Article

Lead and other metals in gestational hypertension

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Abstract

Objectives: To identify any effects that lead, calcium, magnesium, and zinc may have on the development of gestational hypertension. Methods: Third-trimester 110 normotensive and 33 gestational hypertension cases were assayed for various metal levels, using standard techniques, including atomic absorption spectrometry. Results: Gestational hypertension cases showed significantly higher blood lead levels than normotensives. No differences were noticed regarding calcium (ionized and total), magnesium, and zinc levels. Blood lead was significantly related with blood pressure, even after correcting for the body mass indices and age. Blood pressure levels showed no relation to the other analyzed metals. However, the lead:ionized calcium ratio showed a stronger association with blood pressure, than lead alone. Blood lead showed a significant negative relationship with ionized calcium, but none with the other metals. Conclusions: Blood lead evidently influenced blood pressure increments and gestational hypertension development. This implies that all efforts should be made to reduce the population’s exposure.

Keywords: Lead; Calcium; Zinc; Magnesium; Metals; Gestational hypertension

1. Introduction

The functional role of the various metals found in the body remain unclear, especially in relation to pathological conditions that involve multiple complex pathways [1]. Biochemical interactions between various minerals, such as the competition between lead, zinc, and calcium; and calcium with magnesium, further complicate the issue [2,3]. The documented clinical effects of the elements generally refer to extreme cases of toxicities or deficiencies. However, the effects of slightly reduced or elevated concentrations on the general population, rather than on the individual, have now become more relevant [4].

Pregnancy is associated with profound physiological cardiovascular changes, but what precipitates hypertension remains unknown [5]. However, the pathophysiology of gestational hypertension appears to be multifactorial, with several factors having synergistic or protective roles [6]. Some of the metals may have a contributory role in these unclear pathways. Blood pressure control has been shown to be partly dependent on the status of
various elements, such as lead [7,8], calcium [9], zinc [4], and magnesium [2]. These influences were also retained during the pregnant state [3,10], although they are poorly documented.

The present study set out to identify any possible contributory effects that the elements—lead, calcium, magnesium, and zinc—may have on the development of gestational hypertension. The Maltese population was chosen as it was previously shown to have high levels of circulatory lead [11]. Regulatory measures introduced in recent years have managed to reduce the environmental lead levels. In response blood lead levels have also been reduced, though the levels still remain elevated [12].

Additionally, the lead stored in its metabolically inactive form in bones for decades [7], could be released during conditions of increased bone turnover, such as pregnancy [13]. This increased bone resorption results from the increased calcium requirements, especially during the last trimester. Consequently lead’s active form would also be released into the circulation, and could hence affect various systems.

2. Materials and methods

2.1. Population variables

A cross-sectional study was conducted in third trimester primigravid women, where a total of 143 pregnant women, including 33 cases diagnosed with gestational hypertension participated. Prior to initiating the study, all proposed procedures were approved by the ethical research committee. All study participants were Maltese Caucasian females, having singleton pregnancies. Women having a history of hypertension, and a family history of gestational hypertension were excluded from the study, as were those having gestational diabetes, renal disease, and on medication. All women were on unrestricted diets. None of the cases was treated with magnesium sulfate. None of the cases was complicated with pre-eclampsia or eclampsia, so as to exclude any major blood volume difference, which could significantly affect blood metal levels.

Anthropometrical measurements were recorded during the first trimester, so as to eliminate any confounding effects of edema development. Dosage, frequency and period of mineral supplementation use were recorded at time of blood sampling.

2.2. Blood pressure measurements

The criteria used for the diagnosis of gestational hypertension were blood pressure readings above 140/90 mmHg at two successive measurements, at a 4-h interval [6]. Blood pressure was measured using a mercury sphygmomanometer, with the participant seated and her right arm elevated to heart height. To minimize the white-coat hypertensive effect, blood pressure was taken in the same familiar place where the women had previous appointments, and after being seated for at least 10 min [10]. Systolic pressure was taken at the point at which the Korotkoff sound was first heard and the diastolic pressure were recorded when the fifth sound disappeared.

2.3. Laboratory methodology

Blood collection followed a through cleaning of the venipuncture site to eliminate possible lead contamination. Samples for blood lead analysis were collected in 5-ml plastic tubes (KIMA SIL, Italy) containing 50 μl of lead-free EDTA (Spectrosol, BDH supplies) prepared internally. Another 7-ml sample was obtained within a trace element plain Vacutainer tube (Bectin-Dickinson, UK) for sera analyses of the other metals. Lead was analyzed using electro-thermal atomic absorption spectrometry (AAS) according to the modified Fernandez method [14] on a Perkin Elmer 2100 (USA), equipped with Deuterium lamp background corrector and auto-sampler. Serum zinc was measured by flame AAS on a Varian Techtron Model 1100 (Varian, Australia), using the technique of standard addition. Serum calcium and magnesium concentrations were determined colorimetrically on a Hitachi 917 (Boehringer-Mannheim, Germany). Serum ionized calcium was determined using a calcium ion selective electrode (AVL 988-3; AVL LIST, Austria), following standardized procedures [15].
Table 1
Blood concentration of the analyzed metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Normotensive females (mean ± S.D.)</th>
<th>Gestational hypertension cases (mean ± S.D.)</th>
<th>Significant difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood lead (µg/dl)</td>
<td>5.8±3 (n=93)</td>
<td>9.6±6 (n=30)</td>
<td>0.002**</td>
</tr>
<tr>
<td>Upon hematocrit correction</td>
<td>16.6±7 (n=93)</td>
<td>26.7±17 (n=30)</td>
<td>0.009**</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.31±0.17 (n=94)</td>
<td>2.35±0.18 (n=33)</td>
<td>0.71</td>
</tr>
<tr>
<td>Ionized</td>
<td>1.02±0.1 (n=94)</td>
<td>0.99±0.1 (n=33)</td>
<td>0.18</td>
</tr>
<tr>
<td>Serum magnesium (mmol/l)</td>
<td>0.71±0.1 (n=94)</td>
<td>0.71±0.1 (n=33)</td>
<td>0.89</td>
</tr>
<tr>
<td>Serum zinc (µg/dl)</td>
<td>63.6±10 (n=92)</td>
<td>60.6±8 (n=33)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Denotes difference significant at the 99% level.

2.4. Statistical analysis

Statistical significance was evaluated using the SPSS software with a P-value of <0.05 considered significant. The Kolomogrov–Smirnov test was first applied to assess for normal distribution, which determined whether parametric or non-parametric tests were used. All values are expressed as mean ± standard deviation.

3. Results

3.1. Age and gestation

No statistically significant differences were found in the mean ages of the gestational hypertension cases and the normotensive control group (30±6 years vs. 27±6 years, respectively). The gestational week at sampling was similarly comparable between the two groups (both having a mean of 37±3 weeks).

3.2. Metal status

The mean values of the metals investigated in the study are given in Table 1. In line with previously published guidelines [16], lead levels are also given after being adjusted for the hematocrit, so as to correct for technical errors derived from differences in hemodilution. Gestational hypertension cases had blood lead levels that were statistically significantly higher than those of the normotensive controls, before and after correcting for the hematocrit (Mann–Whitney U-test). No significant differences were noticed between the two groups regarding calcium (ionized and total), magnesium, and zinc levels (independent-samples t-test).

3.3. Metal–blood pressure relationships

A statistically significant positive relationship between blood lead levels and systolic and diastolic blood pressure readings was observed. Such an association was maintained even after correcting for the influences of the body mass indices (BMI) and age of the participants (Table 2). This effect of lead on blood pressure had no apparent threshold, as indicated by a continuous relationship observed with both blood pressures (Figs. 1 and 2).

A similar statistical relationship was shown for total calcium levels with the systolic blood pressure readings, but not for the diastolic blood pressure. No relationships were established for ionized calcium, serum magnesium, or zinc levels. However, when the individualized molar ratio of lead to ionized calcium was considered, the asso-
Table 2
Pearson correlation factors for blood lead, after correcting for influencing variables

<table>
<thead>
<tr>
<th></th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood lead</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) All population</td>
<td>0.314 ($P&lt;0.001$)**</td>
<td>0.307 ($P=0.001$)**</td>
</tr>
<tr>
<td>(ii) Corrected for BMI and age</td>
<td>0.236 ($P=0.025$)*</td>
<td>0.221 ($P=0.036$)*</td>
</tr>
<tr>
<td><strong>Blood lead (hematocrit corrected)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) All population</td>
<td>0.276 ($P=0.002$)*</td>
<td>0.283 ($P=0.002$)*</td>
</tr>
<tr>
<td>(ii) Corrected for BMI and age</td>
<td>0.210 ($P=0.047$)*</td>
<td>0.208 ($P=0.049$)*</td>
</tr>
</tbody>
</table>

*Denotes difference significant at the 95% level, **significant at the 99% level. BMI, body mass index.

Association with blood pressure was stronger than when lead was considered alone (Table 3).

3.4. Metal inter-relationships

Blood lead levels of the participants showed a statistically significant negative correlation with extra-cellular ionized calcium levels (Fig. 3). There were no established correlations with total calcium, magnesium or zinc levels (Table 4).

3.5. Effect of supplementation

Of the participants 30% of the cases and 27% of the normotensive females were on calcium supplementation, which averaged on 212 mg per day (18% of the RDA). These same participants were also on magnesium supplementation (average of 52 mg, 16% the RDA), and an average of 19 mg zinc supplementation (127% RDA). No differences were noticed regarding the time supplementation started between the normotensive group (average of $17 \pm 1.7$ week) and the gestational hypertensive group ($18 \pm 1.6$ week). There were also no differences in the period of supplementation prior to blood sampling ($19 \pm 5$ vs. $18 \pm 4$ weeks, respectively).

In spite of this supplementation, no statistical significant differences were noticed between the supplemented and non-supplemented sub-groups of the two groups in any of the measured parameters, including blood pressure readings.

Fig. 1. Presentation of the significant positive relationship between blood lead levels and systolic blood pressure ($r=0.314$).

Fig. 2. Presentation of the significant positive relationship between blood lead levels and diastolic blood pressure ($r=0.307$).
Table 3
Pearson correlation factors for the other analyzed metals

<table>
<thead>
<tr>
<th></th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized</td>
<td>−0.140 (P=0.136)</td>
<td>−0.123 (P=0.193)</td>
</tr>
<tr>
<td>Total</td>
<td>0.212 (P=0.018)*</td>
<td>0.164 (P=0.071)</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td>0.059 (P=0.518)</td>
<td>0.031 (P=0.734)</td>
</tr>
<tr>
<td>Serum zinc</td>
<td>0.137 (P=0.133)</td>
<td>0.004 (P=0.965)</td>
</tr>
<tr>
<td>Blood lead:ionized calcium ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) All population</td>
<td>0.410 (P&lt;0.001)**</td>
<td>0.373 (P&lt;0.001)**</td>
</tr>
<tr>
<td>(ii) Corrected for BMI and age</td>
<td>0.355 (P=0.002)**</td>
<td>0.297 (P=0.011)*</td>
</tr>
</tbody>
</table>

*Denotes difference significant the 95% level, **significance at the 99% level.

Fig. 3. Presentation of the significant negative relationship between blood lead levels and the ionized calcium levels (r = −0.200).

4. Discussion

The etiology behind gestational hypertension remains unknown [5], but its pathophysiological cascades are determined by a number of regulatory factors, possibly involving the metals.

The present study has shown the influence of circulatory lead on gestational hypertension development. Hypertensive females had significantly higher blood lead levels than normotensives, even though none exhibited toxic levels. Other studies have similarly associated blood lead levels with hypertension [7,8], although few investigated this relationship during pregnancy [3,10]. Slightly elevated blood lead levels could influence hypertension development through various mechanisms [8]. Lead may be involved with vasoconstriction through the inhibition of the Na⁺/K-ATPase pump.
Pearson correlation factors for the metal inter-relationships

<table>
<thead>
<tr>
<th></th>
<th>Blood lead</th>
<th>Blood lead (hematocrit corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized</td>
<td>$-0.200 \ (P=0.043)^*$</td>
<td>$-0.188 \ (P=0.057)$</td>
</tr>
<tr>
<td>Total</td>
<td>$0.152 \ (P=0.112)$</td>
<td>$0.118 \ (P=0.220)$</td>
</tr>
<tr>
<td>Serum magnesium</td>
<td>$-0.114 \ (P=0.236)$</td>
<td>$-0.121 \ (P=0.207)$</td>
</tr>
<tr>
<td>Serum zinc</td>
<td>$-0.045 \ (P=0.643)$</td>
<td>$-0.051 \ (P=0.601)$</td>
</tr>
</tbody>
</table>

*Denotes difference significant the 95% level.

[8]; or by enhancing the synthesis of vasoconstrictors and reducing the synthesis of vasodilators. Lead was found to reduce nitric oxide levels [17], which are needed to maintain the vasodilatation of pregnancy [18]. Furthermore, lead was found to enhance the sympathetic nervous system activity [17], as well as to stimulate the renin–angiotensin–aldosterone system [3].

This study demonstrated statistically significant positive relationships between blood lead levels and blood pressures readings. These associations remained significant after adjusting for the confounding effects of body mass indices and age (Table 2). Such positive associations have also been reported in the literature [7], albeit the majority were performed on non-pregnant populations. Even though lead’s influence on blood pressure is assumed to be less defined among women [19], such an association was shown clearly by this study.

Calcium metabolism during pregnancy is still vaguely understood, and the few analytical results of total and ionized calcium are conflicting [2]. This study found that extra-cellular ionized calcium was 2.9% lower in the gestational hypertension group when compared with the normotensives, but such a difference failed to achieve statistical significance. Conversely hypertensive cases had higher, though non-significant, levels of total protein-bound calcium. Since plasma proteins were not assessed, ionized calcium should be considered a more relevant indicator of calcium status, as its level does not depend on protein status [15].

A hypotensive effect has been suggested for calcium [9] and magnesium [2], probably related with smooth muscle relaxation [9], or to endothelial substance release [18]. The apparent reduction in ionized calcium during gestational hypertension could be due to an increased retention of sodium and water. This would increase the sodium–calcium exchanges, thereby raising the intra-cellular calcium levels at the expense of the extra-cellular pool [2]. These extra-cellular reductions could fail to sustain nitric oxide production enough to preserve the vasodilatation of pregnancy, and could also impede the production of vasodilatory prostaglandins [18].

Circulatory lead may also contribute to hypertension development through its inter-relationships with the other minerals [3,20]. This study has shown a significant negative association between blood lead and ionized calcium, suggesting some metabolic relationship. A calcium–lead interaction on blood pressure was exposed when the correlation factor of their molar ratio with blood pressure was greater than when lead was considered alone (Table 3).

Literature findings on this interactive influence are inconsistent. Experimental studies on pregnant animals found that third trimester blood pressure was significantly higher in lead-exposed rats that were also fed a low calcium diet [20]. Studies conducted on non-pregnant subjects failed to prove this calcium–lead interactive effect on blood pressure. Probably calcium intakes have no effect on lead exposure, but could decrease bone resorption and hence lead release from bone stores, which is enhanced during pregnancy [13,24].

The absence of a significant difference in serum magnesium concentrations between the two groups cannot exclude a magnesium imbalance in gestational hypertension, as magnesium is primarily an intra-cellular cation [20]. These findings are consistent with the literature, where most groups failed
to implicate low magnesium levels as a precipitating factor for gestational hypertension [21]. Although this study found that hypertensive cases had mean serum zinc levels that were 4.8% lower than the normotensive group, no statistical significance was achieved. This conforms to previous studies, where results remain inconclusive [22]. Failure of mineral supplementation to affect blood pressure and blood metal levels were probably due to the low levels used. Clinical studies showing blood pressure reductions in response to calcium supplementation used much higher levels of calcium [23]. High levels could maintain sufficient nitric oxide production [18], or could slow bone resorption and hence lead release [24]. This study could not differentiate the effects of zinc and magnesium supplementation from calcium’s, as all supplemented participants used multi-mineral tablets. Zinc supplementation was never shown to reduce the incidence of gestational hypertension, but magnesium supplementation during pregnancy was associated with reductions in the mean arterial blood pressure [2]. However, these findings still need to be confirmed.

5. Conclusions

In addition to the known fetal detrimental effects of lead [25], this work exposed an effect on the maternal side too. It is evident that circulatory lead influenced at least part of the blood pressure variation, and hypertension development. Considering this study’s cross-sectional nature, it could not establish any sequence during gestational hypertension progression, or any cause–effect relationships with any of the metals.

The relationships between lead and blood pressure levels exhibited no apparent threshold from which lead’s influence started. This demands that all possible efforts should be made to reduce the population’s exposure to lead. A speculative means of reducing blood lead levels during pregnancy could be through third-trimester calcium supplementation, so as to reduce bone resorption, leaving the accumulated lead in its metabolically inactive state [24].

Acknowledgments

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References


