Fracture is a structural failure of bone. Its severe consequences in nature have driven the evolution of bone to be strong for loading yet light for locomotion, which is achieved by its structural and material optimisation.1,2 Millions of years of development have defined the diversity of bone from species to species and from site to site along a bone within a species.3 Chick limb buds removed and grown in vitro develop the shape of the proximal femur of a chick, implying that the genetic code pre-determines how the bone should develop.4 However, the bone is also flexible, ultimately allowing the structure to modify its mechanical strength to cope with its load demands starting from the beginning of life, and this capability is best demonstrated during growth.5–7

Earlier reports with twin and family design demonstrated that 65–80% of the variance of bone mineral content (BMC) and areal bone mineral density (aBMD) may be attributed to differences in genetic make-up, with the remainder due to differences in environmental factors in apparently healthy cohorts.8–11 BMC is the lump sum of the mineral within the periosteum and the aBMD is the BMC per unit area in the projected shadow of bones. These two bone traits obscure the complexity of bone structure and oversimplify the pathophysiology of fragility fracture because the bone structure cannot be estimated by a 2D assessment.12 Parameters other than the amount of mass used for construction, such as how it is distributed within the bone (cortical versus trabecular bone, denser but smaller versus lighter but bigger bone, etc.), play no less, if not more, important role than the amount of mass itself in determining the mechanical strength of the bone, and this has not been fully appreciated in our daily clinical practice. For example, ~50% of fragility fractures occur in patients without osteoporosis (as defined by a T-score of aBMD).13,14

The external size of bone and how its internal structure is configured plus the properties of the building materials determine the bone’s mechanical strength. Differences in size and structure determine the majority of the variance in bone strength between species and between individuals as a species, because the properties of the building materials are no different across land-dwelling mammals.15 The size of the bone may affect the internal bone structure; for example, a big cross-section is strongly associated with great bone strength and a big medullar size and a low volumetric BMD in the tibial shaft, indicating that failure to consider the bone structure may lead to an entirely different interpretation of bone strength by the volumetric BMD (vBMD).16 Variance in structural parameters can be partitioned into genetic origin and environmental adaptation. Their relative contributions may vary with examined site, population and species. For example, Mikkola et al. reported that in post-menopausal women genetic factors accounted for 83 and 61% of the variance of compressive strength index (calculated as bone strength index [BSI] = cross-sectional areas [CSA] x vBMD^2) of the distal radius and distal tibia, respectively.17 Therefore, a greater proportion of the total variances of BSI is accounted for by environmental factors in the weight-bearing than in the non-weight-bearing sites, suggesting that the more diverse the environment the bone is subjected to, the greater the proportion of its variance can be accounted for by environment, and less by genetic make-up. This result supports the view that weight-bearing facilitates bone gain in the lower limb.18

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Bone

Variance in Bone Size and Shape – The Macrostructure

The increase in bone size and the modification of bone shape after the completion of growth is minimal, even among individuals who who have undertaken intensive physical training, suggesting that both components of variance – genetic and environmental – in bone macrostructure are almost, if not fully, expressed at maturation. Bone length, like standing height, is largely a genetically determined trait; for example, segmental lengths (humerus, ulna, femur, tibia and spine) do not differ between children with cerebral palsy and normal controls after adjustment of bone age. This is not the case for bone diameter. In children with hemiplegic cerebral palsy, bone length of the humerus, radius and ulna differed by only 1–2%, while their diameter differed by 8–9%. In another study, Binkely et al. demonstrated that tibial length did not differ, but tibial shaft periosteal circumference was one-third less in non-ambulatory cerebral palsy patients than in age- and weight-matched controls. Kontulainen et al. reported on a tennis player who started training early in puberty and who increased the humeral shaft diameter by 6% in the dominant arm relative to the non-dominant arm. This evidence suggests that without mechanical stimulation, growth in bone width is greatly retarded, while loading beyond a certain minimal level that can be easily reached by ambulatory, healthy individuals has only a limited effect on the bone width.

The retarded periosteal expansion is accompanied by a proportional smaller marrow cavity in non-ambulatory cerebral palsy patients compared with age- and weight-matched healthy controls, resulting in a similar growth pattern (but ~1 standard deviation [SD] less) of cortical thickness in these patients. Although there was little difference in cortical thickness, the bone-bending strength index was more than 50% lower in these patients than in their counterparts despite their higher vBMD. In paraplegic young adults five years after spinal cord injury, the cortical thickness of the tibial shaft was ~1 SD less than that in normal controls due to increased endosteal resorption; the bone-bending strength index in these adult patients was ~18% lower than in the controls. Thus, the decreased BMC in physically handicapped patients could have various bone morphological characteristics relative to normal controls; bone diameter is smaller with a higher vBMD in patients whose disability began during growth, while bone size is not different but marrow cavity is bigger with a lower vBMD in those whose disability began after the cessation of growth.

Cortical thickness also varies around and along the bone. Using micro-computed tomography (CT), Zebaze et al. demonstrated that cortical thickness around the femoral neck varied greatly at the neck-shaft junction, being thickest medioinferiorly and thinnest laterosuperiorly; this variation decreased moving proximally and the cortical thickness around the bone varied little at the head-neck junction, even though the bone tissue area did not differ along the femoral neck. It is not clear how this site-to-site variance is established. Whether this is programmed by genetic factors or modified by adaptation according to environmental factors needs further investigation.

Bone modifies its shape to efficiently accommodate the load applied to it by different rates of periosteal apposition around its perimeter. For example, the shape of the tibial shaft became more elliptical with advanced age in pubertal girls, due to a greater periosteal apposition rate at the anterior and posterior sites than at the medial and lateral sites. A similar result was reported in the radius of growing goats. The shape of the radius in small goats is rather circular and becomes semi-circular in adult goats. No study to quantify the modifiable range of the variance in bone shape has examined the variance in bone shape across individuals under different loading circumstances, for example in athletes who participate in various sports.

Variance in Cortical and Trabecular Architecture – The Microarchitecture

The cortical vBMD differs little between individuals; its co-efficient of variation (SD/mean x 100%) is only ~2–4%. Cortical vBMD is also not affected by ‘overuse’ or disuse; for example, there is no cortical vBMD difference between the dominant and non-dominant arm in professional tennis players or between affected and non-affected sides in patients with hemiplegic cerebral palsy.

Cortical vBMD is affected by two factors – tissue mineralisation and porosity – and its variance could be derived from either of them. The degree of tissue mineralisation varies between individuals, from site to site within a bone and from time to time within a site. These variances reflect the rate of bone modelling and remodelling: the higher the bone remodelling rate, the lower the degree of mineralisation, because secondary mineralisation takes several months. For example, the cortical bone is less mineralised in children and the elderly than in young adults, and less mineralised in the outer ribbon than in the middle and inner ribbons of the cortical wall in the femoral shaft cross-section of young adults. Any factors that could influence the rate of bone remodelling would affect the degree of bone-tissue mineralisation. The degree of...
mineralisation is greatly affected by both environmental and genetic factors, as exemplified in patients with osteomalacia due to vitamin D deficiency and with osteoporosis due to osteoclast malfunction. At the tissue level, the degree of mineralisation contributes significantly to bone mechanical features; while this is not clear at the organ level.

Porosity, like mineralisation, also differs between individuals, between sites of a single bone and between times of life in one site (young versus old). Intracortical porosity is associated with growth rate in the chicken; the more rapid the growth, the higher the porosity. Whether this occurs in humans has not yet been studied. If this is the case, it is likely that the variance in cortical porosity is established at the completion of growth, which would corroborate the view that the variance in BMC at aBMD is largely established at the completion of growth because 80% of the total body BMC is in the cortical bone. Cooper et al. and Feik et al. examined the age-dependent change in intracortical porosity and demonstrated that the canal volume fraction in the femoral shaft increased with age but its variance remained unchanged, supporting this view.

As the rate of bone remodelling is largely an inherited bone trait and the cortical porosity is the result of bone remodelling, the intracortical porosity in turn would be greatly affected by genetic factors. Whether the intracortical porosity is associated with environmental factors, such as exercise and nutrition, has not yet been studied. As the cortical vBMD at the shaft of the humerus in professional tennis players did not differ between the dominant and non-dominant arm, the effect of exercise on cortical porosity may not be significant.

Trabecular mineralisation varies very little in individuals, thus, the majority of trabecular bone strength is determined by its architecture. By examining the iliac biopsy, Parfitt et al. demonstrated that the trabecular number in a given volume did not change from two years of age, while trabecular thickness increased.

Gilsanz et al. showed no sex or race difference in pre-pubertal African-Americans and Caucasian-Americans while race difference not sex difference in pre-pubertal African-Americans and Caucasian-Americans while race difference not sex difference emerged after puberty. These data suggest that genetic factors pre-determine trabecular architecture (especially the trabecular structure and vBMD may increase slightly in prolonged sport training, but deteriorate enormously and rapidly after immobilisation.

For example, non-ambulatory children with cerebral palsy have 30% lower bone fraction (B/V) due to reduced trabecular number and thickness, and in paraplegic young adults the trabecular vBMD of distal tibia was reduced to less than half that of the normal controls. These data suggest that, to a great degree, trabecular structural features may be genetically determined in a normal population, while no or loss of loading will lead to dramatic deterioration of its structure. The genetically determined trabecular structure may not change much during growth, as shown in trabecular vBMD in the distal radius and tibia. This would provide an opportunity to identify those individuals with a high risk of skeletal fragility before they are old (see Figure 1).

Conclusion

The diversity of external bone size is largely genetically determined, but environmental factors also make a significant contribution, as shown by the effect of malnutrition on bone length and immobilisation to the bone diameter in children. The external bone shape undergoes modification during growth to optimise bone structure using the least necessary building materials. Relative to bone length, width and shape are more modifiable, thus lifestyle may have a great effect on these characteristics during growth over a lifetime. Bone structure in the periosteal envelope is also strongly influenced by genetics. To adequately express this genetic influence, minimal necessary environmental stimulation has to be present. Without this stimulation, the internal structure of bone will not be adequately developed during growth or will undergo dramatic decay in adulthood.

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