Relationship Between Plasma and Erythrocyte Magnesium and Potassium Concentrations in Fasting Obese Subjects

By William K. Stewart and Laura W. Fleming

During 18-day fasts undertaken by 19 obese patients, plasma magnesium concentrations decreased in those given no mineral supplements or given calcium or sodium supplements, but did not decrease in those given magnesium supplements. The extent of the decreases ranged from 9% in the nonsupplemented group to 25% in the sodium-supplemented group. Plasma potassium concentrations decreased more gradually in all patients, irrespective of magnesium supplementation. Erythrocyte magnesium concentrations remained un-

It has been stated\(^1\)\(^-\)\(^4\) that, in general, plasma levels of electrolytes remain unchanged or are only insignificantly altered, even after fairly prolonged periods of fasting. No reports have mentioned magnesium specifically until Drenick et al.\(^2\) reported unchanged plasma magnesium concentrations in 18 fasting obese male subjects, despite continued urinary magnesium loss and biopsy evidence of magnesium “depletion” in muscular tissue. Their results for plasma magnesium concentrations are at variances with our own, which are reported here.

Decreases in plasma potassium concentrations during fasting have been
reported repeatedly,5-7 but to our knowledge there have been no reports on
erythrocyte concentrations during starvation. Our finding of decreased eryth-
rocyte potassium concentrations during fasting, reported here, is of interest
due to the effect of magnesium thereon.

MATERIALS AND METHODS

Patient Treatment

Obese patients admitted for weight reduction were stabilized on the routine ward diet
for 3-6 days, during which time base-line blood and urine concentrations were measured.
These estimations were repeated throughout a 12-day period of fasting, with oral intake
of noncaloric fluids fixed at 1500 ml or 2000 ml daily, whichever the patient preferred.
One multivitamin tablet (Juvel, Bencard) was taken daily. On Day 13, counting the first
day of the fast as Day 1, 107 g carbohydrate, supplying 425 kcal, were given daily as
demineralized liquid glucose B.P.C. (Hycal, Beechams), in two doses diluted to taste from
the fluid allowance. One bottle of Hycal containing 175 ml supplies this amount. This
carbohydrate intake was continued for 6 days from the 13th to the 18th day inclusive,
with fluids and vitamins as before. Thereafter, the "refeeding" period began, with a
low-calorie diet supplying 600-800 kcal.

Patients were allocated into four test groups (Table 1). Seven, treated as described above,
formed the "no-supplements" group. Six patients (the calcium-supplemented group) were
treated as above, but in addition they were each given calcium supplements as calcium
glucogalactogluconate (Calcium-Sandoz, or SandoCal tablets—Sandoz), such that their
calcium intake remained relatively unchanged over the entire period of study and
approximated to their estimated calcium intake before entering the hospital. In practice,
this amounted to two tablets of Calcium-Sandoz or SandoCal per day for all six patients.
(See Table 1 for sodium and potassium contents of these tablets.)

A further seven patients (the magnesium-supplemented group) were given magnesium
supplements in the form of gelatin capsules containing 83 mg magnesium oxide (Analytical
Reagent Grade), that is, supplying 4.1 meq magnesium per capsule. The magnesium sup-
plements were given in three divided doses during the day, the amount being such that
magnesium intake remained relatively unchanged throughout the whole period of study,
and approximated to the patient's habitual intake (Table 1). In practice, this meant four,
five, or six capsules daily, until Day 19, when one less capsule was given to compensate
for the intake of magnesium contained in the 600-800 kcal diet.

Two patients were given sodium citrate supplements daily (sodium-supplemented group)
in the hope of minimizing the metabolic acidosis of fasting. These patients received 90 ml
of modified Shohl's mixture, in three divided doses of 30 ml. The modified Shohl's solution
contained 98 g sodium citrate and 30 g citric acid per liter, with the glucose and coloring
solution of the original formulation omitted. One ml of solution provided 1 meq of
sodium and 1 meq of alkali, the total intake of sodium being 90 meq daily.

Altogether, nineteen patients fasted for 18-day periods. Three of the nineteen fasted
twice making 22 fasts total. There were no statistically significant differences between
the various groups in respect of age, height, and percentage overweight, the last cal-
culated from the Metropolitan Life Insurance Tables8 of ideal weight at age 25. There
was one diabetic patient in each of the first three groups, but only one was on treatment
(tolbutamide) prior to the fast. Two of the patients in each of the first three groups were
not given the carbohydrate supplement during Days 13-18. There was no detectable
difference between these patients and the others with respect to the blood levels of
magnesium and potassium described here. All patients were weighed daily at 8 a.m. after
voiding urine.

Sampling

Venous blood samples were collected without tourniquets into heparinized containers.
They were taken during the base-line period and on Days 1, 6, 12, 15, and 18 during
<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Carbohydrate Supplements Days 13-18 Only (g/day)</th>
<th>Calcium (meq/day)</th>
<th>Magnesium (meq/day)</th>
<th>Sodium (meq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplements</td>
<td>5</td>
<td>105</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>4</td>
<td>105</td>
<td>38*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sodium supplements</td>
<td>2</td>
<td>105</td>
<td>None</td>
<td>None</td>
<td>90</td>
</tr>
<tr>
<td>Magnesium supplements</td>
<td>5</td>
<td>105</td>
<td>None</td>
<td>17 to 25</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>21 to 25</td>
<td>None</td>
</tr>
</tbody>
</table>

*Calcium-Sandoz: Two tablets provided 12 meq sodium and 9 meq potassium daily.

†Sandocal: Two tablets provided 13.2 meq sodium and 9 meq potassium daily.
During the refeeding period, blood samples were taken on either Day 20 or 21 and on Day 22 or 23.

Hematocrits were measured using a standard centrifugation technique (British Standard No. 4316: 1968). Lysed blood samples for the erythrocyte measurements were prepared by adding 2 ml of whole blood to 3 ml of deionized water, which, to prevent clotting during storage, contained 2 drops sodium heparin B.P.

Twenty-four-hour urine collections were taken using thymol/isopropanol as a preservative. Aliquots were stored at -4°C until analysis using acid as a preservative (0.5% HCl final concentration).

Plasma, blood lysate, and urinary magnesium concentrations were measured by atomic absorption spectrophotometry using the Zeiss FA-2 flame attachment and MM12 double monochromator. Potassium in plasma, lysate, and urine was measured by flame emission spectrophotometry.

Erythrocyte magnesium and potassium concentrations were calculated using the formula:

\[ [E] = \frac{100}{H} ([L] - \frac{H}{100} \times [P]) \]

where \( H \) is the hematocrit and \([L] \) represents the concentration of the cation in meq/liter of erythrocytes \([E]\), lysate \([L]\), and plasma \([P]\), respectively.

Plasma bicarbonate concentrations were measured in the AutoAnalyzer (Technicon method N21A).

For all comparisons of fasting days and base line within the groups the two-sided t test for paired data was used; i.e., \( t = \frac{\bar{d} - 0}{s_{d}/\sqrt{n}} \) where \( \bar{d} = \) mean difference and \( n = \) number of pairs.

**RESULTS**

**Plasma Magnesium**

A decrease in plasma magnesium concentrations (Fig. 1) was apparent by Day 6 of the fast in all but the magnesium-supplemented patients. In the nonsupplemented group the plasma magnesium decreased from a mean base-line concentration (meq/liter ± SD) of 1.81 ± 0.15 to 1.66 ± 0.18 by Day 6, with subsequent mean concentrations remaining at this level (1.64 ± 0.14 on Day 12, 1.67 ± 0.12 on Day 15, and 1.65 ± 0.17 on Day 18; \( p < 0.02 \) to < 0.05 compared with base-line concentrations). The difference was significant even for Day 6 (\( p < 0.02 \)). In the calcium-supplemented group, the decrease appeared more pronounced. By Day 6, the mean plasma magnesium had decreased from 1.76 ± 0.08 to 1.62 ± 0.13, reaching 1.51 ± 0.10 on Day

![Fig. 1. Mean plasma magnesium concentrations during fasting. The normal reference line shows the mean value for 55 blood donors.](image-url)
The level of significance of the decreases ranged from $p < 0.005$ on Day 6 to $< 0.001$ on Days 12, 15, and 18, compared with base-line concentrations. As evidence of the lack of difference in response between those given carbohydrate and those not, the individual decreases ranged between 0.09 and 0.40 on Days 15 and 18 in the carbohydrate-supplemented patients and between 0.21 and 0.35 in those not given carbohydrate. The greatest decrease in plasma magnesium was seen in the sodium-supplemented patients, with mean concentrations of 1.54 ± 0.02 on Day 6 and 1.32 ± 0.08 on Day 12. The low levels were maintained in the carbohydrate-fed period, the mean concentrations being 1.34 ± 0.10 on Day 15 and 1.33 ± 0.14 on Day 18. In contrast, the magnesium-supplemented patients showed no decrease in plasma magnesium levels, the difference from the base-line concentrations being insignificant on all days. The decrease in plasma magnesium ranged from 9% in the nonsupplemented group through 16% in the calcium-supplemented group to 25% in the sodium-supplemented patients.

**Erythrocyte Magnesium**

Unlike the plasma magnesium concentrations, erythrocyte magnesium concentration changes did not exceed ±4% in any of the four groups through-
out the period of investigation (Fig. 2). For some unknown reason the base-line erythrocyte magnesium concentrations in the sodium-supplemented patients were lower than in the others, but the low values were maintained unchanged during the fast.

**Plasma Potassium**

Mean plasma potassium concentrations (Fig. 3) decreased in all four groups, but the decrease was more gradual than it was with magnesium, becoming apparent only by Days 12 or 15, and it was unaffected by either calcium or magnesium supplements. The lowest potassium levels occurred in the sodium-supplemented patients, where the decrease by Day 18 was comparable to that shown by magnesium (i.e., 25%). In the other groups, the decrease by Day 18 ranged between 12% and 17%, being less (4%–10%) on Day 12.

**Erythrocyte Potassium**

A divergence was seen in the changes in erythrocyte potassium concentrations, comparing the four groups (Fig. 4). A decrease of between 5% and 9% in erythrocyte potassium occurred in the nonsupplemented, calcium-supplemented, and sodium-supplemented patients, whereas in the magnesium-supplemented patients the erythrocyte potassium concentrations remained unchanged (−0.3 to +0.1%). In the nonmagnesium-supplemented patients, the decrease from a mean base-line concentration (meq/liter ± SD) of 95.6 ± 4.1 to 85.6 ± 5.6 on Day 6 was significant (p < 0.005). On Days 12, 15, and 18, the concentrations were respectively 89.9 ± 3.4, 89.9 ± 2.7 and 89.7 ± 1.4 (p < 0.001 on Days 12 and 15 and p < 0.01 on Day 18 compared with the base-line concentration).

**Plasma Bicarbonate**

The plasma bicarbonate concentrations (Table 2) suggested that the extent of extracellular acidosis was greatest in the sodium-supplemented and non-supplemented groups, where the concentrations ranged between 19 and 22 meq/liter, and least in the calcium-supplemented group during the fast. Carbohydrate supplementation during Days 13–18 corrected the acidosis in
Table 2. Mean Plasma Bicarbonate Concentrations (meq/liter ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-fast</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 12</th>
<th>Day 15</th>
<th>Day 18</th>
<th>Day 20/21</th>
<th>Day 22/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplements</td>
<td>26 ± 2</td>
<td>26 ± 3</td>
<td>20 ± 3</td>
<td>21 ± 4</td>
<td>26 ± 3</td>
<td>26 ± 2</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>23 ± 3</td>
<td>27 ± 2</td>
<td>24 ± 3</td>
<td>25 ± 3</td>
<td>31 ± 3</td>
<td>33 ± 3</td>
<td>32 ± 3</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Sodium supplements</td>
<td>25 ± 1</td>
<td>26 ± 1</td>
<td>19 ± 0</td>
<td>22 ± 4</td>
<td>28 ± 1</td>
<td>36 ± 2</td>
<td>34 ± 4</td>
<td>—</td>
</tr>
<tr>
<td>Magnesium supplements</td>
<td>27 ± 1</td>
<td>26 ± 2</td>
<td>23 ± 3</td>
<td>22 ± 4</td>
<td>26 ± 2</td>
<td>27 ± 1</td>
<td>27 ± 1</td>
<td>29 ± 3</td>
</tr>
</tbody>
</table>

Table 3. Urinary Excretion of Magnesium and Potassium (meq/24 hr)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Magnesium Excretion</th>
<th>Mean Potassium Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Line</td>
<td>Peak (*)</td>
</tr>
<tr>
<td>No supplements</td>
<td>5.4</td>
<td>6.6 (3)</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>6.4</td>
<td>7.4 (4)</td>
</tr>
<tr>
<td>Sodium supplements</td>
<td>7.4</td>
<td>8.7 (5)</td>
</tr>
<tr>
<td>Magnesium supplements</td>
<td>9.3</td>
<td>16.0 (4)</td>
</tr>
</tbody>
</table>

*Day of peak excretion in parentheses.
†Mean ± SD.
Urinary magnesium excretion (Table 3) during the twelve days of complete fast was fairly similar in the three groups not given magnesium supplements, the calcium- and sodium-supplemented patients having a slightly greater excretion of magnesium during the last few days than the nonsupplemented group. The magnesium-supplemented patients had a much higher rate of excretion, but all four groups showed the same general pattern, namely a temporary "peak" excretion, increased compared with base line during Days 3–5, followed by decreased excretion stabilizing over Days 9–12.

Urinary potassium excretion (Table 3) also showed a slight "peak" over Days 4–7 in all groups, with the greatest excretion seen in the sodium-supplemented patients and the least in the nonsupplemented patients. With the exception of the sodium-supplemented patients, in whom potassium excretion during Days 9–12 continued at the base-line rate, excretion in the other groups stabilized at around half the base-line rate during Days 9–12.

DISCUSSION

Magnesium and the Fasting State

Hypomagnesemia can be readily elicited in fasting animals. The prompt hypomagnesemia that occurs on complete fasting in man has been largely overlooked, judging both by reviews on fasting and by reviews on magnesium metabolism. This lack of comment is unusual when, according to our data, the decrease in plasma magnesium is the first definite plasma cation change seen to occur during short-term fasting, the only other comparable one being the more slowly developing decrease in potassium levels, while plasma calcium, sodium, and phosphate concentrations remain essentially unchanged.

Recently, "magnesium depletion" has been reported to occur, without hypomagnesemia, in obese males during fasting. The evidence of depletion was obtained from the analysis of muscle biopsy specimens taken before and after the fast, in five subjects who fasted between 55 and 63 days, and from estimates of total magnesium losses in six subjects. It would appear that only two of the five were among those subjects in whom magnesium losses were measured. Although we, like Drenick and colleagues, found a peak magnesium excretion during the first few days of fasting, the subsequent stabilized urinary excretion in our patients of between 2.9 and 4.3 meq/24 hr was considerably lower than their reported urinary excretion level of an average 7 meq/day. Despite the lower urinary excretion, our patients showed consistent hypomagnesemia. In 18 of the subjects studied for up to 60 days by Drenick and colleagues, plasma magnesium decreased "modestly" in only five patients, remained steady in seven, and increased slightly in six. Unfortunately, it is not clear which of the eighteen were among those subjects who were also investigated for total losses or muscle concentrations. Clearly, these
reported plasma results are at variance with our experience. Some or all of the patients studied by Drenick and colleagues received allopurinol. Although they assert that allopurinol had no effect on magnesium excretion, the drug might conceivably have influenced plasma magnesium concentrations, particularly in view of the admitted lack of correlation between magnesium loss and plasma magnesium mentioned later in their report. Another difference between our patients and their subjects was that our patients received no potassium supplements whereas they state that “most subjects” received 2 g potassium chloride daily. The difference in vitamin D content between their multivitamin tablets and ours (400 units as compared with 500 units) was probably immaterial.

Runcie and Thomson remark in passing that one patient had a normal plasma magnesium concentration at the time she developed tetany during a long-term fast, but no other details are available, although it appears likely from other statements that this patient might also have received potassium supplements. It may therefore be relevant that the above-mentioned patients, unlike those described here, apparently received potassium supplements. Until this potential influence is explored, the present results remain in sharp contrast.

By further contrast, there has been a single case report describing increased plasma magnesium concentrations at the end of a 45-day fast undertaken for religious reasons, but the actual fast was unsupervised and, although the subject was said to be reliable, the possibility that a magnesium-containing purgative was taken cannot be ruled out. Increased serum magnesium levels have also been reported during 10-day fasts by six nonobese volunteers, but there was in fact no increase after the first day of the fast, the reported mean concentrations being 1.83, 1.90 and 1.80 meq/liter respectively on Days 1, 5, and 10 of the fast. Moreover, their low base-line value of 1.63 was unusual.

That the plasma magnesium decrease of fasting reflects a developing deficiency rather than adaptation is suggested by the fact that the plasma magnesium did not decrease in the fasting patients who received magnesium supplements. Thus, the hypomagnesemia seems to be a consequence of the lack of magnesium intake and is not an indirect, mediated expression of caloric deprivation or of some other fasting attribute.

Magnesium–Potassium Interrelationships

The present fasting studies may shed some light on magnesium–potassium interrelationships. The main feature was the decrease in erythrocyte potassium concentrations in the groups not given magnesium, evident and indeed greatest by the sixth day of the fast, before the development of obvious hypokalemia. The fact that the magnesium–supplemented group alone failed to show any decrease in erythrocyte potassium concentrations suggests an effect of magnesium, or some correlate thereof, on potassium distribution. Such ‘magnesium-sensitive’ factors appear to be capable of influencing intracellular potassium concentrations. It is perhaps relevant that the sodium–supplemented group, which showed the greatest decrease in plasma magnesium concentra-
tion, also showed the greatest decrease in erythrocyte potassium concentration.

A positive correlation between extracellular magnesium and intracellular potassium concentrations has been described previously for muscle in an in vitro system.\textsuperscript{17} Similarly, during investigations on anesthetic agents,\textsuperscript{18} increased magnesium concentrations reduced the loss of intracellular potassium, possibly due to decreased membrane permeability to potassium. Seller et al.\textsuperscript{19} noticed a similar relationship in hypertensive subjects treated with diuretic drugs, in whom serum magnesium decreased in parallel with a decrease in the erythrocyte potassium:magnesium ratio. Severe magnesium deprivation in growing animals is usually accompanied by decreases in tissue potassium content, characteristically without changes in plasma potassium concentrations,\textsuperscript{13} but these experimental states are of uncertain relevance to the condition of adult human subjects temporarily deprived of magnesium or of magnesium and potassium.

Hypomagnesemia preceded the hypokalemia in all groups except in the magnesium-supplemented group, who had no hypomagnesemia yet still developed hypokalemia. This would suggest that the occurrence of hypokalemia in fasting patients is not mediated or potentiated by magnesium deficiency in contrast to the effect on intracellular (erythrocyte) potassium concentrations. Although an increase in plasma potassium concentrations might be expected during the development of extracellular acidosis,\textsuperscript{20} this did not occur during the fast presumably because of the concurrent negative balance of potassium.

It is appropriate to compare the present results with those in other studies of human subjects involving magnesium-deficient but otherwise fully adequate diets.\textsuperscript{21-25} While search for an explanation why his magnesium-deficient patients developed hypomagnesemia while the subjects of other authors cited did not, Shils\textsuperscript{25} pointed out that his subjects had received the lowest potassium intake. This would be compatible with the experience of Carrillo and others,\textsuperscript{26} who reported that a high potassium intake minimized the decrease in plasma magnesium in rats on a low magnesium diet. These two reports suggest that high or even adequate potassium intakes can diminish the hypomagnesemia of magnesium deprivation. Unfortunately, this is in direct opposition to other findings in rats,\textsuperscript{27} and in sheep,\textsuperscript{28} where potassium supplements appeared to aggravate the hypomagnesemia brought about by a magnesium-deficient diet. Since the hypokalemia of Shils' patients was corrected by magnesium supplements, it is therefore notable that a comparable effect was not observed in the completely fasting patients reported here.

It is of interest that there was no very obvious difference in urinary potassium excretion between the magnesium-supplemented patients and the others. The higher excretion in the calcium-supplemented group compared with the nonsupplemented group was probably due to the potassium content of the calcium tablets, which supplied 9 meq potassium daily. It was the sodium and not the magnesium supplements that most obviously influenced the urinary potassium excretion, a feature possibly related to the distal tubular cation exchange mechanism.\textsuperscript{29} Since the magnesium-supplemented patients did not excrete less potassium than the others the urine results indicate that the
effect of magnesium on erythrocyte potassium was not necessarily mediated through a renal tubular mechanism, and was therefore possibly due to an internal redistribution of potassium. Likewise, there was no suggestion that the effect of magnesium on erythrocyte potassium correlated with the extent of extracellular acidosis.

CONCLUSION

In man, fasting induces hypomagnesemia unless magnesium supplements are supplied. If starvation therapy for obesity continues to be employed, there is reason for considering magnesium supplementation as an adjunct to the therapy.

The provision of magnesium supplements prevents the decrease in erythrocyte potassium, which otherwise would occur in the fasting patient. The determining factor was neither intracellular erythrocyte magnesium, which did not change in any group, nor plasma potassium, which decreased in all groups. The reason seems to be the maintenance of normal plasma magnesium concentrations, or some correlate of this, as seen in the magnesium-supplemented group. The results demonstrate that in the fasting patient the concentration of extracellular magnesium affects the distribution of potassium between extra- and intracellular compartments, at least in erythrocytes. Extracellular magnesium could exert this effect through its influence on the adenosine—triphosphatase system,30 which is associated with the cell membrane sodium-potassium transfer mechanism.

REFERENCES

15. Sunderman, W. F.: Studies in serum electrolytes. IXV. Changes in blood and


