Review of: "Magnesium and Longevity"

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Potential competing interests: No potential competing interests to declare.

Strength

Comprehensive Review of Magnesium's Role: The manuscript offers a detailed examination of magnesium (Mg) as a crucial cofactor in various physiological processes, particularly in aging and longevity. It effectively ties Mg to other longevity-related factors, such as vitamin D, melatonin, and short-chain fatty acids, providing a thorough understanding of its potential to extend healthspan. The inclusion of Mg's involvement in over 800 enzymatic reactions and its influence on biomarkers like telomere attrition and HDL-C is well-supported by biochemical principles.

1. **Clear Linkages to Aging Mechanisms**: The author successfully connects Mg to key metabolic pathways involved in aging, including oxidative stress, inflammation, and epigenetic regulation. The discussion on the role of the gut microbiome in aging, and Mg's potential effects on gut health, is both relevant and timely.
2. **Innovative Connections**: The manuscript introduces several novel concepts, such as Mg's interactions with agents like GLP-1, bile acids, and indoles, and the concept of a "chronic latent Mg deficit." These ideas provide fresh perspectives on Mg's role in aging and disease, warranting further exploration.
3. **Organized and Clear Structure**: The manuscript is well-structured, with a logical flow that simplifies complex biochemical processes. Although the figures are not included, the manuscript seems to be carefully organized, making the content easy to follow for readers.
4. **Broad Scope**: The review covers a wide range of topics, including microbiota diversity, epigenetics, and various metabolic pathways related to aging, offering a holistic perspective on Mg's contributions to health and longevity.
5. **Current Research Integration**: The inclusion of recent studies, such as those from NHANES and research on Mg and COVID-19, ensures that the review remains grounded in contemporary scientific developments.

Weaknesses:

1. **Lack of Clinical Evidence**: Despite the extensive biochemical and theoretical evidence, the manuscript lacks robust clinical data or randomized controlled trials (RCTs) linking Mg supplementation to improved healthspan or longevity. Emphasizing existing clinical studies or critically discussing the limitations of current research would lend greater credibility to the review.
2. **Limited Consideration of Confounding Variables**: The manuscript does not fully address lifestyle factors (diet, exercise, etc.) that might influence Mg's role in diseases like cardiovascular disease (CVD) and type 2 diabetes (T2DM). A deeper discussion of the complexities surrounding causality versus correlation would strengthen the

manuscript's claims.

3. **Underdeveloped Discussion of Mg Supplementation**: While Mg's importance is well-addressed, the manuscript lacks a thorough exploration of practical issues related to Mg supplementation, such as bioavailability, dosage guidelines, and potential side effects, particularly for individuals with renal disease or other health conditions. A section on different forms of Mg (e.g., citrate vs. oxide) and their effectiveness would improve the manuscript's practical utility.
4. **Overemphasis on Mg Deficiency**: The manuscript frequently highlights Mg deficiency as a primary factor in aging, but this could be presented more cautiously. The majority of individuals do not have overt Mg deficiency, and the idea of a "chronic latent Mg deficit" needs further clarification and supporting data. A more nuanced approach would help avoid an overly alarmist tone.
5. **Insufficient Mechanistic Detail**: While the manuscript touches on Mg's role in methylation and DNA repair, it lacks sufficient mechanistic detail in these areas. Expanding on how Mg interacts with specific enzymes in these pathways would add depth and clarity to these sections.
6. **Limited Discussion of Alternative Theories**: The review predominantly emphasizes Mg as a key factor in aging, without addressing alternative theories or other potential longevity agents, such as selenium, vitamin E, or polyphenols. Including a broader perspective would provide a more balanced and objective view of the topic.
7. **Dependence on Theoretical Pathways**: Many claims about Mg's role in aging are based on theoretical mechanisms, which are not always supported by solid experimental evidence. For example, the hypothesis that Mg enhances the effects of GLP-1 agonists is intriguing but lacks sufficient data. More empirical studies or potential experimental designs would strengthen these arguments.

Suggestions for Improvement:

1. **Incorporate More Clinical Evidence**: A stronger focus on clinical studies, particularly large-scale RCTs linking Mg supplementation with longevity or healthspan, would enhance the review's credibility.
2. **Address Confounding Factors**: A discussion on the impact of lifestyle factors and the challenges of interpreting Mg's effects would provide a more balanced perspective and strengthen the manuscript's claims.
3. **Expand on Practical Aspects of Supplementation**: Including detailed information on the bioavailability, optimal dosages, and safety concerns related to Mg supplementation—especially for individuals with certain health conditions—would improve the manuscript's practical value for clinicians and researchers.
4. **Strengthen Mechanistic Explanations**: A more thorough exploration of how Mg influences specific biochemical processes, such as epigenetics and mitochondrial function, would provide readers with a deeper understanding of its potential role in aging.
5. **Engage with Alternative Theories**: Introducing and discussing other theories on aging and longevity, as well as alternative agents, would create a more balanced and objective narrative.
6. **Clarify the Concept of Mg Deficiency**: The manuscript would benefit from a clearer explanation of the concept of "chronic latent Mg deficit" and a discussion on how subclinical Mg deficiencies can be identified and addressed.
7. **Improve Structural Flow**: The manuscript would benefit from clearer transitions between topics. For example, the shift from discussions on gut microbiota to the Mg/Ca ratio and then to COVID-19 may confuse readers. More distinct

subsections and improved transitions could improve readability.