PERSPECTIVES

SARS-CoV-2: Influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP)-metabolism and on severity of COVID-19

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RUNNING HEAD

Running head: COVID-19: influence of phosphate, Mg, and ATP beyond vitamin D

GRANTS

This work was pro bono.

DISCLORURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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AUTHOR CONTRIBUTIONS

E.D. conceived the hypothesis; E.D. and T.v.K. build the total case and manuscript.

ABSTRACT

Van Kempen TATG, Deixler E. SARS-CoV-2: Influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP)-metabolism and on severity of COVID-19. *Am J Physiol Endocrinol Metab* – The use of vitamin D to reduce the severity of COVID-19 complications is receiving considerable attention, backed by encouraging data. Its purported mode of action is as an immune modulator. Vitamin D, however, also affects metabolism of phosphate and Mg, which may well play a critical role in SARS-CoV-2 pathogenesis. SARS-CoV-2 may induce a cytokine storm that drains ATP whose regeneration requires phosphate and Mg. These minerals, however, are often deficient in conditions that predispose people to severe COVID-19, including older age (especially males), diabetes, obesity, and usage of diuretics. Symptoms observed in severe COVID-19 also fit well with those seen in classical hypophosphatemia and hypomagnesemia, such as thrombocytopenia, coagulopathy, dysfunction of liver and kidneys, neurologic disturbances, immunodeficiency, failure of heart and lungs, delayed weaning from a respirator, cardiac arrhythmia, seizures, and finally multi-organ failure. Deficiencies of phosphate and Mg can be amplified by kidney problems commonly observed in COVID-19 patients resulting in their wastage into urine. Available data show that phosphate and Mg are deficient in COVID-19 with phosphate showing a remarkable correlation with its severity. In one experiment, COVID-19 patients were supplemented with a cocktail of vitamin D_3, Mg, and vitamin B_{12}, with very encouraging results. We thus argue that COVID-19 patients should be monitored and treated for phosphate and Mg deficiencies, ideally already in the early phases of infection. Supplementation of phosphate and Mg combined with vitamin D could also be implemented as a preventative strategy in populations at risk.

MAIN TEXT

Vitamin D is receiving considerable attention in the fight against COVID-19. Correlations between serum calcifediol and severity of COVID-19 ($R^2 = 0.96$) have been demonstrated with two times higher infection rates for people with low vs. high circulating calcifediol (16, 34), and over 50 clinical trials have been initiated (clinicaltrials.gov, accessed Oct20) to evaluate its impact. The discussion about mode of action focuses foremost on its effect on immunity (31, 34). What we would like to argue is that the more fundamental role of vitamin D in mineral metabolism also should be considered in the etiology of COVID-19. Vitamin D plays an important role in the metabolism of Ca, phosphate (21), and Mg (24), both by stimulating intestinal uptake as well as by preventing renal excretion, while a Mg deficit can also compromise vitamin D status (71). Especially phosphate and Mg are often clinically ignored despite their critical role in energy metabolism, which is clearly perturbed in COVID-19 patients. The role of vitamin D in immunity and its role in mineral metabolism are interconnected and, more specifically, interact via ATP and energy metabolism.

A key deleterious effect of a SARS-CoV-2 infection is the immune hyperreaction and cytokine storm (11). This acute hyperinflammatory response is paramount in the severity of the SARS-CoV-2 infection. Taghizadeh-Hesary and Akbari (58) elegantly explain how SARS-COV-2 may cause a depletion of cellular ATP and a dysfunction of immune cells, and they propose a repletion of cellular ATP to improve the efficiency of the immune system. In line with this, Kouhpayeh et al. (39) propose that SARS-CoV-2 activates PARP-2 (poly [ADP-ribose] polymerase 2), which induces a depletion of NAD^+ and consequently also drains cellular ATP. Scrutiny of this hypothesis reveals that a critical part of the process may have been overlooked. For the synthesis and regeneration of ATP, phosphate and Mg are required. Due to often diminished food intake during infectious diseases, the higher ATP requirements of activated immune cells are mainly covered by mobilization of its components, like phosphate and Mg, from stored reserves in bones and/or muscles through cytokine release (64). This catabolism in bones and muscles in

response to an inflammatory stimulus supports anabolism in immune cells, but it may also lead to an intracellular decrease of phosphate and ATP and finally to a break-down of muscle cells with release of intracellular phosphate and magnesium into the extracellular space (64). When these nutrients are already in short supply (due to age, diabetes, etc.), either cytokine release and catabolism may be enhanced, or ATP depletion may be severe and impede the immune system (47). The observed cases of rhabdomyolysis in COVID-19 patients (45, 70) may be an indication of intracellular ATP-depletion and perhaps also severe hypophosphatemia (13).

Interestingly, most risk factors for a severe course of COVID-19 are associated with a deficiency of phosphate and/or Mg. For instance, type 2 diabetics [COVID-19 odds ratio (C-OR) 5.02 (26)] are three times more likely to suffer from hypomagnesemia [incidence 14-48% (20)] while the incidence of hypophosphatemia is notably higher [62 vs. 0% for controls (54)]. Especially diabetics with a poor glycemic control are affected, because hyperglycemia leads to a reduced renal re-absorption of phosphate and Mg (51, 65). Diuretics (55) routinely prescribed against hypertension [C-OR 3.99 (26)] diminish Mg [incidence hypomagnesemia 72-100% (19)] and phosphate [incidence hypophosphatemia 12.5% in patients treated with Thiazide (42)] through enhanced renal excretion. Certain anticancer medicines, like Ifosfamide or Imatinib, may cause hypophosphatemia (42). Furthermore, degree of obesity [C-OR 6.92 (26)] is associated with hypophosphatemia [r =-0.22 (23)] and hypomagnesemia [r = -0.21 (57)]. While hypomagnesemia in obesity is mostly associated with low dietary intake (22), hypophosphatemia is multifactorial (66) and even suspected to play a role in the development of obesity by impeding ATP production (48). Overweight, particularly in the elderly, leads to diminished mitochondrial ATP production (approximately -30%) with secondary muscle weakness (53).

Another intriguing observation is that renal phosphate and Mg re-absorption and, consequently, serum phosphate [-20% for men comparing 20 versus 70 years (14)] and cellular Mg [-13% comparing <65 and >65 years, -23% for >65 years with non-insulin-dependent diabetes mellitus (8)] levels decline

with age [age > 53: C-OR 2.59 (26)]. For phosphate, this decline is much stronger in older men than in older women (14), which is in line with COVID-19 complications being more severe in older men. The role of smoking in COVID-19 patients appears more controversial; lung damage from smoking may make people more susceptible, but odds ratios are typically close to 1 [e.g., C-OR 0.63 (26)]. Smoking dose-dependently increases serum phosphate [r = 0.67 (28)] and decreases ATP [by as much as 70% in heart mitochondria (27)]. The usage of proton-pump inhibitors has also been linked to a worse outcome in COVID-19 patients [C-OR 1.79 (41)]; such proton-pump inhibitors are known to diminish intestinal Mg absorption (17). African Americans infected with SARS-CoV-2 have two times higher death rates than white Americans (69), twice the incidence of hypomagnesemia (43), and in about 76% a vitamin D deficiency mainly due to the fact that pigmentation reduces vitamin D production in the skin (25). Seasonal effects showing low levels of serum phosphate [-36% (29); -10% (61)] and Mg [-15% (61)] in the winter, which are possibly linked to seasonally fluctuating vitamin D levels, have also been observed in COVID-19 patients, which would make more severe SARS-CoV-2 complications more likely in the winter. COVID-19 patients often develop renal failure which typically begins with an acute necrosis of the proximal tubule [23% develop kidney injury (9), 75% proximal tubule abnormalities (38)]. Since this is the precise location for phosphate and Mg re-absorption, the patients' phosphate and Mg status worsens by urinary wasting of these electrolytes. A pregnancy complication more common in women with COVID-19 is pre-eclampsia/eclampsia (1, 46), an endothelial disease often accompanied by magnesium and vitamin D deficiency (10, 11).

While Mg deficiency may occur without hypomagnesemia, when present, it is usually indicative of an important systemic Mg deficit (8). Hypophosphatemia can exist when total stores are low, normal, or high. Clinically significant hypophosphatemia, however, tends to occur when there is a total-body deficit of phosphorus. Hypophosphatemia and hypomagnesemia impede ATP production, and hypophosphatemia additionally diminishes 2,3-bisphosphoglycerate in erythrocytes, which is essential

for the release of O_2 from hemoglobin. This leads to hypoxia at a tissue level (36). Complications from hypophosphatemia include thrombocytopenia, coagulopathy, dysfunction of liver and kidneys, neurologic disturbances, immunodeficiency, delayed weaning from a respirator, rhabdomyolysis, failure of heart and lungs, and finally multi-organ failure (36), which are in line with complications observed in COVID-19. Hypomagnesemia can lead to, among others, cardiac arrhythmia and seizures (35), also observed in COVID-19 patients (6, 37, 44). Furthermore, Mg is an important co-factor of membrane ATPases (4, 52) which are involved in the pathogenesis of the acute respiratory distress syndrome (ARDS) (60, 63). This severe complication of COVID-19 is also often associated with a vitamin D deficiency (7, 15).

Intracellular ATP depletion due to low phosphate and Mg may cause cell death by necrosis instead of apoptosis associated with membrane instability and ATP release into the extracellular space (40). Extracellular ATP, however, can function as a danger signal and start an (over)activation of the immune system (30) with the possible consequence of a cytokine storm or ARDS (39, 47, 62). This may be an explanation of why people with diseases associated with pre-existing low ATP and low energy reserves due to diminished phosphate and/or Mg more easily develop severe COVID-19 symptoms, like a cytokine storm and ARDS. ARDS, itself, is also often associated with ATP-deficiency diseases like diabetes, severe burns, or sepsis (15, 50, 60). Cellular ATP depletion and cell death by necrosis with subsequent activation of the immune system are also discussed as a possible pathomechanism of autoimmune diseases and may also explain various autoimmune phenomena in COVID-19, like auto-antibodies against Interferon or the Kawasaki-like syndrome in children (18).

Few have reported phosphate and Mg levels in COVID-19 patients. Xue et al. (68) registered serum phosphate levels of 1.11±0.35 mM in non-critically sick, and 0.79±0.29 mM in severely sick and showed a correlation between lymphocytes and phosphate ($r = 0.48$). Javdani et al. (32) ranked patients for the severity of lung damage and showed that phosphate was the sole assessed parameter assessed that

144 correlated. Arenas et al. (5) assessed phosphate in infected renal patients and observed lower levels
145 (0.75 mM vs. 1.45 mM) of phosphate. Alkhouli et al. (3) surveyed 14712 patients for which data were
146 not categorized for severity of the infection. An average value of 1.07±0.033 mM was observed in men,
147 and 1.09±0.028 mM in women. Using the reported standard deviations, however, an estimated 38% of
148 the men and 33% of the women were hypophosphatemic using the threshold defined by Pagana (49).
149 Booth et al. (12) assessed many clinical parameters in patients infected with the closely related SARS
150 and showed that 53% had hypophosphatemia, 57% hypomagnesemia, and 70% hypocalcemia.
151 Tan et al. (59) supplemented COVID-19 patients once daily with a combination of vitamin D_3 (1000
152 IU), Mg (150 mg), and vitamin B_{12} (500 μg); findings were that significantly fewer patients required
153 oxygen support (18 vs. 63%) and/or intensive care support (6 vs. 32%). Our review of available
154 information aligns with this finding. Vitamin D, beyond a role in immunity, can enhance absorption from
155 the intestinal tract and reduce kidney losses of both phosphate and Mg, which may be critical for
156 respiration and energy metabolism. Some kinds of renal proximal tubulopathy (so-called Fanconi
157 syndrome) have already been treated successfully with vitamin D, phosphate and Ca (2), and urinary
158 phosphate and Mg loss in COVID-19 patients may also be reduced by supplementation with vitamin D.
159 Per the above, we would like to suggest that Tan's supplement should be augmented with phosphate,
160 especially in light of the above reported correlations between the severity of COVID-19 and phosphate.
161 This focus on phosphate was also raised by Seers (56) while Mg was raised Wallace (67). For phosphate
162 and magnesium, actual supplementation levels should be guided by the tissue shortages observed.
163 Intriguingly, the rather controversial chloroquine is typically supplied as a phosphate salt (12% P), and
164 doses used [approximately 1 g/d (33)] can supply 10-20% of the recommended dietary intake for
165 phosphate.
166
167 *Conclusion*

In conclusion, we suggest monitoring and, when deficient, supplementation of vitamin D, Mg, and phosphate already during the early phase of COVID-19 or as a preventative in populations at risk, as it may diminish secondary complications.

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