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Perspective Article

Hylonome

Perspective: Cerebral palsy as a model of bone development in the absence of postnatal mechanical factors

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Abstract

To ensure optimal skeletal development, mechanical loading is imperative. The consequences of the removal of, or complete absence of, mechanical loading are illustrated by the clinical condition of cerebral palsy (CP). Clinical and radiological evaluation of children with CP provides an insight into how the growing skeleton develops when mechanical loading is reduced due to non-physiological muscle function. The poor bone status or 'physiologic osteopenia' that these children suffer is multifactorial compromised of both mechanical and non-mechanical effects; primarily it is the lack of normal loading from the musculature which causes the development of a bone incapable of withstanding daily activities. Fractures occur during daily activities such as dressing and handling. Increased bone resorption during periods of immobilisation after fracture or surgery, also increases bone fragility. Trials of physical, nutritional and pharmacological treatments in CP children result in increased bone mineral density. Trials that include fracture prevention as the primary end point are required in this vulnerable group of children.

Keywords: Cerebral Palsy, Fractures, Bone Development, Mechanical Loading, Non-pharmacological Treatment

Introduction

To ensure optimal development of the skeleton, mechanical loading is imperative. During the postnatal period and throughout childhood and adolescence loading of the skeleton drives its development to become a functionally viable structure, which does not fail when physiological loads are applied to it. Whilst hormones and nutrition play a vital role in postnatal skeletal development the removal of either one of these key factors does not have as devastating effect upon the bone as does the removal of mechanical signals. The consequences of the removal of, or complete absence of, mechanical loading are illustrated by the clinical condition of cerebral palsy.

Cerebral palsy (CP) is a non-progressive disorder of posture and movement resulting from an insult to the developing brain. It is one of the commonest chronic disabling conditions of childhood, with a prevalence of 2·4 per 1,000 in children aged 3-10 years[1]. The spectrum and patterns of motor disability are variable but can be classified into the following categories: diplegia, hemiplegia and quadriplegia. Additionally, children with CP often have abnormal muscle tone or movement disorders, such as, spasticity, rigidity, hypotonia, dystonia, athetosis, or a mixture of these disorders[1]. Mildly affected individuals are able to participate in most normal load-bearing physical activities, whilst those who are severely affected will have never walked, or sat or even stood without external support. In addition to motor disability, children with CP often have other problems including communication, learning difficulties, epilepsy, poor growth and musculoskeletal problems such as joint contractures, kypho-scoliosis and hip dislocation. Children and adolescents with CP are also prone to low trauma fractures, which occur for example during normal activities such as dressing and handling[2-4]. In addition to causing pain and suffering, fractures further limit the mobility of these children leading to muscle wasting through disuse, hospitalisation, missed school and further loss of independence. As many as 10,000 children and adults with CP may suffer frac-

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tures in the USA every year costing at least $75-150 million[5]. With a rise in the prevalence of CP due to increased survival of low birth weight infants and increased life expectancy due to improvements in supportive care[1,6,7], pathological fractures are likely to become a more common problem in children and adults with CP. Fracture diagnosis is often delayed due to difficulties in communication, neuro-sensory deficit and possibly reduced pain perception in severely disabled CP children. Indeed, a fracture may only come to light because of the development of a tender swelling along a limb or when the child's carer observes a painful reaction such as the child grimacing or crying when the affected limb is moved[4,8]. Lack of a clear history of the injury causing the fracture and delay in presentation to hospital sometimes leads to suspicion of child abuse[9].

The aim of this article is to consider the pathogenesis of increased fracture risk in children with cerebral palsy and to consider the varying degrees of mobility impairment in this condition and how the skeleton may be affected. Non-pharmacological strategies for the prevention of fractures/treatment of low bone mass will also be discussed.

Pathogenesis of bone fragility in cerebral palsy

Mechanical factors

According to Frost's mechanostat model[10-12] the postnatal development of bones is driven by the mechanical forces to which the bones are subjected, primarily arising from muscles, the ultimate end point being a bone that does not fail under normal physiological loading. Such forces result in changes in the dimensions of the bone or 'strains', which are sensed by a regulatory feedback system in the bone called the "mechanostat"[11-13]. This model allows bone to respond to increased bone loading by increasing bone strength and to decreased bone loading by decreasing bone strength; these adaptations are achieved by processes of bone modeling and remodeling. When large loading events, such as running and jumping, result in bone strains that exceed the threshold range of around 1,500-2,500 microstrains (μstrains), the modelling process is switched on, which allows bones to structurally adapt to mechanical loading by increasing their size, altering their shape (architecture) and increasing the mineral mass contained within their periosteal envelopes. In tubular bones, this adaptation results in deposition of bone on the periosteal surfaces thus increasing their external bone diameter. This deposition of bone mass further away from the centre of the marrow cavity serves to increase resistance to fracture arising from bending and torsional loads[14].

During childhood, the response of the long bones to muscular loading results in longitudinal growth, metaphyseal inwaisting and epiphyseal widening in order to produce a structure through which loads are efficiently transferred from joint surface to joint surface during daily activities and giving the bone its characteristic appearance[15]. In the absence or reduction of mechanical strains bone development is altered with abnormal modelling and the resultant structure reduced in its strength through changes in geometry and mineral content; the bones of children with CP often have a long pencil like appearance, with extremely thin cortices, generalised trabecular osteopenia and narrow epiphyses.

The pathogenesis of fractures in CP is multifactorial, primarily the lack of development of the musculature leads to abnormal bone development, and considering the varying degrees of disability associated with cerebral palsy illustrate how vital the musculature is to the developing bone[16]. By definition the bone disorder suffered by individuals with CP is 'physiologic osteopenia'[11] in that the poor muscle function and lack of weight-bearing leads to normal bone development in response to lower mechanical forces than normal thus resulting in abnormal bone geometry, mineral content and a structure of reduced strength in comparison to the healthy child. The loads required to fracture a bone are therefore much lower than normal, consequently a child with CP may fracture during normal handling or when suffering an epileptic seizure.

As an inevitable consequence of fracture the increased immobility causes further reduction in mechanical forces; increased endosteal bone resorption to adjust bone to the altered loading situation will result. The endosteal bone loss leads to cortical thinning and increases the bones' inability to adequately withstand bending and torsional loads. In a healthy individual this would probably be reversible, but in these children, even those previously mobile, fractures will have poor outcome (please refer to clinical examples below).

In addition to the mechanostat, the importance of postural muscle activity upon skeletal health has also been demonstrated[17-22]. The loads to the bones during postural muscle activity are of much lesser magnitude (<100 μstrains) than those during peak loading (>2,000 μstrains). It is likely that postural muscle activity is also impaired in children with CP and may further contribute to poor bone health in this group. The re-introduction of these low magnitude, high-frequency signals has been shown to be anabolic to the bone[23].

Clinical evidence

Examination of radiographs of the bones of CP children often provides an insight into the adaptation of bones to mechanical loading during growth. The degree of reduction in mechanical forces and how this affects bone development is illustrated well by considering two children, one who has been immobile since birth, and the other who was mobile but has since become immobile (Figures 1 and 2).

Child 1 (Figure 1) developed quadriplegic CP with spasticity secondary to meningitis in the neonatal period. She never walked but participated in a static vertical standing programme at school. From Figure 1 it is clear that the child's femur has altered anatomy with a thin and narrow femoral diaphysis, which, as mentioned above, is likely to have arisen as a consequence of reduced loading from her abnormal muscles. Even if the material density of her

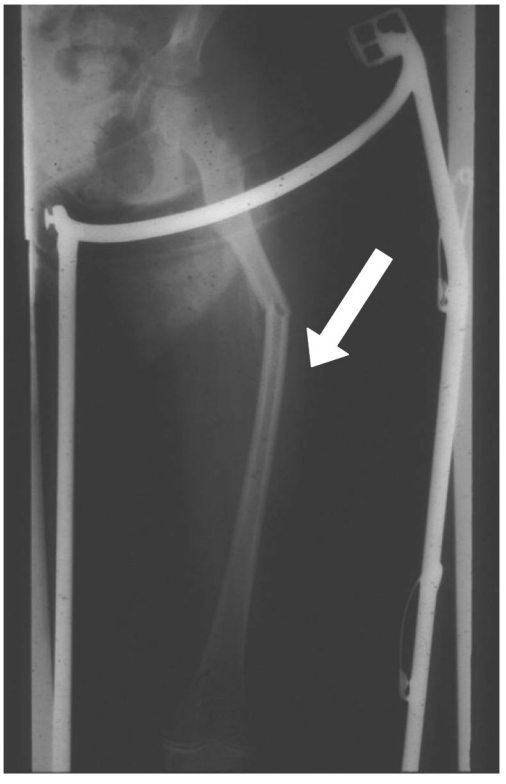

Figure 1. A mid-shaft femoral fracture in a non-ambulant child with spastic quadraplegia secondary to neonatal meningitis sustained whilst being lifted.

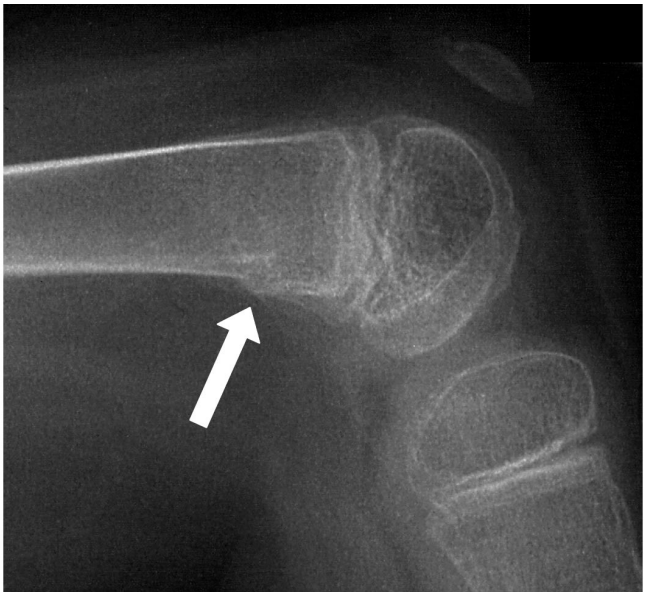

Figure 2. A distal femoral fracture sustained during a flexor spasm during a convulsion.

femoral cortical bone was normal, it is clear from the foregoing discussion that such a bone will have increased risk of fracture from application of bending and torsional forces that might not normally cause a fracture. Such forces, which were generated when she was simply lifted by her carer, resulted in the mid-shaft femoral fracture.

Child 2 is a boy with diplegic CP who was ambulant, albeit with an abnormal gait. He also suffered from a poorly controlled generalised (Grand-mal) seizure disorder and had suffered previous lower limb bone fractures, which were treated by immobilisation in plaster casts. His distal femoral diaphysis (Figure 2) appears to be adequately modelled indicating adaptation by periosteal expansion in response to loading from his more 'normal' muscles than child 1. However, his 'egg-shell thin cortices' are likely to have arisen as a result of endosteal bone resorption secondary to immobilisation of the limb. Therefore, it is not surprising that a muscle spasm during an epileptic seizure resulted in fracture at the metaphyseal-epiphyseal junction of his distal femur.

Non-mechanical factors

There are several non-mechanical factors that also contribute to the poor bone development and fracture risk associated with CP. These include inadequate nutritional intake through oral-motor difficulties, slow feeding, vomiting due to gastro-oesophageal reflux and behavioural disorders; all of which have been associated with lower than normal bone mineral density (BMD)[3,8,24,25]. In a study of institutionalised severely disabled Black South African children and adults with CP, vitamin D status of subjects to be an important factor in the aetiology of fractures[26]; in the same study there was an association between the number of fractures and use of anticonvulsants. Anticonvulsants are known to increase catabolism of vitamin D[27] or lead to a reduction in BMD[28].

Reducing the fracture risk in children with Cerebral Palsy

To the best of our knowledge there are no randomised controlled trials (RCT) of fracture reduction as an outcome measure following nutritional, physiotherapy or pharmacological interventions in children with CP. However a number of studies have reported an improvement in BMD (a surrogate for bone strength) as an outcome measure.

It is clear that the absence of mechanical loading in these children increases fracture risk and it would therefore seem logical that the introduction of loading to stimulate bone development and adaptation in this group may be the best approach to improving their long-term bone health and thus reduce fracture risk. Chad et al.[29], reported that an 8-month programme of physical activity, consisting of upper, lower and trunk exercises significantly improved the estimated volumetric BMD in the proximal femur and femoral neck in children with CP.

Whilst it is known that dynamic loading is more anabolic to bone than static loads[30,31], increasing physical activity in non-ambulant children is not viable. We therefore conducted a RCT of the effects of an increased duration of static standing programme in 26 non-ambulant CP children, aged 4.3 to 10.8 years[32]. We hypothesised that a longer period of standing would result in increased mechanical loading of the lower limb and spine through gravitational forces that would increase muscle tone and thus result in increased volumetric trabecular BMD (vTBMD) at the spine and proximal tibia. The intervention group stood in their standing frames for 50% longer than their normal duration whilst those in the control group continued with their usual duration of standing. After 9 months, the mean vertebral vTBMD, estimated by quantitative computer tomography (QCT), in the intervention group showed a 6% increase ($p=0.01$) compared to the control group; no change was observed in proximal tibia vTBMD. Thus, a longer period of static standing is unlikely to improve strength parameters at the metaphyseal-epiphyseal junction of long bones, where low trauma fractures are known to occur (Figure 2).

In a second RCT we studied the effect of low magnitude, high frequency mechanical loading therapy in a heterogeneous group of disabled but ambulant subjects[23]. The hypothesis was that dysfunctional muscle action in children with CP might deprive the skeleton of small but frequent loading signals[18-22] thereby contributing to their reduced BMD. Therefore, the low magnitude high frequency signals would elicit a response in the bone; more specifically an increase in vTBMD would be seen at the spine and tibia. Twenty pre- or post-pubertal subjects aged 4 to 19 years stood on vibrating platforms (90 Hz, 0.3 gravity) or placebo platforms for 10 minutes/day, 5 days/week for 6 months[23]. Due to the short duration of the trial, we specifically chose to study the effects of vertical vibration therapy on trabecular bone because of its much faster turnover rate than cortical bone[33]. A strong anabolic response was observed in the proximal tibia vTBMD of children who stood on active devices (6.3% increase), in contrast to the significant decrease (11.9%) in subjects who stood on a placebo device; net benefit of treatment 17.7%, $p=0.003$. A positive trend in spinal vTBMD (5.5% increase) failed to reach significance ($p=0.14$), probably due to the relative absence of a decrease in vTBMD in the control subjects (0.3% increase). Post-hoc analysis did not find significant changes in proximal tibia diaphyseal bone geometry or cortical vBMD parameters. The reasons for this might be due to the short duration of the trial, the small number of participants, and because the trial was not specifically designed to look at bone parameters at this site. Despite this, there was a trend for a greater change in whole bone area, circumference and cortical area in the subjects in the intervention group of the trial; change in whole bone circumference was significantly different between intervention and control groups ($p=0.02$).

Pharmacological intervention to improve bone status is a more common management approach in children with CP. Bisphosphonates, which inhibit osteoclastic bone resorption, have been shown to increase spinal BMD by 20% to 40% after 12 to 18 months of treatment in three non-ambulant children with CP[25]. Henderson et al.[34], conducted a placebo-controlled RCT of intravenous pamidronate in CP. Twelve children were randomised to pamidronate or placebo administered for 3 consecutive days at 3 month intervals for 1 year. The BMD of the distal femoral metaphyseal region increased in BMD by 89% in the intervention group whilst the control group had a mean increase of 9%. These agents increase the BMD but to date no study has studied the effect of bisphosphonates on the geometry of long bones in CP, or other disabled children.

The optimisation of a child with CP's calcium intake and vitamin D status is vitally important. The association between vitamin D status and fractures has been shown with subsequent improvements in serum calcium and vitamin D levels after supplementation. Supplementation may prevent or slow further bone loss, which would be highly advantageous to this group. However, it is unlikely that supplementation with calcium and vitamin D will lead to a long-term net benefit to bone strength and prevention of fractures. For the bone to improve its strength mechanical input is required to elicit the response, optimisation of the nutritional status of the child will provide the capacity for accrual of mineral in mechanically relevant sites. We would therefore suggest that an ideal approach would be to use appropriate supplementation as an adjunct to mechanical intervention in this group.

Conclusion

In conclusion, children with CP are prone to fragility fractures and consequently a much reduced quality of life. Their increased fracture risk is due to "physiological osteopenia" associated with poorly and abnormally functioning musculature and associated immobility, both of which reduce loading to the developing skeleton and prevent healthy bone development. The ultimate consequence of this is a skeleton incapable of withstanding daily activities such as lifting and handling or muscle spasms sustained when having an epileptic fit. To compound the problems of these children, fractures result in further bone loss due to further reduction in mechanical forces by immobilisation. From the evidence presented it is clear how vital postnatal mechanical loading is to ensure bone development. The varying degrees of disability that are associated with CP illustrate this, with the most affected group being those that have impaired mobility, immobilisation following surgery, stiff or contracted joints, dislocated joints, quadriplegics and poor nutrition. Secondary to that is the nutritional status and hormonal factors, which also form an important part of bone development and should not be ignored in the future development of therapeutic approaches.

Evidence for fracture prevention using any intervention in children with CP is limited; to date there is no current data of fracture risk reduction in CP. Novel non-pharmacological

approaches show potential although much larger studies are required to support the preliminary evidence. Further randomised controlled trials of physical, nutritional and pharmacological treatments with fracture prevention as the primary end point are required in this group of vulnerable children.

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