

# Correcting magnesium deficiencies may prolong life

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**Abstract:** The International Space Station provides an extraordinary facility to study the accelerated aging process in microgravity, which could be triggered by significant reductions in magnesium (Mg) ion levels with, in turn, elevations of catecholamines and vicious cycles between the two. With space flight there are significant reductions of serum Mg ( $P < 0.0001$ ) that have been shown in large studies of astronauts and cosmonauts. The loss of the functional capacity of the cardiovascular system with space flight is over ten times faster than the course of aging on Earth. Mg is an antioxidant and calcium blocker and in space there is oxidative stress, insulin resistance, and inflammatory conditions with evidence in experimental animals of significant endothelial injuries and damage to mitochondria. The aging process is associated with progressive shortening of telomeres, repetitive DNA sequences, and proteins that cap and protect the ends of chromosomes. Telomerase can elongate pre-existing telomeres to maintain length and chromosome stability. Low telomerase triggers increased catecholamines while the sensitivity of telomere synthesis to Mg ions is primarily seen for the longer elongation products. Mg stabilizes DNA and promotes DNA replication and transcription, whereas low Mg might accelerate cellular senescence by reducing DNA stability, protein synthesis, and function of mitochondria. Telomerase, in binding to short DNAs, is Mg dependent. On Earth, in humans, a year might be required to detect changes in telomeres, but in space there is a predictably much shorter duration required for detection, which is therefore more reasonable in time and cost. Before and after a space mission, telomere lengths and telomerase enzyme activity can be determined and compared with age-matched control rats on Earth. The effect of Mg supplementation, both on maintaining telomere length and extending the life span, can be evaluated. Similar studies in astronauts would be fruitful.

**Keywords:** magnesium, life span, telomeres, telomerase, catecholamines

## Commentary

It has been shown that about 60% of adults in the USA do not consume the estimated average requirement of magnesium (Mg), yet widespread pathological conditions attributed to Mg deficiency have not been reported.<sup>1</sup> One reason for this discrepancy may be that a significant Mg deficiency has not been recognized since only 1% of Mg is in the serum. In a study of geriatric outpatients, for example, serum Mg levels were within the normal range in all patients, whereas the intra-erythrocyte Mg measurements were low in 57% of the patients.<sup>2</sup> In another study, when measuring the total serum Mg concentration as subjects aged, there was no apparent change; however, when the intracellular free Mg concentration was measured, there was clearly a progressive decrease.<sup>3</sup> After 6 months in space, there is a loss of Mg reservoirs, with 35% loss in some leg muscles<sup>4</sup> and 1%–2% bone loss per month.<sup>5–10</sup>

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The International Space Station, at an initial cost of \$100 billion and considerable cost to maintain, which has six laboratories powered by solar energy, provides an extraordinary facility to study the accelerated aging process in space. This process could be triggered by significant reductions in Mg ion levels with, in turn, elevations of catecholamines and vicious cycles between the two. There is invariable malabsorption with microgravity.<sup>10</sup>

Despite the lack of sensitivity of the serum Mg, there are with microgravity significant reductions of serum Mg ( $P < 0.0001$ ) that have been shown in large groups of both astronauts and cosmonauts.<sup>11</sup> The loss of functional capacity of the cardiovascular system, which complicates space flight, occurs over ten times faster than it does during the course of aging on Earth.<sup>12</sup> There is increased vulnerability of the endothelium<sup>13</sup> and the heart because of its high enzyme content and dense mitochondrial structure.<sup>6</sup> Both aging and living in space induce the decline, not just of a single system, but of a composite of almost every body system.<sup>12</sup>

Permanent cardiac muscle injuries have been shown with reparative fibrosis in rats with Mg deficiencies.<sup>14</sup> This would contribute to permanent injuries to the heart from both too much and too little exercise.<sup>6</sup> Mg is an antioxidant and calcium blocker<sup>15</sup> and with microgravity and Mg ion deficiency there is oxidative stress, insulin resistance, and inflammatory conditions with cytokine elevations<sup>16</sup> conducive to endothelial injuries and shortening of the life span. Mg potentiates iron–transferrin binding, an important contribution to offsetting oxidative stress.<sup>17</sup>

The aging process is considered to be associated with progressive shortening of telomeres, repetitive DNA sequences, and associated proteins that cap and protect the ends of chromosomes. Telomeres' function in protecting chromosomes has been likened to the function of the plastic placed on the ends of shoelaces to keep them from unraveling. Telomerase adds telomeric repeats directly to nontelomeric sequences and can elongate pre-existing telomeres to maintain length and, therefore, chromosomal stability.<sup>18–20</sup> Low telomerase activity is associated with increased catecholamines,<sup>18</sup> while the sensitivity of telomere synthesis to Mg ions is primarily seen for the longer elongation products.<sup>19,20</sup>

Mg stabilizes DNA – reducing the potential for oxidative stress<sup>21</sup> and promoting DNA replication and transcription, whereas low Mg might accelerate cellular senescence by reducing DNA stability, protein synthesis, and the function of mitochondria.<sup>22,23</sup>

Mg is also essential in regulating >300 enzymes.<sup>8</sup> Telomerase, in binding to short DNAs, is Mg-dependent.<sup>23</sup>

It is involved in cell proliferation and genetic stability and DNA repair.<sup>23</sup> Telomere dysfunction is associated with impairment in mitochondrial function,<sup>24</sup> conducive particularly to the vulnerability of the heart.<sup>6</sup> Oxidative stress leads to accelerated telomere attrition, cell senescence, and, ultimately, to the progression of atherosclerotic disease.<sup>21</sup>

On Earth, a year might be required to detect changes in telomere lengths in humans.<sup>25</sup> The normal rat life span on Earth is about 3 years. With a predictably much shorter life span, studies in microgravity would be a more reasonable approach in terms of time and cost. Telomere lengths could be assessed pre- and postflight and compared with age-matched control rats on Earth. Additionally, the effect of Mg supplementation, both on maintaining telomere length and extending the life span, could be evaluated. Before and after space mission studies on astronauts could also be fruitful.

Regarding specifically experimental animal studies in microgravity, there have been several Russian studies involving, for example, evaluations of the myocardium of rats, divided into those utilized as controls under normal laboratory conditions and those subjected to microgravity to determine the vulnerability of the myocardium.<sup>26,27</sup> However, the exposure to microgravity has been for only relatively brief durations<sup>27</sup> and up to 4 months using only hypokinesia studies.<sup>26</sup> The Russians have shown, for example, in just 13 days, atrophy of rat heart muscle fibers, metabolic disturbances, and alterations in the structure of mitochondria.<sup>27</sup> In addition, these studies have shown suppression of myocardial protein synthesis, impairment in the repair process, and diminished function and activity of enzyme systems.<sup>26</sup>

Clearly, research involving lengths of telomeres and telomerase measurements would involve studies during long missions of at least 6 months and duration of stay on the International Space Station for at least this time. Results from such studies would have important implications for human aging on Earth as well as providing a way of evaluating the risk and prevention of premature aging in astronauts spending extended periods of time in space. These risks, particularly regarding the endothelium from oxidative stress, are not necessarily related to the effects of radiation in space. With the exception of solar storms, there would be no dangerous radiation on the International Space Station; there were no significant radiation elevations during the Apollo missions.<sup>7</sup>

Corrections of Mg deficiencies – which are very common on Earth, particularly in the elderly who have reduced Mg intakes, and invariably occur in space – may prolong life in microgravity. For studies of this in space, subcutaneous

administration of Mg will be required to supplement oral Mg, since there is malabsorption, as well as close monitoring of Mg levels by serial studies. Since impairment in renal function is a contraindication to administering Mg supplements and the kidneys are vulnerable to injuries in microgravity, close monitoring is also necessary. At this time, however, there is no subcutaneous implantable, replenishable, silicon device available to administer Mg to astronauts.<sup>9,10</sup>

In microgravity, plasma norepinephrine levels have been shown to be approximately twice those in the supine position on earth.<sup>9</sup> This is intensified by ischemia, which in turn triggers reductions in Mg ions with vicious cycles as noted above.

In addition, in microgravity, both experimental animals and humans will require an appropriate exercise program, focusing on avoiding very high catecholamine levels since catecholamines can undergo auto-oxidation which may in turn lead to injuries to telomeres.<sup>18</sup> Since Mg is an antioxidant, correcting Mg deficiencies is equally important in controlling vicious cycles with catecholamines and in turn ischemia.<sup>5,6</sup> This would require serial intracellular Mg studies.

Regarding an exercise prescription, Ludlow et al<sup>28</sup> has shown that a moderate amount of physical activity may provide a protective effect regarding telomere length in comparison with low and high exercise energy expenditures. This indeed supports my hypothesis that extraordinary, unremitting endurance exercise can injure a normal heart.<sup>5</sup> It also shows how difficult it will be to establish a suitable exercise program for experimental animals or astronauts in microgravity with the invariable problem of correcting Mg deficits.<sup>29</sup> Treadmill exercise will be required for both rats and astronauts and there will need to be cautious monitoring of heart rates and rhythm as these rates are higher in microgravity with catecholamine elevations conducive to ventricular fibrillation. This is particularly the case when rates reach 85% of one's predicted maximum heart rate.

There is another major problem with exercise in microgravity that will require careful monitoring with core temperature devices: it was first reported in 1995<sup>30</sup> that with exercise in space there are elevations of body temperature.<sup>31</sup> This could be triggered by the combination of loss of Mg in the sweat and through the kidneys, with the latter complicating increased angiotensin and aldosterone.<sup>8</sup> In addition, there is loss of plasma volume through leaks in the endothelium with decreased thirst and a shift of fluid to the upper part of the body.<sup>10,11</sup> There is a 40% reduction in the vessel dilator atrial natriuretic peptide,<sup>11</sup> with Mg probably necessary both for its synthesis and release.<sup>10</sup> With impairment in blood

flow to the periphery, these core temperature elevations could trigger heat exhaustion or heat stroke. (On the Moon at noon it is 250°F.)

Before and after a space mission, telomere lengths and telomerase enzyme activity would be determined and compared with age-matched control rats on Earth. Similar studies in astronauts would be valuable as well.

In summary, it is conceivable that corrections of significant Mg ion reductions, with their associated catecholamine elevations and potential vicious cycles, will prolong life in microgravity; whether corrections of the very common and often unrecognized Mg deficits on Earth will prolong life remains to be seen.

## Disclosure

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