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Magnesium and the premenstrual syndrome

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SUMMARY. Plasma and erythrocyte magnesium were measured in 105 patients with premenstrual syndrome (PMS) using a simple atomic absorption spectroscopy method. The erythrocyte magnesium concentration for the patients with PMS was significantly lower than that of a normal population. The plasma magnesium did not show this difference. The significance of this apparent cellular deficiency of magnesium is discussed.

The premenstrual syndrome (PMS), first described by Frank in 1931,[1] is now a well recognised clinical entity. A wide variety of features are exhibited by patients with PMS, ranging from psychological symptoms such as irritability, over-reactive emotions and craving for sweets, to physical signs of abdominal bloating and enlargement of the breasts with water retention. The syndrome is common with up to 40% of women being affected at some time in their lives. Although the features of PMS are now better known, the mechanisms are still unclear. Several hormonal factors have been demonstrated, such as excessive circulating oestrogens,[2] increased aldosterone in the luteal phase[3] and progesterone deficiency during the luteal phase,[4] but the cause is unknown.

Magnesium deficiency in PMS was proposed in 1983 by Abraham.[5] He postulated that magnesium deficiency could explain many of the diverse symptoms found in the syndrome. Magnesium nitrate had been used in the treatment of PMS and essential dysmenorrhoea in 1962 by Durlach and Lemierre.[6] Abraham and Lubran showed in 1981 that 26 patients with PMS had lower erythrocyte magnesium levels than did nine normal premenopausal women.[7] As magnesium is an intracellular cation, the erythrocyte concentration should be a more sensitive indicator of body stores of magnesium than plasma magnesium concentration. This small study prompted us to investigate the magnesium status of two groups of patients with PMS in the Brighton Health District.

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Materials and methods

One hundred and five patients with PMS were included in the study from two sources (57 from a private practice and 48 from a Well Woman Clinic). All were shown to have recognisable PMS using a modified MOOS questionaire.[8] Patients receiving preparations containing magnesium or substantial quantities of vitamin B6 were excluded from the study, as high doses of vitamin B6 (100 mg bd) have been shown to elevate a subnormal erythrocyte magnesium.[9] 5 mL venous blood were placed in a tube containing lithium heparin as anti-coagulant. Relevant clinical details, including present and past medication, were noted. Plasma and erythrocyte magnesium were also measured in a control group of 50 normal premenopausal women. The samples were taken in the mid-luteal phase of the menstrual cycle for both groups.

Plasma and erythrocyte magnesium were assayed using atomic absorption spectroscopy. Plasma (20 μL) was diluted in 2 mL of 1% (w/v) EDTA and aspirated into a Rank Hilger Atomspek H1550®, adjusted according to the manufacturer's recommendations. For the erythrocyte magnesium determination the haematocrit of the whole blood specimen was first measured using a micro-haematocrit centrifuge. Whole blood (10 μL) was then added to 2 mL of 1% EDTA followed by 10 μL of 'Zapoglobin'® (a commercially available agent for the lysis of erythrocytes). The resulting suspension containing erythrocyte 'ghosts' was then centrifuged and the supernatant was assayed as for the plasma magnesium. This result was multiplied by two to correct for the smaller sample volume. The magnesium concentration of haemolysed whole blood is made up of contributions from the cells and from the plasma. The relative volumes of these two sources can be obtained from the haematocrit and the proportional contribution to whole blood magnesium expressed as:

$$W = E \times \frac{H}{100} + P\frac{(1-H)}{100},$$

where W = whole blood magnesium (mmol/L); P = plasma magnesium (mmol/L); E = erythrocyte magnesium (mmol/L), and H = haematocrit (%). This can be rearranged to give:

$$E = \frac{(W-P) \times 100}{H} + P .$$

Hence, by measuring W, P and H, E may be calculated. (The calculation ignores the effect of white cells and platelets.)

Normal ranges have previously been established for plasma and erythrocyte magnesium by this laboratory:[10] plasma magnesium 0·7–1·0 mmol/L and erythrocyte magnesium 2·0–3·0 mmol/L. Statistical comparison of results was performed using Student's *t*-test.

Results

ANALYTICAL VALIDATION

Determination of plasma magnesium using the described technique has been reported previously.[11] Recovery of magnesium was calculated by analysing six plasma samples before and after addition of a known quantity of concentrated standard (0·5 mmol/L). The recoveries ranged between 98 and 100%. There was a linear relationship between absorbance and concentration up to 2 mmol/L. Samples with a greater concentration than this were reassayed after further dilution. Because the concentration of whole blood is approximately twice that of plasma, 10 μL of whole blood and 20 μL of plasma were used in the respective assays.

Within-batch precision was determined by replicate measurements (n = 10) of pooled whole blood. The coefficient of variation (CV%) was 1·5% (mean 0·80 mmol/L) for the plasma and 2·5% (mean 2·35 mmol/L) for the calculated erythrocyte magnesium concentration. The between-batch imprecision was determined by daily analysis (n = 10) of aliquots of pooled plasma and whole blood which were stored frozen. For these studies it was necessary to separate the plasma from a portion of the whole blood in advance of the assays. This is because freezing and thawing blood causes haemolysis and results in an elevated plasma magnesium at the expense of the red cells. The CV was 2·5% for the plasma and 4·3% for the erythrocyte magnesium concentration.

SAMPLE ASSAYS

The mean haematocrit of the PMS group was 40·8% and of the control group 41·0%. By applying the *t*-test no significant difference between the haematocrits of the two groups was found ($P > 0·05$). Haematological investigation (Coulter S) of 18 samples from PMS patients with low erythrocyte magnesium concentrations confirmed that there were no gross blood cell abnormalities in this group of patients.

The results for the plasma and erythrocyte magnesium concentration in the PMS patients and the control group are shown in Table 1. The mean erythrocyte magnesium of the PMS patients (2·06 mmol/L) was significantly different ($P < 0·01$) from that of the controls (2·47 mmol/L). There was no significant difference in the plasma magnesium concentration between the two groups. There was no significant difference between the mean erythrocyte magnesium for the two sources of PMS patients (private

TABLE 1. Plasma and erythocyte magnesium concentrations in PMS patients

	This study		Abraham and Lubran (1981)[7]	
	(a) PMS	(b) Controls	(c) PMS	(d) Controls
Plasma magnesium (mmol/L)	0·79±0·06	0·82±0·05	0·74±0·02	0·70±0·02
Erythrocyte magnesium (mmol/L)	2·06±0·25	2·47±0·3	1·28±0·1	1·85±0·1
Mean age (years)	36±8	36±9·5	29±1·2	30±0·9
Number of subjects	105	50	26	9

All values shown are mean±standard deviation.
Columns (c) and (d) have been converted to mmol/L from mg/100 mL by dividing by 2·43.

practice—mean erythrocyte magnesium: 2·07 mmol/L, Well Woman Clinic—mean erythrocyte magnesium: 2·06 mmol/L).

Discussion

Direct methods of collecting red cells for magnesium determination involve separation of the cells, washing them several times and finally lysing them before assay. Although these procedures remove adherent plasma and can also be adapted to remove platelets and white cells, inevitably an uncertain quantity of red cells are lost in the process. Additionally, the washing steps may cause leakage from the cells and some erythrocytes may rupture with further loss of magnesium.

The indirect method, used in this report, does not suffer from these losses and because of its relative simplicity is better suited to studies involving large numbers of samples. The disadvantage of the approach described here is that the haematocrit measurement includes trapped plasma, and the blood haemolysate will also include magnesium from white cells and platelets. However, as pointed out by Abraham, Schwartz and Lubran[9] these sources of error are small enough to be neglected. For example, the amount of trapped plasma is about 2%.[12] In a typical case this would have the effect of causing the erythrocyte magnesium measurement to be underestimated by about 0·05 mmol/L. The average magnesium content of white cells is about 3·5 mmol/L per 10^{12} white cells,[13] corresponding to approximately 0·026 mmol/L of average blood. Platelets contain about 5·7 μmol/L of magnesium per 10^{11} cells,[14] equivalent to about 0·016 mmol/L of blood. Therefore, on average, the combined effect of the platelets and the white cells would be to falsely elevate the erythrocyte magnesium measurement by 0·04 mmol/L. Interestingly, the error caused by the platelets and white cells just about cancels the error resulting from the trapped plasma. In any case, the magnitude of the errors is not significant.

Although the 105 patients had a mean plasma magnesium well within the normal range, the mean erythrocyte magnesium was significantly lower ($P<0·01$) than that of a group of normal women of reproductive age without PMS. In this laboratory we have measured erythrocyte magnesium in patients with a variety of disorders, including myocardial infarction (unpublished observations) and in the elderly.[10] PMS is the only common condition where the mean erythrocyte magnesium has differed from the control population. Of the patients with PMS, 45% had an erythrocyte magnesium below the lower limit of the normal range.

The results obtained by Abraham and Lubran are detailed in Table 1 (columns c and d). Their normal female population has lower mean plasma and erythrocyte magnesium concentrations (0·68–0·72 mmol/L and 1·75–1·95 mmol/L respectively) than those found in this study, although the conclusions concerning the difference in erythrocyte magnesium between normals and PMS are the same. This discrepancy between the normal ranges could be methodological. Their method is similar but uses repeated freezing and thawing to lyse the erthrocytes rather than the commercial agent 'Zapoglobin' used in this study. The range for erythrocyte magnesium found in this study for normal women is very much in accord with the range of means (1·9–3·1 mmol/L) from over 20 studies quoted by Seelig.[15] The mean ages of Abraham and Lubran's PMS patients and normal women are lower than in this study; however, we found that the erythrocyte magnesium did not vary with age in either group of subjects ($r=0·12$; $P>0·05$).

Features of severe experimental magnesium deficiency include anorexia, nausea, apathy and personality change, as well as spontaneous generalised muscle spasm, tremor and vesiculation, and positive Trousseau and Chvostek signs.[16] Thus, a magnesium deficiency in women with PMS could account for some of the symptoms of PMS. The present study did not assess whether the administration of magnesium had any therapeutic benefit, either to those with or to those without deficiency. However, recent reports of dietary improvement and the use of a multivitamin/multimineral preparation, Optivite, at a dosage providing at least 300 mg of vitamin B6 and 250 mg of elemental magnesium per day, show a beneficial effect upon PMS symptoms in a double-blind, cross-over study,[17] and the correction of hormonal abnormalities sometimes associated with PMS.[18]

The reason for an erythrocyte magnesium deficiency in PMS is unclear. There may be decreased intake/absorption or increased renal excretion. The plasma magnesium in most of the PMS cases was normal, so there might be a defect in the cellular mechanism for magnesium regulation. PMS could be the cause of the magnesium deficiency rather than the result of it.

This much larger study confirms the findings of Abraham and Lubran[7] that many PMS patients have low erythrocyte magnesium. Erythrocyte magnesium measurement could be useful in the assessment of PMS patients and a trial of magnesium supplementation in patients with low erythrocyte magnesium may be worthwhile.

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