Bone Stimulus

Summary and Applications

1. Summary

Musculoskeletal tissues, such as bone, muscle, tendon and cartilage, respond and adapt to their local mechanical environment to maintain a stable equilibrium, or homeostasis (Carter et al., 1998). As well as maintaining healthy tissue, mechanical loads can lead to injury and disease. In a broad sense, injury occurs when the loads experienced by the tissue exceed the tissues mechanical strength. These loads might be *traumatic*, such as a direct impact or single loading event causing failure, or *repetitive*, where cumulative loads result in damage to the tissue.

Measuring and monitoring the mechanical loads experienced by musculoskeletal tissue is critical to reducing risk of injury as well as prescribing appropriate training strategies to recover from injury.

IMU Step is a tool to measure and monitor the impact loads and long-term load exposure of an athlete to provide subject-specific insight to assist decision making around training volumes and intensities, and return-to-play.

IMU Step measures tibial shock as a surrogate of the impact load that is experienced by the tibia during running and court-based activities, where impact loads dominate the activity or sport. The *Bone Stimulus* metric that is calculated within IMU Step is NOT a surrogate measure of the ground reaction force, which some people have suggested. The Bone Stimulus represents a cumulative mechanical stimulus that would lead to potential bone remodelling bone stress injury. In the literature this stimulus has been referred to as a Daily Load Stimulus. A reasonable question to ask here is whether we should be monitoring impact loads across an entire day? This might be ideal, but it is also impractical. We will argue here that the high magnitude events that occur during training will dominate the loading stimulus experienced by the musculoskeletal tissues. As such, we measure each training bout and include these events into a cumulative Bone Stimulus metric.

The purpose of this document is to provide an overview of the literature that underpins our current understanding of injury mechanisms and the background concepts and rationale for IMU Step and Bone Stimulus. A review of bone mechanobiology is also provided, for further reading and context.

What is a bone stress injury (BSI)?

A bone stress injury (BSI) represents the inability of bone to withstand repetitive loading, which results in structural fatigue and localised bone pain and tenderness (Warden et al., 2014b). A BSI occurs along a continuum that begins with an initial reaction to a mechanical or chemical stimulus, which is often referred to as a ***stress reaction***. These might be visible as signal changes in MRI or ultrasound imaging (often swelling or edema is visible prior to structural changes in bone). Beyond a stress reaction, continued loading can progress to microscopic failure of the bone**,** often termed a *stress fracture.* It should be noted, however, that ALL fractures are related to mechanical stress, so the term ***fatigue fracture*** is more appropriate when relating to fractures that related to repetitive loading and cumulative damage. Ultimately, continued damage can result in ***macroscopic bone fracture*** [see Warden et al. (2014b) for an excellent review].

How common are bone stress injuries and do they occur in common sites?

Since BSI is related to repetitive loading, it is no surprise that sports such as distance running, track-and-field, and court-based sports have the highest incidence of BSI. The incidence of BSI in competitive cross-country runners across a 12-month time frame is between 5% and 21% (Bennell et al., 1996; Arendt et al., 2003; Tenforde et al., 2016). Half of the BSI in cross-country runners occurs in the shaft of the tibia, whilst the majority of other BSIs occur in the feet (tarsals, metatarsals, and calcaneus), femur, and fibula (Arendt et al., 2003).

What is the mechanical pathway for fatigue fractures?

If we ignore some of the complicated interactions of biological bone remodelling and damage repair, we can present a simplified pathway of the mechanical factors related to fatigue fracture (Figure 1). In this pathway, fatigue fracture occurs when the cumulative stress applied to the tissue exceeds the mechanical strength of the bone. Cumulative tissue stress represents the summation of stresses that occur every time the bone is loaded. In the context of running and court-based sports, we can think of these as the combined, cumulative sum of loading events. The interesting point to make here is that this total load exposure consists of parameters that can be modified, either through *technique changes,* or through the *volume and intensity of training*. The total number of loading events (# cycles) can be easily determined using tibial-mounted inertial sensors.

The bone stress/strain is more difficult to determine, since it depends on factors including bone material properties (i.e. bone density), bone morphology (including size and shape), and the forces placed on the bone. The bone forces are determined by the joint reaction forces (experienced due to intersegmental dynamics, including gravitational loading) and the muscle forces that are causing joint motion.

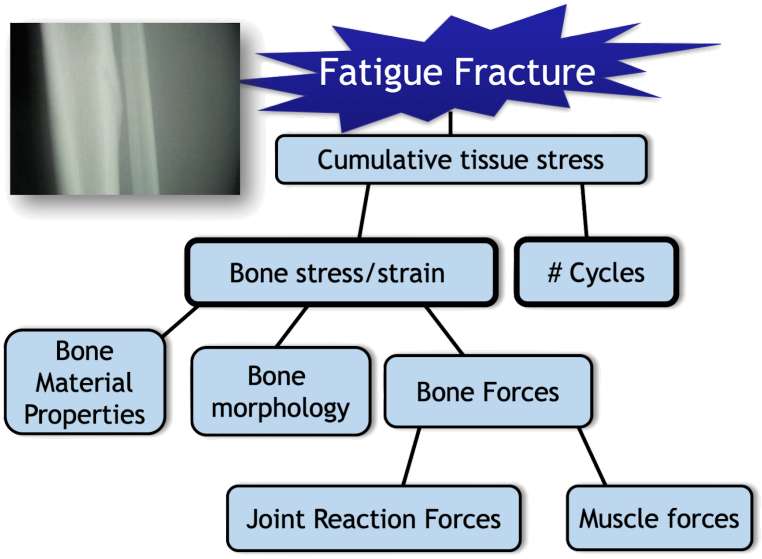


Figure 1: Mechanical pathway for fatigue fractures.

How can we measure bone stress?

The term ‘stress’ here refers to a physical quantity that represents the internal forces within the structure. These forces give rise to small deformations or ‘strains’ of the structure. It is possible to measure these deformations directly using strain gauges attached directly to the bone. This direct measurement of bone strain could then be used as an input to our Bone Stimulus parameter. Although strain gauges have been attached to the tibia previously (Burr et al., 1996; Milgrom et al., 2000a), it is not really feasible for athlete monitoring due to the invasive nature of the procedure.

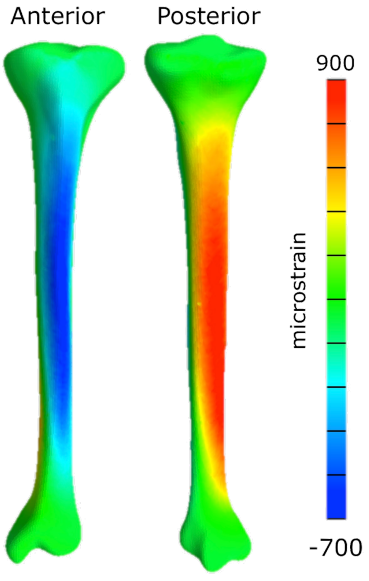


Figure 2: Finite element model of the tibia, illustrating the non-uniform strain distribution during running.

Instead of direct measurement, we develop computational models to estimate the forces and distributions of forces in the tissue. Figure 2 represents a computational, finite element model that illustrates the distribution of strain throughout the tibia during the stance phase of running, when the foot is on the ground. This model takes into account bone material properties, morphology (size and shape), joint reaction forces and local muscle forces. You can appreciate from this image that the bone is experiencing both compression AND tension, indicated by the different colours. At this point in the stance phase, the anterior-medial portion of the bone experiences compression (blue colour), whilst the posterior side of the bone experiences tension (red colour). It is important to note that this distribution changes throughout the stance phase and throughout the bone (here we are seeing just the surface strains).

These computational models are complex and require medical imaging, such as CT or MRI and take a long time to solve. As such, they are also not feasible for real world applications (at least not yet anyway). Therefore, we must rely on indirect, or 'surrogate' measures to estimate bone stresses and strains.

How is tibial shock a 'surrogate' measure of impact load at the tibia?

Biomechanics researchers have long been interested in how impact forces are attenuated by different tissues of the body and have used skin-mounted accelerometers to quantify tibial shock (i.e. peak accelerations) and assess attenuation of shock during walking (Wosk et al., 1981), running (Unold et al., 1974), and landing from a vertical jump (Gross and Nelson, 1988). A skin-mounted accelerometer firmly attached to the anterior-medial aspect of the tibia (inside of the shin) provides a useful 'surrogate' measure of the impact load experienced by the underlying bone. Although it is known that the accelerations measured on the surface of the skin overestimate the accelerations experienced by bone (Lafortune, 1991; Edwards et al., 2009), this method provides a convenient and reliable way to monitor impact loading and assess changes in running technique or environmental conditions (Crowell et al., 2010). Tibial accelerations are also sensitive to changes in running speed (Clark et al., 1985), providing a useful stimulus to monitor events that have impact loads, such as running and landing from a jump; two conditions that give rise to large bone strains (Milgrom et al., 2000a).

It should be noted that there are conditions under which tibial-mounted accelerations do not provide good measurements of the forces applied to the tibia. Imagine performing a squat or a dead-lift with a large load, where the feet are firmly planted on the ground and the tibia is experiencing very small accelerations. The muscle forces in this scenario would be placing significant loads onto the tibia, causing stresses and strains and adding to the cumulative stress. A recent publication by Matijevich et al. (2019) made the point that muscle forces are important contributors to loading of the tibia and measurements based on ground reaction forces are not good predictors of tibial forces. Tibial-mounted accelerations provide a useful surrogate for monitoring lower limb impact loads, but it is important to understand its limitations.

Does tibial shock predict the ground reaction forces (GRFs)?

For every force there is an equal and opposite force. Newton's third law explains that when we produce a force on the ground, there is an equal and opposite force that the ground exerts on us, the *Ground Reaction Force*. Newton's second law states that forces are related to the product of mass and acceleration (F = m x a). As such, the Ground Reaction Force represents the summed product of our individual segment masses and accelerations. It is therefore no surprise to find that the accelerations experienced by the tibia only partly explain the reaction forces measured at the ground during impact. Hennig et al. (1993) explored this relationship and showed that peak tibial acceleration accounted for ~76% of the vertical ground reaction force. If we want to predict reaction forces at the ground, we need more information about the acceleration of the rest of the body segments.

Clark, Ryan and Weyand (2017) developed a simplified model, which represents the body as two segment masses, the first representing the shank and foot segments (~8% of total body mass) and the second mass representing the rest of the body (82% of body mass). Using impulse relationships (force x time) to determine the contribution of each of these masses to the reaction forces at the ground, Clark and colleagues accurately predicted the vertical component of the GRF across a range of running speeds and conditions (including forefoot and rearfoot strikers). It is possible to apply this model using tibial mounted accelerations, and obtain estimates of the vertical ground reaction force.

The important question to ask here is 'why would you want to predict GRFs in the first place?' The magnitude and rate of change of the GRF has gained much interest in terms of its role in injury mechanisms, as high strain rates can cause tissue damage. However, since we really care about tissue strain and tissue strain rate (see mechanism in Figure 1), we need to go beyond just the reaction forces at the ground and estimate how these reaction forces are distributed into our tissues. An inverse dynamic analysis can be performed to estimate the segmental forces and moments that cause movement, but this still does not tell us what the individual muscle forces are, which are important for bone loading. So in terms of the question above, unless you intend to use these data with kinematic information to calculate joint moments, there is greater value in measuring tibial accelerations, which are more sensitive to changes in running technique, fatigue, and running speed (Clarke et al., 1985). For this reason, IMU Step uses tibial acceleration data as a simple surrogate measure as input to our cumulative Bone Stimulus metric, without trying to predict the GRFs.

So what is Bone Stimulus in IMU Step?

Bone Stimulus is an estimate of the mechanical stimulus that would cause the bone to respond and remodel. As outlined in Figure 1, the mechanical factors that are related to fatigue fractures in bone include the bone stress-strain and the number of cycles of loading. Together, these variables provide a total, or cumulative load 'exposure'. We know that bone responds more to the magnitude of bone stress (and strain rate) than the number of cycles (Beaupré et al., 1990), so we integrate these two variables together into a Bone Stimulus metric, which has been referred to in the literature as a Daily Load Stimulus (DLS, Figure 3). We calculate this stimulus for each training session.

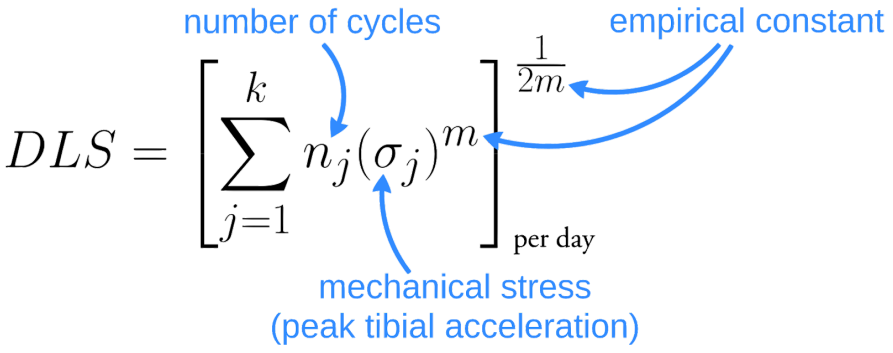


Figure 3. The Daily Load Stimulus (DLS), or Bone Stimulus metric in IMU Step accounts for the number of cycles of loading (n) as well as the stress (here we use the tibial acceleration as a surrogate measure of stress). An empirical constant is also provided to account for the fact that bone responds more to the magnitude of stress than the number of cycles.

This concept has been used to predict changes in calcaneus (heel) bone density due to different activity levels (Whalen et al., 1988), as well as changes in bone density following exercise interventions (Ahola et al., 2010). An important feature of this mechanobiological relationship is that, for example, you can reduce the risk of fatigue fracture in running by increasing your cadence

(Edwards et al., 2010). Even though you might take more steps, the slight reduction in peak mechanical stress with each step that you take will have a greater influence on the total stimulus applied to the bone.

Bone Stimulus does not equate to physiological stress intensity

It is important to acknowledge that the Bone Stimulus does not equate to physiological intensity of a training session. Rather, it represents the mechanical stimulus that will potentially lead to changes in bone remodelling (i.e. altering the shape and/or material properties of the bone). The fact that the Bone Stimulus score reaches a plateau after a certain number of cycles indicates that the continued mechanical stimulation has a limiting influence on the bone response (i.e. the bone cells experiencing this mechanical stimulus have saturated in terms of their response to a mechanical stimulus). The significance of this is appreciated by the fact that a marathon runner does not have a bone mineral density that is 10 times more dense than that of a recreational athlete, even though he or she might run 10 times more.

Is it possible to predict bone failure?

Predicting musculoskeletal injury is a challenging goal. Although it might be possible to obtain reasonable estimates of loading and cumulative load exposure, it is difficult to measure the current mechanical properties, and hence, the strength of a given tissue. It is also challenging to understand how an individual's tissue might adapt to the load exposure (this might be influenced by biological factors, including age and sex). However, if we understand the mechanical aetiology of injury, we can mitigate injury risk by altering these mechanical factors. In this context, IMeasureU Step can be seen as a tool to obtain estimates of load exposure for an individual athlete.

Edwards and colleagues (2010) presented a model to predict the risk of tibial fatigue fractures, where they estimated bone strain using a complex finite element model (as in Figure 2) and used some simplified load exposure (cycles/day) to estimate a probability of failure. These plots look very much like the Bone Stimulus plots, in terms of a plateau that occurs after a period of days, beyond which, the probability no longer increases. Bone is a tissue that can withstand 1000's of cycles of loading without failure. This plateau in fracture risk makes sense from a biological standpoint, because if the probability of fracture continued to increase with every cycle of loading, it would only be a matter of time before our bones would break. If you have an understanding of the mechanical properties of the bone, the rates at which the bone repairs, and knowledge of the load exposure (total number and magnitude of each loading event [i.e. Bone Stimulus]), then you can provide a tool to predict the probability of fatigue fracture at an individual athlete level.

Can I use the Bone Stimulus metric for other musculoskeletal injuries that are due to repetitive loading, such as tendinopathy?

The Bone Stimulus metric is based upon the mechanobiology of bone and the premise that bone tissue responds more to the magnitude of stress, rather than the number of loading cycles. A similar framework might be relevant for soft tissue, such as cartilage and tendon. Indeed, muscle and tendon also adapt to their mechanical environment, so it makes sense that a similar paradigm in cumulative load monitoring could be used for these soft tissues. However, one would have to adopt the stimulus metric to account for the mechanobiology of these tissues. The surrogate measure of tibial shock might be a reasonable proxy for bone loading during impact activities such as running and landing from a jump, but information regarding muscle activation is likely necessary to understand the mechanical environment of muscle and tendon.

Young and colleagues (2016) developed a computational model of the tendon that accounted for various distributions in loading cycles, cumulative damage and adaptation. The model also accounted for the muscle in series with the tendon and it was able to predict biological rates of

collagen turnover, which have been measured experimentally. Pizzolato et al. (2019) illustrate how knowledge of the tissue mechanical environment can be used to develop training regimes to stimulate tendon with the appropriate strain and provide real-time feedback, using computational modelling and wearable sensors. Integrating these types of models with wearable sensor data will provide new approaches and opportunities for soft tissue injury prevention.

2. Potential use-cases

There are many potential use-cases for IMeasureU Step, in terms of load monitoring of athletes. These cases cover a spectrum of athlete health, from monitoring healthy, non-injured athletes, to monitoring of athletes in return-to-play situations, or monitoring those who are considered 'at risk' due to prior injuries. Some of these use-cases are provided by users of the system and are available online as case studies.

Monitoring of healthy, non-injured athletes

Without the ability to measure and monitor athletes in the real-world, either in the training environment, or in competitive game play, we really have little knowledge of an individuals' load exposure. IMeasureU Step can be used to obtain baseline information regarding impact load profiles that are specific to each athlete. This can be useful to see loading profiles across different training protocols and intensities and many interesting questions can be addressed. Does fatigue alter loading profiles? Does asymmetry change with different conditions? Can I alter technique to change my loading profile? Does the intensity of training compare to the intensity of game scenarios? Can I periodise my training intensity in terms of load exposure? These are important areas for new research and the biomechanics community are beginning to investigate these questions. At least now we have the tools to facilitate this research.

Monitoring athletes in return-to-play situations

Bringing athletes back to peak physical condition and performance following an injury is a challenging process, which is as much about mental preparation as it is a physical or biological one. The grand challenge here is providing the musculoskeletal tissue with a loading stimulus that promotes a positive adaptation, yet enabling the tissue to recover from a compromised structural integrity. Where a tissue could once withstand a certain amount of load, a damaged tissue can no longer withstand that same load and further exposure may exacerbate the damage. Ideally we would have non-invasive measurements of tissue health, which would aid the decision-making necessary for athletes to return to sport. Medical imaging, such as CT, MRI, and ultrasound can provide information regarding tissue structure and non-invasive estimation of tissue health is an active area of research in the imaging community.

In the absence of having a 'tissue health' measurement, having prior knowledge of athlete load exposure is useful in setting a baseline for return-to-play load monitoring. However, such baseline data is often not available, so monitoring load symmetry is an obvious application for IMeasureU Step in bringing an athlete back from injury. Adequate rest and recovery is necessary and periodisation of training load intensity can be managed if you have a system to measure and monitor the recovery process. This full case study provides an excellent example of how this can be achieved.

Monitoring athletes who are considered 'at risk' due to prior injuries

Previous injury is typically one of the strongest predictor variables in terms of injury risk. Athletes who have suffered overuse or repetitive strain injuries, such as bone stress injury, patellofemoral pain, tendinopathy, and muscle-tendon strain are all considered 'at risk' of recurring injury. This is in part due to the compromised tissue structure following the repair and remodelling process. Damage and repair of soft tissue in particular, can result in stress concentrations around the region

of injury due to the mismatch in material properties of the native tissue and repaired tissue. Monitoring load symmetry and loading profiles, as in the case of return-to-play, again offers a useful tool to monitor athletes might are considered ‘at risk’ given a prior injury.

3. Bone mechanobiology

This section provides a brief overview on bone physiology and mechanobiology (i.e. how bone responds to a mechanical stimulus).

Different types of bone

Our bones consist of two functionally different types. *Spongy bone*, also known as *cancellous* or *trabecular bone*, is the type of bone that you find at the ends of a long bone and the centre of our spine. The spongy bone is where red blood cells are made (we produce 2.4 million new red blood cells each second! In fact, a quarter of the cells in your body are red blood cells!).

Compact or *cortical bone* is the dense bone you find at the shaft of a long bone, and the surrounding outer shell of the bone. It is responsible for providing structural strength to bone and makes up 80% of skeletal mass.

Bone modelling vs bone remodelling

There are two important processes to consider when thinking about how bone adapts and changes to the mechanical environment. One process is *bone modelling*. This is the process by which new bone is formed during growth and development (i.e. until the skeleton is mature, around age 19 or 20 yrs). The second process is *bone remodelling*. This is the continued adaptation and regulation of bone after skeletal maturity (i.e. adaptations of the adult skeleton).

What is bone remodelling?

Bone remodelling is a tightly regulated process of repairing microdamage and replacement of old bone with new bone. Remodelling occurs through the breakdown (resorption) of old bone with the formation of new bone. The rate of remodelling is regulated by biological factors (hormones, age, etc) and the mechanical environment.

How do the bone cells actually remodel the bone?

In cancellous (spongy) bone, remodelling occurs on the surface of trabeculae (miniature struts) and lasts about 200 days in normal bone. The first step in this process involves resorption of a small tunnel (lacuna) by cells called osteoclasts. This resorption has a median duration of 30-40 days. Following resorption, these microscopic (40-60 micron in length) tunnels are filled with new bone by cells called osteoblasts. This process takes ~150 days. The total surface of cancellous bone is completely remodeled over a period of 2 years. In disease states, such as osteoporosis, the osteoblast cells are unable to completely fill the resorption lucuna, resulting in a net loss of bone. The remodelling process of cortical bone occurs in only 120 days.

How does mechanical loading influence bone remodelling?

Certain athletic activities (or an increase in body weight) can promote bone formation. Severe bone resorption will occur through inactivity or bed rest (i.e bone responds more to inactivity than increased activity, which is bad news for astronauts wanting to travel to Mars!).

The number of loading cycles as well as the stress magnitudes influence skeletal mass. Bone responds more to high strain rate (i.e. larger forces over a shorter time), compared to the number of cycles. The consequence of this is that bone can respond the same way to exercise that is high force-low cycle or medium force-high cycle. For example, animal studies have shown that a 40%

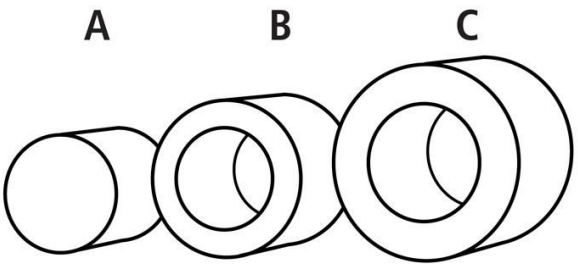
increase in bone mineral density in the mid-shaft of the rooster ulna occurred after only 36 cycles per day at physiologic strain levels. Increasing the number of loading cycles to 1800 per day had no additional observable effect on bone mineral density. This explains why a marathon runner does not have a bone mineral density that is 50x more dense than you or I, even though they might experience 50x more cycles of loading!

Can adults increase bone mineral density by changing our physical activity levels?

Only modest gains in bone density have been achieved in adults with mild exercise added as a supplement to normal daily activity. The amount of new bone formation is not only a function of your daily activity, but also depends on the load history of the bone. For example, an athlete who is already a trained runner, will have very little increase in bone formation if they add some extra miles into their training schedule. However, a sedentary individual who experiences that same mileage might experience a greater response in bone formation. Across the general healthy population we see fairly modest differences in bone density. For example, measurement of the calcaneal (heel) bone indicate ~20% difference in bone mineral density between cross-country runners and a control population of non-runners.

Does bone mineral density determine the strength of the bone, and hence, it's risk of fracture?

The strength of bone is determined by a combination of its density, size, and shape. When we consider strength, we can think of this as a resistance to being squashed (compressive) or pulled (tensile), or a resistance to bending and twisting (torsion). Bones in our body experience ALL of these loading conditions. Adding bone mass is important for strength, but it is equally important to know where the mass is located. For a long bone, the cross-sectional area of the bone and the thickness of the cortical bone have a huge impact on the strength of the bone. Figure below illustrates this. Cylinders A and B have the same unit area of bone (1 square unit) and the same resistance to tensile and compressive forces. However, cylinder B has distributed the bone to the outside and has a hollow centre. This results in a much stronger resistance to bending and torsional forces. Cylinder C has twice the mass (or area in the cross-section; 2 square units) and also a greater moment of inertia (cross-section diameter). The added mass results in a proportional increase in tensile and compressive strength. By contrast, because the moment of inertia is to the 4th power, the bending and torsional strengths become exponentially greater from bar A to C.



	A	B	C
Area	1	1	2
Tensile and compressive strength	100%	100%	200%
Bending and torsional strength	100%	210%	459%

Figure 4. The influence of bone cross-sectional area and size on strength (from https://teambone.com/education-basic/biomechanics-of-bone/).

During growth and development, if we place large bending and torsional loads on our bones, they respond by growing in cross sectional area. This change in morphology during growth and development stays with us for the rest of our lives (Warden et al., 2014a), so it is extremely important to place large loads on the growing skeleton, to ensure strong bones in our ageing years.

Can we predict bone density?

The non-linear relationship between bone density and the loading history means that activity level, body weight, and exercise alone cannot be used as independent variables to correlate with bone density. In order to develop a successful exercise study and predict the changes in bone density, one must carefully quantify the daily loading history and have accurate knowledge of the current bone health.

What are the important mechanical loads that cause bone remodelling?

For most people, the daily history of the ground reaction forces, which account for both body weight and activity level, are the principal source of external forces on the body. The magnitudes of the joint contact forces (which are the forces that are directly applied to the ends of our bones) are related to the magnitude of the ground reaction force and the muscle forces responsible for producing segmental movement. Muscle forces really dominate contact forces, so ideally we would have wearable sensors to tell us what muscle forces cause motion. However, since we cannot easily implant sensors into muscles, we rely on external measures, such as the ground reaction force, or impact experienced from accelerometers, as a relative measurement of the forces applied to the skeleton. We know that elite swimmers and cyclists are at risk of osteopenia or even osteoporosis, because they don't experience large impact loads.

Can we mitigate bone loss due to ageing?

Bone loss can occur at ~0.3% per year after the age of 30yrs. This can be mitigated by physical activity and it only takes a small number of cycles or bone cells to respond. So maintenance of bone is achieved without too much commitment in terms of physical activity! The figure below shows a summary of the human bone life cycle. Early in life, as the skeleton is growing, we see large amounts of bone formation, which is influenced and regulated by mechanical loads (even in utero). After the skeleton has matured, you see little bone mass added. The ‘quality’ of bone here refers to the structural strength, as noted above, which takes into account the size and shape of the bone, not just its density. Note how the quality of bone can be enhanced during growth and development, beyond just the added mass. This is in response to mechanical loads and the additional strength gained from altering the cross sectional area of bone is maintained throughout life (Warden et al., 2014a).

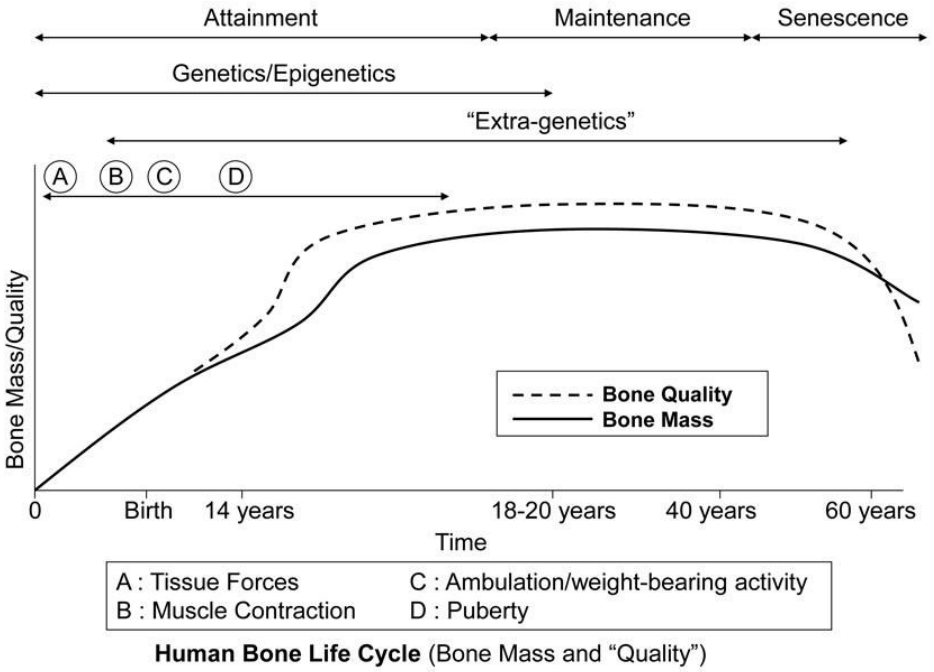


Figure 5. The influence of ageing on bone mass/quality (from https://teambone.com/education-basic/biomechanics-of-bone/).

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