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REVIEW

Calcium revisited: part I

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In February 2013, the US Preventive Services Task Force (see www.uspreventiveservicestaskforce.org) recommended 'against daily supplementation with 400 IU or less of vitamin D_3 and 1000 mg or less of calcium for the primary prevention of fractures in non institutionalized postmenopausal women', which illustrates the divergence of opinions. This review wants to shed an objective light on the importance of calcium for bone health. It cannot compete with an exhaustive analysis of the literature by an institute. It does not mention all significant references. But it highlights some pivotal studies from the past and it refers to recent studies that opened new views or added essential data to known facts. It also reflects the personal perception of the author. The first part deals mainly with intake, absorption, needs and recommendations; the second part will discuss the effects of calcium and its supplements on bone.

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Introduction

About 99% calcium is included in the skeleton. The circulating calcium is strictly controlled and does not reflect the calcium stores in the bone. This control seems to function in a totally independent way from bone. Variations in plasma calcium do not act directly on bone cells, but via PTH or vitamin D. However, there is also a direct action through the calcium-sensor receptors on osteoblastic lining cells. They transfer changes of the blood calcium concentration into specific cell functions. Therefore, changes in blood calcium concentration influence osteoblast proliferation, differentiation and function,[1] and osteocytic osteolysis might be triggered by a low calcium level. As the surface of the osteocytic canalicular system is several times greater than bone surface, even a minimal resorption can immediately raise the blood calcium level.[2] The relative importance of these mechanisms is not known; they might be essential for short-term regulations. The long-term regulation of calcium in bone obviously needs a normal hormonal environment, but it also depends on the availability of bone minerals, mainly of calcium, the topic of this review.

Calcium Deficiency

Calcium deficiency means low bone density and low bone mass due to low calcium intake or low calcium absorption. As none can be assessed easily in clinic, the diagnosis remains mostly hypothetical for a given patient. PTH can be slightly elevated in low calcium intake (see below), but this is only recognizable in studies of cohorts and large populations. The markers of calcium metabolism are usually normal, except that the urinary calcium excretion can be low. On a population basis the diagnosis results from correlations between calcium intakes and bone mineral density (BMD) or other health issues, and from the positive effects of calcium supplementation.

Calcium deficiency has bone-related manifestations and extraskeletal ones. The skeletal manifestations vary with age.

Calcium deficiency in children. Very low calcium intake retards growth and leads to a relatively low peak bone mass, as shown by cross-sectional studies.[3] Populations with a low calcium intake are shorter (Asians and Eskimos for example); it is supposed that in addition to genetic factors, the growing body adapts to the low calcium intake. As to be discussed in part II, calcium supplementation stimulates growth and the development of bone mass, an indirect argument in favor of calcium deficiency.

In children of Asian and African countries, calcium deficiency was found to go along with mineralization defects, such as seen in rickets, which can be healed by calcium alone.[4]

Calcium deficiency in adults. In adults a correlation between calcium intake and bone density can only be found in populations with a low intake.[5,6] With the average calcium intake in Western countries, no correlation with bone density can generally be shown, because calcium is a threshold nutrient, where intakes higher than recommended do not produce an additional benefit. But calcium deficiency is considered as a pathogenetic factor of osteoporosis since more than 50 years.[7]

Calcium deficiency in the postmenopause and senescence. Postmenopausal women with low dietary calcium intake showed a significantly greater risk for osteoporosis.[8] Vertebral bone loss was accelerated with a calcium intake below 450 mg/day compared with an intake of more than 777 mg/day.[9] Almost the same figures were found in early

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postmenopausal Chinese women.[10] In a large prospective Swedish cohort study, the risk of hip fractures rose when the intake was below about 800 mg/day.[11]

Extraskeletal manifestations. A Swedish study[12] showed an increase of cardiovascular diseases and deaths when calcium intake was low and a Japanese study showed an increase of strokes.[13] Low dietary calcium constitutes a significant risk factor for primary hypertension (see McCarron and Reusser[14] for review). Calcium deficiency is also associated with metabolic syndromes and type 2 diabetes mellitus (see Pittas *et al*.[15] for review). Recently, low-calcium diets and a lack of supplementation were associated with a higher incidence of parathyroid adenoma formation.[16]

Low calcium intake has been reported to increase the total cancer incidence,[17] but strong evidence has only been produced for colorectal and breast cancer. There is also some evidence for an association with the development of renal, gastric, pancreatic, ovarian, endometrial and lung cancer as well as multiple myeloma (see Peterlik *et al*.[18] for review).

In conclusion, although calcium deficiency can only be suspected in the presence of low bone density or mass, due to low calcium-intake or absorption, it has been found to be frequent and not only harmful for bone, but also for many other health issues.

Calcium Intake

Calcium intake varies with age, sex, ethnics, cultures, countries and changes over adult life.[19] In general, calcium intake is higher in boys than in girls, decreases during adolescence and again in senescence; it is higher in whites than in blacks, lower in Asia than in the Western world. Studies on calcium intake can only be considered when the technique of assessment is known, such as food frequency questionnaires (FFQ), 1–3-day recalls, food diaries, etc. The more detailed the assessment, the higher the recorded intake. For example, the calcium intake was 1104 mg/day with a calcium-focused FFQ in postmenopausal American women, versus only 800 mg/day with a 24-h recall[20] with enormous individual variations: 592–1449 mg for the interquartile differences only. Therefore, results from different surveys can only be compared when they applied the same technique and accuracy for assessment; and many published figures on calcium intake are underestimations because of inaccurate assessment.

Calcium intake is often insufficient in schoolchildren, adolescents and young women of childbearing age, particularly in Southeast Asian countries, although the requirements may be lower in this region for ethnic reasons. For example, in young adults, median daily intake is 562 mg in Canada and 270 mg in Indonesia; in adults it is 611 mg in Canada and 485 mg in China; and in elderly women it is 1082 mg in Germany and 527 in Japan (see Peterlik *et al*.[1] and FAO/WHO[21] for review). Already in the past, many studies revealed low intakes, especially in elderlies,[22] and this was recently reconfirmed.[23]

Absorption

General comments. Calcium absorption is important to be known for assessing the needs. Low absorption is also associated with increased risk of hip fracture in women with low calcium intake.[24] But it cannot be easily measured in clinical practice. Calcium is absorbed primarily in the duodenum by an active transcellular and saturable system, which is stimulated and regulated by $1,25(OH)_2D$,[25] and through a passive and vitamin D-independent paracellular transport in the jejunum and ileum, and even in the colon (about 4%), when the intake is high. Absorption occurs mostly in the first hours, but absorption from a breakfast meal is 96% complete only after 7 h;[26] absorption from a supplement is faster. The bioavailability of calcium is determined as calcium fractional absorption, measured by metabolic balance, or more preferably using tracer techniques with radio- or stable isotopes of calcium. Clinical absorption tests often use the increase in the 4-h urinary calcium output as a parameter of absorption. But this catches only the first phase of absorption, and rather indicates speed than quantity of the absorptive process.

Fractional calcium absorption depends mainly on the amount of intake. At low intakes, it increases, especially at young age, and at high intakes it decreases. In middle-aged women it is about 45% when intake is 200 mg, about 30% at an intake of 500 mg, and about 25% at an intake of 1000 mg.[27] These figures cannot be applied to an individual patient, because of the three-fold individual differences. At very high intakes, fractional absorption does not decrease any more. Therefore, with increasing intakes the net amount of calcium absorbed continues to rise, but only by a very small amount. It seems that net calcium absorption has no limit, because the component of passive transport is independent of control mechanisms and is related to intake only. Nevertheless, no intoxication occurs at very high calcium intakes, because urinary calcium excretion increases accordingly.[28] Indeed, very high intakes—about 3000 mg daily and more—do not offer any advantage, confirming the concept of a plateau effect. For this reason, calcium is considered as a threshold nutrient.

Absorption efficiency is high in infants and adolescents.[29] Breast-fed infants absorb about 55–60% of the calcium in human milk, and about 40% of formula milk preparations.[30] In pregnancy it increases,[31] whereas in postmenopausal osteoporosis it is lower.[32] With aging it decreases, which has been known since 40–50 years, and fractional calcium does not adapt anymore to a low intake as it does in young subjects. This explains why elderly persons get more easily into a negative calcium balance at a low intake than younger subjects.

In older women, calcium absorption, although highly variable between subjects, is quite consistent within subjects.[33] But there are no simple methods for assessing it in a patient. Therefore it has to be feared that each elderly patient with osteoporosis can be a low absorber, needing a high calcium intake to cover the needs.

A low gastric pH is necessary for an optimal dissociation of calcium salts making calcium available for absorption. For this reason the long-term intake of protein pump inhibitors (PPI) preparations is considered as a risk factor for calcium deficiency, and by that for osteoporosis.[34] Other studies question this thesis,[35] and trials with radioactive tracers did not confirm it, but radiolabels probably do not need a low pH to be absorbed. A recent long-term cohort follow-up study reconfirmed this significant, although weak, negative effect on calcium absorption.[36]

The addition of bioactive compounds to the diet might improve bioavailability of dietary calcium. Galacto-oligosaccharides are non-digestible substances and are fermented in the colon by the microflora, resulting in the production of short chain fatty acids, which in turn lower pH and enhance calcium absorption.[37]

Role of 25(OH) vitamin D. Only about 20% of calcium absorption depends on vitamin D. The major part of calcium is absorbed by diffusion. Absorption is weakly related to serum 25OHD levels within the normal range. A study in elderly persons found that absorption was decreased only when serum 25OHD was below 4 ng/ml (10 nmol/l).[38] It is widely assumed that the main effect of vitamin D is promoting calcium absorption, but this is only true in very severe vitamin D deficiency, when serum 25OHD is below 10 ng/ml (25 nmol/l),[39] because the plasma $1,25(OH)_2D$ is maintained by PTH until its substrate (25OHD) is virtually exhausted.[40]

The small effect of 25OHD on absorption is illustrated by several studies: 50 000 IU vitamin D_2 daily for 2 weeks increased absorption of a 300-mg calcium load (double-isotope method) by only 3%,[41] and different doses of vitamin D_3 for 1 year with a calcium intake of 1200–1400 mg, showed that the absorption of a 100-mg calcium isotope dose increased by only 6 mg. Such a small increase could also be obtained with half a glass of milk or 100 mg calcium.[39] The calcium absorption correlated better with final serum 25OHD than with vitamin D dose.

The ongoing discussion on the 25OHD level necessary for optimal calcium absorption is not part of this review.

Role of $1,25(OH)_2$ vitamin D. $1,25(OH)_2D$ is the primary regulator of calcium absorption. It stimulates and mediates active transcellular calcium absorption.[25] It is long known that $1,25(OH)_2D$ increases calcium absorption almost 10 times more than 25OHD. Cross-sectional data have shown significant correlations only between calcium absorption and serum $1,25(OH)_2D$ and not with serum 25OHD.[42]

Interaction of Food

Phytic acid. A number of dietary components can inhibit intestinal calcium absorption; these include fibers, phytic acid from cereals and vegetables, and oxalic acid from vegetables. Calcium absorption from cow's milk, which is 38%, was reduced to 31% with high-phytate soybeans, whereas it was 41% from low-phytate soybeans.[43] These small differences are probably of no clinical importance.

Proteins. For obtaining positive bone effects from calcium, an adequate protein intake is required and vice versa.[44] A high protein intake stimulates calcium absorption, which leads to an increase in urinary calcium excretion. But some large follow-up and some cross-sectional studies demonstrated that a high protein intake together with a low calcium intake, a rather rare combination, increases fracture risk.[45]

Caseinophosphopeptides (CCP). Calcium-binding CPP are produced *in vivo* and industrially from casein. They may enhance calcium bioavailability during growth and prevent bone loss in older animals.[46] However, studies in humans have given inconsistent results, as often observed in nutritional research when animal data are applied to humans.

Cereals. Cereal-based diets with limited variety and little access to dairy products are characteristic of low dietary calcium intake.[47]

Calcium Losses

Obligatory losses of calcium occur in the urine, the feces and through the skin. 'Obligatory' means that they persist during low intake, causing a negative calcium balance with growth retardation in children and bone loss in adults, especially in elderly persons. They were assessed about 20 years ago. Without referring to the original literature, they can be summarized as follows: average obligatory daily loss in the urine 116 mg, through the skin 30–60 mg, with the stool 120 mg (i.e., endogenous fecal calcium, secreted by the intestinal mucosa and not reabsorbed) with large individual differences, and 160 mg in adolescents. The total obligatory losses sum up to 200–300 mg/day, minimally 150 mg/day. Exact figures can be found in the referenced balance studies (see below). It is not very well known how much these losses can decrease when intake is very low on a longer period, because almost no research was devoted to this question.

Calcium Balance

Balance studies served to establish the needs in calcium, which are discussed below. Balance studies, which evaluate the intake against the urinary and fecal losses, are the most precise technique for assessing the body's retention of calcium. They are difficult and need a run-in period when the intake is modified.

The balance becomes negative in adults when the intake falls below 800 mg/day.[48] Children can maintain a slightly positive balance ($+80$ mg/day) even when the calcium intake is as low as 300 mg/day.[29] But this is not enough for optimal growth. Consider that in the first 20 years of their life women retain 140 mg/day in average and men 165 mg/day. It has to be reminded that from a low to a high calcium intake the retention varies in average by about 300 mg, while the individual variation is ± 500 mg![49] In other words, the published figures on absorption, retention and balance are average values of groups, and cannot be applied to individual subjects and patients.

Effect on PTH and bone metabolism. Dietary calcium intake influences the PTH level. Several studies showed an inverse association between calcium intake and the PTH level on a population or group basis.[50] Dietary calcium has an immediate and a chronic effect on PTH and on bone resorption markers. Obviously, the acute effect is easier to be demonstrated with calcium supplements. But 200 mg calcium in the form of milk[51] or 172 mg in mineral water[52] was shown to decrease PTH for 4 h and sCTX for more. This effect is not only transient. A high-calcium diet was associated with a significantly decreased PTH level and decreased resorption markers, even after 3 years.[53] In addition, a long-term follow-up in the Nurses Health Study I revealed that increased calcium intake was independently associated with a reduced risk of primary hyperparathyroidism.[16]

Needs and Recommended Intakes

General observations. The need for calcium has to be covered every day; a transient excess intake cannot be stored, and a transient insufficient intake accelerates bone loss. The need for calcium varies by life stages for assuring bone accretion during growth and maintenance of bone mass in adulthood. To make recommendations for the calcium intake, the needs must be known. But the assessment of the needs is difficult. It can be achieved by different techniques, and the results vary with sex and age. This explains the variability of the recommendations.

First, the assessment can be done by short-term balance studies, which determine the amount of calcium necessary to

replace losses or the calcium intake that leads to maximal retention.[29,54,55]

Second, it can be achieved by controlled intervention trials (RCTs) with nutrients or calcium supplements. But RCTs encounter the difficulty to standardize and stabilize the intake, to work with control groups of variable intakes, and to avoid bad compliance as RCT imply administration of diets or supplements for longer periods. Despite these sources of error, public health policies still favor the use of evidence-based reviews that prioritize high-quality RCTs.[56] According to Weaver,[56] this shifts the questions from efficacy to effectiveness, which may be more relevant to public health recommendations surrounding calcium supplementation than determining calcium requirements.

The calcium needs can also be estimated, with less precision, by longitudinal studies that measure the changes in bone density, growth in children and adolescents or loss in postmenopausal women and elderly people. These estimations lead to lower recommendations than balance studies.

In the last report of the IOM of the USA,[57] the recommendations (daily recommended intakes, DRIs) take the form of estimated average requirements (EARs) and recommended dietary allowances (RDAs) or adequate intakes (AIs). The DRIs for calcium established in the USA in 1997[58] relied on bone health as the indicator, but no EARs or RDAs were indicated because of uncertainties concerning balance studies, lack of concordance between observational and experimental data, and lack of longitudinal data to verify the relationship between calcium intake, retention and bone loss. Since then, newer evidence was produced by large-scale randomized trials and calcium balance studies.

The RDAs are set about 200 mg higher than the EAR; in children, adolescents and young adults to ensure a level of skeletal retention of calcium for maximal peak bone mass, and in adults and elderly persons to minimize bone loss and to guarantee that the majority of the population takes enough calcium. The EAR represents in fact rather the average minimal requirement.

Requirements by Age

Fetus: The development of the fetal skeleton occurs mainly in the third trimester of pregnancy, when it needs 200–250 mg/day.[59] The mother delivers this amount partially thanks to an increased absorption rate.[60] The effect of calcium intake on the fetal skeleton is poorly examined.

Infants: The adequate intake in the first year of life is not sufficiently established. The average amount of breast milk consumed is 780 ml/day. Breast milk contains in average 259 mg calcium per /liter, which brings the intake of calcium in infants fed exclusively with human milk to 202 mg/day; this should meet the requirements.[58] According to balance studies in 1–4-year-old infants, adequate intake adjusted for the high-absorption efficiency is 474 mg/day.[61] Infants can retain almost 50% of the calcium intake. At high intakes of about 1200 mg/day and with adequate vitamin D status, they are able to retain 400–500 mg calcium per day. They can even keep the balance positive at low intakes. The mechanisms for this adaptation are not well known.[29]

Children: The calcium balance of children has to be positive by the amount needed for bone accretion. For this reason the required intake is relatively high. But during the ages 2–8 years the rate of growth slows, and the adequate intake was estimated at 800 mg/day according to balance studies.[29] Therefore, the RDA of the IOM for this age is 1000 mg. As already mentioned, the RDAs are set 200 mg higher than the amount currently established to ensure a level of skeletal retention of calcium for maximal peak bone mass.

For children and adolescents 9–18 years of age, the daily needs for bone accretion are estimated at 92–210 mg and can peak at much higher values. At intakes of about 1100 mg/day, maximal calcium retention is around 240 mg/day in girls and 400 mg/day in boys depending on the technique of evaluation, balance or longitudinal studies.[62,63] Therefore, the daily intake should be 1000–1100 mg for the age 9–13, and 1000 mg for girls, 1200 mg for boys of the age 14–18 years.[64] During this period of growth, calcium absorption is high, but the variation in calcium intake accounts for 12–15% of the variance in calcium retention. When the intake is increased, bone mass is transiently enhanced,[65] but the longest follow-up study in children showed some remaining effects.[66] Inadequate calcium intake in children and adolescents may lead to a reduced peak bone mass.

Adolescents: The assessment of calcium requirements for white adolescents based on balance studies[54] led to the conclusion that the balance was equal at an intake of 741 mg and to the recommendation of 1035 mg/day, which is the upper confidence limit of the study's results. An analysis of 477 published balance studies[29] revealed that the requirements are highest during infancy and adolescence, when growth is at its peak. To meet these requirements (and for compensating the urinary losses), adolescents have higher calcium absorption rates, as do infants. Although the calcium balance stays positive even at a very low calcium intake up to the age of 8 years, at the age of over 18 years it becomes negative at an intake below 700 mg/day, and calcium consumption should be about 1200 mg considering the decreasing absorption efficiency. The higher the intake, the more calcium is retained. This applies to adolescents for intakes up to 1500 mg/day, for young adults for up to 1000 mg/day.

The figures for bone accretions, urinary losses, endogenous fecal excretion, losses through the skin and absorption rates, extracted from various studies, lead to relatively high recommendations: for female adolescents 1276 mg/day, which—at a absorption rate of 38%—delivers the required 485 mg (212 mg for bone accretion and 273 mg for total losses), and for male adolescents 1505 mg/day (282 mg for accretion and 190 mg for the losses).[67] In adolescence, calcium balance depends mainly from calcium intake; net calcium absorption increases with intake while urinary calcium does not change and does not correlate with intake. In any case, the accelerated skeletal development needs greater intakes than in children or adults. For this reason, maximal peak bone mass can only be reached when the calcium intake is several 100 mg above the RDA.[68]

Adults: In adults, the obligatory losses of calcium are estimated at ±250 mg. At an average absorption rate of 20–25%, the intake should therefore be 1000–1250 mg/day to avoid a negative balance. Considering the individual variation in absorption efficiency and in obligatory losses, and respecting the necessity to cover 95% of the population, the RDA for the adult US population could be higher than often proposed. It was 1500 mg for adults over 65 years in 1984,[69] and became 1000–1200 mg in 2011.[57] In the postmenopausal period an even higher intake of about 1400 mg/day would be necessary for an

equilibrated balance, considering that the obligatory losses increase with higher intakes.[70]

As already discussed, calcium balance becomes negative and bone loss is accelerated at an intake below about 800 mg/day.[9,10,29,48] Below 800 mg/day the risk of hip fracture increases.[11] The same limit can be seen for bone density of the radius.[71] Therefore, 800 mg/day can be considered as a minimal requirement. To guarantee this 1000 mg/day is recommended. For Chinese women, 900 mg/day is recommended as a minimal value.[10] Nordin and Morris[55] consider that the needs can be set at lower levels. They recommend an RDA of 900 mg/day for adults over 60 years in order to cover the minimal intake of 750 mg/day. Hunt and Johnsons[72] also concluded that the needs, resulting from balance studies, are 741 mg/day, which would lead to an RDA of about 900–950 mg/day only.

The discussion on the optimal intake has never been settled, and there is some evidence that indeed lower intakes might still be sufficient. According to cross-sectional and follow-up studies, there is indeed no evidence that intakes of calcium higher than 900–1000 mg offer a benefit for bone health in the context of bone maintenance for adults 19–50 years of age. In elderly Americans too, a high intake beyond the RDA, usually achieved with calcium supplements, did not provide any benefit for hip or lumbar BMD according to a recent NHANES analysis.[73] A higher intake also does not seem to lower hip fracture risk,[11] although this is eventually explained by the frequent general vitamin D insufficiency. But it has to be reminded that many studies showed that calcium supplements are beneficial, as to be discussed in part II. Despite these restricting observations, the official recommendations are higher in most countries. In European and North-American countries, and in Lebanon and Brazil they are at 1300 mg. In Canada they are at 1000 mg, as well as in many Asian countries.[74] Special attention is given to women in the early postmenopausal years where bone loss is accelerated. IOM recommends a 200-mg increment for this period although it is still not evident if calcium intake can mitigate the loss of bone during and immediately following the onset of menopause. The effect of the estrogen-deprivation prevails and cannot be corrected by nutritional means.

Senescence: In elderly persons the fecal loss is higher,[75] and absorption efficiency is substantially decreased. Therefore, the intake should be higher than actually recommended, especially for increasing passive absorption. But the IOM sets the recommendation for men of 51–70 years at 1000 mg/day, the same amount as for younger adults, and at 1200 mg for both sexes over 70 years, with an EAR of 1000 mg/day. This might be enough when the vitamin D level is adequate. Many study results that contributed to these recommendations were obtained in populations that, according to actual knowledge, should have been considered as vitamin D deficient.

In can be concluded that, in order to cover the whole population and to respect the absolute limit of minimal intake (800 mg), the recommendations according to this literature should rather be generous, as were the recommendations of the IOM: 700–800 for small children, 1000–1200 mg up to puberty, then 1300 or more during puberty, about 1200 (IOM only 1000 mg until the menopause) mg/day for adults, 1200–1400 mg/day for postmenopausal women and 1200 mg after the age of 70 years. This amount seems difficult to achieve, but calcium intake is often underestimated, because the intake with non-dairy food and with water is insufficiently taken into account. As no adverse effects are know from calcium overload by nutrition, the recommendations have to be high enough to ensure deficiency. They might be slightly lower in vitamin D sufficiency.

Summary

The importance of calcium for bone, its intake and absorption are known and reinvestigated since 40–50 years. Calcium intakes vary by large amounts and are difficult to be assessed in an individual, and in clinics, calcium absorption can only be approximated. Both should be known for defining the needs. Nevertheless, calcium intake can be approximated in clinics by simple questionnaires, and assessed in research by detailed FFQs, while low calcium absorption can be suspected when urinary calcium excretion is low in the presence of an adequate intake. Pessimistic figures for intake and absorption have to be supposed for defining recommendations that should cover the majority of the population. Because inadequately low calcium intake not only leads to the development of a weaker bone and accelerates bone loss later in life, it is also associated with higher fracture risk and with many extraskeletal diseases, including cardiovascular mortality.

The needs are based on balance studies and also by cross-sectional data, preferably by controlled intervention studies, which, however, are almost impossible to be designed for this purpose. Therefore, the needs are debated, and the recommendations for the intake vary with time and nation. They might be slightly higher than indicated by the IOM, especially when vitamin D insufficiency is suspected.

Conflict of Interest

The author declares no conflict of interest.

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