Proceedings of the Nutrition Society (2016), **75**, 415–419 doi:10.1017/S0029665116000252
 First published online 12 May 2016

The Nutrition Society Irish Section Meeting was held at the University College Cork, Cork on 16–19 June 2015

Conference on 'Nutrition at key life stages: new findings, new approaches' Symposium 1: Nutritional issues in adolescence and adulthood

Factors influencing bone mass accrual: focus on nutritional aspects

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Until recently, much of the research exploring the role of nutrition on bone mass accrual has focused on single nutrients. Although randomised controlled trials have provided key information about the effects of calcium and vitamin D on bone, they also have limitations, e.g. generalisation, implementation of the results and long-term consequences. Human subjects do not eat single nutrients, but foods, and describing healthy food patterns for optimising bone mineral accrual is warranted. Recent advances in research suggest that the effects of whole diet are larger than those of single nutrients on bone health. Research should focus on younger age groups to identify the life-course determinants of osteoporosis during prenatal, infancy, childhood and adolescence that would help to maximise peak bone mass. Food patterns that describe the variability, quality and choices of individuals give broader insight and may provide new strategies for preventing osteoporosis.

Nutrients: Bone mineral accrual: Food pattern: Milk: Osteoporosis

Bone mass accrual occurs with growth and is enhanced during pubertal growth[1]. Peak bone mass is achieved between 16 and 24 years, somewhat earlier in girls than in boys. Interestingly, the timing of peak bone mass varies according to skeletal site: axial skeleton is maturated before peripheral skeleton[2]. A number of factors affect bone mass accretion, including health and disease as well as environmental factors such as physical activity, nutrition and their interactions.

Nutritional factors affecting bone mineral accrual are calcium, vitamin D and protein[3,4]. These are the main constituents of bone, biologically relevant compounds that are beneficial for bone growth and bone mineral accrual. Beyond them are phosphorus, potassium, other trace minerals, *n*-3 fatty acids, vitamins C and K, which are suggested to be meaningful but for which the scientific evidence is still to be gathered.

A 10 % increase in peak bone mass is estimated to halve the risk of an osteoporotic fracture in adult life[5]. Different kinds of strategy to maximise peak bone mass in children have been studied and these are considered to be primary prevention strategies against osteoporosis. The focus of the present paper is on nutritional aspects. The review will not provide comprehensive insight into the topic, but rather highlight the recent advances and discuss these and derive approaches to be used in the future to confirm the information provided in this field.

Proof of evidence

In medical science, the evidence relies on randomised controlled trials (RCT), which are able to prove causal relationships between nutrient intake and bone mineral accrual. With a delicate design, a dose-responsive effect can also be explored[6,7]. Highest in the hierarchy are meta-analyses[8–10] and systematic reviews, which offer an overall picture of the state of evidence and may therefore modify the focus of research.

RCT still represent a simplified approach, as they typically focus on a single, specific nutrient. RCT have several limitations, such as focusing on a selected population. Especially in children and adolescents, only single centre studies are reported, and it is not clear how generalisable the results are into other populations. Another challenge is confounders and being able to

Abbreviation: RCT, randomised controlled trial.
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control for these in the study design. A confounder such as physical activity is shown to enhance bone mineral accrual independently[11], as well as acting together with calcium[12]. Likewise, the pubertal stage may vary across age groups. The timing of accelerated growth in terms of peak height velocity occurs during the mid-pubertal stage in girls, but somewhat later in boys[1,4,7], while weight status modifies both puberty and the bone mass accretion itself[13]. In addition, compliance with the study protocol could affect the results. A dilution effect will be marked with poor compliance and both intention-to-treat and per-protocol analysis should be reported. Without an attempt to follow compliance, an RCT should not be considered high-quality, since it is likely to give false-negative findings[14]. The final concern is drop-outs, for which the researcher should be prepared from the outset. According to ethical guidelines, subjects are allowed to cancel their participation whenever, but researchers are eager to know the reason. This could reveal something about the acceptance of the dose or product. We are interested in long-term effects, as they mimic lifestyles that are beneficial for bone throughout the life. So far, only a few RCT have been able to answer this question and in fact many of them do not plan to look at long-term effects.

Calcium

In 2008, a meta-analysis by Huncharec *et al.*[10] identified twenty-one original RCT and summarised their findings on the effect of dairy/calcium supplementation on bone in children. Increased dietary calcium/dairy products modestly but significantly increased total body and lumbar spine bone mineral content in children. The effect was most profound in children with low baseline intakes. More recent RCT have focused on populations with low habitual calcium intakes and these have reinforced the message: calcium supplementation enhances bone mass augmentation in children and adolescents[7,15,16].

An elegant continuum for this was provided by a supplementation study of Gambian boys with extremely low habitual calcium intakes (<300 mg/d). Prepubertal boys were randomised to receive either a placebo or 1000 mg calcium from supplements for 12 months[17]. The group started to follow the long-term effects 1 year after ending the trial. Of forty boys in each arm, twenty five and twenty nine completed the 12-year follow-up. The key finding was that although the peak velocity occurred earlier in the supplemented group, the total amount of bone accrued was not affected. In line with earlier study[15], the effect of supplementation on bone was short-lived, which highlights constant adaptation to the prevailing circumstances.

Vitamin D

In 2010, a combined meta-analysis and systematic review was undertaken on the effects of vitamin D on bone mineral accrual[9]. At the time, the authors identified six high-quality vitamin D RCT to be included. The challenge was that these were based on rather diverse populations in many aspects: Pakistani immigrants in Denmark, Finnish girls, Saudi Arabian teens and Chinese girls; enrolment age varied between 10 and 17 years; vitamin D doses varied from 3·3 μg/d and 350 μg week and baseline 25-hydroxy vitamin D concentration 7·3–49·5 nM/l; and only one study included boys. Changes in bone mineral accrual were measured with dual-energy absorptiometry from different sites. The results from individual studies were optimistic, but still not conclusive: the effect of vitamin D supplementation on changes in bone mineral density was without effect or positive. The review summarised that 'vitamin D supplementation is unlikely to be beneficial for children and adolescents with normal vitamin D level,' although the greatest effect sizes were noticed in those with higher than deficient vitamin D status (25-hydroxy vitamin D > 25 nM/l)[6,18,19].

Based on the meta-analysis[9] children with severe vitamin D deficiency could be optimal targets for vitamin D supplementation, as clinically relevant improvements in bone mineral accrual are anticipated. But in very poor, underprivileged societies, severe vitamin D deficiency coexists with multiple nutrient deficiencies, e.g. stunting of growth, anaemia and protein malnutrition[20], and focusing entirely on vitamin D may not be sufficient. Conversely, supplementing Bangladeshi women for 12 months with vitamin D solely or in combination with micronutrients improved bone mineral density in the femur similarly in both groups[21] while effects on overall wellbeing were not evaluated.

Protein

Dietary protein intake is shown to be associated with bone health, at least in elderly subjects. Optimal linear growth requires adequate dietary intake of protein, and protein may play a role in bone mineral accrual, but the scientific evidence is scarce. The association of protein intake with bone status was evaluated in a longitudinal study including 229 German children[22]. Growth and multiple lifestyle factors were followed annually for four preceding years. Bone and muscle parameters were assessed using peripheral quantitative computed tomography in the study. A positive association was observed between dietary intake of protein and several bone characteristics in the forearm: cortical cross-sectional area, periosteal circumference, bone mineral content, and stress and strain index. Interestingly, an inverse association was marked between potential renal acid load and bone mineral content and cortical area, which suggest that the type of protein source is also meaningful. These observations have been confirmed in more recent studies[23].

Food pattern

Until recently, much of the research exploring the role of nutrition on peak bone mass has concentrated on single nutrients. While this approach has provided data on the effects of various vitamins and minerals on bone, it

https://doi.org/10.1017/S0029665116000252 Published online by Cambridge University Press

also has limitations. Human subjects do not eat single nutrients, but foods, and the RCT described here do not answer the question as to which are good dietary sources of nutrients. In addition, in epidemiological studies, separating the effect of a single nutrient has proved to be problematic, and in most cases the effect of a single nutrient may be too relatively small to be detected in epidemiological studies. This gives rise to conflicting results and confusion for policy-makers. Food or dietary pattern-oriented studies avoid some of the fundamental challenges of studies assessing the role of single nutrients. Such studies also provide practical information for the public and may be more directly utilised when revising dietary guidelines. Dietary pattern is a rather stable measurement compared with the day-to-day variation in certain nutrient intakes. Approaches that apply foods or dietary patterns could teach us novel things about bone health.

An example of the approach is milk. Milk contains over thirty nutrients, including calcium, phosphorus, protein, magnesium and potassium, that could be considered as bone agents, and these may have additive or synergistic effects on bone. What evidence is there? A number of studies have looked at the association between milk consumption and bone mineral accrual. One of the earliest RCT was performed in Sheffield, UK[24]. A total of 82 girls aged 12 years took part in this RCT. For randomly chosen girls, milk was delivered at home. At baseline, the intake of milk was relatively low, only 150 ml/d, but it increased by 300 ml during the 18-month trial. Bone mineral density increased in both groups, but more in the milk group: 9·6 *v.* 8·5 %. Serum concentrations of insulin-like growth factor I increased more in the milk group compared with the control group (35 *v.* 25 %)[24].

Similarly, in a prospective study, milk intake was associated with higher axial growth in a 6-year follow-up of American girls[25]. Further evidence from a Copenhagen study cohort of 17-year old boys and girls suggested that bone mineral accretion is associated with both total protein and milk protein intakes, but less so with meat protein intake[26], which implies that milk is an optimal protein source and synergistic effects are likely to occur. How about elimination of milk from the diet? In a Polish case–control study of 5–20-year-old children and adolescents, milk allergy was associated with an increased risk of fractures in girls[27]. Similarly, in a New Zealand study, milk-avoiding children (*n* 50) had a higher incidence of fractures (twenty fractures) than a birth cohort of 1000 children from the same area (eight fractures)[28]. In addition, higher hip fracture incidence has been reported in elderly subjects consuming at most one portion of milk per week in the Framingham Osteoporosis Study[29]. The decrease in hip fracture risk was 40 % in the milk-favouring group; this is a major effect that could not be achieved with any single nutrient.

Longitudinal studies with dietary assessment contain data on habitual use of foods and are able to create food patterns that describe the variability, quality and choices of individuals. Compared with nutrient intakes, this gives broader insight and allows new strategies for preventing osteoporosis. There are several ongoing prospective studies, e.g. the Framingham Osteoporosis Study, Women's Health Initiative, Canadian Multicentre Osteoporosis study, Kuopio Osteoporosis Study, but these have focused on older populations and are considered as secondary prevention studies for osteoporosis. The findings from the Canadian Multicentre Osteoporosis study have been appealing: a diet rich in vegetables and fruits, evidently a nutrient-dense diet, prevents bone loss and low-energy fractures in Canadian women, but an energy-dense-nutrient-poor diet seems not to accelerate it[30]. Future research should focus on younger age groups to identify the life-course determinants for osteoporosis during prenatal, infancy, childhood and adolescence that would help to maximise peak bone mass. Diet and physical activity are the modifiable factors, but being able to describe these in more detail and the opposite as well, being able to identify lifestyle risk factors for impaired bone mineral accrual is important. In addition, the interaction of lifestyle factors with genetic factors has remained unclear. This would give us tools to recognise subjects at risk more easily and readily, and furthermore to be able to educate them (Fig. 1).

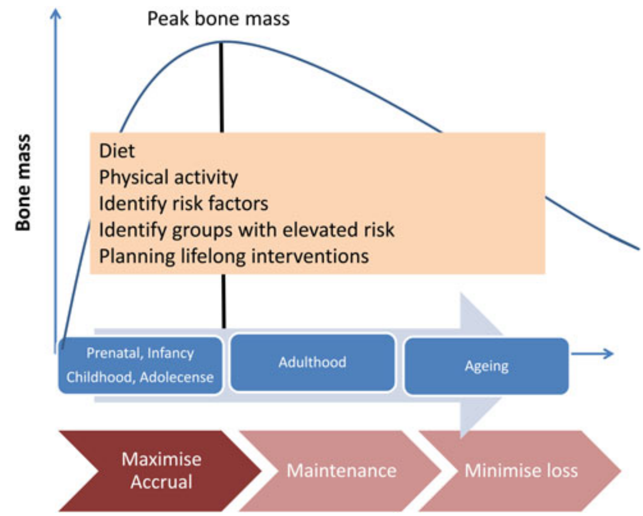

Fig. 1. Life-course determinants of osteoporosis and future perspectives.

Conclusion

Bone mass accrual is affected by multiple factors, of which nutrition is a modifiable one. Recent RCT have confirmed the effects of single nutrients on bone health, but the effects may be too small to be detected in epidemiological studies. Food or dietary pattern is a rather stable measurement compared with day-to-day variation in certain nutrient intakes. Typically dietary patterns evolve during growth, but remain stable from late adolescence. The effects of a whole diet are larger compared with a single nutrient. Research on recognising dietary patterns that benefit bone mineral accrual is warranted

https://doi.org/10.1017/S0029665116000252 Published online by Cambridge University Press

side-by-side with RCT to broaden our understanding of nutrition and bone health. We are interested in long-term effects, and cohorts with longitudinal follow-up are needed to provide real-life data on nutrition and bone health.

Financial support

The work was supported by the Academy of Finland; Sigrid Jusélius Foundation; and Päivikki and Sakari Sohlberg Foundation.

Conflicts of interest

None.

Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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