Beta-hydroxy-beta-methylbutyrate and sarcopenia: from biological plausibility to clinical evidence

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Purpose of review
Given the role of leucine as a major regulator of muscle protein turnover, the consumption of protein sources enhanced with this essential amino acid, or its metabolite beta-hydroxy-beta-methylbutyrate (HMB), is assumed to give the greatest benefit in terms of maintenance of muscle mass and function during aging. The aim of this review is to discuss recent literature about HMB metabolism, its pharmacokinetics compared with the metabolite leucine, effectiveness of HMB to improve outcomes in older adults, and novel approaches for HMB use.

Recent findings
Overall, this review article highlights the potential relationship between HMB dietary supplementation and parameters related to maintenance of muscle mass and strength in older people. However, there are limitations in the studies conducted so far, including low number of participants per study group, heterogeneity of study designs, methodologies, and outcomes. The combination of HMB with other amino acids or supplements limits the ability to determine the direct impact of HMB alone.

Summary
It is proposed that HMB may be utilized to protect or rebuild muscle mass in older people with reduced lean body mass.

Keywords
amino acid, anorexia, frailty, leucine, malnutrition, sarcopenia, supplementation

INTRODUCTION

An appropriate consumption of proteins with the usual diet is important for muscle mass maintenance as it guarantees the right amount of essential amino acids and consequently stimulates protein synthesis. Usually, older adults are at risk for inadequate protein intake. As people age, insufficient intake of protein is correlated with reduced muscle reserves, increased skin fragility, lower immune function, poor wound healing, and longer recovery time from illness [1]. Older individuals are less reactive to the stimulatory effect of amino acids on muscle protein synthesis, but recent evidence has demonstrated that a higher amount of protein/amino acid intake might preserve this stimulation and result in enhancements in lean body mass, strength, and physical function [2]. In this respect, the current WHO recommended dietary allowance (RDA) for protein (0.8 g/kg/day) might be inadequate for maintaining muscle mass and quality in frail old people [3]. Therefore, it is discussed whether the RDA for protein intake is appropriate to prevent major adverse events and negative outcomes in older persons [4]. Given the fact that protein–energy malnutrition is one of the major risk factors for the onset and progression of sarcopenia [5▪], a nonoptimal nutritional status may mediate the association between sarcopenia and negative outcomes in older and frail individuals. Protein and/or specific amino acids supplementation may therefore be required to increase muscle mass and muscle function in malnourished older people [6].

Beta-hydroxy-beta-methylbutyrate (HMB) (Fig. 1) is an active metabolite of leucine, a branched-chain essential amino acid. HMB is found in very small amounts in some foods, such as avocado, citrus

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KEY POINTS

- Protein is the principal component of muscle, and adequate dietary supply is required for muscle maintenance, particularly in older adults.
- Recent research has focused on the use of HMB to preserve or rebuild muscle mass in populations at risk of lean body mass loss, especially older adults.
- The effective amount of HMB (3 g/day) is extremely difficult to obtain from the normal diet, given the low quantities of HMB available in foods and the low conversion rate of leucine to HMB.
- Several studies have shown positive effects of HMB supplementation on body composition, muscle mass and strength, and physical function in older adults.
- HMB supplementation has also been shown to reduce the risk of mortality by 50% through 90 days post hospital discharge in malnourished, cardiopulmonary patients, 65 years or older, as compared with standard nutrition care and placebo.

fruit, cauliflower, and catfish. HMB is synthesized from leucine in a two-step process occurring in muscle and liver cells [7]. Leucine has a specific role in regulating and controlling protein synthesis at muscle cell level, and HMB acts as a key active metabolite in such regulation (Fig. 2). However, only nearly 5% of leucine is transformed to HMB, which results in the production of 0.2–0.4 g of HMB per day in a person weighing 70 kg [8]. Traditionally, bodybuilders and athletes have been using HMB supplements to increase performance and to build muscle mass, in the form of its calcium salt HMB monohydrate (CaHMB). More recent research has also focused on the use of HMB supplementation to preserve or rebuild muscle mass in populations at risk for sarcopenia, particularly the older people. Several studies have demonstrated the benefits of HMB supplementation, alone or in combination with other amino acids and exercise training, for maintaining and restoring lean body mass, muscle strength and function in older adults.

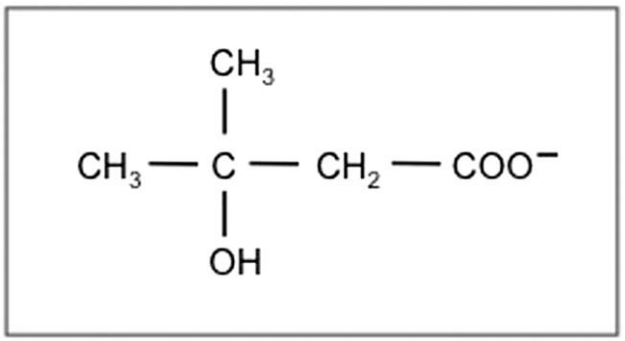

FIGURE 1. Chemical structure of hydroxy-beta-methylbutyrate.

HYDROXY-BETA-METHYLBUTYRATE TO SUPPORT MUSCLE HEALTH: BIOLOGICAL ACTIVITY

HMB has important effects in activating protective and anticatabolic mechanisms and, at the same time, it has been shown to directly influence protein synthesis [9] (Fig. 3). HMB has been demonstrated to stabilize the muscle cell membrane, to downregulate protein degradation, and to upregulate protein synthesis [10▪].

As a substrate for cholesterol synthesis in the muscle cell, HMB contributes to the reinforcement of the cell membrane. In this way, HMB helps stabilize the sarcolemma to maintain the muscle cell intact [10▪].

HMB increases protein synthesis directly by activating mTOR (mammalian target of rapamycin), the major checkpoint for protein synthesis. It is the active leucine metabolite that consistently activates the mTOR signal pathway [10▪]. Insulin-like growth factor-1 (IGF-1) is one of the growth factors that activate mTOR in muscle cells, too. As a consequence, HMB directly activates mTOR and its effects are boosted by IGF-1. In this way, HMB may help overcome the age-related reduction in tissue response to endogenous growth hormones, such as IGF-1 [11] (Fig. 3).

In addition, HMB selectively hinders intracellular inflammation attenuating protein degradation pathways. In fact, HMB inhibits the activation of caspase-8, thereby reducing protein degradation.

PUTATIVE MECHANISMS OF HYDROXY-BETA-METHYLBUTYRATE ACTION ON MUSCLE CELLS

The plasticity of skeletal myocytes is controlled by the intricate interaction of many factors; nonetheless, it is certain that the balance between protein synthesis and protein breakdown has an essential role in this process. Substantial losses or enhancements in muscle mass are mainly the result of changes in muscle protein synthesis and breakdown rates, or of a balanced combination of such mechanisms. On the other hand, muscle protein metabolism is significantly related to the intake of an adequate quantity of dietary-derived proteins and amino acids [12].

Muscle protein synthesis rates are controlled mainly by sensitivity to anabolic stimuli, such as physical activity and specific foods. Proteins from

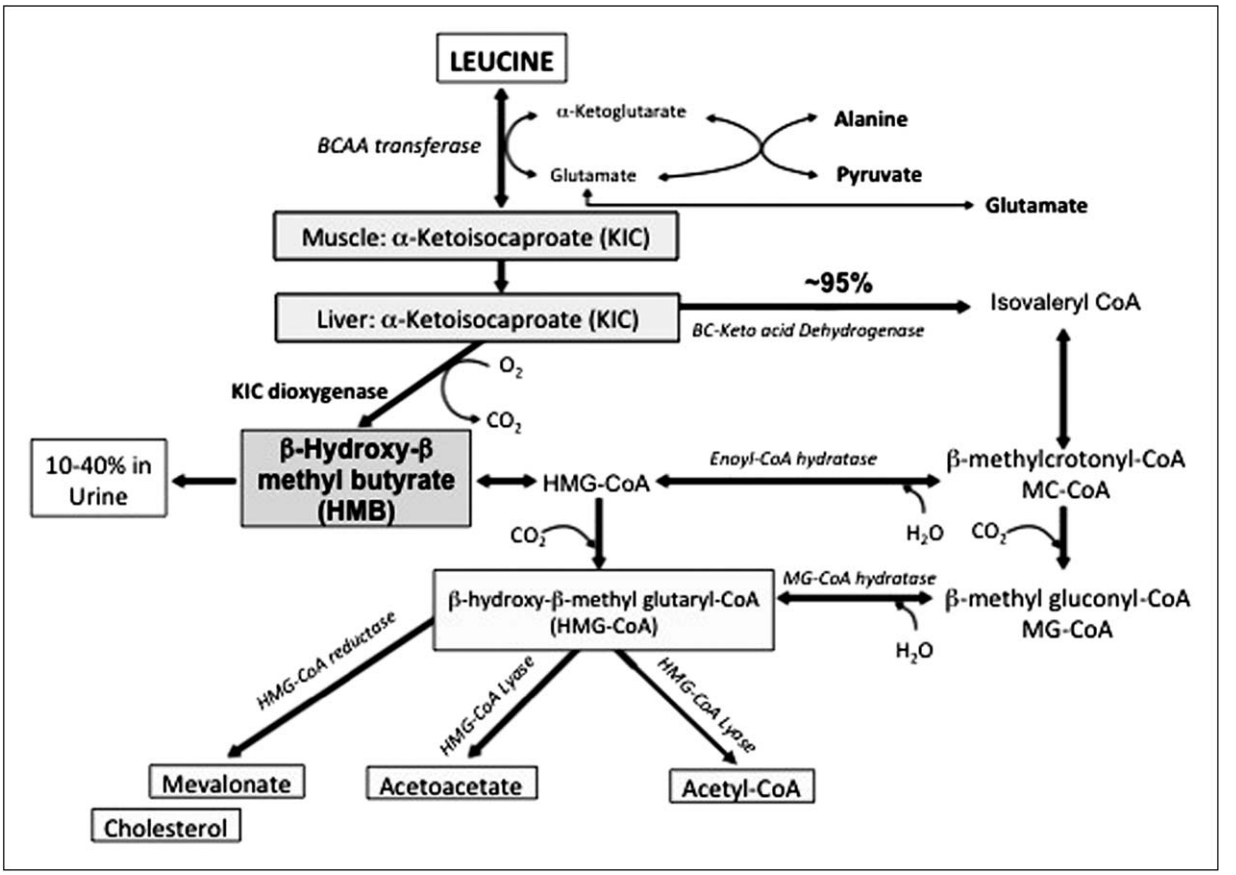

FIGURE 2. Metabolism of hydroxy-beta-methylbutyrate in the body.

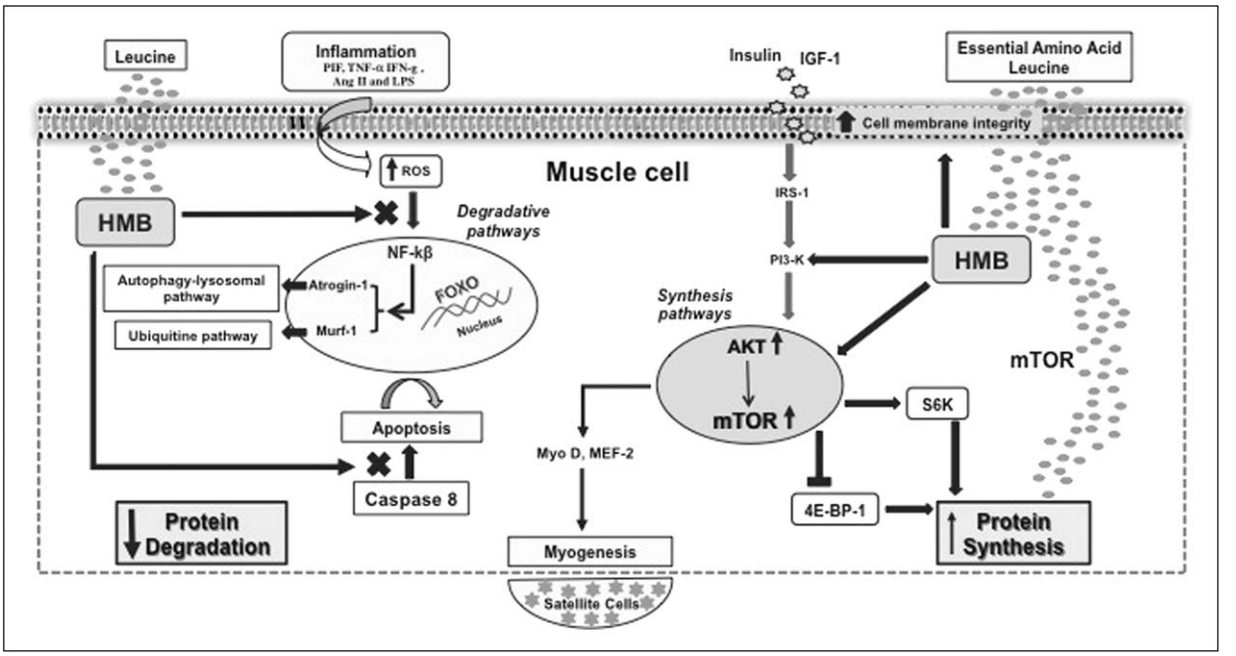

FIGURE 3. Overview of potential pathways whereby hydroxy-beta-methylbutyrate influences cellular events implicated in the regulation of muscle homeostasis.

usual diet and/or specific nutritional supplementations, such as HMB, are able to increase muscle protein synthesis rates and to inhibit protein breakdown, thus supporting net muscle protein accumulation. Aging process *per se* does not impact skeletal muscle protein breakdown rates [13]. Hence, targeting muscle protein synthesis response may hold more promise in the prevention of muscle loss and sarcopenia during aging.

Leucine and its active metabolite HMB are considered the most important regulators of muscle protein anabolism, due to the ability to stimulate the mTOR pathway and inhibit the proteasome [3]. Even though during the aging process muscle presents a reduced anabolic response, higher protein intakes (with at least 3 g of leucine) are able to overcome the anabolic resistance and trigger a protein synthetic response comparable with that found in younger people [3].

Indeed, physical inactivity and muscle disuse lead to the fast development of anabolic resistance in both young and older subjects [14,15]. Sedentary life style *per se* is also likely to lower basal muscle protein synthesis rates [16]. As a consequence, a harmonized prescription of HMB supplementation and physical exercise may be important for middle-aged and older adults suffering from catabolic stressors such as illness, inflammation, injury, or experiencing persistent physical inactivity. The combination of physical exercise (in particular, resistance exercise) and HMB intake has a positive and synergistic effect on skeletal muscle protein synthesis [17,18▪▪]. In fact, studies clearly indicate that physical exercise provides the greatest benefits to the aged muscle cells when combined with a dietary protein intake that exceeds the current RDA [4,15].

HYDROXY-BETA-METHYLBUTYRATE INTAKE FROM STANDARD DIET IS LOW

Recent studies have demonstrated that 2.4 g of HMB per day are helpful for muscle health [19]. However, this quantity is difficult to obtain from usual diet, considering the low amounts of HMB available in foods and the low transformation rate of leucine to HMB [20▪]. In addition to HMB content of food being low, the quantity of leucine obtained from the diet is inadequate, too. For the human body to produce 2.4 g of HMB per day (the amount provided by 3 g of CaHMB), it is calculated that 60 g of leucine would need to be daily consumed from usual foods, which is really hard to reach even for a young person [21]. For example, according to the USDA Food Composition Databases, black beans are one of the highest leucine food sources (~1.7 g of leucine in 100 g of product), so an ingestion of around 3.5 kg of beans would be needed to introduce 60 g of leucine, which would be unreasonable.

This means that even using high leucine protein sources (dairy, meat, eggs), the daily amount needed to reach 3 g/day of HMB is well above that consumed in a usual diet. As a result, HMB supplementation is a realistic alternative, and may be beneficial particularly for individuals with or at risk of sarcopenia, such as older persons or those with disease-related loss of lean body mass. In addition, a recent study conducted by Kuriyan *et al.* [22] documented an age-related decline in endogenous plasma HMB concentrations, which was correlated with appendicular lean mass (aLM) and muscle strength in young and older adults.

EXAMINATION OF HYDROXY-BETA-METHYLBUTYRATE SUPPLEMENTATION IN OLDER ADULTS

Strong evidence indicates that anorexia of aging is one of the major causes for overall and selective malnutrition. Anorexia is correlated with a higher risk of quantitative malnutrition (e.g., protein–energy malnutrition) due to insufficient food intake. However, especially in the initial stages, anorexia increases the risk of qualitative malnutrition, due to suboptimal intake of specific nutrients, like proteins and vitamins [23]. Studies have demonstrated that selective malnutrition is related to the development of sarcopenia and other negative health outcomes, including morbidity and mortality [24]. Specific nutritional supplementations – such as HMB – do not treat anorexia of aging but only its consequences, such as weight loss, muscle wasting, sarcopenia, and energy–protein malnutrition. Nevertheless, the heterogeneity of the supplementation protocols implemented hinders their applicability to standard patient care. As it stands, the only convincing evidence is currently limited to protein supplementation.

Different studies over several years have shown the effects of HMB supplementation on body composition, muscle mass and strength, and physical function in older adults. Since 1990 there have been more than 90 publications using HMB alone or in combination with amino acids, of which more than 20 were done in healthy elderly and more than 20 included specific clinical conditions in adults [25▪▪]. In addition, many reviews, systematic reviews, meta-analyses, and position articles have been published so far [26]. The dose of HMB provided to the treatment groups was typically 3 g/day and was considered by most researchers the optimal dosage. Only a few tested a lower

dose, 2 g/day, and it seems that a dose of 6 g/day did not make a difference [27].

Overall, these articles emphasize the potential relationship between HMB supplementation and specific parameters correlated with the preservation of muscle mass and strength in older individuals. Though, there are some limitations in the studies conducted so far, including low number of participants per study group, heterogeneity of study designs, methodologies, and outcomes. Furthermore, the mixture of HMB with other amino acids or nutritional supplements (vitamins) limits the ability to establish the direct impact of HMB alone or its effectiveness in specific formulations. However, it is important to highlight that nutrition is a part of a multimodal intervention approach that should usually include other healthy lifestyle components, such as healthy diet and exercise. Even within nutrition, it is always difficult to clarify the contribution of single ingredients in nutritional formulations. This is because a wide variety of factors contribute to the positive effects observed in interventions, and combinations of ingredients may also modify these effects. It is proposed that the real benefits of ingredients in nutritional preparations be best achieved as a full product rather than any a single ingredient alone.

Combined nutritional intervention comprising controlled diet, nutritional supplementation containing HMB, and vitamin D and calcium supplementation can induce weight gain, decrease functional limitations, and reduce the number of falls, as well as the length of hospital stay, and the incidence of clinical complications, which can have important cost implications [20▪].

Hydroxy-beta-methylbutyrate in hospitalized patients

The Nutrition Effect on Unplanned Readmissions and Survival in Hospitalized Patients [28▪▪] study was one of the largest clinical trials using a nutritional intervention conducted so far. It was a multicenter, prospective, randomized, double blind, placebo-controlled, parallel-group study conducted in the United States. The study assessed the effects of nutritional intervention including a specific nutritional supplement – containing 350 kcal, 20-g protein, 1.5-g CaHMB, 11-g fat, 44-g carbohydrate, and other essential micronutrients – on the postdischarge incidence of hospital readmission, nutritional status, and morbidity among older, malnourished, hospitalized adults versus a placebo supplement containing only carbohydrates and vitamin C. Patients included in the study were 65 years of age and older with a recent hospital admission (within 72 h) and with primary diagnosis of congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease and with malnutrition-related disease as determined by the Subjective Global Assessment tool. A total of 622 patients were included in the analysis (313 patients in the experimental and 309 in the control group). Although there was no significant difference between groups for the primary composite endpoint and 90-day readmission rate, the 90-day mortality rate was significantly lower with the nutritional supplement containing HMB, compared with the control supplement (CONS) (4.8 versus 9.7%; $P = 0.018$).

Changes were observed in nutritional status, too; patients receiving the experimental supplement (EONS) had higher odds of achieving a better nutritional status at day 90 [odds ratio, 2.04 (95% confidence interval, 1.28–3.25); $P = 0.009$]. In addition, muscle strength was evaluated by dynamometer at baseline, hospital discharge, days 30, 60, and 90 postdischarge. Handgrip strength was significantly higher in the experimental group supplemented with HMB versus the control group ($P = 0.03$). At day 90, there was a significant positive association between handgrip strength and nutritional status; 49% of participants with increased muscle strength from discharge had improved nutritional status compared with 31% with unchanged or decreased handgrip strength ($P = 0.003$). In conclusion, this study showed that a nutritional supplement containing high protein and HMB decreased postdischarge mortality and improved nutritional status, handgrip strength, dietary intake, and nutritional markers compared with placebo or the standard of care.

Hydroxy-beta-methylbutyrate in postacute patients

A multicenter randomized trial conducted by Malafarina *et al.* [29▪] in 2017 explored whether nutritional supplement enriched with CaHMB, proteins, and vitamins improved muscle mass and nutritional markers in older patients with hip fracture. Ninety-two older patients (mean age 86 ± 6 years) with hip fracture admitted to rehabilitation facilities received standard diet and two servings per day of nutritional supplement with HMB or standard diet for 30 days. BMI and aLM were stable in supplemented patients, whereas these parameters decreased in the control group, with a significant difference between groups ($P < 0.001$ and $P = 0.020$, respectively). As expected, supplemented patients showed higher intake of proteins ($P = 0.007$) and vitamin D ($P = 0.001$). In addition, a greater percentage of supplemented patients showed functional

recovery (68%) as compared with the control group (59%), although the difference was not statistically significant ($P = 0.265$). This study concluded that supplementing the standard diet with HMB resulted in muscle mass preservation and improved functional recovery and nutritional status in older patients with hip fracture during the rehabilitation period.

Hydroxy-beta-methylbutyrate in community older people

The 2016 randomized trial by Cramer *et al.* [30▪▪] evaluated the effects of two high-quality oral supplements differing in amount and type of key nutrients (including HMB) in older adults. The study included malnourished and sarcopenic men and women, 65 years and older ($n = 330$). Participants were randomized to receive a CONS (330 kcal, 14-g protein, including vitamins and minerals) or an EONS (330 kcal, 1.5-g CaHMB with 20-g protein, including minerals and vitamins) twice a day for 24 weeks. Both groups improved isokinetic peak torque, muscle quality, grip strength, and gait speed from baseline, with no treatment differences. Participants with severe sarcopenia (44%) exhibited lower baseline isokinetic peak torque and muscle quality, without differences in strength improvements between treatments. However, participants with mild–moderate sarcopenia exhibited higher baseline isokinetic peak torque and muscle quality, with differences in strength improvements at 12 weeks (EONS > CONS, $P = 0.032$) compared with enrollees with normal grip strength. There were no treatment differences based on sarcopenic severity for either grip strength or gait speed. The authors concluded that nutritional supplements improved strength outcomes in malnourished older adults with sarcopenia and in those with mild–moderate sarcopenia, but not severe sarcopenia, consumption of the EONS improved leg muscle strength and quality compared with the standard supplement (CONS).

CONCLUSION

The identification of sarcopenia as one of the major risk factors for adverse outcomes in frail older individuals suggests that skeletal muscle may represent a critical target for nutritional interventions. The association between low intake of energy and protein and reduced muscle mass and strength in older adults, shown by several studies [5▪,31], emphasizes the importance of a comprehensive dietary assessment for the early identification of nutritional deficits, which may promote muscle loss [6].

Experimental research indicates that HMB has many effects that may counteract sarcopenia, and this is confirmed by the use of HMB in younger athletes [32]. Though, research on the effects of HMB in sarcopenia is limited by the small number of studies, heterogeneous methodological approaches, lack of agreement on significant outcome measures, and issues on the interaction of HMB with other nutrients and with physical activity programs. Some findings suggest that, at least in some settings, HMB may prevent muscle atrophy or improve muscle mass, and at the same time increase muscle strength/function and physical performance. Even though the limitations in research preclude solid conclusions, evidence provided by recent investigations may serve as the foundation for future studies examining whether the implementation of nutritional interventions targeting the skeletal muscle (including HMB supplementation) improves the clinical outcomes of frail older persons [13]. In this respect it is important to highlight that the European Society of Clinical nutrition and Metabolism guidelines on nutritional support for polymorbid internal medicine patients suggest that in malnourished inpatients or in those at high risk of malnutrition, nutrient-specific supplementation (with HMB) should be administered, as they may maintain muscle mass, reduce mortality and improve quality of life [33].

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Conflicts of interest

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