

# The structural adaptations of cortical bone to loading during different stages of maturation

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## Introduction

Exercise during growth has the potential to result in large (and clinically important) increases in bone mass that would reduce the risk of fracture if maintained into later life<sup>1-3</sup>. However, the clinical significance of this increase in bone mass is influenced by whether the bone is laid down on the periosteal or endocortical bone surfaces. Expansion at the periosteal surface (i.e., increasing bone size) provides the optimal biomechanical advantage. For instance, if two bones have a similar cortical area (i.e., bone mass) but one is a bigger bone (i.e., larger in diameter), then the larger bone will be stronger when bent or twisted. This is because in the bigger bone, the mass of the bone is further from the central axis which translates to increased load-bearing capacity (because the moment of inertia increases as a function of radius raised to the power of four<sup>4</sup>).

These biomechanical principles have important implications for the interpretation of bone density data because it is possible that changes in bone geometric structure may affect bone strength with or without significant changes in bone density<sup>5,6</sup>. Consequently, understanding where bone is accrued is a critical component of understanding the success of any intervention aimed at increasing bone strength.

Changes in bone geometry in response to exercise in children or adults have rarely been investigated, and little is known about how loading affects the size and shape of cortical bone during different stages of maturation<sup>7-10</sup>. It has been proposed that loading during growth would result in an increase in bone accrual at the surfaces undergoing apposition<sup>7</sup>. This hypothesis has sound biological basis because the development of the skeletal phenotype is dependent on the interaction between

genes regulating body size and bone mass, hormones and the loading environment experienced in everyday living<sup>11,12</sup>. Thus, it would follow that additional loading would enhance the effect of growth. Therefore, to understand the effect of loading during growth one must first understand how the surfaces of cortical bone are shaped during the growth process.

## Changes in bone geometry during growth

Growth in the external size of a long bone, its cortical thickness and the distribution of cortical bone about the neutral axis is determined by the absolute and relative behavior of the periosteal and endocortical bone surfaces along the length of the bone<sup>8,13</sup>. Before puberty, periosteal apposition accounts for most of the increase in cortical area, this is partly offset however by the enlarging marrow cavity due to endocortical resorption. The net result is an enlarged cortical area located further from the neutral axis, leading to increased resistance to bending<sup>4</sup>. Late in puberty, periosteal apposition continues and is now accompanied by endocortical apposition<sup>14</sup>, leading to an increase in cortical thickness.

The temporal sequence of events in boys tracks that of girls before puberty. Sexual dimorphism occurs during puberty and is characterized by boys exhibiting greater periosteal expansion late in and post-puberty, and the absence of any endocortical contraction. Thus, in boys, the net result is the attainment of a greater cortical area that is located further from the axis of rotation compared to girls<sup>13</sup>.

The skeleton's temporal sequence of events due to growth are not only surface-specific but also region-specific with more rapid maturation of distal than proximal regions. Distal segments of the appendicular skeleton mature before the proximal segments<sup>14</sup>. Similarly, contraction of the medullary cavity occurs in a distal to proximal pattern<sup>8,14</sup>.

## The effect of additional loading on bone geometry during growth

If additional loading does enhance the effect of growth

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then it would follow that exercise during childhood would result in an increase in periosteal but not endocortical apposition. Late in puberty, and in the immediate years following puberty the predominant effect would be narrowing of the medullary cavity due to endocortical apposition. This maturity-dependent preferential change in cortical surfaces with mechanical loading has been demonstrated in animals<sup>15-17</sup>. Younger animals showed greater periosteal expansion, while older animals showed greater medullary cavity narrowing. Reduced mechanical loading through limb immobilization or weightlessness also leads to preferential changes at the cortical surfaces: younger animals show a greater periosteal response (inhibition of bone formation), while older animals showed a greater endocortical response (increased resorption)<sup>7,16,18</sup>.

The results of human studies however are equivocal; for instance, consistent with this proposal is the finding that pre-pubertal female gymnasts had a larger total bone area (periosteal expansion) of the forearm despite a smaller stature<sup>19</sup>. While the playing arm in adult tennis players resulted in no detectable change to the total bone area of the radius, it did however result in thicker trabeculae<sup>20</sup>. Exercise also led to medullary contraction (but no periosteal expansion) at the tibia in adult military recruits<sup>21</sup>. In contrast, loading in pre-pubertal female gymnasts and non-athletic boys resulted in increased cortical area at the mid-femoral shaft due to endocortical contraction, not periosteal expansion<sup>2</sup>.

The aforementioned inconsistencies in the literature are likely to partly reflect the limitations imposed by two-dimensional measures (i.e., X-ray) of a three-dimensional structure (i.e., bone). Radiographs and dual energy X-ray absorptiometry (DEXA) provide a two-dimensional projection of bone in the coronal plane which integrates periosteal and endocortical changes in the medio-lateral, not antero-posterior direction. Predicting changes using two-dimensional projections makes the flawed assumption that the bone is cylindrical and that the osteogenic response is uniform. These measurements in one plane do not provide information about changes that may occur cross-sectionally because of bone modelling. The cortical bone could be contracting in one plane but expanding in the other to resist bending moments. For this reason analysis of the cross sectional bone geometry is imperative. Furthermore, inferences from one or two measures at a site may not provide an accurate representation of changes that occur along the length of the bone<sup>8,22</sup>. Measuring techniques (MRI or CT) that provide a cross sectional view in the transverse plane is required for a more accurate assessment of surface specific changes in long bones. MRI is useful (particularly in children) because of the ability to collect images along the whole length of the bone without any radiation exposure.

In a recent study, MRI was used to compare the side-to-side differences in bone traits in the arms of competitive female tennis players during different stages of maturation<sup>8</sup>. The key findings were that loading did magnify the structural changes produced during growth. Prior to puberty, loading

magnified periosteal apposition along the length of the shaft; at the mid-humerus loading resulted in increased endocortical resorption (medullary expansion). During the post-pubertal period loading magnified the effect of endocortical apposition (medullary contraction), which makes an important contribution to cortical thickness in females. In fact, endocortical apposition accounted for most of the greater side-to-side difference attained in the post-pubertal years.

Most of the structural changes due to loading occurred early in the pre-pubertal years because adaptive changes in response to loading were sufficient to reduce the strains in bone that may lead to microdamage if not decreased<sup>23,24</sup>. The only additional benefit achieved from tennis training later in puberty was contraction of the medullary cavity. The rising estrogen levels during puberty are thought to lower the bone (re)modeling threshold on this surface, and thus sensitize bone next to marrow to the effect of mechanical loading<sup>25</sup>. Interestingly, medullary contraction did not confer any additional increase in the structural rigidity of the bone.

### Sex-specific effect of additional loading on bone geometry during growth

Little is known about how gender may influence the structural response to loading during growth and aging. For instance, it is not known if the effect of loading on the surfaces of cortical bone is similar in boys and girls during different stages of puberty. Pre-pubertal growth of the male and female skeleton is regulated by growth hormone and IGF-1<sup>13</sup>. During pubertal skeletal growth, estrogen production in females inhibits periosteal apposition but stimulates the acquisition of bone on the endocortical surface by either stimulating bone formation or reducing bone resorption<sup>13</sup>. In contrast, testosterone secretion in males results in continued periosteal expansion and has little effect at the endocortical surface. Thus, in females, peak bone size and cortical area are the result of periosteal and medullary expansion in the pre- and peri-pubertal years, and medullary contraction in the post-pubertal years. In contrast, in males, peak bone size and cortical area is predominantly determined by movement at the periosteal surface.

As the skeletal response to loading appears to be regulated in part by the growth process, loading during and after puberty may result in different surface-specific responses in males and females. Importantly, loading before puberty may result in periosteal expansion in both sexes, whereas loading after puberty may result in periosteal expansion in males but only endocortical contraction in females. This notion is supported by our work in female tennis players<sup>8</sup> and our preliminary work in male tennis players (SL Bass, unpublished). If these data in boys are validated then it would follow that the window of opportunity for exercise to increase bone size would be greater in males than in females. This would then have important implications for the prescription of exercise for improved bone health in males and females.

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