Significant positive relationship between serum magnesium and muscle quality in maintenance hemodialysis patients

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Abstract. Background/Aims: Serum magnesium (Mg) levels have been associated with muscle performance in the general population. We hypothesized that serum Mg would be associated with muscle quality in hemodialysis patients. Methods: A total of 310 patients were examined (age: 58 ± 12 years, hemodialysis duration: 6.4 ± 6.0 years, 60.6% men, and 36.1% diabetics). Arm lean mass was measured by dual energy X-ray absorptiometry (DXA) on the dominant side. Arm muscle quality was defined as the ratio of the handgrip strength to the arm lean mass of the same side (kg/kg). Results: Serum Mg was 1.15 ± 0.16 mmol/L (2.8 ± 0.4 mg/dL), being higher than the reference range of normal subjects. There was a significant negative correlation between muscle quality and age (r = -0.326, p<0.0001) and duration of hemodialysis (r = -0.253, p<0.0001). The muscle quality of the diabetics was significantly lower than that of the non-diabetics (p<0.001). There was a significant, positive correlation between muscle quality and serum Mg (r = 0.118, p<0.05), but not serum calcium or phosphate. In multiple regression analysis, age, gender, hemodialysis duration, diabetes, and serum Mg (β = 0.129, p<0.05) were significantly and independently associated with muscle quality (R² = 0.298, p<0.0001). Conclusion: These results demonstrated that a lower serum Mg concentration was significantly associated with poor muscle quality in hemodialysis patients. Further studies are needed to explore the mechanism by which lower serum Mg affects muscle quality.

Key words: magnesium, muscle quality, hemodialysis, hand grip strength

Magnesium (Mg) acts as a co-factor for numerous enzymes and plays an essential role in a wide range of fundamental cellular reactions. Skeletal muscle is one of the tissues affected by Mg deficiency. Ingestion of an Mg-deficient diet has been shown to induce myopathy within one week in growing rats [1]. Ultrastructural changes have also been observed in Mg-deficient rats [2]. In diabetic rats, Mg treatment has been shown to prevent the decrease in muscle isometric twitch tension [3]. In older adults, intake of Mg has also been reported to be a positive predictor of changes in appendicular lean mass [4]. In elite, male sports players, magnesium intake has been associated with all isokinetic strength variables [5]. In older persons, serum Mg concentrations have been
associated with indices of muscle performance [6]. However, no studies have reported any relationship between serum Mg and muscle strength in dialysis patients, who can exhibit significantly higher Mg levels than the normal, healthy population [7-9]. We hypothesized that serum Mg in hemodialysis patients would be associated with muscle quality, as was assessed by the maximum hand grip strength of the dominant side relative to the lean mass of the arm, as measured by dual X-ray absorptiometry (DXA).

**Patients and methods**

**Patients**

A total of 310, stable, maintenance hemodialysis patients (188 males and 122 females) at Shirasagi Hospital, Osaka, Japan, who had undergone hemodialysis for more than three months were examined. In all patients, 4- to 5-hour hemodialysis was performed three times a week with bicarbonate dialysate. The Mg concentration of the dialysate of all patients was 0.5 mmol/L (1.0 mEq/L). None of the patients received supplemental Mg. All patients provided informed consent prior to participation in the present study. This study was approved by the ethics review committee of Shirasagi Hospital.

Blood was collected prior to each hemodialysis session. Serum calcium, phosphate, and Mg levels were measured using routine laboratory methods. Serum Mg was measured by the isocitrate dehydrogenase enzymatic method (Aqua-auto Kainos Mg Test Kit, Kainos Co. Ltd., Tokyo, Japan). The mean values of six measurements in three months were used for the analysis.

**Measurement of lean mass by dual X-ray absorptiometry**

At Shirasagi Hospital, annual measurements of bone mineral density are performed routinely, near to the birthday of each patient, using dual X-ray absorptiometry (DXA; QDR-4500A, Hologic, Waltham, MA, USA), 21-24 hours after completion of a dialysis session. Fat mass and lean mass of the patients were also measured at the same time as the bone mineral density measurements [10]. Lean mass of the upper limb was measured by DXA, and was regarded as representative of the muscle mass of the upper limb, as reported previously [11]. Handgrip strength was determined using a hand dynamometer by experienced research staff that were blinded to all clinical and biochemical data. The patients were instructed to apply as much handgrip pressure as possible using their dominant hand. The measurements were repeated three times and the highest score was recorded in kilograms. Muscle quality was calculated by division of the handgrip strength by the lean mass of the upper limb on the dominant side [11].

**Statistical analysis**

Data are presented as the mean ± SD. Correlation and linear regression analyses were performed to examine the relationships between muscle quality and several parameters. Multiple regression analysis was performed to examine the independent association of several parameters with muscle quality. In the analysis, gender and diabetes were entered as dummy variables (male 0, female 1; non-diabetes 0, diabetes 1). P-values <0.05 were considered significant. All analyses were performed using StatView 5 (SAS Institute Inc., Cary, NC, USA), designed for a Windows personal computer.

**Results**

*Table 1* presents the clinical characteristics of the 310 patients. There were 188 males and 122 females, and the mean age (± SD) of the participants was 58 (± 12) years. The duration

**Table 1. Clinical characteristics of 310 patients.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>58 ± 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>188/122</td>
</tr>
<tr>
<td>Duration of hemodialysis (years)</td>
<td>6.4 ± 6.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.4 ± 2.8</td>
</tr>
<tr>
<td>Diabetes (no/yes)</td>
<td>208/102</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.28 ± 0.15</td>
</tr>
<tr>
<td>Serum phosphate (mmol/L)</td>
<td>1.94 ± 0.42</td>
</tr>
<tr>
<td>Serum magnesium (mmol/L)</td>
<td>1.15 ± 0.16</td>
</tr>
</tbody>
</table>

(mean ± SD)
Figures 1 and 2. Relationships between muscle quality, age, body mass index (BMI) and duration of hemodialysis. There were significant negative correlations between muscle quality and age ($r = -0.326, p < 0.0001$) and duration of hemodialysis ($r = -0.253, p < 0.0001$), but not between muscle quality and body mass index (BMI).

Among these patients, there were significant negative correlations between muscle quality and age ($r = -0.326, p < 0.0001$) and duration of hemodialysis ($r = -0.253, p < 0.0001$), but not between muscle quality and body mass index (figure 1). Muscle quality was $10.6 \pm 2.8$ kg/kg in the diabetics compared with $12.1 \pm 4.0$ kg/kg in the non-diabetics. Muscle quality was significantly lower in the diabetics compared with the non-diabetics ($p < 0.001$) (figure 2). While there was a significant positive correlation between muscle quality and serum Mg ($r = 0.118, p < 0.05$), there were no significant correlations between muscle quality and serum calcium or serum phosphate (figure 3).

In multiple regression analysis, serum Mg ($\beta = 0.129, p = 0.0198$) was significantly and independently associated with muscle quality, in addition to other significant and independent variables of age, gender, duration of hemodialysis and diabetes ($R^2 = 0.298, p < 0.0001$), after adjustment for other factors, i.e., body mass index, serum calcium, and phosphate (table 2).

Discussion

In the present study, we demonstrated that muscle quality, as assessed by the maximum hand grip strength of the dominant side relative to the lean mass of the arm measured by DXA in hemodialysis patients, correlated significantly and positively with serum Mg concentration. This showed that patients with lower Mg concentrations exhibited poorer muscle quality, compared with those with higher Mg concentrations. Muscle quality was significantly and independently associated with serum Mg after adjustment for several confounders.

Several studies have examined the relationship between Mg deficiency and muscle disorders in rats. In these studies, Mg deficiency led to a complex array of biochemical, electrophysiological and morphological abnormalities in skeletal...
Mg and muscle quality in dialysis patients

Ca (mmol/L)

P (mmol/L)

Mg (mmol/L)

Figure 3. Relationships between muscle quality, serum calcium (Ca [mmol/L]), phosphate (P [mmol/L]) and magnesium (Mg [mmol/L]). There was a significant positive correlation between muscle quality and serum Mg ($r = 0.118$, $p < 0.05$), but not between muscle quality and serum Ca or P.

Table 2. Factors associated with muscle quality (multiple regression analysis).

<table>
<thead>
<tr>
<th>Factor</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.412</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (female versus male)</td>
<td>-0.040</td>
<td>0.4176</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>-0.089</td>
<td>0.0792</td>
</tr>
<tr>
<td>Duration of hemodialysis (years)</td>
<td>-0.414</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (yes versus no)</td>
<td>-0.280</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>-0.074</td>
<td>0.1766</td>
</tr>
<tr>
<td>Serum phosphate (mmol/L)</td>
<td>-0.105</td>
<td>0.0677</td>
</tr>
<tr>
<td>Serum magnesium (mmol/L)</td>
<td>0.129</td>
<td>0.0198</td>
</tr>
</tbody>
</table>

$R^2 = 0.298$

$\beta < 0.0001$

muscle [1-3, 12]. Ingestion of an Mg-deficient diet induced myopathy within one week in growing rats [1]. Electron microscopic evaluation of the skeletal muscle tissue from Mg-deficient rats revealed ultrastructural changes, including swelling of the mitochondria and disorganization of the sarcoplasmic reticulum network [2]. Pelit et al. showed that Mg treatment prevented the hyperglycemia-induced decrease in the isometric twitch tension of the gastrocnemius, and increased the resting membrane potential in diabetic rats [3]. Thus, skeletal muscle is considered to be damaged by Mg deficiency, and to be protected by Mg supplementation.

Several studies have examined the relationship between Mg and muscle in the general population, the elderly, and in adolescents [4-6, 13]. Energy-adjusted Mg intake was reported to be a positive predictor of changes in appendicular lean mass in 740, non-institutionalized, older adults, sampled randomly from the electoral rolls [4]. In elite, male sports players, Santos et al. reported that intake of Mg was directly associated with maximal isometric trunk flexion, rotation and handgrip, independent of total energy intake [5]. Domínguez et al. reported that serum Mg concentrations were significantly associated with indices of muscle performance, such as grip strength, lower-leg muscle power, knee extension torque and ankle extension strength, in older persons, after adjustment for age, sex, body mass index, and laboratory variables [6]. They further demonstrated that serum Mg concentrations were significantly associated with muscle performance after adjustment for muscle area and muscle density [6]. Their findings suggest that serum Mg was significantly and independently associated with muscle quality, i.e., muscle strength adjusted for muscle mass, which was consistent with the results of our study. Brilla et al. demonstrated significant differences in pre- and post- quadriceps torque gains between those with an Mg supplemented diet and those with a control diet, following a seven-week strength training program in 26 untrained subjects [13]. In their study, Mg supplementation was associated with muscle strength. To the best of our knowledge, there have been no studies on muscle strength in relation to Mg status in hemodialysis patients, who can exhibit significantly higher Mg levels than the normal, healthy population [7-9]. The present study examined the muscle quality of patients undergoing hemodialysis, and our findings are consistent with the above studies of patients without end-stage renal disease, in that lower Mg status was associated with poorer muscle strength or quality. As regards the relationship between diabetes and muscle quality,
type 2 diabetes has been associated with accelerated loss of leg muscle strength and quality in a three-year follow-up of 1840 older adults [14]. In the present study, we found that the muscle quality in diabetic hemodialysis patients was significantly lower than that of non-diabetic hemodialysis patients.

Several mechanisms have been hypothesized to explain the significant association between poor muscle strength and decreased Mg status. As an early consequence of Mg deficiency in rats, polymorphonuclear leucocytes become activated, whereas increased extracellular Mg concentrations inhibit the generation of free radicals [15]. Mg deficiency in rats is associated with increased oxidative stress through a reduction in plasma antioxidants and increased lipid peroxidation, suggesting that the increased oxidative stress in Mg deficiency may be due to increased susceptibility of body organs to free radical injury [16].

In humans, Mg intake has been reported to be inversely associated with systemic inflammation in middle-aged and older women [17]. Guerrero-Romero et al. reported that low serum Mg levels were independently related to elevated C-reactive protein (CRP) in non-diabetic, non-hypertensive obese subjects [18]. These reports suggest that systemic inflammation of the muscle due to Mg deficiency may bring about decreased muscle quality. Mg deficiency inhibits the expression of genes related to myogenesis in the gastrocnemius muscle, as well as in C2C12 myogenic cells [12]. The results of the present study, in which lower Mg was associated with poorer muscle quality, may be caused by an increased oxidative condition, increased systemic inflammation, and decreased myogenesis, although further studies are needed to explore the underlying mechanism. Although, in the present study, CRP, a marker of inflammation, was not measured in relation to serum Mg concentrations, the relationship between CRP, serum Mg concentrations, and muscle quality may be an interesting target to be examined in the future studies.

There are some limitations in the present study. Firstly, because of the observational nature of this cohort study, the association between lower serum Mg and poorer muscle quality does not necessarily indicate causality, i.e., it is not known whether low serum Mg leads directly to poor muscle quality. It may be necessary to demonstrate clinically that Mg supplementation to increase serum Mg concentrations leads to improved muscle quality. Secondly, we did not know the Mg intake of the patients in the present study. Serum Mg concentrations are reported to be affected by Mg intake [19]. In future studies, it will be necessary to examine Mg intake, possibly by using a nutritional questionnaire. Thirdly, our study was limited to a Japanese population, which may limit extrapolation of our findings to other ethnic groups. Finally, although in our study, muscle quality was assessed by hand grip strength divided by the lean mass, as measured by DXA, more precise methods to assess muscle quality will be necessary in future investigations.

In conclusion, the present study demonstrated that muscle quality was significantly associated with lower serum Mg in hemodialysis patients, independent of other significant variables of age, gender, duration of hemodialysis and diabetes. It may be necessary to consider Mg supplementation for hemodialysis patients with lower serum Mg concentrations. Further studies are needed to explore the mechanism by which lower serum Mg affects muscle quality.

Disclosure


References


