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Serum ionized magnesium and calcium in women after menopause: inverse relation of estrogen with ionized magnesium

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Objective: To study the serum concentrations of the sex steroid hormones and free divalent cations Mg^{2+} and Ca^{2+} in healthy women at or past menopause and to compare them with the serum concentrations of healthy, cycling women of child-bearing age at different stages of the menstrual cycle.

Design: Controlled clinical study.

Setting: An academic medical center.

Patient(s): Women of varying age and duration of menopause, and healthy, cycling women.

Intervention(s): None.

Main Outcome Measure(s): Serum levels of the sex steroids (estrogen, progesterone, and testosterone) and of Ca^{2+} and Mg^{2+} were measured in menopausal and postmenopausal women, and in healthy, cycling women at five different stages of the menstrual cycle.

Result(s): The Mg^{2+} and total Mg levels of the postmenopausal women were inversely related to the serum level of estrogen and were similar to the levels present during the early follicular phase of healthy women of child-bearing age. The Ca^{2+} level was unrelated to the sex steroid hormones present, but it was increased compared with that of younger women in both the follicular phase and the luteal phase.

Conclusion(s): Serum levels of Mg^{2+} and total Mg were inversely correlated with the estrogen concentration in menopausal women. Serum levels of Ca^{2+} were significantly elevated in menopausal women compared with younger women, but the ratio of Ca^{2+} to Mg^{2+}, a measure of cardiovascular problems, was not elevated in the postmenopausal women. (Fertil Steril® 1999;71:869–72. ©1999 by American Society for Reproductive Medicine.)

Key Words: Estrogen, progesterone, testosterone, ionized magnesium, ionized calcium, ionized Ca/Mg ratio, menopause

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We previously examined serum levels of ionized magnesium (Mg^{2+}) and ionized calcium (Ca^{2+}) in healthy women of reproductive age in conjunction with their hormone profiles. These women showed recurring changes in their serum levels of Mg^{2+} and total Mg, and alterations in the ratio of Ca^{2+} to Mg^{2+} as their serum levels of estrogen, testosterone, and progesterone rose and fell (1). With low levels of estrogen and testosterone, levels of Mg^{2+} and total Mg were comparatively elevated, whereas the level of Ca^{2+} was comparatively low. As the estrogen level peaked, the Mg^{2+} level fell and the Ca^{2+} level rose; the rise in the Ca^{2+} level was associated with an increase in the hormone that was shown previously (2). When the progesterone level peaked, levels of both Mg^{2+} and total Mg were low and the ratio of Ca^{2+} to Mg^{2+} was significantly increased (1).

We recently demonstrated that an elevated ratio of Ca^{2+} to Mg^{2+} is associated with vasospasm (3) and the onset of migraine and tension headaches (4–6). Our clinical trials indicate that these headaches are relieved in most women by the IV administration of $MgSO_4$, which normalizes the elevated ratio of Ca^{2+} to Mg^{2+} (5, 6).

In the present study, we evaluated 25 menopausal and postmenopausal women of different ages, and compared their serum levels of estrogen, testosterone, and progesterone, as well as Mg^{2+}, total Mg, and Ca^{2+}, with those of women of child-bearing age.

TABLE 1

Baseline characteristics of the 25 menopausal women at study enrollment.

Characteristic	Mean ± SD (range)
Age (y)	53.56 ± 27.37 (42–65)
Height (m)	1.65 ± 0.08 (1.40–1.81)
Weight (kg)	77.19 ± 12.42 (55.33–105.69)
Body mass index (kg/m^2)	29.04 ± 4.198 (20–36)
Duration of menopause (y)	4.71 ± 5.74 (1–20)

MATERIALS AND METHODS

Patient Selection

Twenty-five menopausal and postmenopausal volunteers of varying ages were selected, none of whom were receiving hormonal medications. This study was approved by the institutional review board at our center. Informed consent was obtained from the volunteers. Fifteen premenopausal women with normal cycles were studied for comparison.

Blood samples were drawn under anaerobic conditions, and serum was separated out and stored at −10°–20°C for cation analysis and at −79°C for hormone assays. We drew samples from the young women at five different stages of the menstrual cycle, as described previously (1).

Hormone and Cation Assays

Levels of E_2, progesterone, and testosterone were determined with the use of Coat-A-Count RIA kits (Diagnostic Products Corporation, Los Angeles, CA). Levels of Ca^{2+} and Mg^{2+} were measured with Nova Biomedical Stat (Nova Biomedical, Waltham, MA) Profile 8 ion-selective electrodes for Ca^{2+} and Mg^{2+}, respectively (7). The level of total Mg was measured with a Kodak DT 60 colorimetric instrument (Rochester, NY), which uses a formazan dye complex (7). The ratio of Ca^{2+} to Mg^{2+} was calculated (measured Ca^{2+} divided by measured Mg^{2+}), as was the percentage of Mg^{2+}. The normal reference ranges for our laboratory are as follows: Ca^{2+}, 1.09–1.33 mmol/L; Mg^{2+}, 0.54–0.64 mmol/L; total Mg, 0.74–0.96 mmol/L; and percentage of Mg^{2+}, 61%–75% (7).

Statistical Analysis

Where appropriate, the data are presented as means ± SD. The relations between two variables were analyzed by simple linear regression (with 95% confidence limits) using Microcal Origin software (Microcal Software, Inc., Northampton, MA). Correlation analyses were accomplished with Pearson's two-tailed significance tests. The unpaired Student's *t*-test was used to ascertain relations between two groups. $P<.05$ was defined as statistically significant.

RESULTS

Table 1 shows the characteristics of the menopausal women enrolled in the study. The premenopausal women were 23–35 years of age. Table 2 shows the mean (±SD) serum levels of estrogen, progesterone, and testosterone for all the women. In comparing the data, we found, as we expected, that the serum estrogen levels of the menopausal women were significantly lower than those of the healthy, cycling women, even during the early follicular phase. The progesterone levels of the postmenopausal women also were significantly lower, whereas the testosterone levels were similar to those of the normally cycling women during the early follicular phase (8).

TABLE 2

Serum hormone levels of all the study participants.

	Hormone level		
Subject	Estrogen (pg/mL)	Progesterone (ng/mL)	Testosterone (ng/dL)
Normal cycling			
Follicular phase	41.05 ± 13.15	0.68 ± 0.34	18.55 ± 8.15
Ovulatory phase	184.19 ± 63.78	3.31 ± 5.65	26.97 ± 14.21
Menopausal	16.48 ± 9.45	0.26 ± 0.18	17.90 ± 9.48

Note: Values are means ± SD.

Table 3 shows the mean (±SD) serum levels of Mg^{2+}, Ca^{2+}, and total Mg, the mean (±SD) ratio of Ca^{2+} to Mg^{2+}, and the mean (±SD) percentage of Mg^{2+} in all the women, determined from the same samples that were used for the hormone analyses. The serum Mg^{2+} and total Mg levels of the menopausal women were similar to those of the healthy, cycling women during their lowest estrogen and progesterone phase (i.e., the early follicular phase). The mean serum Mg^{2+} level, however, was significantly higher in the menopausal women than in the healthy, cycling women during their highest estrogen phase ($P<.01$). There was no statistically significant difference in the percentage of Mg^{2+} compared with the values during either of these phases. On the

TABLE 3

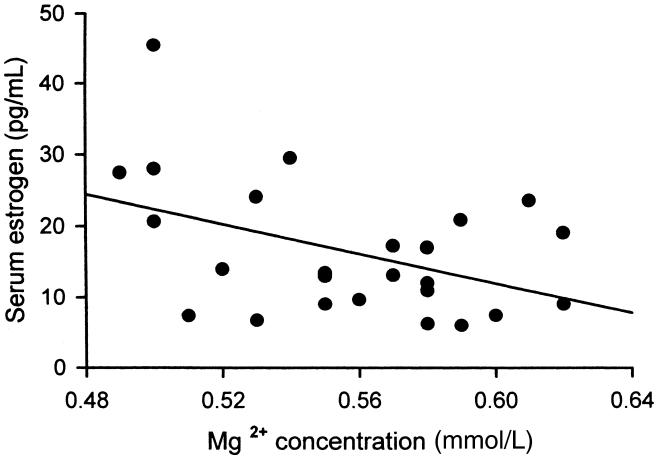
Serum cation levels of all the study participants.

	Patient group		
	Healthy cycling		
Cation	Follicular phase	Ovulatory phase	Menopausal
Mg^{2+} level (mmol/L)	0.55 ± 0.04	0.53 ± 0.04	0.56 ± 0.04
Ca^{2+} level (mmol/L)	1.19 ± 0.04	1.20 ± 0.05	1.24 ± 0.04
Mg total level (mmol/L)	0.83 ± 0.07	0.80 ± 0.07	0.83 ± 0.08
Ca^{2+}/Mg^{2+} ratio	2.17 ± 0.18	2.29 ± 0.20	2.24 ± 0.18
Percentage of ionized Mg	66.67 ± 3.98	66.33 ± 4.30	67.24 ± 4.89

Note: Values are means ± SD.

FIGURE 1

Relation between serum estrogen levels (pg/mL) and serum ionized magnesium (Mg^{2+}) levels (mmol) in menopausal women. $P=.04$.



other hand, the mean level of Ca^{2+} in the menopausal women was significantly higher than that in the younger women during their low estrogen and progesterone phase ($P<.01$). The mean ratio of Ca^{2+} to Mg^{2+} in the menopausal women, however, was not different from that in the cycling women at either low estrogen levels or high estrogen and progesterone levels.

Figure 1 shows that the serum level of Mg^{2+} was inversely related to the serum level of estrogen in the menopausal women. The level of total Mg showed a similar trend, which approached statistical significance. This is similar to what we found in the healthy, cycling women when we compared each woman's values at different times during her cycle. That is, when the estrogen level increased, the Mg^{2+} level decreased, and there was an opposite trend for the Ca^{2+} level, whereas the ratio of Ca^{2+} to Mg^{2+} rose as the estrogen and progesterone levels peaked. We found no correlation between the level of Ca^{2+} and the concentration of any of the sex steroid hormones in the menopausal women, and no correlation between the level of Mg^{2+} or total Mg and the concentration of testosterone or progesterone. Finally, neither the divalent cations nor the hormone concentrations were related to body mass index in our study group.

DISCUSSION

It can be surmised from our recent study of adult women of child-bearing age (1), the results of which are largely confirmed by our present study of menopausal women, that serum levels of Mg^{2+} and total Mg are related in some way to serum levels of estrogen. This also was true when we examined young women undergoing stimulation for IVF, (unpublished observations), whose estrogen levels are greatly increased. Further, it has been reported repeatedly that women who are pregnant have a decreased level of total Mg, as do menopausal women who are treated with estrogen (9, 10).

Thus, in the menopausal and postmenopausal women, mean levels of Mg^{2+} and total Mg were similar to those in the cycling women during the early follicular phase, when estrogen and progesterone levels are comparatively low (Table 2). However the Mg^{2+} level was significantly higher in the menopausal women than in the healthy, cycling women during the high estrogen stage (around the time of ovulation) ($P<.02$). In addition, in the menopausal and postmenopausal women, the Mg^{2+} level was inversely and significantly related to the estrogen level ($P<.04$) (Fig. 1), and the same tended to be true for the total Mg level.

The serum level of Ca^{2+} was significantly higher in the menopausal women than in the cycling women during the early follicular phase ($P<.0006$) or in the cycling women during the high estrogen stage ($P<.02$).

The fact that the Ca^{2+} level was increased in the blood of menopausal and postmenopausal women should not come as a surprise. It has been well documented that, during this stage of a woman's life, bone metabolism is increased to the point where breakdown is more prevalent than buildup (11). An increase in serum Ca and total Mg levels in women after menopause was reported previously (9, 10). The increases in serum Ca and total Mg levels associated with the loss of estrogen were thought to result in increased bone breakdown (10).

Another group of investigators reported an increase in the total Mg level in serum and in urine, but found no change in erythrocyte Mg related to menopause or estrogen therapy (12). Therefore, they also concluded that the increases in divalent cation concentrations were due to increased bone breakdown. A third group interpreted their findings of increased Mg in the blood and urine as indicative of increased absorption of the cation from the gut (13).

An increase in bone metabolism has been cited often as the cause of osteoporosis in postmenopausal women. A recent study, however, explains why all postmenopausal women do not have this disease (14). The investigators demonstrated that, in addition to low serum estrogen levels, patients with osteoporosis had kidneys that did not reabsorb as much calcium as the kidneys of women without osteoporosis (14).

We cannot explain the increased risk of cardiovascular disorders in menopausal and postmenopausal women, as we had anticipated, solely by the concentrations of circulating divalent cations in their blood. Although the serum Ca^{2+} level is increased, which would make the vascular system more prone to contractions and spasms, the comparatively higher Mg^{2+} level should act as a balancing ion (15) to ameliorate the tendency toward increased blood pressure and

increased peripheral resistance. Estrogen is known to be responsible for other protective mechanisms that affect the blood pressure and cardiovascular system, such as vasodilation, the release of nitric oxide, and the inhibition of vascular smooth muscle cell growth (16–18); these mechanisms would be reduced at menopause. In addition, progesterone has been found to have beneficial effects on the cardiovascular system (18–20); these also would be lost during menopause because the concentration of progesterone is greatly reduced.

It is possible that women who have low serum levels of Mg^{2+} could be at risk for the development of cardiovascular disease. We showed that certain patients with heart disease, diabetes, hypertension, and stroke have low serum Mg^{2+} concentrations (4, 15), lower than the mean concentration in our healthy menopausal women, and that these patients invariably have a high ratio of Ca^{2+} to Mg^{2+}. Therefore, it would be efficacious to study more postmenopausal women and to study some of them in series, to strengthen this hypothesis.

In any case, it would seem that a low estrogen level (no more than the amount that circulates in the blood during the follicular phase in premenopausal women) is beneficial to the cardiovascular system, both because of its direct effects on blood vessels and the heart, and because it seems to "allow for" the presence of an adequate (protective) amount of Mg^{2+} circulating in the blood.

In our previous article (1), we indicated that premenstrual syndrome and cyclically recurring migraine headaches, which some women of child-bearing age experience, were related in part to the increase in estrogen and accompanying decrease in circulating Mg^{2+} (and increase in the ratio of Ca^{2+} to Mg^{2+}) that is found in these women during the luteal phase. Therefore, it seems possible that the known dramatic decrease in migraine headaches that occurs after menopause (21) may be due to the basically steady, comparatively elevated concentration of Mg^{2+} (compared with the usual significantly decreased level that occurs in the ovulatory-luteal phase) (1) that we found in the blood of menopausal women.

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