Proceedings of the Nutrition Society (2012), **71**, 27–37 doi:10.1017/S0029665111003375
 First published online 5 December 2011

A meeting of the Nutrition Society hosted by the Irish Section jointly with the American Society for Nutrition was held at University College Cork, Republic of Ireland on 15–17 June 2011

70th Anniversary Conference on 'Vitamins in early development and healthy aging: impact on infectious and chronic disease'

Symposium 2: Vitamins in muscular and skeletal function
Musculoskeletal phenotype through the life course: the role of nutrition

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This review considers the definition of a healthy bone phenotype through the life course and the modulating effects of muscle function and nutrition. In particular, it will emphasise that optimal bone strength (and how that is regulated) is more important than simple measures of bone mass. The forces imposed on bone by muscle loading are the primary determinants of musculoskeletal health. Any factor that changes muscle loading on the bone, or the response of bone to loading results in alterations of bone strength. Advances in technology have enhanced the understanding of a healthy bone phenotype in different skeletal compartments. Multiple components of muscle strength can also be quantified. The critical evaluation of emerging technologies for assessment of bone and muscle phenotype is vital. Populations with low and moderate/high daily Ca intakes and/or different vitamin D status illustrate the importance of nutrition in determining musculoskeletal phenotype. Changes in mass and architecture maintain strength despite low Ca intake or vitamin D status. There is a complex interaction between body fat and bone which, in addition to protein intake, is emerging as a key area of research. Muscle and bone should be considered as an integrative unit; the role of body fat requires definition. There remains a lack of longitudinal evidence to understand how nutrition and lifestyle define musculoskeletal health. In conclusion, a life-course approach is required to understand the definition of healthy skeletal phenotype in different populations and at different stages of life.

Mechanostat: Bone: Growth: Aging: Muscle: Life course

A healthy bone is one that is fit-for-purpose, has mechanisms for maintenance and repair, is responsive to changes in musculoskeletal environment and will not fail during normal physiological activities. To assess bone health, measures have been developed to quantify the amount of mineral within the bone (bone mineral density (BMD) or bone mineral content (BMC)). However, it has become increasingly important to move beyond a definition of bone health only in terms of BMD/BMC to one of 'optimal bone strength' that encapsulates the contributions from multiple components such as bone shape and size, internal structure and metabolism and loading conditions[1]. Bone strength in later life may depend on optimal skeletal growth and development during childhood, adolescence and reproduction. Over the last decade the focus of research in human bone strength has altered to include early life and childhood in addition to aging, and to prevention rather than treatment of bone disease. Bone strength may be compromised at different times in the life-course (Fig. 1). It is during periods of rapid growth that the developing skeleton is at most risk. Conditions that may manifest during childhood are rickets (failure of mineralisation of the growing bone) and osteomalacia (weak and soft bones), low trauma fractures and stunting (failure or delayed longitudinal growth). Peak bone strength is reached at the end of longitudinal growth. In young

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CSMA, cross-sectional muscle area; 25(OH)D, 25-hydroxy-vitamin D; DXA, dual energy X-ray absorptiometry; QCT, quantitative computed tomography.

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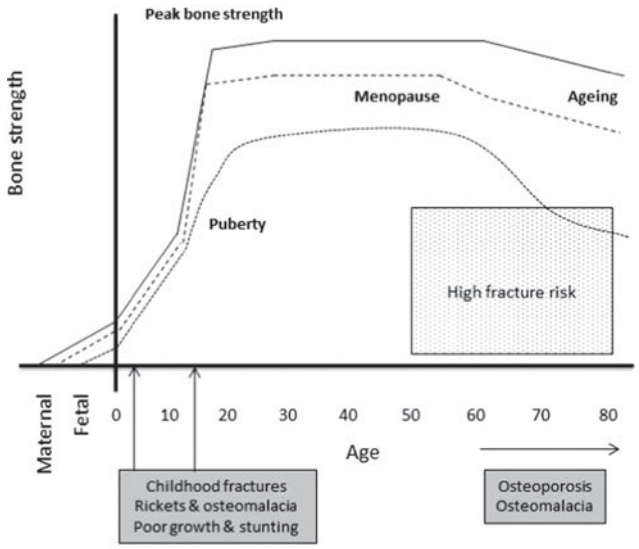

Fig. 1. A conceptual diagram of bone health through the life course: the solid line denotes male, dashed female and dotted the consequence of not achieving peak bone strength at the end of development.

adulthood, bone is in a steady state of maintenance with no net loss or gain of strength. The menopause and aging in women and aging in men lead to bone loss and increased susceptibility of the skeleton to fragility fracture (osteoporosis); osteomalacia is also a common disease of the elderly. The aim of this review is to consider the definition of a healthy bone phenotype through the life course and the modulating effects of muscle function, Ca, vitamin D and other nutritional factors.

Definition of healthy skeletal phenotype

Changes in biomechanical environment through the life-course require bone to be a dynamic, modifiable tissue capable of sensing and responding to these changes. As muscles contract and relax, the bone is loaded, which changes the shape and length of the bone and induces strain. Strain is defined as the change in length divided by original length of the structure. It is generally accepted that a change in bone strain is one of the key mechanisms for adapting skeletal mass and architecture so that the skeleton is as light as possible for normal daily activities with a sufficient margin of error to avoid failure (fracture). During a 24 h period, the bone is subjected to a characteristic range of strains of defined magnitude and is adapted to this range[2,3]. Strain sensing cells (osteocytes) detect any changes in strain outside of the 'steady state' and drive bone gain (modelling by osteoblasts) or loss (resorption by osteoclasts) in response to this. Where no gain or loss is necessary, a steady state is maintained through remodelling, a balance of osteoblast and osteoclast activity. The mechanostat describes the mechanism by which bone strength is maintained as 'fit-for-purpose' for daily living (Fig. 2)[3]. Together, the response of the mechanostat to muscular loading and/or external modulators, form a functional model of bone development and aging, referred to in this review as the mechanostat model[4,5]. Nutrition and lifestyle factors are key examples of external modulators and interact with the mechanostat model through muscle and bone (Fig. 2).

The mechanostat model describes how bone strength is modified in response to changes in strains. The four main determinants of bone strength are (i) material properties, (ii) bone mass, (iii) structural (shape and geometry) design and (iv) the loading conditions (including the direction of load) to which the bone is subjected.

Material properties: A bone is composed of organic and inorganic matter, collagen and ground substance (osteoid) and mineral (hydroxyapatite), respectively. The ratio and arrangement of osteoid and hydroxyapatite determine the mechanical quality, or stiffness, of bone and describes the ability to withstand strain without permanent deformation or damage, i.e. an elastic material. The material properties also determine bone toughness, which describes the energy required to break the bone[6].

Fig. 3 illustrates how stiffness contributes to the bone phenotype. Changes in stiffness of the bone alter the elastic, plastic and fracture thresholds of the bone. Nutrition, lifestyle status or certain conditions may change the stiffness of a bone. For example, in severe vitamin D deficiency there is bone formation without adequate mineralisation and the bone deforms easily due to low stiffness. Toughness is high compared to a healthy bone, meaning more energy would be required to break the bone. The structural changes in response to low stiffness are driven by overestimation by the mechanostat of the loads applied. Increases in cross section are required to maintain the bone strains within the elastic range and not cause damage. In contrast, excessive mineralisation increases stiffness and decreases toughness, creating a brittle structure[7]. In this situation, strains are underestimated by the mechanostat; as the material is not able to deform to the same degree as the healthy bone the cross section is smaller than a bone with 'healthy stiffness' (Fig. 3). An analogy would be two tubes of pasta, one cooked and one uncooked, if the same load were applied to each the cooked tube would deform easily (overestimation of load by mechanostat), while the uncooked tube would break easily (underestimation of load by mechanostat).

Bone mass: It is the amount of matter within the whole bone (i.e. collagen, mineral and extracellular fluid). By definition mass is the product of volume (cm^3 or mm^3) and density (g/cm^3 or mg/mm^3). The 'mineral mass' or BMC (g or mg/mm) is the amount of mineral within the tissue and is quantified by bone measurement techniques that are discussed later.

Structural properties: The shape, spatial distribution and internal organisation of the bone are also important determinants of strength. The different bone compartments adapt in different ways to increase, maintain or lose strength throughout the life course[8–11]. The observed sexual dimorphism in the changes in structure are thought to explain differences in fracture rates in males and females and have evolutionary significance for the demands of pregnancy, lactation, menopause and aging[11–13].

For cortical bone, the further away that bone mineral is distributed from the axis of the bone, the greater the

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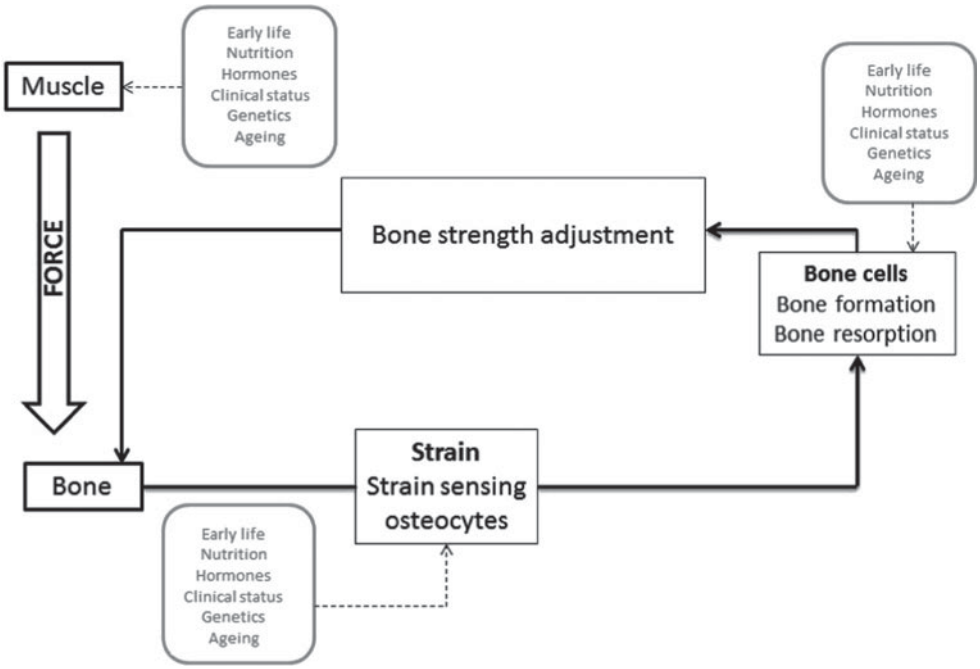

Fig. 2. A summary diagram of the Mechanostat model: the grey boxes indicate non-mechanical factors, including nutrition, and where they may interact with the Mechanostat. These interactions may be through alterations in the ability of muscle to generate forces (load), the bone ability to detect or respond to changes in load. For example, vitamin D causes proximal muscle weakness, which would reduce loading to bone and from this 'sub-optimal' bone accretion or increased bone loss may occur. At the bone level, vitamin D causes under-mineralisation of bone which would change the way it responds to loading. Both of these examples would result in changes in bone phenotype and strength. Adapted from Frost[3].

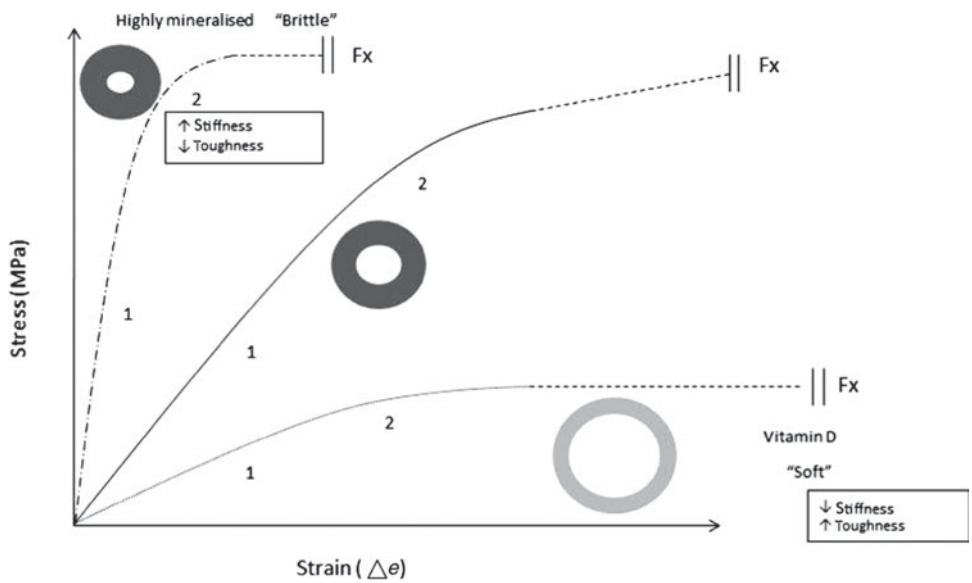

Fig. 3. Schematic stress–strain curve to demonstrate how phenotype may respond to changes in stiffness: the solid line denotes a healthy skeleton 1. Elastic portion of the curve where load does not permanently deform the bone or induce damage, 2. Plastic region where damage is starting to accumulate, Fx = fracture load; note there is a long period before the fracture load is reached under normal circumstances. The dash-dot line is a bone with high stiffness (mechanostat underestimates loads from muscle) and the dotted line is low stiffness (mechanostat overestimates loads from muscle); note the differing length of the elastic and plastic regions in each of these situations.

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strength. Therefore, two long bones of differing cross-sectional area with identical amounts of mineral distributed in different ways will have markedly different moments of inertia, or resistance to bending, which are proportional to the radius of the cross section of bone. Redistribution of mineral within bone when cross-section remains the same may also increase bone strength, but to a lesser degree.

In trabecular bone, the arrangement and interconnectivity of the trabeculae are important for strength. Trabeculae thicken and change orientation during growth and development. As trabecular bone is lost during aging, the most supporting trabeculae to the direction of load are maintained to prevent fracture for as long as possible, for example, trabeculae in the vertebrae, radius or tibia[14,15].

Loading conditions: Increases or decreases in muscle strength will drive a modification of bone by the mechanostat. For example, during growth, peak height velocity is followed by peak muscle mass velocity and then peak bone mineral accumulation; during aging, declining muscle function precedes bone loss.

Imaging and musculoskeletal phenotype

The direct measurement of bone strength, resistance to fracture load, is not possible *in vivo*. Quantification of the skeleton using imaging is thus based upon measurement of parameters related to bone strength. Currently, the most common measurements are BMD or BMC, which only act as proxies for bone strength, but are related to fracture risk in populations at high risk of fracture[16–18].

When using imaging methods to measure the skeleton, it is important to consider the measurements being taken and the information they actually provide about the bone as an organ both as a whole and constituent compartments. BMD, by definition, is the mass of mineral divided by volume (g/cm^3). There are two types of BMD that can be measured *in vivo*: BMD_{TOTAL} measures everything within the periosteal envelope, including bone marrow, cortical and trabecular bone; $BMD_{COMPARTMENT}$ is the BMD of the separate compartments of bone, for cortical bone this includes the pores and Haversian canals, for trabecular bone this also includes bone marrow[19].

As a two-dimensional measurement, dual energy X-ray absorptiometry (DXA) estimates both areal BMD_{TOTAL} (g/cm^2) of the axial and peripheral skeleton and $BMD_{COMPARTMENT}$ of cortical bone at sites where little trabecular bone is present, e.g. midshaft femur and radius. DXA cannot take into account the depth of the bone and data acquired are thus size dependent; considerations must be made when using the technique in the growing skeleton and when measuring populations which may differ in size[1,20,21]. DXA images have vastly improved in quality in recent years and the method now provides assessment of vertebral fracture, bone structure and detailed body composition.

Areal BMD_{TOTAL} by DXA has been used for many years as a predictor of fracture risk and diagnosis of osteoporosis, predominantly based on evidence in post-menopausal populations. The method is now used in males, pre-menopausal females and children and is considered the gold standard in terms of clinical practice. However, there are limitations to DXA both for clinical and research applications[1,20,22,23]. Clinically, not all people with fracture have low BMD_{TOTAL} or BMC indicating that factors other than bone mass are important[24]. More recently, an audit of fracture cases in UK showed obese people who fracture do not have a low BMD_{TOTAL}[25]. Research in females from The Gambia and China found that they had low BMD_{TOTAL}/BMC in comparison with an age-matched UK population, yet these populations are known to have lower fracture risk[26,27]. The Gambian population still had lower BMC after adjustment for their smaller bone size and lower body weight, contradicting the assumption that low BMD_{TOTAL} equals higher fracture risk[28]. Therefore, although DXA measures of BMC/BMD_{TOTAL} are strong predictors of fracture risk in older people and children in populations at high risk of osteoporosis these measures are of limited value in different populations and at different times of life.

Quantitative computed tomography (QCT) is a three-dimensional technique providing size-independent measures of volumetric BMD (g/cm^3). QCT is the forerunner in three-dimensional assessment of the axial and peripheral skeleton being the only technique to measure volumetric BMD_{TOTAL} and $BMD_{COMPARTMENT}$ of trabecular and cortical bone. QCT also provides measures of multiple components of cortical and trabecular bone (shape and geometry), which allow the measurement of some parameters of bone strength[29–36]. The use of QCT to measure the spine and hip is limited due to radiation dose considerations and accessibility of scanners; although radiation dose is considerably less than diagnostic computed tomography[37–39]. The invention of peripheral (p) QCT and more recently high-resolution pQCT, has led to wider application of QCT to define phenotype including assessment of trabecular microarchitecture and metaphyseal cortical bone[35,36,40–42].

The utility of axial and peripheral QCT has been shown in studies investigating differences in bone phenotype related to nutrition, aging, hormone status, chronic disease and treatment, i.e. the external modulators of bone and muscle; DXA has not always had the sensitivity to such detect differences[34,43–47]. The agreement between DXA and QCT is generally poor[48,49]. This is due to the ability of each technique to measure estimated or actual BMD_{TOTAL} and $BMD_{COMPARTMENT}$; different patterns of regional bone loss (e.g. spine *v.* hip); and the disease-specific effects on bone compartments. The selection of scan site and measurement method is therefore extremely important when designing study protocols.

Body composition: Muscle strength is a composite term and is determined by muscle mass (e.g. volume, composition, fibre number and size) and structure (e.g. fibre type and pennation angle), which in turn determine force-generating capacity and power. Muscle force is a measure of the load applied to bone, whereas power is a measure of function[50,51]. A full assessment of body composition methodology, particularly the measurement of muscle mass, density and function, is beyond the scope of this review. Lean tissue mass by DXA and cross-sectional muscle area (CSMA) from pQCT or MRI have been used as proxies for muscle strength in a similar way to BMD/BMC being proxies for bone strength. The acquisition of

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https://doi.org/10.1017/S0029665111003375 Published online by Cambridge University Press

data at the same time as skeletal assessment is a particular advantage of these techniques, yet the sensitivity of measurement of muscle mass or CSMA to detect changes in muscle function has been questioned[50,52,53]. For example, CSMA measured by pQCT showed less decline with age than functional tests such as chair rising and jumping mechanography (which measures lower-limb muscle function using a ground reaction force platform)[50]. Infiltration of muscle with fat is another reason for the lack of sensitivity of CSMA or lean mass measurements. For example, CSMA by pQCT did not change in response to vitamin D supplementation, whereas lower-limb power improved, likely due to changes in intramuscular fat not being detected by CSMA measurements[53]. Measurement of intramuscular fat is possible with some techniques and may provide vital information regarding muscle development and aging and the effects of nutrition[54–56].

In summary, measurements of BMD/BMC provide information about the amount of mineral within a given volume or area of bone and thus provide some indication of bone strength. However, bone strength is also determined by shape, geometry and loading conditions. The separate measurement of cortical and trabecular bone compartments in respect of all these aspects of bone strength is important to fully understand the definition of a healthy bone phenotype. This requires technologies that move beyond BMC/BMD by DXA. The critical evaluation of the existing and newer technologies for assessing bone and muscle *in vivo* is a research priority in order to fully determine their potential, appropriate use and interpretation.

Nutrition and musculoskeletal health though the life course

The dietary factors and lifestyle determinants that have been associated with bone strength and with longitudinal growth include the bone-forming minerals (Ca, P, Mn and Zn); vitamins involved in Ca–P homoeostasis and/or bone metabolism (e.g. vitamins D, K and C); energy, amino acids and ions (e.g. Cu, Mn, CO_3 and citrate)[57]. Either the bone matrix and composition is altered (Ca, P, vitamin D, vitamin C and vitamin K) or deficiencies in single nutrients or food groups result in poor bone development and longitudinal growth (e.g. protein, Ca and Zn)[1,58]. The majority of these nutrients are also associated with muscle strength, including protein and vitamin D[59–61]. There is also emerging evidence for an interaction between the musculoskeletal system and adipose tissue[25,62–64].

Therefore, nutrition may influence bone strength at several points in the mechanostat model through changes in muscle strength, longitudinal growth, bone stiffness and consequent response to strain or through the function of the cells which drive the response (Fig. 2)[5]. Most of the evidence of the effects of nutrition on bone strength is for Ca and/or vitamin D. Protein intake and adiposity are emerging areas of research. These four areas will be the focus of this review.

Ca

Ca is the most abundant bone-forming mineral in the diet. As such, the role of Ca, in the tempo of bone growth and development, and the timing and level of peak bone strength, has been widely studied[21,65]. The assumption that increased dietary Ca intake translates into sustained benefit for bone health has been challenged by the many published supplementation trials[1,66–69]. There are several reasons for this. Increased Ca may temporarily increase BMD/BMC through a slowing of bone turnover known as a remodelling transient. The transient effect is related to the amount of mineral being quantified by DXA or QCT. Slowing of bone turnover would result in fewer bone sites undergoing resorption and more mineralised or mature bone being measured, temporarily increasing BMD/BMC. When normal bone turnover resumes, the increased number of bone sites undergoing resorption and the less mineralised new immature bone would result in a lower BMD/BMC[21,66]. Secondly, evidence from a pQCT study showed extra Ca may be deposited on the endosteal surface; once the source of Ca was removed the effect was lost[69]. If extra Ca was required to increase bone strength, bone would be laid down on periosteal not endosteal surface. Finally, the type of supplementation is crucial for the maintenance of effects whereby Ca salts do not always provide sustained changes in bone and dairy sources of Ca show lasting benefit[21,70–72]. It is important to note, dairy sources also contain growth factors such as insulin-like growth factor 1 and protein and therefore the observed effects of the intervention might be through increases in intakes of all of these factors rather than Ca *per se*[21]. The assessment of whole diet rather than single nutrients is important to determine relative contributions of the single nutrients. Combined benefits of Ca and physical activity interventions have been found at some skeletal sites[73–75], but again there is lack of evidence for maintenance of effect of the Ca supplement, whereas physical activity effects remain once the intervention stops[69]. These observations of a sustained effect of childhood physical activity on bone are consistent with the studies of adults[76–79].

The majority of evidence for the association between a high Ca intake and greater BMD is based on studies from countries with moderate to high Ca intake. Low Ca intake is characteristic of some population groups. Increasing Ca intake from 300 to 700 mg/d increased BMC and size adjusted BMD, but not bone width (perhaps indicating deposition of Ca on endosteal surface), growth rate or pubertal stage in a group of Gambian children[80]. Bone turnover was reduced and parathyroid hormone lowered in the Ca group, indicative of a bone remodelling transient effect[81]. However, after a year, the differences in size-adjusted BMC remained despite normalisation of bone turnover[82]. These data suggest a sustained effect of Ca salt on the skeleton; if, as the continued suppression of parathyroid harmone levels suggest, there is permanent disruption of the adaptation to low Ca intake in these children, this may not be beneficial for future growth and development[81].

The long-term role of Ca in skeletal health in adults with low Ca intakes has also been challenged by previous studies from The Gambia[28,83]. In an older population of Gambian women, significant age-related decreases in lumbar spine BMC were observed; these were of similar magnitude to those in Western populations[28]. Differences

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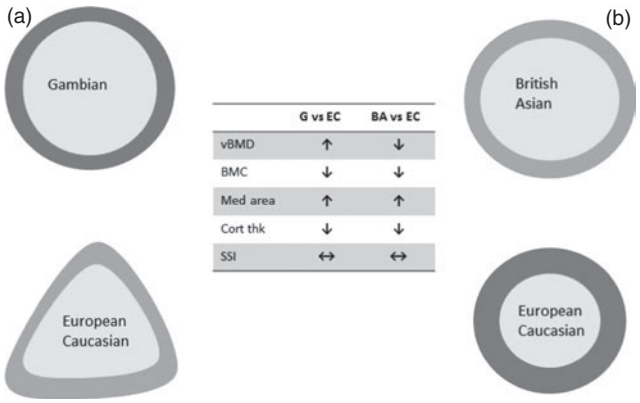

Fig. 4. Overview of how nutrition may alter phenotype at age of peak bone strength: (a) low Ca intake – comparing Gambian to European Caucasian tibia; (b) vitamin D status – comparing British Asian compared to European Caucasian radius. The table summarises the differences. vBMD, volumetric bone mineral density; BMC, bone mineral content; Med area, medullary area; Cort thk, cortical thickness; SSI, bone strength.

in body segment proportions (lower ratio of sitting:standing height) and bone biochemistry (increased parathyroid hormone in response to low Ca intake) were proposed as possible explanations for the lower incidence of fracture in Gambian women[26]. Another explanation is provided in Fig. 4(a), which illustrates how phenotype may alter, to maintain strength in response to long-term low Ca intake. Pre-menopausal Gambian females had lower BMC and thinner cortices, yet higher cortical BMD and rounder bones in comparison with a group of age-matched UK women[47]. These data illustrate discrepancies between measurements by DXA and pQCT, DXA measures lower $aBMD_{TOTAL}$ in spine and forearm, whereas pQCT measured higher cortical $BMD_{COMPARTMENT}$. Despite the differences in geometry and lower BMC, there were no differences in bone strength; in the long term these data may explain lower fracture risk in the Gambian population. Causality cannot be inferred from these cross-sectional data; however, they highlight the importance of using techniques to measure more than BMD/BMC when exploring population differences.

Vitamin D

Vitamin D has a role in Ca homoeostasis and skeletal mineralisation through endocrine effects on bone, intestine and kidney. Vitamin D also promotes protein synthesis and Ca and PO_4 transport in muscle, thus influencing muscle strength[59]. Given these multi-factorial effects, vitamin D may interact with the mechanostat model at multiple levels (Fig. 2): directly, through bone mineralisation and muscle strength; and, indirectly, through decreases in physical activity due to muscle weakness and fatigue caused by deficiency. Through these mechanisms vitamin D may have a role in prevention of falls and subsequently fractures in older people, although evidence does not conclusively support this[84–86].

The possible implications of poor vitamin D status for long-term musculoskeletal health and rising incidence of vitamin D deficiency in teenagers in the UK prompted a study into the effects of vitamin D supplementation in adolescent South-Asian girls in Manchester[53,87]. Over 60% had serum 25-hydroxy-vitamin D (25(OH)D) levels less than 25 nmol/l[87]. 25(OH)D is a measure of an individual's vitamin D status, 25 nmol/l is the current cut-off for serum 25(OH)D level to prevent the occurrence of rickets and osteomalacia. Despite this, none had symptoms associated with vitamin D deficiency, although muscle function was related to 25(OH)D status[60]. After supplementation with ergocalciferol 3579 μg ((150 000 IU) every 3 months equivalent to 35 μg (1400 IU) per day), 25(OH)D levels rose from 18 to 56 nmol/l. However, there were no effects on BMD/BMC, geometry or strength[53]. Muscle function improved, with greater response in those who had the lower baseline 25(OH)D. In general, the evidence for positive effects of increases in serum 25(OH)D on the developing musculoskeletal system is inconclusive[53,88,89]. The baseline 25(OH)D levels, timing and dose of intervention could be crucial for sustained, positive effects[53,88–90].

Fig. 4(b) illustrates how low vitamin D status may contribute to bone phenotype through the life course. South Asians had lower volumetric BMD, BMC and cortical thickness compared to age-matched Caucasians. The South Asians had slightly larger bones suggesting that the bone mineral was distributed further from the bone axis. The consequence of this was that despite lower BMC in South Asians, bone strength was not different between the groups[46]. Longitudinal data are required to confirm these observations and the multi-factorial role of vitamin D status on the mechanostat model.

Protein

Dietary protein intake has been shown to have positive associations on bone and muscle by increasing serum insulin-like growth factor 1, Ca absorption and bioavailability[1,61,91]. During childhood and adolescence these positive associations may be through effects on growth or mineral acquisition[1,92,93]. Reductions in protein intake during aging have been linked to loss of muscle mass and an increased number of falls, both of which contribute to fracture risk[61,93]. In contrast, animal protein may promote an acidic environment, which may lead to bone loss through $CaPO_4$ being released as a buffer[1,93]. Consistent with this, large amounts of animal and dairy protein have been associated with increased risk of hip fracture[61,94]. The complexity of the differential effects of the type of dietary protein and how they interact with bone and muscle at different times during life requires further study.

Adiposity

Although low body weight, including anorexia nervosa, is well recognised as a strong risk factor for fracture, and higher body weight associated with protection, there is emerging evidence that obesity may also be a risk factor for fracture[25,62]. The rising levels of obesity and evidence for an interaction between skeletal and adipose tissue is

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of increasing importance within musculoskeletal research[25,62,63,95,96].

The amount and distribution of the adipose tissue are important in determining fracture risk in children and adults, with visceral rather than subcutaneous fat being a risk factor for fracture[97]. The interaction between adiposity and other nutrition and lifestyle components, for example, vitamin D status, gives added complexity to the understanding of the relationship between adipose tissue, muscle and bone.

Adipokines are the secretory products of adipose tissue; adiponectin is inversely and leptin positively related to fat mass[95]. The potential role of circulating adipokines in fracture risk has not been clearly described or elucidated. The majority of evidence is for positive associations between leptin and BMD/BMC, which would support the observations that higher body weight (greater fat mass) is protective of the skeleton. Other studies suggest leptin acts as a marker of fat mass with little extra independent effect on the bone. However, infusion of leptin into the central nervous system of leptin deficient and wild-type mice-induced bone loss[95,98]. Recent data from our group showed negative associations between skeletal shape, geometry and strength and leptin, independently of fat mass[99]. Higher circulating leptin was associated with smaller bones, thinner cortices and lower strength. These data provide supporting evidence for increased fracture risk in overweight or obese individuals, irrespective of BMD/BMC. Adiponectin, a marker of insulin sensitivity, was negatively related to body mass, BMD and bone shape. This is supported by work from other groups and may explain increased fracture risk in low-body-weight individuals[100,101]. Longitudinal data are required to substantiate these observations.

In summary, Ca and vitamin D have been the most widely studied nutrients but many questions remain unanswered to be able to define how Ca intake or vitamin D status over the long term may determine bone and muscle phenotype in later life. The inclusion of follow-up measurements after cessation of Ca or vitamin D supplementation is vital to understand whether effects of an intervention are sustained. Longitudinal bone, muscle, dietary and/or biomarker data (e.g. 25(OH)D status) are required to understand how and where nutrition may contribute to the relationship between muscle and bone. Fat and bone have a complex inter-relationship with multiple pathways implicated; these require confirmation in human studies. Including the effects of adipose tissue in the mechanostat is an important focus moving forward.

Perspectives on future research

The preceding section illustrates how differences in dietary intake and lifestyle may challenge the ability of the mechanostat to successfully modify bone strength to cope with daily physiological demands. Current evidence highlights the need to define phenotype at different stages of life and in different populations. For nutrition and the mechanostat model, there is an inconsistency of evidence between males and females, age groups, limited data for muscle and many studies do not investigate the interactive effects on muscle and bone. One reason for this may be the reliance on studying the effects of single nutrients rather than taking a whole diet approach. In comparison with analysing individual foods and nutrients, dietary patterns have the advantage of taking account of total food intake and the potential synergies between foods and nutrients consumed together. Furthermore, public health messages about overall dietary patterns may be easier for the public to interpret.

Moving forward, there is therefore a need to understand how the interaction between muscle and bone drives bone development and aging, to identify factors that modulate this, and to obtain more detailed characterisation of a healthy skeletal phenotype using existing and novel technology. The following text provides an overview of the author's research approach within the Nutrition and Bone Health Group at MRC Human Nutrition Research which aims to achieve this objective. Skeletal health is most likely to be determined during childhood and adolescence and aging, when growth rates are highest, and bone loss greatest. Studies of bone health often focus on a particular life stage, such as pre-puberty, post-menopause or aging. Although these data provide invaluable insights about the determinants and definition of a healthy bone, there are limitations. It is not necessarily correct to assume that these factors are the same at different times through life or between populations. This is illustrated by considering the differences in the response of the developing skeleton to physical activity or nutritional interventions[76,88,102]. Therefore, to address on-going research needs, a threefold approach is being taken to study childhood and adolescence, aging and life-course data.

During childhood and adolescence, the longitudinal effects of low Ca intake and poor vitamin D status on peak bone strength are still not clearly defined. Using comparative populations of differing Ca intake or D status provides to possibility to study the effects of each on phenotype.

For aging, the aim is to characterise bone and muscle phenotype within and between populations to study the interactive effects between muscle and bone and modulators to this relationship: the European Male Ageing Study studies musculoskeletal aging in different ethnic groups during early to late adulthood[52,103]; The Gambian Bone Ageing Study is being carried out in a country of characteristically low Ca intake and currently rapidly transitioning towards a more Western diet and lifestyle; the National Survey for Health and Development is a birth cohort in whom bone mass has been gathered at age 60–64 years[104].

Birth cohorts provide prospective data through the life-course: the National Survey for Health and Development has collected growth, nutrition and physical capability data through the life course, providing the opportunity for the study of the relationship between bone and dietary patterns through adulthood[105–108], the Hertfordshire Cohort provides information on early life (pre- and post-natal) determinants of osteoporosis[109–112]; ongoing longitudinal studies of bone development in children and young adults in The Gambia to study the impact of poor growth, delayed puberty and nutrition on peak bone strength[21,57].

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By taking an approach to study the interaction between muscle, bone and nutrition at defined time points and throughout the life course a better understanding of the definition of a healthy bone phenotype should lead to effective strategies for prevention of bone disease during childhood and aging.

Key messages

A healthy bone is one that is fit-for-purpose that does not fail under normal physiological loading. The response of bone to muscle loading is the primary determinant of a healthy bone phenotype and is described by a functional feedback model that incorporates the mechanostat.

The study of different life stages and populations is important when defining a healthy skeletal phenotype which should be defined by bone strength rather than bone mass. The shape, geometry, mineral content and turnover of bone determine bone strength. Although all techniques have strengths and limitations, the ability to refine the definition of bone phenotype is increasing as developments allow better resolution, separate assessment of bone compartments, measurements of most aspects of bone strength and body composition. Techniques are also readily available to quantify muscle function. The critical evaluation and interpretation of newer technologies is important.

Nutrition acts as a modulator of the mechanostat through effects on bone and/or muscle, inadequate or excess nutrition may alter the bones response to loading altering phenotype.

For public health messages to be developed, it is important to understand the relative contribution of diet across life stage, between sexes and different populations.

For lifestyle and dietary recommendations, a life-course approach in different populations and age groups and not a 'one size fits all' approach should be used. Collection of longitudinal data is vital. The definition of a healthy phenotype and interaction between bone, muscle and nutrition require further study.

Acknowledgements

The author is grateful for the contributions to her research of Dr Ann Prentice, Dr Inez Schoenmakers, Dr Gail Goldberg and other colleagues in the Nutrition and Bone Health Group in MRC Human Nutrition Research, Cambridge and MRC Keneba, The Gambia; Dr Zulf Mughal and Professor Judith Adams and European Male Ageing Study Team, University of Manchester and Dr Nigel Loveridge, University of Cambridge for his comments on this manuscript. The author declares no conflicts of interest. This work was conducted within the core programme of the MRC Nutrition and Bone Health Group at MRC Human Nutrition Research, funded by the UK Medical Research Council (Grant codes U105960371 and U123261351). There was no other specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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