The Effect of Orally –Administered Calcium Carbonate to Pregnant Women with Mild Pre-eclampsia

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Abstract

Pre-eclampsia is the most common medical complication of pregnancy associated with increased maternal and infant mortality and morbidity. Its exact etiology is not known, although several evidences indicate that various elements might play an important role in pre-eclampsia. This study was carried out to analyze and to compare the concentration of calcium, in mild pre-eclampsia and in normal pregnant women , and to determine the effect of oral supplementation with calcium on mild pre-eclampsia , and whether this effect is related to the change in the level of serum calcium. Forty-five women in the third trimester of pregnancy were selected to participate in this study and divided into: fifteen apparently healthy, normotensive pregnant women served as a control group; thirty clinically diagnosed patients with mild pre-eclampsia (15 mild pre-eclamptic un-treated group , 15 mild pre-eclamptic treated with calcium carbonate 500 mg twice daily) , the serum calcium were estimated with an atomic absorption spectrophotometer .the data were analyzed using the un- paired Student's-test.The serum calcium in mild pre-eclmpatic un-treated group was significantly lower than that in normal pregnant women (8.84 ± 1.14 *Vs.* 9.66 ± 0.87 , $p<0.05$) , Serum calcium level significantly increased in mild pre-eclamptic treated with calcium carbonate 500mg twice daily as compared to mild pre-eclamptic un-treated group (9.76 ±0.96 *Vs* 8.84±1.14 ,$p<0.05$) . Systolic ,diastolic, and mean arterial blood pressure were significantly reduced after one month of treatment with calcium carbonate 500 mg twice daily as compared to mild pre-eclamptic un –treated group.(134.83 ± 7.5 Vs139.33 ± 5.30, 88.46 ± 3.27 Vs 91 ± 3.38, 103.90 ± 3.8*Vs*106.66 ± 3.08 ,$p<0.05$) respectively.This study showed that serum calcium level in mild pre-eclampsia are lower than in normotensive pregnant women ,this finding support the hypothesis that hypocalcemia is a possible etiology in pre-eclampsia ; additionally this study showed the possible beneficial effect of calcium supplementation in controlling pre-eclampsia and reducing blood pressure by increasing serum calcium level .

Key words: **Mild Pre-eclampsia, Calcium carbonate tablet, Pregnant women, Serum calcium**

الخلاصة

يعد مرض ارتفاع ضغط الدم أو مرض سمدمية الحمل من أكثر المضاعفات الطبية للحمل مصاحبة لزيادة الضرر والموت في الام والطفل. لايزال السبب الرئيس لمرض سمدمية الحمل مجهولا بالرغم من ان هنالك اثباتات تدل على ان مستويات العناصر المختلفة قد تلعب دورا في ارتفاع ضغط الدم للام الحامل. صممت هذه الدراسة لبيان التأثير المحتمل لمادة كاربونات الكالسيوم في حالة سمدمية الحمل البسيط على مستوى الكالسيوم بالمقارنة مع ذلك التركيز في النساء الحوامل ذات الضغط الطبيعي ولتحديد هذا التأثير وعلاقته بتغيير في مستوى الكالسيوم في مصل الدم للنساء. تم اختيار خمس واربعون امرأة في الاشهر الثلاثة الاخيرة من الحمل وتم تقسيمهن الى ثلاثة مجموعات: المجموعة الاولى: خمسة عشر امرأة حامل ذوات ضغط دم طبيعي اعتبرن كمجموعة سيطرة. المجموعة الثانية: ثلاثون امراة حامل مصابات بسمدمية الحمل البسيط. قسمت هذه المجموعة الى مجموعتين (١٥) امراة حامل شخصت حديثا باصابتهن بسمدمية الحمل البسيط ، (١٥) امراة حامل مصابات بسمدمية الحمل البسيط اعطين جرعة ٥٠٠ ملغم من حبوب كاربونات الكالسيوم مرتان يوميا. تم قياس مستوى الكالسيوم في مصل النساء الحوامل في المجموعات اعلاه . بينت نتائج هذه الدراسة ان تركيز مستوى الكالسيوم في مصل النساء المصابات بسمدمية الحمل اقل بصورة معنوية عند مقارنتها بالحمل الطبيعي والذي زاد وبصورة معنوية بعد استعمال كاربونات الكالسيوم لمرضى سمدمية الحمل البسيط. كما بينت الدراسة ان مستويات ضغط الدم الانقباضي ، الانبساطي وضغط الدم الشرياني قد انخفض بصورة معنوية بعد شهر من استعمال كاربونات الكالسيوم ٥٠٠ ملغم مرتين باليوم بالمقارنة مع مجموعة النساء الحوامل المشخصات حديثا على انهن مصابات بسمدمية الحمل البسيط . بينت هذه الدراسة ان مستوى مصل الكالسيوم في النساء الحوامل المصابات بسمدمية الحمل البسيط هو أقل من مستواه لدى النساء الحوامل ذوات ضغط الدم الطبيعي. ان النتائج التي تم الحصول عليها من هذه الدراسة تدعم النظرية ان قلة مستوى الكالسيوم في الدم قد يكون السبب المحتمل في سمدمية الحمل ، بالاضافة الى ذلك، بينت هذه الدراسة الى التأثير المفيد والمحتمل لمادة كاربونات الكالسيوم في السيطرة على مرض سمدمية الحمل البسيط وتخفيض ضغط الدم وتحسين التدهور الحاصل في مستوى مصل الكالسيوم.

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Introduction

Preeclampsia is one of the most common causes of maternal and fetal morbidities and mortalities [(1)]. Its incidence is 4-8% of pregnancies[(2)].The patho physiological mechanism is characterized by failure of the trophoblastic invasion of the spiral arteries, leading to mal adaptation of maternal spiral arterioles, which may be associated with an increased vascular resistance of the uterine artery and decreased perfusion of the placenta[(3)]. However, the exact etiology of preeclampsia is still unknown. On the physiological basis, calcium plays an important role in muscle contraction and regulation of water balance in cells. Modification of plasma calcium concentration leads to the alteration of blood pressure. The lowering of serum calcium and the increase of cellular calcium can cause an elevation of blood pressure in pre-eclamptic mothers. Therefore, the modification of calcium metabolism during pregnancy could be one of the potential causes of preeclampsia[(4,5).] However, the role and status of serum calcium, is still being discussed. The aims of the present study were to measure serum levels of calcium in mild pre-eclamptic pregnancy and compared with normal pregnancy and to investigate whether the oral supplementation of calcium decrease the incidence of pre-eclampsia, control the blood pressure, and affecting the plasma level of calcium.

Methods

Forty- five women in the third trimester of pregnancy attending the Karbala hospital; department of obstetrics and gynecology were selected to participate in this study with age ranged between (20-45) years (mean 30.99±0.47). Diagnosis was carried out according to WHO criteria [(1)], which are bases on clinical, laboratory diagnostic measures to detect hypertension and proteinuria in all patients. These women were classified into:

1. Fifteen healthy normotensive pregnant women(blood pressure 120/80) the mean gestational age (32.73 ± 2.49) weeks and mean age (30.46 ± 6.79)years, mean systolic blood pressure(115.33 ± 5.4) mmHg , mean diastolic blood pressure(78.66 ± 5.49)mmHg , mean arterial blood pressure (90.78 ± 4.22) mmHg . These pregnant women served as control group. Blood pressure measurement and blood samples were taken every two weeks until the day of delivery.
2. Thirty pre- eclamptic pregnant women in the third trimester of pregnancy, after blood pressure measurement and protein in urine assessment in addition to clinical and diagnostic measures this group can be classified into two groups
   - **A.** Fifteen pre-eclamptic women, their gestational age mean (31.6 ± .46) weeks , age mean (31.31 ± 5.89)years, their mean systolic blood pressure (139.33 ± 5.30) mmHg ; mean diastolic blood pressure(91 ± 3.38) ; and mean arterial blood pressure(106.66 ± 3.08) .they served as mild pre eclamptic un- treated control group .
   - **B.** Fifteen pregnant women with mild pre-eclampsia in the third trimester of pregnancy , They received calcium carbonate 500 mg twice daily . their mean gestational age (32.6 ± 1.88) weeks, mean age(32.13 ± 6.15)years ,mean systolic blood pressure (140.83±2.60) mmHg, mean diastolic blood pressure (91.70 ± 2.85)mmHg , mean arterial blood pressure (108.05±2.20)mmHg. Blood pressure measurement and blood samples were taken every two weeks after starting the treatment until the day of delivery.

Mid stream urine was collected from women in a clean plastic tube, and utilized to perform a test for protein. Venous blood samples were collected and their sera were isolated by centrifugation . Measurement of calcium in serum by colorimetric method , which based on combination of calcium with reactant O-cresolphthalein (O-CPC) complexon, to form a stable , colored reaction product .the developed colored is measured at 570 nm ; Serum calcium levels were expressed as mg / dl . None of the women had cardiac, hepatic or renal dysfunction .and none had any obstetrical abnormalities (diabetes mellitus, rhesus immunization). none had essential hypertension.

Statistical analysis

Data were presented as mean ± SD . Comparison of means of parameter tested between groups was performed by un-paired Student's t test and $p<0.05$ was considered as statistically significant.

Results

The present study enrolled 45 pregnant women. The clinical characteristics of the participant shown in Table 1. There were no statistical difference between mild pre-eclamptic un-treated group and normotensive control group for age and gestational period. The results showed that systolic, diastolic ,and mean arterial blood pressures were

significantly higher in mild pre-eclamptic un-treated group when compared with the normal pregnant women , serum calcium levels in mild pre-eclamptic un-treated women were significantly lower when compared to normotensive pregnant controls($p<0.05$).

Table 1 : Clinical characteristics of the study population.

variables	Normotensive pregnant controls n=15	Mild pre-eclamptic un-treated group n=15
Maternal Age(years)	30.46 ± 6.79	31.31 ±5.89 NS
Systolic B.P. (mmHg)	115 .33 ± 5.4	139.33 ±5.30*
Diastolic B.P. (mmHg)	78.66 ± 5.49	91 ± 3.38 *
Mean Arterial B.P.(mmHg)	90.78 ± 4.22	106.66 ± 3.08*
Gestational age (weeks)	32.73 ± 2.49	31.6 ± 2.46 NS
Serum Calcium (mg/d)	9.66 ± 0.87	8.84 ± 1.14*

Data are shown as mean ±SD ; *: $p < 0.05$ compared to normotensive control group; NS:no significant differences.

Figure 1 shows that in mild pre-eclamptic women, mean arterial blood pressure levels were inversely correlated with serum calcium level (r = - 0.811) ($p<0.05$).

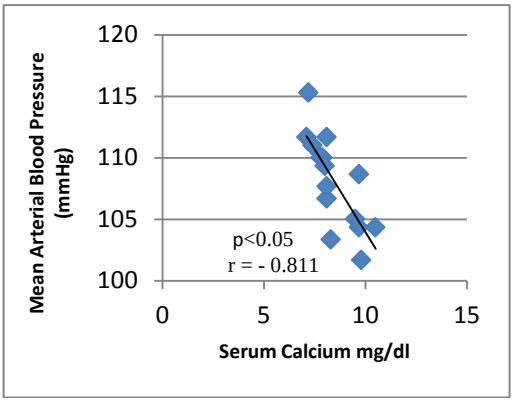

Figure 1: Relation between Mean Arterial Blood Pressure and serum calcium in mild pre-eclamptic patients.

Mild pre-eclamptic women treated with oral tablets calcium carbonate 500 mg tablets twice daily showed a significant decrease in the levels of systolic - , diastolic -, and mean arterial blood pressures compared to mild pre-eclamptic un- treated control group ($p < 0.05$) as shown in table 2. The levels of systolic - , diastolic- and mean arterial blood pressures in mild pre-eclamptic treated with calcium carbonate twice daily showed a significant difference with the corresponding levels in normotensive controls ($p< 0.05$).as shown in table 2 and figures 2,3 and 4.

Table 2: Systolic- ,Diastolic- , and Mean arterial- blood pressures in mild pre-eclamptic women treated with calcium carbonate (500mg tablets) compared to mild pre-eclamptic un-treated control group and normotensive pregnant control groups.

	Systolic blood pressure mmHg	Diastolic Blood pressure mmHg	Mean Arterial Blood pressure mmHg
Mild Pre-eclamptic treated with Calcium carbonate n=15	134.83 ± 75^{c}	88.46 ± 27^{c}	103.90 ± 3.8^{c}
Mild pre-eclamptic Un - treated Control n=15	139.33 ± 5.3^{b}	91 ± 3.38^{b}	106.6 ± 0.08^{b}
Normoten-sive Pregnant Control n=15	115 ± 5.49^{a}	78.6 ± 5.49^{a}	90.87 ± 4.2^{a}

Data shown as mean ± SD ; Values with non- identical subscripts (a, b, c) within each parameter are significantly different ($p < 0.05$).

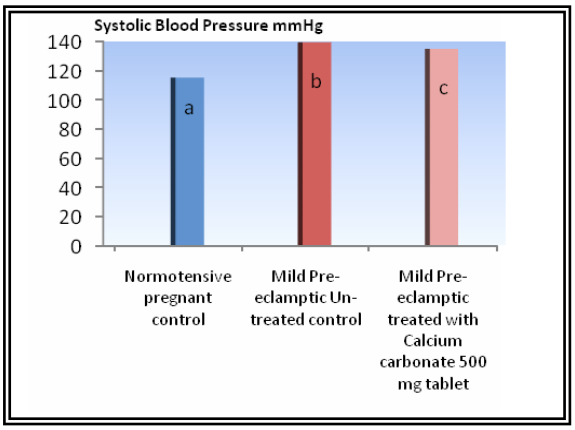

Figure2:The effect of treatment with calcium carbonate 500 mg tablet on systolic blood pressure levels in mild pre-eclamptic women .

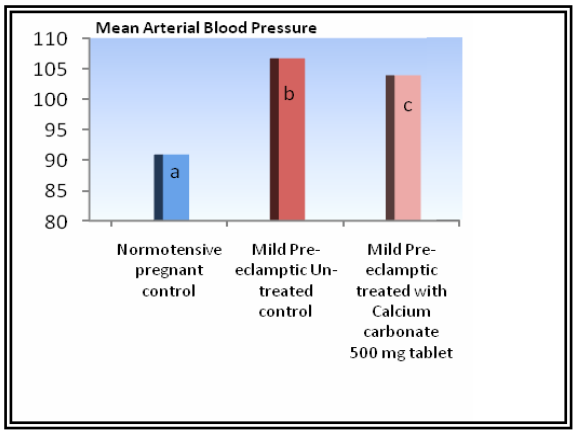

Figure 4: The effect of treatment with calcium carbonate 500 mg tablet on mean arterial blood pressure level in mild pre-eclamptic women .

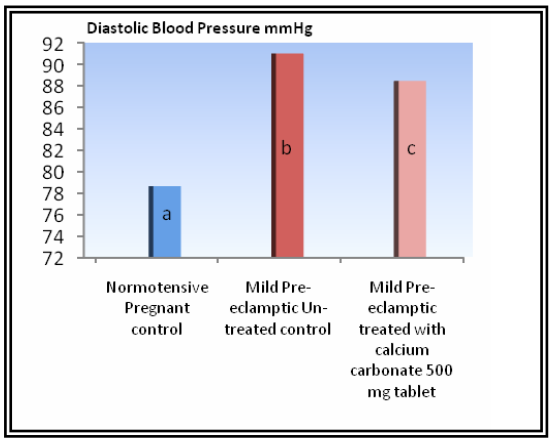

Figure 3: The effect of treatment with calcium carbonate 500 mg tablet on diastolic blood pressure levels in mild pre-eclamptic women.

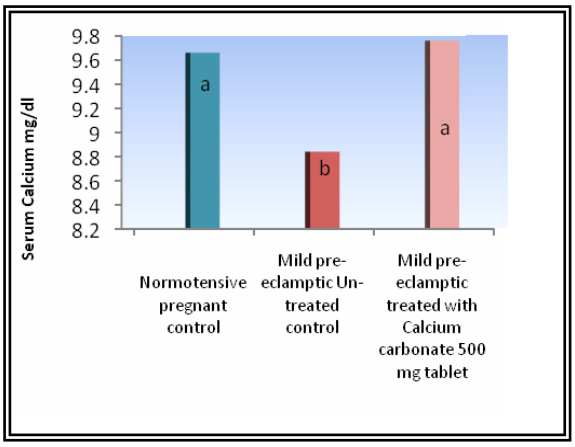

Figure 5: The effect of treatment with calcium carbonate 500 mg tablet in mild pre-eclamptic women on serum calcium level.

Table 3: serum calcium in mild pre-eclamptic treated with calcium carbonate 500 mg tablet compared to mild pre-eclamptic un-treated and normotensive control groups.

	Normotensive pregnant Control n=15	Mild pre-eclamptic Un-treated Control n=15	Mild pre-eclamptic treated with Calcium carbonate 500 mg tablet n=15
Serum Calcium (mg/dl)	9.66 ± 0.87^{a}	8.84 ± 1.14^{b}	9.76 ± 0.76^{a}

Data shown as mean ± SD ; Values with non- identical subscripts (a,b) within each parameter are significantly different ($p < 0.05$).

A significant increase in the serum calcium level were seen in mild pre-eclamptic women treated with calcium carbonate 500 mg tablet compared to pre-eclamptic un –treated control group ($p< 0.05$) , the level of serum calcium were reached levels of corresponding normotensive pregnant control group as shown in table 3. and Figure 5.

Discussion

It has been proposed that the pathophysiological processes in pre-eclampsia began with a reduction in placental perfusion [6,7] and, ultimately, placental ischemia and infarction [8].The resultant placental damage is believed to result in the release of a variety of placental factors [9]such as Soluble fms- like tyrosine kinase (sFlt1), the angiotensin II type-1 receptor autoantibody (AT1-AA), and cytokines such as tumor necrosis factor (TNF)-α that generate widespread dysfunction of the maternal vascular endothelium [10]. Which in turn resulted in enhance formation of factors such as endothelin, reactive oxygen species (ROS), thromboxane, , and augmentation the sensitivity to vascular angiotensin II, In addition, preeclampsia is also associated with the decreased formation of vasodilators such as nitric oxide (NO) and prostacyclin[11].These alterations in vascular function not only lead to hypertension but multi- organ dysfunction, especially in women with early onset preeclampsia[12]. In the present study , in mild cases of preeclampsia showed an elevation in systolic ,diastolic ,and mean arterial blood pressures compared to normotensive control pregnancies ($p< 0.05$), Table1.Deficient or excessive levels of blood electrolytes and trace elements can be an adverse factor on human pregnancy. The results from many clinical studies demonstrated the relationship between the aggravation of the hypertensive complication of pregnancy and the change in the serum concentration of electrolytes [13-15] .In the present study, Mean serum calcium levels in mild pre-eclamptic un-treated women were significantly lower than normotensive pregnant women ($p< 0.05$), Table1. This finding is similar to the previous studies [16,17] , and is contradictory to others[18-20], where no significant differences in serum calcium levels in pre-eclampsia were observed compared to normal pregnancy. Furthermore, our study showed an inverse relationship between serum calcium level and mean arterial blood pressure in mild pre-eclamptic patients, Figures 1.The biochemical mechanism responsible for the possible decrease in extracellular calcium and concomitant increase in intracellular calcium is presently unclear. It has been suggested that parathyroid hormone plays a crucial role in influencing cation transport [21]. it was postulated that, in preeclampsia, the defective placenta is unable to produce sufficient levels of 1,25 (OH)2 D, resulting in inadequate gastrointestinal calcium absorption, low ionized calcium levels, and a secondary rise in PTH, which in turn may increase cytoplasmic Ca^{+2} or alter the production of endothelium – derived vasoactive factors [31]. Low calcium levels may also contribute to hypertension via stimulation of renin release from the kidney[22]. Also The decreased serum total calcium concentration in preeclampsia may be an alteration of the plasma protein concentration (primarily albumin) results in parallel changes in total plasma calcium[23].It is widely accepted that vascular smooth muscle contraction is triggered by increases in intracellular free Ca^{+2} concentration due to Ca^{+2} release from the intracellular stores and Ca^{+2} entry from the extracellular space [24,25]). Several studies have investigated the role of angiotensin II as an agonist for receptor-mediated intracellular calcium transients in vascular smooth muscle[26]. These studies have consistently shown an increase of intracellular free calcium concentration in platelets and lymphocytes in response to stimulation with angiotensin II and vasopressin in patients with pre-eclampsia[27]. In addition ,Ang II may enhance Ca^{+2} entry through plasma membrane Ca^{+2} channels [28] , Furthermore, there is evidence that several ion-transport pathways are highly sensitive to oxidative stress, and the resulting modulation of ion transport by ROS will affect Ca^{+2} homeostasis[29].Treatment of mild cases of pre-eclampsia with calcium carbonate 500 mg tablet twice daily for one month resulted in a significant decrease in the level of systolic ,diastolic , and mean arterial blood pressure ($p< 0.05$) ,Table 2. figures 2,3,and4.. Our findings were similar to those reported by others[30,31]. Calcium supplementation enhances vasodilation and reduces blood pressure[3,4] by suppression of the parathyroid hormone [21], which in turn reduces the intracellular calcium concentration in vascular smooth muscle cells ,diminishing their responsiveness to pressure stimuli and reducing angiotensin II sensitivity in women with pre-eclampsia [32].However, several different mechanisms have been proposed by which Ca supplementation could reduce blood pressure in pre-eclampsia. Some have focused on neural ,humoral, and renal effects ,whereas others have attempted to relate the antihypertensive action of Ca^{+2} supplementation to improved vascular function[33]. It has been thought that the improved vascular function following Ca supplementation in experimental animals has been attributed to decreased α-adrenoceptor responsiveness[34,35], reduced permeability of plasma membrane to Ca and other cations[36], improved function of cell membrane Na-K ATPase[37], improved vasodilator function of the vascular endothelium ,and to increased

sensitivity of the smooth muscle NO[38].An interesting link between the intake and metabolism of calcium and the control of arterial tone may be the extracellular receptor , the activation of which cause vasorelaxation via the release of hyperpolarizing mediators[39]. The results of this study showed that mild pre-eclamptic patients treated with calcium carbonate showed a significant increase in serum calcium level ($p< 0.05$) Table 3. ,Figure 5., and the result of increasing serum calcium is consistent with the others[40] which demonstrated that calcium supplementation for women with a low baseline calcium intake was associated with an increase in serum calcium concentration. thus calcium supplementation could have a meaningful impact on calcium metabolism regulation by maintaining serum calcium level within the narrow physiological range and reducing serum PTH[21]. Moreover ,when calcium is present in optimal concentration, it stabilizes vascular membranes, blocks its own entry into cells and reduces vasoconstriction[41], Calcium in combination with other ions such as Na+, K+ ,Cl- and Mg2+ provides ionic balance to the vascular membrane[42], since membrane potential in vascular smooth cells is governed by the membrane permeability to these ions, and they are act as a major determinant of membrane potential under resting condition.From this study we conclude that the reduction in serum level of calcium during pregnancy might be possible contributor in etiology of pre-eclampsia, and supplementation of this micronutrients may be of value to prevent pre-eclampsia by controlling blood pressure ,improving endothelial function , and modulating the deterioration of serum level of calcium.

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