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THE INFLUENCE OF MUSCULAR ACTION ON BONE STRENGTH VIA EXERCISE

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Abstract: Mechanical stimuli influence bone strength, with internal muscular forces thought to be the greatest stressors of bone. Consequently, the effects of exercise in improving and maintaining bone strength have been explored in a number of interventional studies. These studies demonstrate a positive effect of high-impact activities (*i.e.* where large muscle forces are produced) on bone strength, with benefits being most pronounced in interventions in early pubertal children. However, current studies have not investigated the forces acting on bones and subsequent deformation, preventing the development of optimized and targeted exercise interventions. Similarly, the effects of number and frequency of exercise repetitions and training sessions on bone accrual is unexplored. There are conflicting results as to gender effects on bone response to exercise, and the effects of age and starting age on the osteogenic effects of exercise are not well known. It also appears that exercise interventions are most effective in physically inactive people, or counteracting conditions of disuse such as bed rest. Bone strength is only one component of fracture risk, it may be that exercise resulting in improvements in *e.g.* muscle force/power and/or balance are more effective than those whose effects are solely osteogenic. In summary, exercise is likely to be an effective tool in maintaining bone strength but current interventions are far from optimal.

Keywords: Bone, BMD, Muscle, Exercise, Osteoporosis

Introduction

It is no longer in doubt that mechanical stimuli (or their absence) have an effect on bone [1]. Evidence for this include the increase and decrease of functionally isolated *in vivo* avian bone mass in response to unloading and loading, respectively [2] and the loss of bone mass after bed rest [3] or spaceflight [4]. Harold Frost's Mechanostat [5] is the current prevailing theory on bone adaptation to mechanical stimuli, which proposes that bone adaptations serve to keep habitual bone strain within defined thresholds. However, the origin of these mechanical stressors is not encompassed within the theory.

	Standing	Hopping
Body Mass [kg]	70	70
Ground reaction force [kN]	0.7	2.5
Torque [Nm]	84	300
Acceleration [g]	1	3
$Force_{AchillesT}$ [kN]	2.1	7.5
$Force_{Tibia}$ [kN]	2.8	10

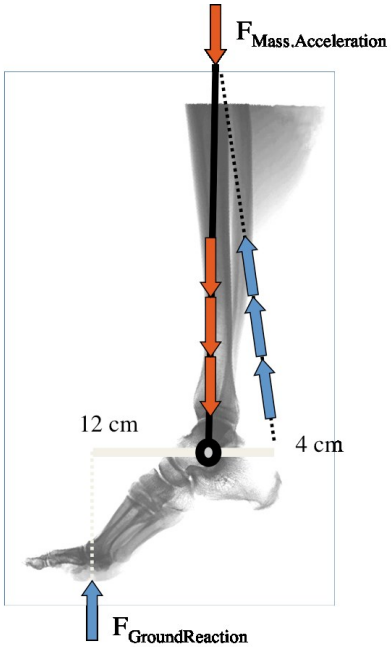


Figure 1. Reaction and tendon forces during standing and hopping. Reproduced with permission from [8].

Ground reaction forces are important stressors of bones of the lower extremities and vary greatly dependent on the type of physical activity undertaken. Walking results in ground reaction forces roughly equal to body mass [6], whereas peak ground reaction forces of up to 15 times body mass have been recorded during the step phase of a triple jump [7]. However, given the short levers that muscles work against, internal muscular forces (often produced in reaction to an applied external load) must be expected to substantially exceed the external loads applied. For example, Achilles tendon force during standing and hopping is approximately three times greater than the ground reaction force [8] (Figure 1) – this disparity can be even more pronounced in other limb segments dependent upon the length of the moment arm. Provided that bone strength is governed by peak strains it should be maximal muscle force that dictates the influence of the muscle on bone. Given that muscle mass and power or force generating capacity are normally correlated it is not surprising then that not only have close relationships between maximal muscular strength and power and bone strength been found [9, 10], but also between muscle mass (as a surrogate for maximal force) and bone size, mass or strength. These associations have been found

in children and adolescents [11], adults and older individuals [12], and even in spinal cord injury patients that suffer from extreme disuse [13]. The distinctly different muscle:bone relationships within the two arms of tennis players suggest, however, that muscle mass may be too simple a proxy to accurately describe the influence of muscle on bone [9]. In addition, the temporal nature of the relationship between muscle and bone (*i.e.* changes in muscle (the stressor) should precede those in bone) has been well demonstrated in several studies. For example, in the case of a woman suffering cruciate ligament injury, the instantaneous loss of muscle force upon ligament rupture preceded a delayed reduction in bone strength (Figure 2) [14] and the increase in muscle strength during rehabilitation preceded the return of BMD to pre-injury values. Also during the pubertal growth spurt the peak rate of lean body mass accrual precedes peak bone mass accrual rate [15]. Besides the direct influences of muscular loading on bone, muscle and bone strength may also be linked through common endocrine signaling pathways [16, 17].

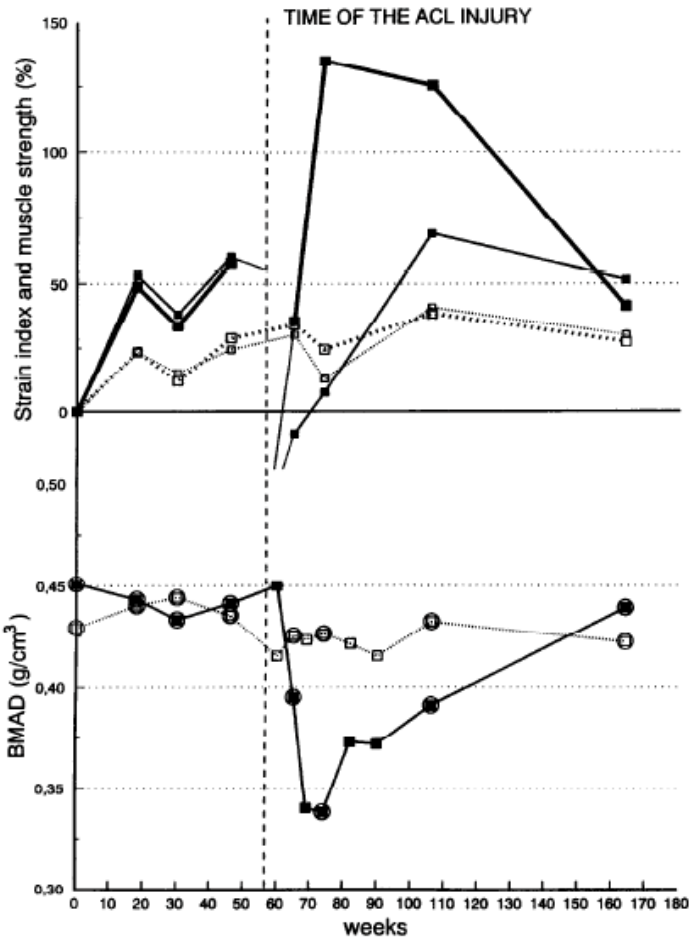


Figure 2. Time course of changes in strain index, muscle strength and patellar bone mineral density following anterior cruciate ligament (ACL) injury and subsequent rehabilitation. Upper panel: wide solid line indicates injured limb strain index, narrow solid line indicates isometric strength – wide and narrow dotted lines indicate respective values in the unaffected limb. Lower panel: solid and dotted lines indicate patellar aBMD in the injured and unaffected limbs respectively. Reproduced with permission from [14].

If indeed maximal strains govern bone adaptation and internal muscle forces are the dominant effectors of bone strain, then maximal muscle force should determine the osteogenic potential of an exercise modality. Therefore, according to Hill's muscle model [18] exercise involving eccentric contractions at high rates of muscle lengthening should result in the highest forces and hence largest bone adaptations. Such contractions occur during sudden application of a large external force, as in what are known as high-impact exercise modalities such as sprinting or jumping [19]. In support of the significance of high-impact exercise modalities is the greater femoral bone strength in athletes who regularly train in these sports than sedentary controls, whereas in athletes in sports without an impact element (*e.g.* swimming and cycling) there was no such effect on femoral bone strength [20]. This association of high peak force with bone adaptation is also demonstrated in master athletes of different locomotory disciplines (*e.g.* race walking, long/middle distance running and sprinting) – whereby tibial bone strength is positively associated with the speed of the event (and hence the magnitude of ground and presumably muscular forces) [21]. In addition, differences between athletes and controls follow site-specific patterns – greater bone strength in epiphyseal areas resulting from greater bone mineral density and bone cross-sectional area, whereas differences in diaphyseal bone strength are a result of greater bone area and differing geometry (larger periosteal/endocortical circumferences) but not bone density [22]. It is possible, however, that part of these differences between athletes and non-athletes is a result of self-selection bias. The largest adaptations thought to be attributable to exercise alone are those in the racquet arm of tennis players – distal radius and mid-humerus bone mass being 45% greater in adolescent boys' favoured arm than the contralateral limb, these side differences being 10-20 times greater than those found in sedentary males [9, 23]. In addition, these side differences follow the same site-specific pattern as outlined above.

Considering the dominating influence that physical activity has on bone strength parameters, it is not surprising that a large number of studies have been conducted to investigate the effects of controlled exercise interventions on bone. A difficulty in comparing these studies is the use of either pQCT or DEXA to measure bone strength indicators. pQCT offers several advantages over DEXA analysis – cortical and trabecular bone can be analysed separately, bone geometry can be examined and volumetric bone density is given (rather than a 2D areal bone density measure which is influenced by bone size). However, pQCT cannot examine proximal limb segments (*e.g.* femoral neck) or axial bone (such as the spine).

Exercise in children and adolescents

Size and strength of both bone and muscle change greatly with age – adult bone and muscle mass being 4-5 times greater than that of young children [24]. Whilst there is a strong association of bone mass and height (and hence long bone length) the size and mass of bone cross-sections also greatly increases - young adult distal tibial bone mass being around 10 times greater than bone mass at birth [25, 26]. Puberty is associated with pronounced bone accrual - bone mass more than doubles in females and nearly triples in males between the ages of 8 and 18 [27], with peak bone accrual

rate occurring at ~12 years of age in females and ~14 years in males [15]. Changes in bone length and mass do not occur synchronously during puberty, with peak height velocity preceding peak bone mass accrual by around 9 months (and peak lean mass accrual rate by around six months, with these peak differences more pronounced in females [15]. Longitudinal bone growth occurs at the metaphyses, and during rapid growth (such as during puberty) a less pronounced age gradient in metaphyseal bone occurs (Figure 3) [28]. This results in much younger, weaker bone at these sites, and may well be a contributing factor (together with asynchronous muscle:bone development) to the increased incidence of long bone fracture during early puberty [29].

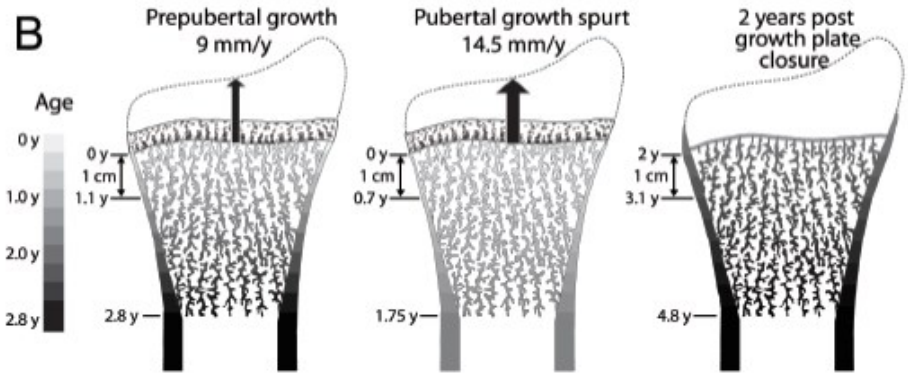


Figure 3. Effect of growth rate on the age gradient in metaphyseal structure. For the 'prepubertal growth' and 'postpubertal growth spurt' scenarios, the simplifying assumption is made that the entire metaphysis has been built under the conditions of the indicated growth rate. The 'post growth plate closure' situation assumes that the speed of growth is constant 9mm/year and then abruptly decreases to zero. Note that 'age' in this context refers to the time that has passed since the growth plate – metaphysis border has moved across a given location. Modified and reproduced with permission from [28].

This period of rapid bone growth has been identified as a window of opportunity to obtain a high peak bone mass, with the potential exercise benefits of bone thought to be limited after puberty [30, 31] or epiphyseal closure [32, 33]. In line with this, a large number of interventional exercise studies have been completed in the young with positive effects on bone found in a number of studies – particularly those involving early pubertal children [34]. Whilst the magnitude of exercise benefits varies greatly between studies, the most effective interventions led to 5-10% greater bone mass or density gains than observed in controls [35, 36]. A problem for the interpretation of many of these studies is the multi-modal nature of interventions, incorporating activities as diverse as weight training, ball sports and isolated jumping exercises within the same programme – making it impossible to isolate the effectiveness of individual exercise modalities. However, jumping exercises are a common component of the most successful interventions, and even jumping exercises alone were effective in improving bone strength [36, 37] – while no such effect was found for resistance exercise [38]. Ground reaction force (GRF) data (as a surrogate for bone loading) was not collected in all studies – however, within those which

reported values the study with the highest recorded GRF (~9 times bodyweight) also recorded the most marked positive effects on bone strength [36].

A number of jumping intervention studies incorporating pQCT measurements of tibial bone have been conducted in children and adolescent populations. In contrast to findings in DXA-based studies, no significant effects of exercise were found in bone measures between exercising children and controls [39-42]. The exception to this was a greater periosteal and endocortical circumferences in exercising children in one study [40], although only one other study reported these geometrical parameters [42]. However, the effects of exercise on bone are site-specific – it may be that jumping exercise preferentially affects areas such as the femoral neck and lumbar spine (measurable with DEXA) rather than sites commonly measured by pQCT, such as the tibia.

In additional to controlled intervention trials, there are many studies investigating differences between exercising children and control counterparts – although these are likely subject to selection bias on the part of participants. Girls of 4-8 years of age who selected to start gymnastics classes gained 3.3% greater forearm bone mass and 2.2% greater lumbar spine BMD in the following 24 months than non-exercising controls [43]. The effects of starting age on benefits in bone have also been examined in tennis players. Those who began playing prior to menarche had 2-4 times greater side differences in bone strength (in favour of the racquet arm) than those who began more than 15 years after menarche [44]. Similarly, pubertal stage was found to affect responses in bone geometry to exercise in tennis players [45]. However, as yet it is unclear whether it is end of puberty or epiphyseal closure at which the periosteal expansion in response to exercise is attenuated.

Exercise in adulthood

The so-called 'peak bone mass' (PBM) occurs in the second or third decade, with age at peak bone mass being site specific [46, 47]. The determinants of PBM are still unclear, and it seems that its relevance has been over-exaggerated in the past, given that there seems to be very little, if any, age-related losses from the tibia [48, 49], and that immobilization-induced losses are readily recovered, at least in adulthood [50]. By comparison with child and adolescent studies, there are few interventional exercise studies in young adult populations. Exercise interventions generally resulted in bone accrual compared to controls, albeit less pronounced (1-3%) than in children and adolescents. However, resistance training was effective in premenopausal females [51] (in contrast to findings in children), which may relate to reduced physical activity in adulthood, hence similar exercise represents a greater departure from habitual loading in premenopausal women than in children. That exercise interventions may be more effective in participants with lower pre-intervention activity levels is supported by findings from a controlled intervention in monozygotic twins that exercise only resulted in significant bone accrual when participants were not already regular exercisers [52]. The lack of pQCT-based controlled intervention studies in this age group prevents analysis of any effects on bone geometry following end of puberty/epiphyseal closure.

It is important to know whether any exercise-induced benefits on bone can be maintained after cessation of regular exercise. Exercise benefits in racquet arm bone

of female adult tennis and squash players were found to be well-maintained despite a 70% reduction in training volume [53]. Results of comparisons of bone strength in retired gymnasts [54], weightlifters [55, 56] and ballet dancers [56] with non-athletic controls are mixed – however these studies are more likely to be subject to a self-selection bias. Similarly, the volume of exercise required to improve bone strength is an important consideration when planning exercise interventions – bone strength in adult women improved following an intervention in which they completed only 10 jumps three times a week [57].

Exercise in older age

Ageing is associated with loss of muscle mass and concomitant loss of force and power generating capacity. Whilst muscle atrophy is a factor in strength loss, other neuromuscular and tendinous changes contribute significantly [58]. Firstly neural factors such as reduced neural activation, loss of motor units [59] and more pronounced denervation of fast motor units [60]. Muscular factors including changes in muscle architecture [61], decreased muscle fibre shortening velocity and specific tension [62, 63], whilst decreased tendon stiffness [64] may also contribute. In addition, there is some evidence that the mechanosensivity and osteogenic response of bone cells to strain diminishes with age [65-67].

Given that the greatest stressor of bone (muscular forces) declines with age and that older bone also seems less responsive to mechanical stimuli, bone strength may decrease with age. Indeed, whilst bone size continues to increase slightly with age, more sizeable age-related reductions in BMD suggest that bone strength is reduced in older age [49]. Accordingly, the incidence of osteopenia and osteoporosis (defined by the World Health Organisation as BMD more than one, and more than two-and-a-half standard deviations lower respectively than mean values in 30 year olds) increases with age as does risk of bone fracture [68]. However, these age effects may be site-specific – hopping force appears to decline little with age [69], as does tibial bone mass [48].

In comparison to studies in children and younger adults, there are quite a number of pQCT-based studies investigating the effects of exercise interventions on bone strength in older people [70]. This should allow analysis of effects of exercise on bone geometry. Unfortunately with few exceptions [71] relevant parameters such as endocortical or periosteal circumferences are not reported. Whilst effects of exercise interventions are mixed, the effects of high-impact exercise such as jumping and volleyball [72, 73] are most pronounced. The gains or attenuated rate of bone strength loss are similar (1-3%) to those found in interventions in young adult women. The effects of low-impact exercise are mixed; whilst tai chi training was found to have a beneficial effect in reducing the rate of bone loss [74], benefits of resistance/vibration training are less pronounced or absent [71, 75].

Physical activity levels decrease with age [76], hence the exercise stimulus required to stimulate osteogenesis may be less in older people. There are few studies reporting the effects of exercise on bone in older men – however, a hopping intervention was found to increase bone area 2.4% and bone mass 1.3% relative to controls [77], with similar results found in women [78]. There are likewise few studies comparing effects of similar interventions on bone strength in people of different ages –

however, bone density in premenopausal women increased significantly more than in postmenopausal women as a result of a jumping exercise intervention (despite ground reaction forces during exercise in the postmenopausal women being 33% greater relative to bodyweight) [79]. Master athletes are known to have greater bone strength than age-matched controls, with the magnitude of advantage in bone strength related to running/walking speed of their chosen event [21]. However, this advantage appears to diminish with age [48].

Exercise in men and women

Sexual differentiation also has an effect on bone strength. Whilst sex-dependent differences are not evident at birth [80], by 14 months bone mass and size are significantly greater in boys than girls [26]. This persists into adulthood where, even when body size is controlled for men have greater bone strength than women [49]. During puberty, extra bone mineral deposition on the endocortical surface and in trabecular bone areas in females (thought to be required to help meet the demands of pregnancy and lactation) results in a higher bone mineral to lean mass ratio than in males [81]. This extra mineral is lost upon estrogen withdrawal, e.g. after child birth or menopause [82, 83] primarily in trabecular bone, and thus likely contributing to post-menopausal fractures. Male osteoporosis rates also increase with age, and the two sexes experience similar mechanisms of bone loss, being driven by increases in osteoclast activity rather than reduction of bone formation by osteoblasts [84].

There are a limited number of studies which examine the effects of similar exercise interventions in men and women. Exercise benefits in older men and women following a hopping intervention were similar [77, 78], as were those found in boys and girls following the same school-based exercise intervention [85, 86]. However, hip BMD in boys but not girls was found to be related to levels of physical activity in a cross-sectional study [87] and male adolescent tennis players were found to have greater side differences in bone strength than females of similar age and training volume [9]. In contrast, side differences in adult tennis players were found to be similar regardless of gender [88]. It has been suggested that estrogen affects bone mechanosensitivity [89] – this may explain these dischordant sex differences between groups of different age/maturity.

Discussion and perspective

In conclusion, exercise interventions have the potential to greatly improve bone strength – particularly in children. However, it is clear that as yet this potential is relatively unexplored. At the most basic level, it is unclear which modalities of exercise are most beneficial for bone strength. This review has focused on traditional exercise interventions (running, jumping, resistance training, *etc*.) for which controlled intervention trial data exists. It may be that new (or even yet to be invented) exercise modalities may be more efficient at improving and maintaining bone strength. For example, whole body vibration (WBV) training has attracted research interest over the past decade. As it may not require as much voluntary effort on the part of the participant, it could be an effective way of encouraging participation in those not keen on traditional exercise. Perhaps more importantly, it will also be applicable to those with movement restrictions ranging from bed rest to spinal cord injury. At present studies on the impact of vibration exercise on bone are often limited

by *e.g.* cohort size [90] and the combination with resistance training [91] which make it difficult to assess the benefits of vibration exercise *per se*. Whilst some positive effects of WBV on bone strength in ambulatory children and adults have been found [75] they are quite small. Therefore it may be that WBV training is most effective in those with restricted movement capabilities. Observational studies report that bone strength in the lower and upper limbs is greatest in sprinters and tennis/squash players [9, 21, 93] – however these sports (or even modified variants) have not been used in interventional studies. In fact, not a single high-impact exercise intervention study in the upper limbs has been completed – despite prevalence of upper and lower limb bone fractures being similar [68].

It should be possible to identify or design exercise actions that cause large amounts of strain to occur at clinically desirable sites (*i.e.* those where fracture incidence is high) such as the femoral neck, distal radius and proximal humerus. However, a number of other factors will contribute to effectiveness of an exercise programme and are currently unknown in humans. Recovery periods between repetitions of an exercise and between exercise bouts have been shown to greatly affect bone formation rates. In rat studies, allowing 14s of recovery between exercise repetitions resulted in 66-190% greater bone formation rate compared to shorter recovery periods – similarly, after 8 hours between bouts mechanosensitivity was restored (compared to a 50% decrement in shorter recovery times). In addition, mechanosensivity of bone decreases after a small number of loading cycles with bouts in excess of 36 cycles having no additive effect on avian ulnae adaptation [2]. Similarly, 5 jumps per day increased bone strength in rats, with diminishing improvements in bone strength gains with increased numbers of jumps [94]. Loading magnitude and frequency also appear to interact – as magnitude of loading increases, the number of loadings required to elicit a bone response diminishes [95]. In adult women only 10 jumps three times a week was enough to result in significant improvements in bone strength [57] – but the threshold for bone adaptation may be even lower than this amount. The effect of training frequency has also been examined – with postmenopausal women completing daily hopping exercise accruing greater benefits in bone density than non-exercisers or participants who exercised less frequently [78]. An interaction of exercise by nutrition was revealed in studies including both exercise (3 x 20 min jumping exercise per week) and nutritional (calcium supplementation) interventions – highlighting the importance of adequate nutrition in the ability to maximize the osteogenic potential of exercise [96, 97]. In addition to nutritional influences, hormonal effects on exercise efficacy for bone health have been found – bone strength being lower in amenorrheic athletes compared to healthy athletes and controls [98]. Bone adaptation appears – at least from observational and within-subject models – to be site-specific, with epiphyseal and diaphyseal adaptations following distinctly different patterns [9, 22, 23]. However, due to the preference for DEXA-based scanning in intervention studies (and incomplete reporting of pQCT-obtained values in other studies) the effects of exercise interventions in the two sites are unclear. As the majority of fractures occur in epiphyseal areas of bone [68], these site differences in bone adaptation would seem to be of key clinical importance.

Fracture incidence is multi-factorial, and bone strength is certainly associated with fracture risk [68]. However, fracture incidence is strongly related to incidence of falls independent of bone strength [99] – fall incidence hence relates also to balance and hence the muscular and tendinous factors discussed previously as well as *e.g.* age-related decrease in procrioception [100]. Another useful factor that could be

considered for inclusion within exercise interventions aimed at bone health could be measures such as balance or co-ordination. Exercise is effective in reducing incidence of falls and risk of falling, whereas other interventions (*e.g.* nutritional and home safety interventions) have not been proven to be effective [101].

Although peak forces acting on bones are thought to determine their structure, few intervention studies report these forces as measured during exercise, and it is entirely unknown what kind of deformation modes these forces engender in exercising human bones. The few available studies report ground reaction forces, neglecting even calculated values (as opposed to direct tendon measurement) of the internal muscle forces. Indeed, comparison of these reaction forces between different studies may not represent even relative differences between exercise modalities. Due to several factors such as tendon compliance, pre-activation of the muscle and rate of force development the time course of bone loading by muscle (via the tendon) and by external forces may differ. For instance, during walking two peaks in ground reaction force are normally seen, where Achilles tendon force only shows a single peak [102]. Similarly, calculated ankle joint forces peak prior to 'toe-off' (*i.e.* relating to the peak Achilles tendon force) rather than heel-strike that might have been expected [103]. Inter-joint differences in muscular loading in reaction to applied external forces may also differ temporally – loading patterns in achilles tendon and patellar tendon differ during squat and counter-movement jumping [104]. Future research therefore must try to identify the exact loading and deformation modes of bones during exercise, so that optimized and targeted exercise prescriptions can be developed.

The physical status of intervention participants may also affect the benefit accrued. For instance, exercise intervention in monozygotic twins was only effective in twins who did not already participate in high-impact sports [52]. Analogous to this are the observations that exercise is most effective in conditions of disuse – *e.g.* 30% of bone lost following spinal cord injury was recovered following 24 weeks of daily electrical stimulation of muscle [105], and that resistive exercise largely prevented bone loss during bed rest [91]. This is promising as it may mean that physically inactive or frail participants may in fact have a good response of bone to exercise. This is particularly pertinent when we consider that frailty is associated with much higher rates of falling, fractures and mortality [106].

However, the pursuit of high bone mass has previously been questioned [107], as – for instance - higher bone mass in older men is associated with greater incidence of osteoarthritis [108]. It may be that impact loading causes osteoarthritis – firstly, directly through an increased rate of incident osteoarthritis [109]. Alternatively, it has been suggested that resulting higher bone mass and increased bone stiffness could indirectly lead to progression of the disease [110]. These negative effects may well be ameloriated by exercise during growth – when bone size seems more responsive to exercise [111], hence reducing joint stress. Alternatively, those with low bone mass and strength may not be at as great a risk from these complications if the effect of exercise interventions are to improve their bone strength to 'normal' levels.

Compliance is another important issue when designing exercise intervention programs to improve bone health. Drop-out and compliance rates vary greatly between studies – the former being as high as 67% in children [86], although withdrawal of school and teacher support greatly affected this value. Across adult studies, retention rates from exercise

groups is 79% with compliance to exercise during the interventions averaging 76% [112] - this is much higher than adherence to pharmacological interventions targeting osteoporosis [113]. In addition, men and older participants (as well as postmenopausal women) were found to have greater adherence rates. Conversely, high-intensity training and unsupervised training are associated with lower compliance rates. After all, it is quite naturally difficult to motivate people to exercise just for the sake of their bones when the goal fracture prevention is equally abstract and remote. Future exercise interventions thus should either involve a greater 'fun' component, or use other secondary incentives in order to engage test subjects or patients.

In summary, exercise is a likely method of improving and maintaining bone strength throughout lifespan. However, current interventions are likely far from optimal as – amongst other factors – the effects of different exercise modalities and volume/intensity of training have not been identified. In addition, due to the lack of pQCT or MRI-based studies the site-specific effects of exercise interventions and effects on bone geometry are not well known. Further studies investigating effects of different exercise modalities, bout timing and program design are required to improve the efficacy of exercise-based interventions aimed at improving bone health. In addition, study of age/maturity and sex-related differences in bone adaptation – as well as differential response based on habitual physical activity levels - may reveal important information pertaining to the personalization of exercise programmes for individuals.

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