60–0·97), particularly in women whose risk of preparing pre-eclampsia was high (RR: 0·45, CI: 0·24–0·83). The total combined outcome for severe maternal morbidity or mortality was significantly lowered by supplementing calcium (RR: 0·80, CI: 0·65–0·97) [14]. The outcomes of a survey conducted on Korean pregnant women had suggested that serum calcium levels could be an individual determinant for pre-eclampsia [15]. Serum calcium concentration in Indian pregnant women, with either mild or severe forms of pre-eclampsia, was also considerably lowered compared to normal healthy controls [16]. However, other analogous clinical trials did not substantiate calcium supplementation to be beneficial. An example of a randomized trial conducted on Australian pregnant women with supplementation of 1.8 g calcium, beginning at twenty-four weeks of gestation and persisting until parturition, had not led to a significantly obvious decline in the risk associated with developing pre-eclampsia (RR: 0.44, P: 0.22) [17]. Moreover, another auxiliary trial conducted among pregnant women with a lower than required intake of calcium (<600mg/day) demonstrated a small, statistically insignificant decline in the rate of incidence of pre-eclampsia (4.1% vs. 4.5%; RR: 0.91, CI: 0.69-1.19) on supplementation of 1.5 g calcium [18]. In another study, supplementation with 2 g elemental calcium on a daily basis was linked with a large decline in the risk associated with developing pre-eclampsia (66.7%) and a decline in the risk associated with preterm deliveries (44.9%). This may have occurred as a result of the baseline intake of calcium of the study population being less (85.71–910.71 mg/day) when compared to the Recommended Daily Allowance (RDA) of 1g/day required throughout the pregnancy and all through the lactation period [19]. In this study, the 24-hour urine collection presented a urine calcium excretion value of 130.82 ± 67.44 mg/d. Among the pregnant women who did develop pre-eclampsia, supplementing calcium had neither diminished the severity or degree of maternal high blood pressure nor had it helped in improving obstetric and neonatal outcomes [20]. Another trial conducted in populations with a lower dietary calcium intake showed that even though pre-eclampsia was not prevented by supplementing 1.5 g/day of calcium, it had lowered its severity along with an overall decline in maternal-neonatal morbidity and mortality. Supplementation of calcium was also associated with a decline in Severe Pre-eclampsia Complications Index (SPCI) scores (RR: 0.76, CI: 0.66–0.89). There was also a decline in Severe Maternal Morbidity and Mortality Index (SMMMI) scores observed in the group supplemented with calcium (RR: 0.80, CI: 0.71–0.91), as well as the pace of mortality among neonates (RR: 0.70, CI: 0.56–0.88) [21].

Supplementation of calcium has also been discovered to boil down the incidences of both, elevated blood pressure present in pregnant women whose risk for developing gestational hypertension was high (RR: 0.35, CI: 0.21–0.57) as well as pre-eclampsia (RR: 0.2, CI: 0.11–0.43) [22]. Another study found a consistent tendency of a greater decline in the blood pressures of the calcium-supplemented group compared to the placebo group at both of the trial visits- at twelve weeks and twenty-four weeks

after randomization, which was conformable with such an effect, but the differences were statistically insignificant except for the diastolic pressure in the sub-group of women who previously suffered from severe pre-eclampsia. These women who had previous forms of severe pre-eclampsia (as well as eclampsia and HELLP syndrome) may be increasingly sensitive to the supplementation effects of calcium, especially on diastolic blood pressure than women who had previous non-severe pre-eclampsia. The latter finding is concordant with the hypothesis that women who have a susceptibility to pre-eclampsia may be particularly sensitive to calcium deficiency, either due to a greater dietary deficiency or an inherent sensitivity to calcium deficiency [23]. The most recently conducted meta-analysis, which had calcium supplementation commencing as early as at twelve weeks of gestation found that an intake of additional calcium during pregnancy led to a decline in the occurrence of pre-eclampsia, suggesting that the commencement of supplementation of calcium early in a pregnancy may be beneficial [24]. Another study had suggested that initiating calcium supplementation prior to pregnancy may provide improved protection against developing pre-eclampsia than compared to starting after twenty weeks of gestation [25]. In 2006, the WHO published the resultant outcomes of a multi-center large randomized placebo-controlled double-blind trial suggesting that a supplementation of 1500 mg/day of calcium, in pregnant populations whose mean intake of calcium was <600 mg/day, lowered the severity of maternal pre-eclampsia and decreased fetal mortality [26].

A stratified analysis had been conducted for pre-eclampsia and the severe pre-eclamptic complications index, based on the (1) baseline intake of calcium, (2) mother's age at the time of entry, as well as (3) treatment compliance. Despite having some tendencies towards a preventive effect as a result of calcium in a few strata, neither of the relations between treatment and the sub-groups were significant statistically; with the subsequent results not being elaborate, except for the investigations and analyses conducted by the mothers' ages, where a clinically consistent trend was recognized. A decline in pre-eclampsia among 2889 pregnant women whose ages were of ≤twenty years was indicated here (RR: 0.74, CI: 0.47-1.16), with a greater effect on the SPCI (RR: 0.72, CI: 0.51-0.99). Supplementing 1.5 g/day of calcium, however, did lead to an obvious decline in the most severe complications induced by pre-eclampsia by 25% approximately. This is observed further in the decline in the SMMMI and in the lowered rates of mortality in neonates, with both results being statistically and clinically significant [27]. While the large WHO calcium supplementation trial conducted did demonstrate a decrease in maternal morbidity once pre-eclampsia had occurred, it did not result in a decline in the disease incidence, even though subsequent meta-analyses incorporating the results of the WHO study suggest a small effect in reducing the disease incidence as well [28]. In this context, the results of the ancillary study provide added support to the importance of calcium supplementation being incorporated in preventative strategies against pre-eclampsia [29]. Calcium has recently been found to significantly affect uteroplacental blood flow by causing a decline in resistance of the umbilical and uterine arteries [30]. A systematic review involving 13 RCTs- randomized controlled trials (15,730 pregnant women) conducted recently assessed calcium's effectiveness in preventing pre-eclampsia [31]. Dietary calcium intake was found to be low in about two-thirds of the women (10,678 pregnant women) with 587 of them at a high risk. In the studies, the daily average intake of calcium was 1.5–2 g of several preparations, which include calcium gluconate (one RCT), elemental calcium (three RCTs) as well as calcium carbonate (eight RCTs). Calcium was deemed an effective choice in pre-eclampsia prevention (RR: 0.45, CI: 0.31-0.65). Beneficial effects were observed mainly in the group with a high risk (RR: 0.22, CI: 0.12-0.42), as well as the group with low dietary intake of calcium (RR: 0.36, CI: 0.20-0.65). No substantial effect or consequence in the incidences of pre-eclampsia in the analysis for the subgroup of women who had an adequate dietary intake of calcium was observed (RR: 0.62, CI: 0.32-1.2). It is likely that the beneficial effect that has been recorded in the group which has a low intake of calcium could have probably been induced by the epiphenomenon of calcium's effect in reducing blood pressure in the active stage of the conducted trials which involve these pregnant women. An intake of 1 g at least (e.g. 1.5–2 g) of calcium regularly on a daily basis leads to a decline in the incidence of pre-eclampsia in pregnant women who are highly at risk and/or women with a low intake of dietary calcium [32].

## Cellular $Ca^{2+}$ metabolism in pre-eclampsia

It is hypothesized that high blood pressure may be caused due to low calcium intake by stimulating parathyroid hormone and/or renin release, thereby

resulting in a rise in the intracellular concentration of calcium in the VSM cells and therefore causing vasoconstriction [33]. Supplementation of calcium may function by reducing the concentration of intracellular calcium and parathyroid calcium release, resulting in increased vasodilatation and decreased smooth muscle contractility. Also, the magnesium levels increasing due to the calcium may have an effect on the function of the smooth muscle. A study had shown that the intracellular free $Ca^{2+}$ concentrations in the basal lymphocytes of pregnant normotensive women tend to increase with gestational age, as well as in women suffering from chronic hypertension and is highest during the 3rd trimester in pre-eclamptic women. Furthermore, significant changes in the lymphocytes intracellular free $Ca^{2+}$ concentrations were caused by experimental manipulation in-vitro of the extracellular $Ca^{2+}$ milieu. Substantial increases in lymphocyte intracellular free $Ca^{2+}$ concentrations were observed in both low-calcium as well as calcium-free mediums. The presence of increased concentrations of intracellular free $Ca^{2+}$ observed in pre-eclamptic women's platelets have hence been demonstrated as an affirmation of the increased vascular reactivity and generalized vasospasm commonly linked with the condition [34].

## Calcium supplementation as a choice of therapy

Novel therapies aimed at the pre-eclampsia focus on various aspects of the pathogenesis of pre-eclampsia and are in progress, yet placental delivery appears to be the only definite cure presently for pre-eclampsia [35]. Intravenous administration of magnesium sulfate is used for effectively treating and preventing eclampsia [36]. The cost of a daily dose of 1·5–2 g of calcium, which is recommended by the WHO, may be a drawback in low-resource environments [37]. A review conducted of randomized trials demonstrated a consistent decline in pre-eclampsia by low-dose (usually 500 mg daily) calcium supplementation compared with placebo [38]. A meta-analysis conducted recently has concluded that calcium supplementation resulted in a decline in the risk associated with pre-eclampsia, along with a decline in the occurrence of maternal mortality or severe morbidity [39]. Women high at risk and/or those with a lower baseline dietary intake of calcium, after being supplemented with calcium, were observed to have the largest decline in risks associated with pre-eclampsia [40].

## Conclusions

Most of the studies conducted do indeed point to calcium supplementation playing a role in reducing the risk associated with pre-eclampsia quite significantly in pregnant women having a previously low intake of dietary calcium <1 g/day. However, further research is required to substantiate the consistency of these findings, which indicate a possibility of calcium deficiency being one of the etiological factors of pre-eclampsia.

### Conflict of interest

The authors declare that they have no conflict of interest.

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