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Bone Health in Children with Cerebral Palsy

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Bone Health in Children with Cerebral Palsy

Craig Campbell

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In partial fulfillment of the requirements
For the Masters degree in Epidemiology and Community Medicine

Department of Epidemiology and Community Medicine
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Abstract

Background: Children with cerebral palsy (CP) encounter a number of orthopedic complications as a result of abnormalities in motor function. One of the most significant complications is fragility fractures, occurring in up to 23% of children in prior reports. Despite a growing literature on how to best interpret bone densitometry in children, little research has determined optimal utilization of dual x-ray absorptiometry (DXA) in children with CP in order to characterize the patients' bone health status. This study outlines the use of the mechanostat theory of bone physiology to classify osteopenia and interpret bone complications in this population. The mechanostat theory posits that muscle forces have the greatest impact on bone strength and that low bone mass will result from one of two pathologic circumstances: a primary disorder of abnormally low bone mass despite normal muscle forces, and a secondary disorder of bone mass due to abnormally low muscle forces on bone. The later category, secondary osteopenia, is hypothesized to be the bone health state of most children with CP, due to the motor dysfunction resulting from brain injury in these children. Bone morbidity is expected to be greater in those with osteopenia.

Methods: Single, community-based, rehabilitation centre, cross sectional study of 53 subjects with CP age 2-15 years of age. Subjects underwent a baseline interview, examination, x-ray, laboratory and DXA bone densitometry. Calculations of z-score values for total body bone mineral content and muscle mass were made based on published normal children. The z-scores determined the classification of osteopenia with -2 defined as abnormally low bone mineral content or muscle mass.

Results: The subjects (51% females) had a mean age of 9 years (*s.d.*=3.8, *range*=2.5-15.8). All types and severity of CP were represented in the sample. Normal DXA bone parameters were seen in 24 children, with 11 children classified as having primary osteopenia, five having secondary osteopenia and three with both primary and secondary (mixed). Three children had fragility fractures. Using the classification proposed herein, the fractures occurred only in children defined as having osteopenia. Having at least one bone complication and joint subluxation were more prevalent in the osteopenic subjects compared to non-osteopenic subjects (Chi square, $p<0.05$). Using z-scores for bone mineral content as an outcome variable, only one CP specific factor, the Gross Motor Function Classification System, was an important independent variable (β=-0.48, R^2=0.18, $p<0.05$). The final model also included age (β=0.52, R^2=0.34, $p<0.05$) and gender (β=-0.36, R^2=0.12, $p<0.05$), showing lower z-scores in males and those of younger age. Use of anti-convulsants, type of CP, family history, calcium and vitamin D intake did not contribute to the model. Measures of pain or quality of life, although worse in osteopenic subjects, were not significantly related to reductions in bone mineral content, when severity of CP was controlled.

Conclusions: Using the mechanostat theory to interpret bone density DXA measurements is a more physiologic way to interpret bone health in children and appears foundationally sound in this sample of children with CP. In the reported subjects orthopedic complications were more common in those with osteopenia, and fragility fractures were accurately classified in functional terms according to whether the osteopenia resulted from a primary or secondary bone defects.

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Glossary

Bone strength: The property of bone that defines how able it is to withstand mechanical forces imposed on it. Bone strength mechanically is contributed to by both the architecture of bone, as well as the amount of mineral (principally calcium) deposited in that bone. Thus one can lose bone strength based on disorders of bone tissue depletion (osteopenia) or due to disorders of bone mineralization (osteomalacia). Bone strength can be directly observed via the occurrence of fragility fracture. Otherwise it is assumed only through surrogate measures such as bone mineral content or bone mineral density.

Bone mass: The amount of bone tissue in a unit of bone. The bone mineral content is a measure of bone mass.

Bone mineral content (BMC): the mass of bone mineral (calcium principally) contained in a unit of bone. The unit of bone can be variable for example a whole bone or a segment of bone. This is measured by bone densitometry as the attenuation of a radiation beam across this unit of bone.

Bone mineral density (BMD): The mass of a unit of bone divided by the volume of that unit of bone is the physical density of bone. In clinical practice bone density usually refers to the measurement of the attenuation of a radiation beam as it passes through a bone divided by the surface area of that bone (areal BMD) or the volume of the bone (volumetic BMD).

Fragility fracture (FF): A fracture occurring with minimal force or trauma. A fracture that occurs with the equivalent force of falling from a standing height while walking on a level surface.

Lean body mass (LBM): This is the amount of muscle mass in a certain body unit. Much like BMC the LBM can be measured using densitometry and the body unit can be variable.

Muscle force: The maximum momentary amount of tension or strain a muscle places on a bone. In the clinical setting this remains a concept. Only surrogate markers of this concept such as measuring muscle power or quantifying muscle mass can act as indicators of potential muscle force on a bone.

Osteopenia: A decreased amount of bone tissue. In the current study this disorder of bone strength has been operationalized into three categories: primary osteopenia where BMC is less than expected for muscle mass; secondary osteopenia where BMC is normal for muscle mass but muscle mass is low; and mixed where both muscle mass is low and BMC is also lower than expected for muscle mass.

Osteomalacia: see above in definition of bone strength.

Introduction

Cerebral Palsy (CP) is a term applied to a group of non-progressive impairments of movement, strength, or posture that is secondary to a brain lesion occurring in the developing brain (1, 2). CP is one of the most common chronic medical problems in pediatrics. In fact the disorder affects approximately 1-2.4/1000 children (1) with a spectrum ranging from mild disability through to profound motor impairment. Conditions that are often associated with CP include: cognitive impairment, seizures, vision and hearing impairment, gastrointestinal motility problems and orthopedic complications (2). The orthopedic complications that can accompany CP include: scoliosis, joint subluxation or dislocation, fractures and torsional bone deformities (3). Children with CP, and their families, can suffer from a large burden of illness as a result of orthopedic and other associated problems. Furthermore, with CP being a common motor disability in children, these issues are of significant concern to pediatric health care providers.

The clinical problem that has driven this study is the observation that children with CP experience many bone complications. One of the most concerning orthopedic complications of CP is bone fractures. This problem has been estimated to occur in 7-23% of children with CP (4-9). When a fracture occurs the patient can suffer a range of repercussions from minor pain through to the need for surgical intervention and prolonged casting. Many fractures in children with CP have been described as pathological or fragility fractures which are defined as those that occur with minimal trauma or during usual activities (10). The term spontaneous fracture has been used to describe fractures with no known trauma history (8, 11). Observations of radiolucent bones on x-rays have led to the implication that low bone mass is an important factor in

the development of fractures in children with CP (5-8, 12). Children with CP also experience other orthopedic complications such as scoliosis, femoral bone rotational abnormalities and joint dislocations. These latter complications have not been clearly linked to bone strength and are largely felt to be a result of abnormal muscle forces. However, as will be discussed below the relationship between muscle forces and bone strength is an important one and may have some implication for these other orthopedic complications.

This project seeks to explore the factors that impact on bone strength in children with CP and then to explore the relation between bone strength and bone complications, principally fragility fractures.

Literature Review

Measurement of bone strength in children

In regards to the measurement of bone strength in children, testing of bone strength is done in an attempt to predict those children who will have a risk of clinical problems related to poor bone health. To date, both in adults and children this risk has been conceptualized almost exclusively as the risk of fracture, although in some populations with primary bone disorders, pain is also a major implication of poor bone health. Those experiencing a fracture with minimal force, equivalent of less than falling from standing height, are said to have experienced a fragility fracture and if associated with a low bone density they are deemed to have osteoporosis.

To date, there have been two main conceptualizations of bone physiology prevalent in the literature. The first is the concept of 'peak bone mass' or the theory that the objective of bone is to be the strongest it can be. This hypothesis has led to the idea

that the more modifications one can make to the factors that control bone strength the more able one will be to increase bone strength indefinitely and prevent bone complications. An example of the peak bone mass concept involves the role of calcium in bone strength. It is thought that if a bone is exposed to calcium then it will accrue this mineral and become stronger. This association between calcium and bone strength may be partly true but research suggests the association also involves other factors (13). The importance of muscle-bone interactions and the concept that bone is only as strong as it needs to be to resist regular muscular forces applied upon it are important factors to consider in the conceptualization and measurement of bone strength. This emerging conceptualization is called the mechanostat theory (13). This theory conceptualizes that bone only becomes as strong as it needs to be in order to adapt to its surroundings (see Figure 1). And the greatest factor in those surroundings is muscle action on the bone. Even more so than gravity, muscle forces on bone generate large forces that impact on how bone forms and adapts. Studies, have demonstrated that the main influence on bone density is some measure, either direct or surrogate, of muscle strength acting on the bone (14-16). If bone strength did not have to have any response to the surrounding environment (the muscle) then the evolution of bone would simply have been to be as strong as possible at any expense and bones would have become solid masses of calcium. This is not the case and bone is a complex design of solid portions (cortical bone) surrounding a swiss cheese array of what is referred to as trabecular bone. Bone is originally formed by specialized connective tissue that becomes calcified or mineralized. The physical bone is made larger or of greater mass not only by the proper laying down of connective tissue but also by adequate deposition of mineral into the bone matrix. This

allows the bone to be strong enough to resist the regular forces applied to it yet light enough that mobility remains optimum.

Following from the conceptualization that muscle mass is the main determinant of bone strength, one can think about bone problems, such as fracture, as falling into one of three groups. The first group includes primary bone diseases where the bone mass is reduced in relation to the degree of strength, or muscle mass, that the child has. The second group includes the situation where the bone and muscle unit are appropriately matched but because the muscle is weak, the bone is consequently weak. This is the situation in those with physiologic or secondary osteopenia. The final group is a mix of primary and secondary bone disruption. The ideal measurement of pediatric bone strength should be able to decipher these various groups with some accuracy.

Bone mineral density is the amount of bone mineral content in a given bone and is usually indicated as bone mineral content per unit of area (areal bone mineral density) or volume (volumetric bone mineral density) of a bone or set of bones. This is the property of a bone that is felt to best represent its strength and in adults has been found to be a predictor of fracture risk (17). Measurement of bone density can be done through a number of methods. A qualitative assessment of bone can be obtained by observation of x-rays. Quantitative methods include dual-energy x-ray absorptiometry (DEXA), Computed Tomography (CT), MRI and Ultrasound. DEXA is used far more frequently than the other methods, due to its low radiation doses and ease of use, and will be discussed exclusively here as it was the method used in this study. Further information of the other methods can be found in recent reviews (18). DEXA works by passing a radiation beam across various tissues and analyses the degree of attenuation of the

radiation beam. Through this method, both total and regional estimates of bone mineral content can be determined and thus a quantitative measure of bone mineral density can be determined by dividing the bone mineral content by the estimated area of bone in the body. As indicated above, bone density is determined in one of two ways: total body bone density and regional bone density. The latter examines a particular region of interest, with the femoral neck and the lumbar spine being most typically measured. DEXA can also measure tissue compartments other than bone so that an accurate measure of fat mass (fat body mass) and muscle mass (lean body mass) can be obtained. Measurement of muscle mass is particularly useful in assessing the relationship between muscle mass and bone strength.

In adults (particularly females) the conceptualization that low bone density is related to health problems is a robust finding with clear risk of fracture associated with low bone density as measured through multiple techniques. Typically, a comparison is made between a measured bone density to the expected young normal value divided by the population standard deviation to derive what is commonly referred to in bone densitometry as a T-score, named after the investigator, Dr. T. Kelly, that first proposed it (19). Again, in otherwise healthy normal sized adults this measure of bone density has been helpful to identify those at risk for fractures and subsequent treatment has undoubtedly reduced the risk of fracture. In children the measurement of bone strength is more complex and the relationship between measured bone density and fracture risk is less well established (20). The principal problem is that children have a greater variability in their size for any given age and as such using age matched controls to generate a z-score value has not been accepted as an adequate means of representing bone density in

children. Additionally, the common measure of bone density used clinically, the areal bone mineral density as measured by DEXA, finds that bone density actually increases as children grow. This phenomenon is a reflection of an increase in the size of the bone and not necessarily an increase in the strength of the bone. Thus, no absolute value can be relied upon across childhood. Several strategies exist to bypass the problems related to measurement of bone mineral density in children.

In regards to measurement of total bone density in children, studies have provided regression equations that allow for correction of measured bone content for size, age, gender and race. One study (21) took a large sample of healthy children and performed DEXA on them and derived regression equations for total body bone mineral density and bone mineral content allowing comparison of predicted and measured values. Unfortunately this study did not use lean body mass as measured by DEXA as part of the equation and this marker of muscle mass is typically found to account for the greatest amount of variability in bone mineral content in childhood populations (14, 22, 23) and theoretically is thought to be more sound (16). More recently, reference values including lean body mass as the main predictor of bone mineral content have been established for normal children and used to demonstrate diagnosis of primary, secondary and mixed osteopenia in select patient populations including two children with CP (14). The algorithm used includes determining first if lean body mass is normal for height, then assessing whether bone mineral content is normal for the amount of lean body mass. If lean body mass is low for height this means a child would have weak muscle forces acting on their bone and must then have a relatively weak bone on this basis alone- or secondary osteopenia. If the muscle mass is normal for height but the bone mineral

content is low for the degree of muscle mass then this represents a primary disorder of bone, and finally if both conditions exist it is a mixed osteopenia. Figure 2 demonstrates this classification and shows results of this classification applied to several patient groups from the study by Crabtree et al. (14) This paradigm will be used in this study to understand if CP children truly have only a secondary or mixed type of bone defect.

A similar approach to measuring total bone density is to use a ratio of bone mineral content to lean body mass (15, 24). Again the theoretical argument here is that lean body mass is the main determinant of bone strength and that a ratio of these two variables will provide a continuous variable with a normal distribution. This ratio could be used to establish 'normal' ranges for healthy populations from different body sites, and those individuals with ratios falling outside these ranges would represent abnormally low (or high) bone mineral content for lean body mass. A ratio similar to control populations would suggest that the bone is as strong as it needs to be for the amount of muscle force acting on the bone. If the bone mineral content is relatively low compared to the lean body mass then the ratio would be lower and represent a bone that would be expected to be weaker than it need be. Few studies have used this approach and normal values are not available for different sites of the body or for different methods of bone mass determination (i.e. DEXA, CT). This makes it difficult to apply this method for study with other population groups. One study, however, has determined this ratio in a healthy sample of 459 people age 3-30 years on a DEXA machine (brand name Lunar) (15). The sample was all white subjects of Australian nationality. Similar to other investigators they found that lean body mass predicted almost all of the variation in bone mineral content in regression models including other standard growth parameters. This

study generated normal value tables of bone mineral content/lean body mass ratios plus standard deviations for differing heights in boys and girls. Similar to the study by Crabtree et al. (14), these investigators applied the combination of low lean body mass for height and bone mineral content/lean body mass ratio to determine primary, secondary and mixed osteopenia. However, this group of investigators used one standard deviation below the mean as the cut off value for determining if a value is below normal. The author's note that this cut off is an arbitrary decision as there is no consensus in pediatrics on what should be defined as osteopenia. The ratio of bone mineral content /lean body mass could also be used as a parameter to explore the impact of other factors on bone strength. For example, if this ratio is used as the outcome variable in a linear regression equation then the impact of other factors on bone health can be examined such as age, gender, mobility status, type of CP, use of anti-convulsants and nutritional factors.

In regards to measurement of regional bone density in children, the main approach is to calculate a volumetric bone mineral density by dividing the bone mineral content measured by DEXA by the calculated volume of the bone. Different methods of calculating the volume of the lumbar vertebra or femur neck have been used with the information on the height and width of the bones measured by DEXA scanning. This method of measurement of regional bone density in children has also been criticized as not accurately representing the strength of bone (22) or for being too general for the range of shapes of the bones in the body (15). Regional approaches using a DEXA derived ratio of lean body mass to bone mineral content have not been fully described but may be a source of important data and could potentially be developed for any bone site with DEXA data. Again, using this mechanostat theory the regional bone muscle

relationship might be the best approach and is increasingly being used in studies with Quantitative CT. In one study total body lean body mass has been shown to be a predictor of lumbar bone mineral content (14). This study suggests that regional bone mineral content at the lumbar spine should be corrected for total body lean body mass and may be useful for predicting if an individual is osteopenic. When applied to two patient populations the results were similar to the total body bone mineral content corrected for lean body mass results described above, with those with frequent fractures and Osteogenesis Imperfecta having low lumbar bone mineral content for lean body mass (primary osteopenia) (14). Notwithstanding these results, very little consensus has been reached as to how best to address the issue of regional bone mineral density in children.

Cerebral palsy and the mechanostat theory

Although, the causes of CP are wide ranging, the final pathway of disrupted motor control is related to the central nervous system. Motor control is disrupted in CP ultimately causing differences in muscle tone with the predominant result being spasticity or dystonia, both states of excess and abnormal muscle tone. As explained above, the interaction between bone and muscle must be considered as a unit, for it appears that bone architecture is largely determined by muscle forces and bone strength ultimately is driven by the need to withstand the muscle forces applied to that bone. This is an important, yet under-recognized concept in normal children and may have an important role in children with CP as well.

In the literature, there is actually very little data on muscle mass in children with CP. In two previous studies examining body composition, by anthropometric measurements, in children with spastic quadriparetic CP both showed that mean lean

body mass was lower in these children compared to age matched controls (25) or to children chosen to have a similar lean body mass (26). In the latter study the method of recruiting the control subjects is unclear because the investigators chose control subjects "...to be comparable in fat-free mass..." to study subjects, however they still found a significant difference in lean muscle mass between the groups (26). Only one study published lean body mass results from a population of ten children with CP by DEXA, but no control group was used presumably because the study was not examining lean body mass specifically (27). This limited literature supports the assumption that children with CP have low muscle mass and may then have low bone strength on this basis.

Studies of bone density in children with CP

Bone fragility is a known issue for children with CP. Original studies of institutionalized children with CP have demonstrated osteopenia on x-ray and fractures (8, 11). Most fractures in this population have been found to be in the femur, are generally situated in the mid and distal portions (6, 9) and occur most commonly in the second decade of life (10). The fractures have been often termed pathologic (6) or even spontaneous (if no trauma is evident) (8). However, currently, no clear operationalized definition is in place to define the degree of force considered acceptable to cause such a fracture. In adults or other populations with a high risk of fracture, the typical conceptualization of a fragility fracture is that which occurs with less force than falling on a level surface from a standing or walking position (28). Although this serves as a reasonable marker in neurologically normal populations, it is sometimes difficult to translate this to children in wheelchair who are being moved by forces other than their own muscle power. Furthermore, for those who are independently ambulant, balance and

coordination is often an issue perhaps causing falls from standing height to occur with more force given the lack of normal protective mechanisms.

In almost all cases the studies of the strength of bone in children have focused on the surrogate marker of bone mineral density assessed by DEXA scan or an alternative. In almost every study the CP group has been noted to have lower bone mineral density than control groups, with the exception of a small study of ten children (29). In view of the understanding of the muscle-bone relationship as a principal determinant of bone mass this finding of reduced bone mineral density compared to healthy controls is not surprising. As mentioned before, children with CP have weakness and imbalance of muscle forces due to an alteration in central nervous system (CNS) motor function. This results in a lack of movement and when it does occur the movement is often abnormal. Thus, it is not surprising that in children with CP, bone becomes weak and does not adequately match the muscle forces that influence the bones. For the most part this adaptation is appropriate, in that, when a child is moving less, they are presumably at a lower risk of fracture. However, CP children still do move about and are moved about by caregivers, which open the possibility of a fracture with forces greater than that which the body may routinely produce itself. This process is much the same as the mechanisms that cause fractures in those with normal bone mass in the setting of excessive force. However, perhaps in addition to normally adapted bone strength for a state of abnormal muscle, there is a group of children with risk of fracture greater than that expected for their muscle mass. This can only be determined by controlling this factor and then looking at other influences on bone mass such as medications, diet, lack of weight

bearing, genetic factors, etc. Unfortunately no study has used lean body mass as a factor in the analysis of bone mineral density in CP populations.

In one of the earliest studies of bone mineral density in children with CP (30), 139 children with spastic CP of various severities were examined by DEXA of the lumbar spine and the proximal femur. Using z-scores for age matched controls, multiple correlation analyses revealed that decreased lumbar and hip bone mineral density were related to lower ambulatory status, history of prolonged immobilization, poor nutritional score, lower calcium intake and quadriparetic type of CP. Anticonvulsant use was associated with lower bone mineral density z-score in the lumbar spine only. No relationship was seen for those with a history of fracture versus those without a fracture history. Also, no relationship was found for any of the serum markers of bone physiology; however, very few children had values outside the normal range. When the above factors were analyzed using regression analysis, the most significant factors in the model were ambulatory status and a nutritional score (which was a parameter including body measurements) (R^2=0.316, p=0.0001, cumulative $R^{2=}$ 0.377 p=0.006, respectively). Keeping in mind the mechanostat theory, what is important to note from the results of this study is that mobility status may be an important risk factor simply because non-ambulant children have low muscle mass. However, in the Henderson et al. (30) study, there was no clear attempt to describe and interpret bone density measurement in those with fragility fracture (n=19, 14%), nor was a substantial difference found in bone mineral density in children with or without fracture. This study used the theory of peak bone mass to suggest that increases in the length of time a child was made to stand and better nutrition will result in increased bone density. Additionally, a finding important to

the purposes of this study, although not emphasized by the authors, is that bone mineral density was lower in the affected proximal femur in hemiplegic children compared to the opposite side which suggests that all other factors being even, muscle forces are an important determinant of bone strength.

A second study conducted by Tasdemir et al. (31) examined bone mineral density in 24 children with CP, age 10 months to 12 years, compared to a control group of healthy children. The sample included both ambulant and non-ambulant children within the CP group. Blood parameters of calcium homeostasis were measured in all children and only calcium and phosphate levels were higher in CP patients compared to controls. However in neither group were they out of the traditionally accepted normal range. Quantitative CT of the lumbar spine was used as the measure of volumetric bone mineral density. Volumetric bone mineral density was found to be lower in the children with CP, especially the non-ambulant group. In this study the bone density was negatively correlated with age suggesting that in CP bone density is reduced over time. The authors of this study conclude that children with CP be made to bear weight more often. However, the conclusions of this study do not take into account that body size and low muscle mass are principal determinants of bone mineral density.

In a third study investigating bone mineral density in children with CP, King et al. (32) examined a cross sectional study of 48 non-ambulant children and adults with CP with DEXA scans of the lumbar spine. Lumbar bone mineral density z-scores were determined (presumably from the manufacturers data base, but not explicitly stated) without correction for body size. The authors hypothesized that bone mineral density would decrease with age. However, in contrast to the Tasdemir et al. study, no

statistically meaningful relation was found between the variables of bone mineral density and age. This still implies that there is an abnormality in bone mineral density status as bone mineral density should actually increase in normal children as they age. The study also compared bone mineral density in those with fracture and without fracture and found a significant difference in bone mineral density for those having a past history of fracture compared to those with no such fracture history. No abnormalities in serum markers of bone physiology were noted.

In a large study of 117 children, by Henderson et al. in 2002 (33), regional distal femur areal bone mineral density scans were used in order to assess risk factors for low bone density in this population. The distal femoral technique of bone mineral density testing is used by this group because in previous studies the authors have found it difficult to perform femoral neck and lumbar spine bone mineral density in CP populations due to positioning (34). Findings on multivariate analysis showed that worse severity of CP, increasing feeding problems, use of anticonvulsant medication and low triceps skin folds were the contributing variables to low areal bone mineral density z-scores. No biochemical parameter was significant, nor was calcium intake. This study did use a health related quality of life score but found no relation to bone mineral density.

In 2004, Henderson and colleagues(35) studied another sample of 107 children with moderate to severe CP using regional distal femur areal bone mineral density scan in order to assess risk factors for low bone density in this population. No measurement of the regional lean body mass was made in this study either. The risk factors for low bone mineral density in this study were low weight for age z-score, increasing age, severe CP, feeding difficulty, previous fracture and use of anti-convulsant medications. The first

two factors, weight and age, were found to be most influential in predicting bone mineral density. Again, no use of lean body mass was used to explain bone mineral density in this study and is likely the major confounder with several of these variables. A subgroup from this same sample of children were recently reported on by Henderson et al. (36) related to follow-up areal bone mineral density evaluations measured and converted into an annualized percentage change in bone mineral density. The increase in bone mineral density was consistent across all sites at about 2-5% per annum despite a decrease in z-scores compared to age matched controls. Again, no clear correlations were noted between baseline factors and annualized percentage change in bone mineral density, save for a positive correlation with tricep skinfold thickness.

Although the previously cited studies have not shown biochemical markers to be abnormal in this population, three studies have documented high fracture rate and recurrent fractures in persons with CP with evidence of rickets and osteomalacia biochemically (4, 6, 7). In all three studies, treatment with adequate levels of vitamin D and calcium improved biochemical parameters to normal and in one study no report of recurrent fractures occurred in six subjects in a follow-up of one year (6). These children are likely an anomalous group as most studies noted above have not identified calcium and vitamin D deficiencies as frequent in children with CP. According to one study in nine children with CP, three with recurrent fragility fracture, no clear abnormality was found on laboratory measures of bone physiology (12). In another study, comparing thirteen children with CP treated with vitamin D and calcium for nine months, to seven children with CP that did not receive the treatment, a significant increase in the areal bone mineral density of the lumbar spine was found for the treatment group and a

decrease in the areal bone mineral density was found for the control group (37). Although in the normal range at baseline the mean alkaline phosphatase, a bone breakdown marker, of the treated group did drop considerably, no other significant changes in biochemical markers were noted. Unfortunately no data were presented on the nutritional status of these children or why the control group children's parents refused vitamin D and calcium supplements. Of note is that the treatment group also had an increase in weight during the treatment as well. Similar findings of biochemical normality and increases in bone density with vitamin D supplement were seen from an earlier study, but no control group was used and measurements of bone mineral content were from the upper extremity (38).

All the studies of biochemical markers of bone physiology suggest that aside from occasional patients with severe nutritional deficiencies of calcium and vitamin D that osteomalacia is not a significant clinical problem in children with CP and has little impact on bone strength.

Overall, each of these studies continue to view bone mineral density as a factor independent of muscle forces which likely explains the relatively weak findings of the relation between bone mineral density with other factors. When an apparent relation is determined, such as between immobility and bone mineral density, it is quite possibly a reflection of muscle mass reduction. Studies focusing specifically on mobility status in relation to weight bearing show reduced bone mineral density in less mobile children (39), whereas other studies show no such difference (40). In one study of 20 mobile and immobile CP children randomized to an intense physical therapy session compared to controls with no intervention showed that over an eight month period, bone mineral content and volumetric bone mineral density of the femoral neck improved significantly

compared to controls (41). This study may well have had positive results based on improvements in muscle mass from increased exercise, which again points to the importance of considering muscle force as the prime predictor of bone strength. A randomized study examining the use of increased time in a standing frame in 26 non-ambulant children with CP showed improved volumetric bone mineral density in the lumbar spine over a nine month period, but no change in volumetric bone mineral density in the tibia as measured by Quantitative CT (42).

In analyzing the findings of the above research related to CP and bone strength, a gap in the research becomes evident, namely the lack of consideration of muscle mass as a prominent determinant of bone strength and the lack of conceptualizing osteopenia in the using the mechanostat paradigm. Therefore, in order to further this important area of research, investigation into examining whether bone mineral content is still related to immobility or weight bearing when lean body mass has been controlled for is needed. Putting children in a standing frame will not necessarily improve bone mineral density, or do so only marginally, if no improvement in lean body mass is occurring. If this is so then interventions aimed at ambulating may help improve bone mineral density in some children. Similar arguments can be made for the relationship between bone mineral density and nutrition status and anti-convulsant use. These may all be confounded by low muscle mass and as such a misunderstanding has likely developed in the determinants of bone mineral density in children with CP.

In essence, no study of CP children has tried to classify subjects as having a primary, secondary or mixed osteopenia based on the mechanostat theory. This study tries to address just these issues, by first examining if bone mineral content is strongly

correlated with lean body mass in this sample. Additional variables will be examined in bivariate analysis as well with development of a model to assess the relative contribution to bone mineral content. If the relationships of lean body mass to bone mineral content are suggestive of what is described by Crabtree et al. (14) then the sample will be examined using their reference data to determine if any of the study children fit into an osteopenic category. Once each child's data has been converted to a z-score for bone mineral content as a function of lean body mass then the z-score can be used as a dependant variable to examine the relative contribution of other factors such as type of CP, mobility status, anti-convulsant use and nutritional parameters. In addition a model using a ratio of bone mineral content to lean body mass will be used to explore the impact of these factors unique to CP on bone mineral content. The expected findings, based on previous literature, is that most children with CP will have secondary osteopenia and that few other factors (i.e. ambulatory status, type of CP, anti-convulsant use, and nutritional factors) will significantly impact on bone mass other than the change in muscle mass. As mentioned previously the only other complicating possibility is that the dynamics of the muscle forces in children with CP may alter the expected impact of lean body mass to bone mineral content. For example, because the agonist/antagonist muscle actions are rarely normal in CP the bone mineral content may appear lower than expected for the amount of muscle mass or alternatively the abnormal muscle forces may cause bone to be larger (thicker, higher bone mineral content, etc.) than expected for lean body mass but not have the appropriate strength because bone architecture is abnormal.

Bone density and outcome measures

To our knowledge no study of bone density in children with CP has yet used a prospective or case control design to determine if those with low bone density, however defined, are associated with a specific outcome measure such as fracture. In fact as seen in the study by Henderson et al.(30) measurements of bone mineral density did not differ significantly between those with and without a history of fracture, calling into question the value of DEXA in identifying those at risk. Other data currently available from treatment trials with various interventions such as bisphosphonates (a class of drug that inhibits osteoclast function thus building bone matrix) may help to clarify the issue of fracture and bone mineral density. As the literature is reviewed below, one will have to remember the problems faced in the measurement of bone mineral density in children and in those with CP, few of which are addressed in the following studies.

A study published only in abstract form (43) followed three children with fractures and six without, all with severe CP. They all received treatment with vitamin D and calcium supplementation and despite increases in bone mineral density by 5-10%, the group that had prior fractures continued to have fractures even following treatment.

Allington et al. (44) examined fracture rates and parents' general perception of their child's comfort following treatment, in a case series of seven CP and four 'CP-like' children between 5 to 16 years old. Nine of the children had had preceding fractures and all had a bone mineral density score less than 2.5 standard deviations below the mean, but it is not clear which site was measured and it appears to be a total body measurement that was not corrected for stature. All were said to have 'bone pain', however this is not defined in the paper nor is a questionnaire used to determine the degree of comfort. All

patients received IV pamidronate, a bisphosphonate, over a year and bone density and pain measurements were repeated. Every child's parent reported improved comfort and no further fractures were experienced over the year. Additionally, the total body bone density measurements improved with an increase of 13% (*s.d.*=15%) with the most clear increases in the regional lumbar spine bone mineral density of 31% (*s.d.*=14%). No control group was used in this study and the results are not separated out from seven additional children with neuromuscular diseases included in the study. In a similar case series of three children with recurrent fracture treated with bisphosphonate, no recurrent fracture was seen over an 8-18 month follow up with marked improvement in lumbar areal bone mineral density (12).

Henderson et al (45) randomized 14 children with non-ambulant quadriparetic CP, to receive one year treatment with IV pamidronate or placebo. The study was double blind and the children were initially matched into pairs based on age with one subject in each pair then randomized to treatment or placebo. All but one child had had a fracture and all had an age-matched bone mineral density score of less than two standard deviations. Six pairs of participants finished the protocol. This group uses lateral femur scans to assess areal bone mineral density, a practice not used in other populations and not routinely used clinically. Percent change in areal bone mineral density was the primary outcome for this study with lumbar spine areal bone mineral density a secondary measure with all z-scores compared to age, gender and race matched healthy controls. Areal bone mineral density and z-scores improved significantly over placebo controls in all but one region of the lateral femur. Furthermore, three subjects in the control group

and no subjects in the treatment groups had fractures in the 18 month follow-up period. No other baseline features correlated with changes in areal bone mineral density.

Despite the small numbers and disregard for controlling for lean body mass or correcting for other growth parameters, these studies demonstrate that bone density is improved with bisphosphonate therapy and that this may translate into a reduction in fractures in this population. As yet, low bone mass has not been definitively associated with fracture in the CP population. Nevertheless, the link is well established in other populations (17, 46, 47) and biologically plausible it would appear that two possible explanations exist. First, methodological problems in previous studies such as small sample size of fracture patients or failure to account for lean body mass as an important parameter have been the cause of the lack of a clear association. The second is that bone density is not entirely related to a bone problem or bone mineral density, as outlined above, but may be accounted for by forces experienced by a child that are beyond the capacity of their bone to withstand, much like what happens in an otherwise normal individual who experiences a fracture. This explanation is what is known as secondary osteopenia. Regarding the problem in this fashion may be simply an exercise in conceptual manipulation, but accurate conceptualization is the underpinning for rational analysis of the problem. For example, increasing calcium intake, the use of standing frames, or reducing anti-convulsant medications may have little impact whereas more care in the handling of a child, or better yet, tipping the balance toward increased bone density beyond that which the child's own muscle can generate through the use of bisphosphonates may be the most effective route to improve physiologic osteopenia.

Needless to say, this relation needs to be clearly defined as it has implications for risk factor management and treatment.

To our knowledge, no study in children with CP or other populations has explored the relation of bone density to scoliosis or joint dislocations. Scoliosis is quite common in children with metabolic bone disease and normal muscle (osteogenesis imperfecta) as well as in those with abnormal muscle function yet presumably normal bone (Duchenne muscular dystrophy). As such, the interaction of paraspinal musculature and spine bone strength is of some interest and this study will explore this relationship. Additionally, no study has adequately examined pain or quality of life in relation to bone density or after treatment with bisphosphonates. Only a cursory examination of pain has been completed (44). The foundation for these outcome measures will be explored in this study. By using regression analysis we will examine the relationship between bone mineral content and pain, Health related quality of life (HRQL), and degree of scoliosis. For pain and HRQL linear regression equations controlling for severity of CP and age will be used to try to isolate the impact of bone mineral density on these variables.

Objectives

This study intends to determine clear, clinically important factors related to bone mass in a population of children with CP. A conceptual diagram of the objectives and hypothesis can be found in Figure 3.

Primary Objectives:

In children 2-15 years of age with CP:

(a) To determine the factors contributing to bone mass by examining the relation between bone mineral content (the dependant variable) and lean body mass, other

growth parameters, type and severity of CP, vitamin D intake, calcium intake, anticonvulsant use, and family history of osteoporosis (independent variables).

(b) To determine if the prevalence of fragility fractures, scoliosis, and joint sub/dislocation is more frequent in those with low bone mass or osteopenia.

Secondary Objectives:

In children 2-15 years of age with CP:

(a) To determine the prevalence of low bone mass.

(b) To determine the prevalence of fragility fractures, scoliosis, joint dislocation.

(c) To describe the biochemical disturbances associated with low bone mass.

(d) To examine the relation between bone mass, pain and quality of life scores.

(e) To describe the morbidity associated with fragility fractures.

Hypotheses

1. The greatest contributor to bone mineral content in children with cerebral palsy will be lean body mass (muscle mass). Other factors such as type and severity of CP, use of anti-convulsant medication and calcium and vitamin D intake, which are specific to cerebral palsy will not be significant in explaining bone mass.

2. Children with cerebral palsy will have a state of low muscle mass which in turn will be associated with low bone mineral content, or secondary osteopenia.

3. A state of secondary osteopenia will be associated with fractures, scoliosis, joint subluxations, and pain. Health related quality of life will be related to osteopenia but will not be significant when other factors such as the severity of CP are considered.

Method

The study, including the screening and recruitment of subjects, was approved by the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board (protocol # 02/28E) (see Appendix A). Approval for the study was obtained from the Ottawa Children's Treatment Centre (OCTC) Research Advisory Board (Appendix B). Funding for the study was provided by the CHEO Research Institute and the Ontario Federation for Cerebral Palsy (Appendix C and D)

Study Population:

All children followed at the Children's Hospital of Eastern Ontario or the Ottawa Children's Treatment Centre and who met the inclusion criteria below were eligible for the study. These centres are regional tertiary care centres serving approximately 1.5 million population in Eastern Ontario (CHEO, OCTC) and Western Quebec (CHEO).

The inclusion/exclusion criteria were the following:

Inclusion criteria:

(1) Age 2-15 years,

(2) Diagnosis of CP: Non-progressive motor impairment due to a static encephalopathy in the developing brain initiated either in the pre-natal, peri-natal, or the first 30 days post-nataly.

Exclusion criteria:

(1) current or past steroid use (excluding inhaled or short course oral i.e., less than 5 days)

(2) primary bone dysplasias such as osteogenesis imperfecta

(3) primary growth disturbances such as achondroplasia or growth hormone deficiency

(4) disorders of mineral metabolism (i.e. Rickets)

(5) chronic inflammatory diseases such as active lupus, juvenile rheumatoid arthritis and dermatomyositis

The investigators are interested in generalizing results to all children with cerebral palsy. The study population however, was recruited from the Eastern Ontario-Western Quebec region. The age range defined for the study permitted a wide cross-section of children with CP. Age two years, was felt to be the youngest that participants might experience bone complications of CP and that this would be the youngest that we could justify doing laboratory investigations, x-rays and bone density testing on to look for issues related to bone health. The upper age limit was chosen as we felt that eventually we wanted to follow these children in a cohort for the subsequent three years and that this would allow us time to do that while they were still considered in the pediatric age group (under 18 years). We also felt based on our clinical experience that by 15 years of age most children with CP would have encountered bone health complications if they were going to happen.

Recruitment:

Initially notices announcing the study were placed in the neurology clinic area at CHEO and near the elevators (Appendix E). An initial five children were recruited in this manner. The main recruitment was carried out with the clients of the OCTC. The OCTC client data base was searched for all children with a diagnosis of Cerebral Palsy seen at the centre in any clinic in the year prior to initiating the study. These records were

examined to identify any children who may have died, have inactive files, incorrect diagnoses, or be outside the required age range. The total number of clients identified was 405 and letters of invitation to participate (Appendix F) were sent to each of the client's homes. Additionally, all Quebec clients followed in a CP clinic run from CHEO were considered for the study. These subjects were identified by the physician and nurse running this clinic and names and addresses were provided. A total of 35 potential participants were identified from this clinic and a French language version of the letter of invitation was sent to each client's home. In the original proposal the plan had been to include clients from LaRessource, a pediatric rehabilitation centre in Gatineau, Quebec; however after discussion with the centre and the physician running the CHEO French language CP clinic we felt that most of the clients would be able to be contacted through the above methods already in place. Thus a total of 440 potential participants were identified. Approximately 20 letters of invitation were returned due to having an incorrect address.

A dedicated phone line was maintained for the study and when not directly monitored by a research assistant, it was checked for messages on a daily basis. Subjects leaving contact information were called back as quickly as possible. All participants contacting the study number were assigned an ID number and a master list was kept with this number and their contact information

Once a telephone contact was made the subject's parent or guardian were given information about the nature of the study and any questions were answered. Telephone consent was obtained to review the child's medical chart. An appointment was made for the baseline interview. A package was sent to the family which included a confirmation

of the initial appointment and a request for completion of a three day dietary diary (Appendix G) that they were instructed to complete prior to the baseline visit.

Procedure:

The baseline visits were scheduled on weekdays during the evening or weekend days and were carried out by the investigator or the research nurse. Prior to the interview all subjects received an information letter and consent form (Appendix H) and were asked to read it in private, then pose any questions and, if in agreement, to sign the document. The interview followed the format of the data collection sheet (Appendix I). Any unclear data from the interviews were clarified by the use of the medical chart. The interview was followed by a brief physical examination which focused primarily on growth related parameters. The interview took anywhere from 30 minutes to one hour. The baseline interview collected the following information:

a) Demographic information: age, gender, date of birth, gestational age at birth
b) Medication list: any current medication including name, dose, and duration of treatment. This included vitamins and other complimentary medications.
c) Fracture history: The fracture history form can be seen in Appendix J.
d) Presence and severity of orthopedic complications: scoliosis, joint sub/dislocations and femoral torsion.
e) Family history of osteoporosis
f) History of other medical complications related to CP: vision and hearing impairment, cognitive impairment, feeding dysfunction, reflux, constipation, seizures (excluding febrile seizures).

A number of specific measurements were taken during the baseline appointment, including:

1. The Gross Motor Function Classification System (Appendix K): This measure is a common classification system used for children with Cerebral Palsy (48) and has been applied to all clients of the OCTC. In instances where the GMFCS was not evident in the clients chart the research coordinator or the investigator applied the measure. Both had been trained with a standard video instruction session and had any questions answered by Dr. J MacLean one of the study investigators.
2. The Hoffer scale (Appendix L): Similar to the GMFCS, this scale is a functional scale originally developed for use in children with myelomeningocele (49). The scale was applied at the time of the baseline visit.
3. Knee Height: This was applied as described by Stevenson (50). A standard baby length board used regularly in the neurology clinic was used. This consisted of a metal tape measure mounted on a Plexiglas frame. The subject's heel was placed on a Plexiglas platform at the zero mark and a sliding rule was brought down to their knee which was bent at 90 degrees. An indicator on the sliding rule showed the length and this was recorded to the nearest half centimeter. All measurements were done by the same person. The knee height was then used to estimate body height through the formula: body height =(2.69x knee height)+24.2. The standard error of the estimate is +/- 1.1 cm (50).

4. Height: Measured in centimeters to the nearest millimeter in the fully extended standing body on an SR scale in the OCTC outpatient clinic. All measurements were done by the same person.
5. Weight: Weight was measured on either a Health-o-meter infant scale, Scaletronics wheel chair scale, or SR scale used in the OCTC outpatient clinics to the nearest tenth of a kilogram. Subjects in wheelchairs were weighed on their own when possible but in some cases parents and subjects were weighed together and then the parent alone with the subject's weight being arrived at by subtraction.
6. Tanner staging system (Appendix M): This is a common pubertal staging system used in pediatric practice.
7. Testicular volume: This measure was applied to all males in the study. A Genentech Orchidometer to record the testicular volume in centimeter cubed. The research coordinator was trained by an endocrinologist in applying the measurement

The guardian or child then filled out a series of questionnaires facilitated by the research coordinator or principal investigator. These included the following:

1. The Non-communicating Children's Pain Checklist- Revised (NCCPC-R) (Appendix N): This questionnaire is a standardized and validated measure for assessing both recent and recalled pain in children who are principally non-verbal (51-53). The measure was completed in this study as a retrospective recall of the child's pain in the past two weeks. We asked additional

questions on this form regarding causes of pain and medication use, etc. which can be seen in the Appendix.

2. The Health Utilities Index Mark 2 and 3 (Appendix O): These Health Related Quality of Life (HRQL) scales are widely used and are standardized, validated measures originally developed in Canada and using neonatal intensive care graduates. The HUI2 scale measures seven specific health related domains. One of these domains is a fertility domain and was excluded in this sample as is commonly done when it is not relevant. The HUI2 has eight domains of health. The measure can be applied via a questionnaire or through a facilitated interview. Due to the cost of the test materials we opted in this study to have the research coordinator apply the measure during the baseline interview with the help of the family if needed. Although the use of this method is not recognized as a validated form of application of the model it is essentially equivalent to the short form multiple choice questionnaire available from the HUI Corporation. The HUI2 and 3 have been used in many national and provincial studies of health including the National Longitudinal Study of Children and Youth (54) and the Ontario Child Health Survey (55). Only the HUI3 has been reported on in a sample of children with CP (56).
3. The Caregiver Questionnaire (CQ) (Appendix P): This measure is the only disease specific quality of life measure we could identify at the time of developing the study. The measure has been validated (57) and we contacted the authors to make sure we were applying the scoring appropriately. The

measure consists of four domains that are primarily aimed at functional quality of life.

The family's three day dietary diary was collected at this time. Three day dietary diaries have been demonstrated to accurately determine average daily intake of the variables of interest (58). If not completed they were asked to fill it out and send it back in a stamped envelope provided. The dietary information was entered into a software program called Food Smart, Sasquatch Software Corporation (1994-2001) by one of two research assistants. Two registered dieticians supervised this and provided final analysis of total daily calorie, calcium and vitamin D intake. Adequate dietary intake of calcium and vitamin D were assumed if the child was taking equal or greater than that recommended from the Health Canada Daily Adequate Intakes (AI) 1997. For calcium the AI is greater than 500mg/day for children less than 4 years, 800mg/day for those less than 9 years and 1300mg/day for those 9 and older (http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/ref_elements_tbl_e.html). For vitamin D the AI is 200 IU or 5 mcg / day for all childhood ages (http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/ref_tbl_e.html).

Following the interview the subject was given a study requisition for blood work and x-rays which could be done at that time or at the family's convenience. An appointment was made for bone density testing at that time. Subjects received free parking for the all the study visits as well as a five dollar voucher for the cafeteria.

Blood work and urinalysis was done through the CHEO laboratory. The following blood tests were completed: calcium, phosphate, vitamin D, dihydroxy vitamin D, alkaline phosphatase, parathyroid hormone; as well as the following urine tests:

phosphate, N-telopeptides, and calcium/creatinine ratio. These are all markers of bone metabolism.

X-rays were done on standard radiography equipment at CHEO. The children had three x-rays done including a (a) bilateral hip, (b) a full spine anterolateral and lateral views and (c) wrist for determining bone age. The x-rays were all read by a single radiologist involved in the study. A quantitative report of the percentage of hip subluxation (migration percentage) (59) and scoliosis (Cobb angle measurements) was indicated for each x-ray. A bone age was indicated. The x-rays were not viewed in a blinded fashion.

Bone mineral density was completed on a GE Lunar Digital Fan Beam Prodigy dual energy x-ray absorptiometry system by a single technologist at the CHEO. The precision of the machine is +/- 0.01 gram/cm^2 (+/- 1%). Quality assessments are done daily using a phantom and patient studies are performed three days per week. The child had whole body, lumbar spine, and femoral neck determinations done. The studies were all interpreted in a non-blinded manner, by the same radiologist who also interpreted the x-rays. Contrary to other studies in children with CP (34) only one child could not be positioned adequately for hip bone mineral density determination but lumbar spine and total body were felt by the radiologist to be adequate. Two children had hardware in the proximal femur area but not directly in the area of the femur neck, but due to possible influence on the total body bone mineral density their results were not used in the analysis. Despite arranging for possible sedation with anesthesiology there was no child who needed sedation.

A fragility fracture (FF) was defined as any fracture that occurred with minimal force or with the equivalent or less force than falling from a standing height on to a level surface (28) or any vertebral compression fracture. Each fracture history was transcribed so that they were free of identifying information and any indication of the severity of CP, and distributed to an orthopedic specialist, a neurologist and an endocrinologist to determine whether they felt the fracture was a fragility fracture (see Appendix Q). These clinicians had no knowledge of the bone density testing at the time of fracture rating. All other fractures were typical fractures. Children having either a parent reported scoliosis or joint complication, or a FF, or a finding of scoliosis, joint dis/subluxation or compression fracture were said to have a bone complication. If a parent reported a complication which was not substantiated by x-ray then the parent report was discounted. Only spinal curves greater than 20 degrees were considered clinically important and counted as scoliosis (60, 61).

Statistical Analysis:

All data were entered onto data collection sheets and then transferred into an SSPS version 12 database. All data were screened for missing variables and inaccuracies. Analysis was carried out using SSPS version 13. All correlations will be presented with confidence intervals and p value in the form (lower limit of CI, upper limit of CI, p value). All means will be presented with standard deviations and ranges in the form (*s.d.*, range) unless otherwise indicated. In all cases actual p values will be presented except where they were less than 0.001 at which point threshold values are presented. All regression equations were done using the stepwise regression command with a probability for inclusion set at p=0.1.

The original sample size calculation was based on a pragmatic approach to linear regression techniques by estimating approximately 10 subjects for each independent variable used in the regression equation. In the planning it was felt that up to ten independent variables might be employed so the target enrollment was 100 subjects. This approach was used due to the exploratory nature of the study.

The analyses and results are divided into four sections (see conceptual diagram of the study Figure 3.) Section one of the results describes the sample in detail. Descriptive statistical methods were used to characterize the variables for the first section of the results. The second section of the results is based on the first objective of the study, to determine which factors are the most significant contributors to bone mass in children with CP through univariate techniques and multiple linear regression. Section three of the results explores the relationship between measures of osteopenia and orthopedic complications, pain and quality of life measures through univariate and multiple linear regression. These latter variables are viewed as potential outcomes of having low bone mass or osteopenia and as such are referred to for simplicity as outcome variables, but it is recognized that the temporal and causal relationship is not established in a cross-sectional study. Section four of the results describes analyses done with bone mineral content measures from the lumbar spine.

Variables:

The following variables were used in the analyses:

Independent Variables:

Age: Continuous variable calculated at time of baseline interview or time of bone densitometry.

Height and Weight: continuous variables measured as described above. In those children where standing height was impossible to measure accurately due to joint contractures and scoliosis, knee height was converted to an estimated height as described above.

Type of CP: A nominal variable that was categorized into spastic quadriplegia, spastic diplegia, spastic hemiplegia, or dystonic.

GMFCS: An ordinal variable described above. Because of the small numbers in the GMFCS groups II, III and IV, the children from group II were reassigned to group I, as both of these classes are children who are independent ambulators without assistance. Group III and IV children were placed together as these children both ambulate with assistive devices to some extent; whereas GMFCS level V do not weight bear at all.

Anti-convulsant use: An ordinal variable categorized as never, past or current use of anti-convulsant medication. No distinction is made for type of medication or length of treatment time in the analyses.

Family history of osteoporosis: This is an ordinal variable that will be categorized as none, either paternal or maternal family history, or both.

Calcium intake: This was both a continuous variable, of average daily calcium intake in milligrams, and a dichotomous variable of normal or below normal daily intake of calcium.

Vitamin D intake: This was analyzed both as a continuous variable, of average daily vitamin D intake in micrograms, and a dichotomous variable of normal or below normal daily intake of vitamin D. The values used to determine this are described above.

Total body lean body mass (TBLBM): This is a continuous variable measured in kilograms derived from DEXA measurement. This represents the body's total muscle

mass. A z-score can be derived for TBLBM using height, gender and pubertal stage matched controls (14). Formulas for calculating this z-score can be found in Table 1. This z-score provides a continuous variable reflecting the muscle mass relative to other children. A z-score of -2 is used in this study to define someone who has abnormally low muscle mass (14).

Total body fat mass (FBM): This is a continuous variable measured in kilograms derived from DEXA measurement.

Dependant variables:

Bone mineral content (BMC) and BMC z-score: This is a continuous, normally distributed variable measured in kilograms derived from DEXA measurement. This represents the body's total bone mineral content. A z-score can be derived for TBBMC using height, TBLBM, gender and pubertal stage controlled formulas based on a normal sample of 646 white children aged 5-18 years old (14). Formulas to calculate the z-score can be found in Table 1. This z-score provides a continuous normally distributed variable reflecting the bone mineral content relative to other children (see Figure 4). A z-score of -2 was used in this study to define someone who has abnormally low BMC (14). In the third stage of the results this variable was used as a predictor (independent) variable for analyses examining the 'outcome' variables.

Bone mineral content/lean body mass ratio (BMC/LBM ratio) and BMC/LBM ratio z-score: This is a continuous, normally distributed variable derived from a ratio of TBBMC to TBLBM as described by Hogler (15) (see Figure 5). A z-score was derived for this sample from charts of height and gender matched ratios taken from a normal sample of 459 white subjects age 3-30 years old (15). This z-score provides a continuous, normally

distributed variable reflecting the bone mineral content relative to other children. A z-score of -1 was used in this study to define someone who has abnormally low BMC (15). In the third stage of the results this variable was used as a predictor (independent) variable for analyses examining the 'outcome' variables.

Lumbar spine bone mineral content (LSBMC) and LSBMC z-score: This is a continuous, normally distributed variable measured in kilograms derived from DEXA measurement. This represents the regional bone mineral content of the L2-L4 lumbar vertebral bodies. A z-score can be derived for LSBMC using height, TBLBM, gender and pubertal stage controlled formulas based on a normal sample of 646 white children aged 5-18 years old (14). Formulas to calculate the z-score can be found in Table 1.This z-score provides a continuous normally distributed variable reflecting the bone mineral content relative to other children. A z-score of -2 was used in this study to define someone who has abnormally low LSBMC (14).

Osteopenia categories: These categories have their origins in the mechanostat theory described in the literature review. The categories used in this study correspond to those described by both Crabtree (14) and Hogler (15). The use of the TBBMC z-score and TBLBM z-score are used to define four possible osteopenic states: Normal (LBM for ht > -2 *s.d.* and BMC for LBM >-2 *s.d.*), Primary osteopenia (LBM for ht > -2 *s.d.* and BMC for LBM <-2 s.d), Secondary osteopenia (LBM for ht < -2 *s.d.* and BMC for LBM >-2 s.d), or Mixed osteopenia (LBM for ht < -2 *s.d.* and BMC for LBM <-2 s.d). In the case of the BMC/LBM ratio the categories are identical except the cut-off value for a low BMC for LBM was defined as -1 *s.d.* as described by Hogler (15).

'Outcome' Variables

Scoliosis: This is a dichotomous variable defined as either no scoliosis (less than 20 degrees) or scoliosis (greater than 20 degrees) as measured by the Cobb method on standard spine x-rays.

Joint dislocation/subluxation: This is an ordinal variable which is categorized by normal (migration percentage <5%), subluxed (5-99%), and dislocated (>99%) (59). No child in this study had completely dislocated hips so the variable was dichotomized to normal or subluxed hip.

Fragility Fracture: This variable is a continuous count variable. Defined as a fracture occurring with minimal force. No child had vertebral compression fractures in this study.

Any bone complication: This variable is a dichotomous variable reflecting whether a subject had no bone complications or any bone complication (a fragility fracture, scoliosis or joint subluxation).

Number of bone complications: This is a continuous count variable of the number of bone complications. A score of 0 to 4 was possible.

Pain Score: A continuous variable ranging from 0 to 90 taken from the NCCPC-R described above. Higher scores represent worse pain.

Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) score: A continuous variable. HUI2 scores can range from 0 to 1.0 and on the HUI3 from -0.34 to 1.0 with zero reflecting a value associated with death and 1.0 being perfect health. In the case of the HUI3 health states with a value worse than death can be obtained.

Caregiver Questionnaire (CQ): This is a continuous variable with a range from 0 to 10 with higher values representing worse state of quality of life.

Study Termination:

Children were not offered entry into a cohort study to measure bone density as the resources both financially and logistically were not in place to do so. Instead of follow-up interviews the families were sent a letter indicating any abnormal findings identified during the study. This letter also indicated there would not be a follow-up portion to the study and also thanked them for their participation. Participants were given an option to receive a summary of the results of the study which have not yet been released. No child had abnormal tests that required intervention or referral beyond the care they were currently receiving.

Results

A total of 87 people contacted the study line for more information, 77 of these from the OCTC and CHEO clients and ten from the French language clinic. From these 87 potential participants 53 met criteria and agreed to participate. Thirty-four potential subjects were not included. The vast majority of these latter subjects either could not be re-contacted, canceled, or did not show up for their scheduled appointments. Two children were excluded for not having the correct diagnosis and a further two children were excluded from the study because they did not meet the age requirements for inclusion. No child was excluded due to the predefined exclusion criteria. Figure 6 demonstrates a flow diagram of the subjects enrolled in the study.

Six participants gave written consent completed various portions of the study, but never came to the baseline interview. For these six participants a chart review and phone call to parents was used to obtain their data.

Section 1. Demographic characteristics:

Of the 53 children enrolled in the study, there were 29 females and 24 males with an average age of 9.0 (*s.d.*=3.8, *95%CI:*2.5-15.8) years. Forty patients were Caucasian, four black and five indicated another race with the remainder not collected adequately due to the subject not presenting for the baseline interview (see Table 2).

Cerebral Palsy and associated problems:

As can be seen in Table 1, the number of children per GMFCS levels were represented as follows: level I= 46%, level II=4%, level III=10%, level IV=12% and level V=28%. Most subjects had spastic hemiplegic type of CP (48%) followed by spastic quadriparesis (40%), and then spastic diplegia and dystonic CP (both 6%).

Participants had a gestational age ranging from 26 through to 42 weeks with 51% participants born at term and 49% born prematurely. In regards to the etiology of the CP, the majority of caregivers reported that the cause of the CP was unknown (30%), 21% reported the cause to hypoxic ischemic events during labour and delivery, and 11% reported the cause to be a stroke in utero. Infection in utero, cerebral malformations, intra –ventricular hemorrhages and non-specific in utero events each accounted for 4% of the etiologies. Four percent of the sample had post-natal causes for their CP with hyperbilirubinemia and neonatal meningitis noted.

Cognitive impairment was present in 45% of the sample. Parents' estimates of mental age varied from infancy (months old) through to just below chronological age. Feeding difficulties and reflux were each problem in 19% of children. In the children with feeding problems a g-tube was used in eight children while pureed foods and avoidance of milk products were used in the other children. Medical treatment of reflux

was needed in 8% of children and included antacids, prokinetic agents and in one child an esophageal fundoplication. Constipation was noted in 23% of children. Twenty-two children had visual impairments and only three had hearing impairments.

Seizures were noted as an associated problem in 36% of children, with 13% of children using anti-convulsant medication in the past and 19% (n=10) on medication at the time of the study. Of those ten children with a current seizure disorder the majority had seizures well controlled with less than one seizure per month, but one child had daily seizures and two children had weekly seizures. The ten children with current seizure disorders had used from one to six anticonvulsant medications and had been on treatment for as long as eight years. In the children with seizure disorders, both current and past, the most common medications were: valproic acid (n=7), phenobarbital (n=6), clobazam (n=5), topiramate, vigabatrin, carbamazepine, phenytoin (each n=2), ACTH, rivotril, zonisamide and the ketogenic diet (each n=1).

Other medications including vitamins and herbal medications that children were using were recorded as we wanted to understand how many children might have been receiving supplemental calcium and vitamin D. The most common medications used were multivitamins of different variety in 25% of subjects. Calcium and/or vitamin D specifically was taken by an additional 8% making a total of one third of children getting some supplementation of calcium and vitamin D. Bowel medications (other than antacids described above) were taken by 8% of subjects. Asthma and anti-spasticity medication were taken by 6% of children each, and urinary tract prophalaxis, pain and sedative medication by 4% each. Other medications used by at least one child included:

anti-depressant, herbal medication, cortisone cream, carnitine, digestive enzymes and ditropan.

In order to determine if this sample was similar to those followed at OCTC who did not enroll in the study a random sample of 50 patients was taken from the non-responders and chart review was completed. The review focused only on those aspects which could be found in the charts up to the mid point of enrollment (Feb 2002). This included: age, gender, type of CP, and GMFCS. From the 50 randomly selected three were discovered not to have CP and four files were not found leaving 43 subjects in the comparison group. Table 3 shows the characteristics of the two groups and statistical comparisons. The average age was similar, as were the type of CP and the severity of CP as demonstrated by the GMFCS. The number of females in this group was low compared to the study sample.

Growth parameters, dietary information and other parameters impacting bone health.

Forty-four children had the physical examination required for the study. The weight and height percentiles for age were assigned using standard growth curves by the software program Genencalc (ver 1.1 2001, Genentech Inc.). In 34 subjects both height and knee height were taken and the knee height converted to a height estimate based on validated formula (50). The correlation coefficient between the two measures in this sample was 0.722 (*95%CI*:0.602, 0.842) which is less than described in the original study (50) but still strong. Therefore, for those five children who could not be accurately measured standing or lying straight a knee height was recorded and converted to an estimated height using the method described by Stevenson (50)(see methods) that was used in the rest of the evaluations. In the whole sample the mean weight percentile was at

46th percentile (*s.d.*=32, *range*= 0-100) and the mean height percentile was 28 (*s.d.*=29, *range*=0-93). The frequency bar chart shows a moderate leftward skew to the data in both distributions suggesting the children were relatively small for age (see Figure 7).

Of the 26 males in the study 22 had Tanner staging completed. Of the 27 females 21 had Tanner staging completed. The results are seen in Table 4. Seventeen males had testicular volumes recorded.

Three day dietary data was received from 28 participants. Despite telephone reminders other participants did not return their forms. Data generated from the nutrition software showed an average daily calcium intake of 1215.7 mg (*s.d.*=500.2, *range*=334-2386). Average daily vitamin D was 197.0 (*s.d.*=145.6, *range*=3.3-557). These totals included all supplementation that the patients were taking in vitamins and supplemental nutritional products. The number of children taking less than the recommended AI from Health Canada of calcium was 46%. A similarly concerning number of inadequate diets in vitamin D were noted in 61% of subjects.

Two thirds of subjects indicated no family history of osteoporosis on either side. Nineteen percent had either a maternal or paternal history of osteoporosis and the remainder did not know. No one indicated a family history of osteoporosis on both sides of the family.

Blood and urine laboratory indicators of bone health were examined in only 26 children and 23 children respectively. Many subjects did not go to the laboratory at their second visit presumably due to inconvenience, but additionally, people refused to have the blood samples done to avoid unnecessary pain in their children. Few values fell outside the normal range on any of the tests. One child had high serum calcium, one

child each a high and low serum phosphate, two children low alkaline phosphatase, and two children a low parathyroid hormone. Ten children had high serum vitamin D levels and six high 1, 25 dihydroxyvitamin D. Although those subjects with a high vitamin D level had higher daily vitamin D intake this did not reach statistical significance ($p>0.05$). Calcium creatinine ratios in the urine were elevated in six children. Urine Cross-linked N--telopeptides (NTX) levels appeared to be markedly elevated in every child. It is felt that this results from a technical issue but have not been able to determine the exact reason with the laboratory.

Health related quality of life and pain issues

Forty-seven children had a parent or caregiver complete the HUI's and Caregiver Questionnaire (CQ) at the baseline interview. Ages ranged from 2.5 to 15.8 years (*mean* = 9.1, *s.d.*=3.9). In this sample HUI2 utility scores ranged from 0.07 to 1.00 with a mean of 0.567 (*s.d.*=0.295). The HUI3 scores ranged from -0.340 to 0.973 with a mean of 0.328 (*s.d.*=0.444). CQ scores ranged from 0.1-7.1 with a mean of 3.0 (*s.d.*=1.8). Pearson correlation between the utility score of the HUI2 and the full scale CQ scores was highly statistically significant (r=-0.801, (*95%CI:*0.714, 0.888)) as was correlation between the HUI3 and the CQ (r=-0.754, (*95%CI:*0.656, 0.852)). The HUI scores were also highly correlated with each other (r=0.869, (*95%CI:*0.795, 0.943)).

HRQL scores were poorer with increasing severity of CP. Mean HUI3 scores were 0.706 and -0.202 for GMFCS level I and V, respectively. In general the HUI scoring system is considered to have a clinically significant difference value of 0.03 which clearly is small compared to the magnitude of difference between these two groups of children representing opposite ends of the spectrum of CP. CQ values increased with

increasing CP severity with a mean of 1.94 in GMFCS I and rising to 4.13 and 4.76 in levels IV and V respectively. Kendall's tau b correlation was used to examine the relationship of GMFCS and the HRQL measures, but due to the small numbers in the GMFCS II and III levels these were dropped for the analysis. Both HUI2 and 3 showed strong negative correlation with the GMFCS level with tau b=-0.702 ($p<0.001$) and tau b= -0.754 ($p<0.001$) respectively. The CQ was positively correlated with GMFCS (tau b=0.568, $p<0.001$).

Pain questionnaires were completed by 44 parents/caregivers for their children. Only eight children were reported as not having regular painful episodes. Of the other 36 subjects 19 children had pain once per month or less, eight had pain weekly, and nine had pain daily or several times per day. All parents of children with regular pain completed the NCCPC-Revised Edition. The score can range from 0 to 90 with greater scores reflecting more significant or frequent pain. In the children with pain episodes the scores ranged from 0 to 62 with a mean of 13.5 (*s.d.*=17.5). Looking at the children by CP severity showed that more severe pain appeared to accompany more severe CP. Pain scores on the NCCPC went from a mean of 7.4 (*s.d.*=12.8, *range*=0-47) at GMFCS level I, to 11.2 (*s.d.*=25.0, *range*=0-62) in level IV, and 16.9 (*s.d.*=18.9, *range*=0-58) in level V. This was not a statistically significant ($p>0.05$) difference using a non-parametric correlation analysis. Also frequency of pain varied in a similar manner as reported by caregivers with only 1/20 children with daily pain in GMFCS level I compared to 5/12 in level V. Sixteen children never used pain medication, and 15 used it less than once per month. Five children used pain medication once per month and five used it weekly.

Only two children were taking daily pain medication despite nine parents reporting daily pain in their child.

Discussion with a health care professional about pain had occurred with 26 of the 44 caregivers who completed the pain questionnaires. Causes of pain from the caregiver's perspective are included in Table 5. In most cases pain was discussed with a specialist (85%) and/or a family doctor (46%). Only five subjects spoke to a nurse about pain and three to an occupational or physical therapist. Approximately half of the caregivers felt they received an adequate response to their questions with the remainder unsure or negative about the interaction. In regards to the significance of their child's pain compared to "other problems" their child had to deal with, the majority of parents (62%) rated it as least significant and only two parents rated pain as the most significant problem.

Five children in this sample (9%) were admitted to hospital specifically for pain at some point in their life. Of those admitted, none of the children turned out to have a bone related complication as the cause of the pain. One child had severe spasticity, one was discovered to have an ear infection, one a shunt malfunction, one gastro-esophageal reflux and one urinary retention.

Bone complications and factors impacting on bone health:

Forty-one children underwent the x-ray studies required of the study. Significant scoliosis was present in six patients by x-ray and another eight by parent report only. Unfortunately these eight patients did not have x-rays to support the parent's reports. Two parents felt their child had scoliosis but on x-ray the curve was below the clinically significant 20 degree mark. The scoliosis in those x-rayed ranged from 20-80 degrees and

no one in the study had had scoliosis surgery. Joint subluxation was noted in ten children on x-ray and an additional four by parent report. In six children the hip subluxation was unilateral and in four bilateral. Ranges for both right and left hip subluxation were from 20-50% of the femoral head displaced from the acetabulum. Three parents were inaccurate in their reporting of joint dislocation suggesting their child had problems which were not demonstrated on x-ray. No child had a vertebral compression fracture.

Fractures were reported in seven children (13%) during the interview. Of the seven children who had fractures a total of ten fractures occurred. One child had three fractures and another had two. Six of these fractures in five different children (9.4% of total sample) were considered to have occurred with minimal force and were defined as fragility fractures (FF). There was complete agreement between the physicians in the clinical rating in eight of the total of ten fractures (four FF and four typical fractures). In one fracture two physicians agreed that the fracture was a FF and the other was unsure, and in one fracture two physicians rated it as a typical fracture whereas one rated it as fragility. A description of each fracture can be seen in Appendix Q and fractures #1, 5, 7-10 were considered fragility.

The FF occurred at ages ranging from 7.3-15.5 years. Three children had a total of four femoral shaft fractures, one child a tibia/fibula fracture and one child a fracture of one of the intrinsic foot bones. The fractures took up to 14 days to diagnose in one child. Three children required hospitalization either to diagnose or treat the fracture. In the child with the foot fracture only observation was needed, while in the other three children closed reduction and casting were required. One child had a cast for three months. All four children were said to experience their worst pain as a result of the fracture and all

needed regular analgesics daily. Two children returned to their regular functioning by six weeks after the fracture and one child was never able to use a standing frame again. On a five point scale of the impact of the fracture on the child compared to other medical difficulties they had to deal with (with 1 being the least impact), the average score was two (*range*=1-3). One parent did not complete these portions of the questionnaire.

Of the five children (3 females) with FF there were several defining characteristics. Four of the children had spastic quadriparesis and one was described as a dystonic CP type, but all had a GMFCS at level IV or V. The children had relatively normal weights for age but were all restricted in their height with the height percentile all below the 15th percentile. They all had low HUI and high CQ scores. Two children reported pain on a regular basis but in one of these children it was severe with a score on the NCCPC of 35. Only one child had a known history of osteoporosis in the family. None of these children had any blood work that would alert one to the presence of poor bone health. In only two children the vitamin D levels were high. Only one child with a FF filled out a dietary questionnaire so this was not useful in assessing risk. Of the two children taking anti-convulsants one was on phenytoin and the other on a combination of clobazam and valproic acid. The other three children had never been on anti-convulsants.

Fifty one percent of children had some form of bone complication identified in the study compared to 49% with no bone issues. Of the children with bone complications 56% had only one complication, 26% two complications and 15% had three. Only one child (4%) had four complications (both hips subluxed, scoliosis and a FF).

Bone age was completed in 41 children. In 19 of these children the result was a bone age less than chronological age. The mean bone age for this group was reduced by

one year with a range from -0.1 to -4.3 years. In the remainder of the children it was either equal to or greater than the chronological age with a range of 0-2.2 years.

Section 2. Bone Mineral Density

Forty-four children had bone mineral density testing completed for the study. No child had previously had bone mineral density testing done for other reasons. One child had bilateral metal plates in his proximal femur and so the total body BMC and LBM values were not used due to possible over estimation due to metal artifact.

In order to establish whether LBM was the body parameter of greatest importance in predicting BMC, multiple bivariate correlations were done to examine the relationship between total body BMC and LBM, height, weight, age and FBM (see Table 6). This shows that LBM is the most highly correlated factor, followed by weight, height, age and finally FBM. Similar relationships were seen with the lumbar spine, and the femoral neck BMC. In the case of the femoral neck the regional LBM in the corresponding leg was even more highly correlated than any other variable.

A multiple regression equation was used to determine the relative importance of these related variables with the additional inclusion of gender. The variables were entered using a stepwise approach with the criteria for inclusion set at $p<0.1$. These results are shown in Table 7. The best fit model included LBM which accounted for the greatest variance in the model ($R^2=0.85$), FBM ($R^2=0.02$), weight ($R^2=0.06$), and gender ($R^2=0.01$). For the lumbar spine BMC a similar model was generated however only LBM and gender remained significant variables in the model. In the case of the femoral neck BMC model the best model was either TB LBM alone or left leg regional LBM alone.

Total Body Bone Mineral Content

Given the similarity between this study sample and the normal population described by Crabtree, in the strength and order of independent variables in the regression analysis of bone mineral content, we felt comfortable using the equations generated from the Crabtree study to generate z-scores for LBM for height, and predicted TBBMC for LBM for the subjects in our study (see Methods section). Using the classification, which will be referred to as the Crabtree system (14), the children were then grouped into four possible osteopenic states (see methods).

The total group was noted to have a mean LBM z-score of -0.07 (*s.d.*=2.08, *range*=-4.00-4.40) and a TBBMC z-score of -1.19 (*s.d.*=1.90, *range*=-6.5-3.4). As a group they would be classified as normal (not osteopenic) with a LBM appropriate for body size and a BMC within normal for LBM. Individually however, the subjects were quite heterogeneous with 24 subjects classified as normal (normal LBM and TBBMC z-scores), 11 classified as primary osteopenia, five as secondary osteopenia and three as mixed. The characteristics of each of these groups will be discussed and the graphs of the LBM z-scores and BMC z-scores as well as a tabular form of these results can be seen in Figure 8 and Table 8 respectively.

The 15 girls and 9 boys classified as normal (not osteopenic) had an average age of 10.2 years (*s.d.*=3.4, *range*=3.3-15.8). The majority had hemiplegic type CP (65%), with spastic quadriparesis (30%) and diplegia (4%) accounting for the rest. Most had a GMFCS of I (76%) or III (19%). Only one subject was taking anticonvulsant medication with 78% never having taken these medications. A familial history of osteoporosis was present in 25%. None of these subjects had had a FF, but two subjects did have a history

of four fractures, however, these were all judged to be from considerable force that would reasonably cause fracture in a normal child. No orthopedic complications were seen in 63%. In the rest of the group (nine subjects) with bone complications the average number of complications was 1.2. Only 9% had clinically significant scoliosis and these were mild and only 12% had joint subluxation.

The five children classified as having secondary osteopenia had an average age of 10.7 (*s.d.*=4.0, *range*=4.7-15.5) with four females and one male. Three children had spastic quadriparesis with one diplegic and one hemiplegic subject each. Most children were GMFCS III (3 children), with one each at GMFCS levels I and V. One child was taking anti-convulsants and one had in the past. Only one child had a known family history of osteoporosis. One of these subjects had had a FF but only three had at least one orthopedic complication.

Eleven children were defined as primary osteopenia and most were male (73%). These children tended to be younger at 6.0 years of age (*s.d.*=3.5, *range*=2.5-13.2). Most of these children were spastic hemiplegia (55%), with spastic and dystonic quadriparesis making up 18% each. These children were spread quite evenly across the GMFCS levels, and only 2 (18%) were currently taking anti-convulsants with the rest never using these medications. Two-thirds had no family history of osteoporosis. One of the children had a FF and also had scoliosis and joint subluxations. This child had a very low TBBMC z-score of -4.5 and had a LBM z-score almost in the abnormal range at -1.8 thus almost appearing to be more of a mixed osteopenia case. Only one child in this group had a lower z-score but he was young at 2.5 years and may be at high risk for fracture in the future. Most children in this group had at least one bone complication

(64%) with the average number of bone complications of 1.7. Only one child had significant scoliosis and a total of seven hips were subluxed.

The mixed osteopenia group consisted of only three children, a 10 year old girl, and a 9 and 13 year old boy. All had spastic quadriparesis with GMFCS level V. One had never been on anti-convulsants and the other two were currently on them. One child had a FF. All children had bone complications with the children not having the FF suffering from scoliosis (both children) and bilateral joint subluxations (one child).

As described in the introduction, another method, of examining BMC in relation to LBM is to generate a ratio of these two variables. Normal reference ranges with standard deviations are available to generate z-scores controlling for gender and height, from this point on referred to as the Hogler system (see Methods). Using this classification system only six patients were classified differently than the system by Crabtree (see Table 9). In three cases called normal under the Crabtree system, the subjects were called primary osteopenia using this system, and likewise three called primary osteopenia in Crabtree system were normal in the Hogler classification. Regardless, all had borderline results in both classification systems with z-score values very near the cut off values of -1 or -2. None of these subjects had FF and 5/6 had no bone complications at all. The exception had a significant left hip subluxation. Thus, although six subjects moved categories, an equal number moved into pathologic categories as moved out. All were between the primary and normal groups, and all sat on the borderline of these cutoff values in both classification systems.

Yet another way to view the utility of such a classification of osteopenia is by treating fragility fracture as a gold standard of osteopenia, and determining the sensitivity

and specificity of the classification using different cut off values for defining someone as having osteopenia. In this sample the children who experienced FF all had either TB BMC or LBM z-scores of less than -2.5 *s.d.* below the mean. Table 10 (a) and (b) demonstrates the sensitivity, specificity, positive predictive value and negative predictive value of using a cut off value of -2 *s.d.* versus -2.5 *s.d.* for our sample with all osteopenic groups put together. Lowering the cut off value any further than this would eliminate two children with FF thus lowering the sensitivity considerably.

Risk factors and bone mineral content

The finding that most of the children with CP in this sample were classified as primary osteopenia or mixed osteopenia implies that there is something intrinsically abnormal about the bone itself that is creating a state of low bone mass. Given this, the next approach was to see what additional factors, especially those specific to CP, might be impacting on bone mass in this sample. Two approaches were taken to examine the impact of factors other than LBM on BMC. The first approach used the previously calculated TB BMC z-scores as the outcome (or dependent variable), and the other approach used the ratio of BMC/LBM as the dependant variable, in linear regression models with factors specific to CP as independent variables. Initially, multiple bivariate correlations or comparison of means between groups were performed with known possible risk factors for low bone mass. The significant variables were then used as independent variables in the linear regression equations.

Univariate analysis

The factors traditionally and theoretically felt to contribute to bone mass and collected for this study included: gender, race, family history of osteoporosis, use of anti-

convulsant medication, calcium and vitamin D intake. In addition some factors specific to children with CP such as type of CP and GMFCS were used. The results of the analyses are presented in Table 11.

No significant difference in the mean TBBMC z-score or BMC/LBM ratio were found between those with/without a family history of osteoporosis, race, or status of anti-convulsant use or adequate/inadequate intake of calcium and vitamin D (all independent sample t-tests non-significant). In addition to the dichotomized variable of calcium and vitamin D intake a Pearson correlation analysis was done with the TBBMC z-score and BMC/LBM ratio and average daily calcium and vitamin D intakes. Initially the correlation was significant however examining the scatter plots of TBBMC to vitamin D and calcium showed one outlier with very low levels of calcium and vitamin D intake and a very low TBBMC z-score and BMC/LBM ratio. This patient presumably had osteomalacia due to poor calcium and vitamin D intake or rickets, however his serum calcium was high and he had a normal PTH. When this subject was excluded there was no relationship between calcium and vitamin D intake and BMC z-score.

Gender showed a significant difference with males having a lower BMC z-score and BMC/LBM ratio than females ($p=0.002$). In previous studies the ratio of BMC/LBM has been shown to increase with age, especially in females (22, 23) so the analysis was performed on the whole sample and showed a significant correlation of age with both TB BMC z-score ($r=0.505$, (*95%CI:*0.373,0.637), $p=0.001$) and BMC/LBM ratio ($r= 0.638$,(*95%CI:*0.520,0.756), $p<0.001$). Examining the scatter plots of BMC z-score against age in males and females separately it appeared that the effect of age is only evident in females, and then doing analyses separately for males and females showed that only in

the latter group is age positively correlated to BMC z-score (r=0.623,(*95%CI:*0.471,0.775), p=0.001).

Correlation with GMFCS using a non-parametric test showed that higher GMFCS level was associated with lower BMC z-score (tau b= -0.352, p=0.006) and BMC/LBM ratio (tau b= -282, p=0.025). The statistical significance of this relationship was also tested comparing the mean BMC z-score between level I and V and this just reached statistical significance at p=0.05.

Thus, for the regression equations the GMFCS, age, gender and an interaction term of age x gender were used as the main predictor variables for the model.

Regression equations

The regression model analysis is shown in Table 12. GMFCS (R^2=0.0.18), age (R^2=0.34), and gender (R^2=0.12) were all important predictor variables for TBBMC z-score. No interaction of age and gender was noted when the interaction term was included in the model as both the model fit and coefficient for the interaction term were not significant. Of note, the regression equation changes very little when excluding the one child that appears to be an outlier due to extremely low total body BMC z-score and total body LBM z-score, thus the model shown in Table 12. includes this child. The results are essentially identical when the dependent variable is the ratio of BMC/LBM (results not shown).

Section 3. Outcomes of low bone mineral content

Comparisons between those with and without bone complications

This section will examine is the relationship between low bone mass and orthopedic complications, pain and quality of life. Thus, a number of univariate and

bivariate analyses were completed to understand the relationship between BMC and pain, HRQL, and bone complications. These results can be seen in Table 13.

Comparing groups with and without joint subluxation on mean BMC z-score and BMC/LBM ratio showed that those with a subluxation had lower mean values for both measures of BMC. There were no differences in BMC in either scoliosis or the combined bone complication measure. Likewise, there was no statistically significant correlation for pain scores and BMC z-score ($p=0.329$) or BMC/LBM ratio ($p=0.267$) although the direction of the relation was for greater pain in those with lower BMC. For BMC z-score the HUI 2 ($p=0.020$) and HUI 3 ($p=0.043$) both showed a significant relation with lower HRQL scores in those with lower BMC z-score.

The number of bone complications, pain and HRQL were tested between different osteopenia groups. Complications were compared between the normal and all osteopenia groups combined, between the normal group ($n=24$) and the primary osteopenia group ($n=11$) and the normal and secondary osteopenia groups ($n=5$). Given the small number of subjects in the mixed group, comparison of means or Chi square testing was not reliable. Thus, for the purposes of exploring this relation, we have done comparisons including this group combined with the other groups for each comparison. These results are shown in Tables 14, 15, and 16.

Comparing the normal and primary osteopenic groups showed that proportionally a greater number of subjects had bone complications and joint subluxation if they were osteopenic. Scoliosis was not more frequent in the primary osteopenia group. No other significant differences were noted between groups unless the mixed osteopenics were added to the primary group. In this case, some of the HRQL measures showed a

significant difference, but it must be noted that the mixed osteopenic were all GMFCS V and hence had low HRQL scores on that basis alone. There were clinically important differences noted in pain scores, number of bone complications and joint subluxations between the groups but none of these reached statistical significance.

Comparing the normal to secondary osteopenic group created problems in statistical testing as cell counts were quite small in many of the 2x2 tables, and small numbers made comparing means through a t-test of questionable validity. Using Fisher's Exact test however to accommodate small cell counts shows no significant difference between groups on joint subluxation or all orthopedic complications. Scoliosis is more frequent in the secondary osteopenic group but only when the mixed group was added. As noted above, important clinical differences appeared between the groups with the osteopenic group having greater number of bone complications, higher pain scores, and poorer HRQL. HRQL scores between groups became significantly different when the mixed group was combined with the secondary osteopenic group.

When comparing the normal group to all the osteopenic groups combined, (primary, secondary and mixed grouped together) the results were similar to what is noted above with clinically important differences between the groups noted in all variables: osteopenic children had greater bone complications and pain, and worse HRQL than normal children. Several results showed statistically significant results including: the proportion of children with bone complications and joint subluxations, in addition to HUI 2 and 3 values.

Regression models for pain and quality of life

In most of the above analyses HRQL measures were related to the different measures or BMC (BMC z-score and osteopenia class). Recalling the previous results (see above) on HRQL measures that showed that HRQL is related to severity of cerebral palsy as measured by the GMFCS, and that GMFCS is also related to BMC z-score, these two factors were included in a regression model for HRQL to understand their individual contribution. The results of the model for both the HUI2 and 3 are shown in Table 17. The model including BMC z-score did not explain the variance in the HUI3 or the HUI2 as demonstrated by non-significant R Squared change of the models with this term included and the lack of significance of the beta coefficient in the model. Thus, low BMC z-score did not appear to have an additional important role in explaining HRQL in this sample when controlling for severity of CP.

Section 4. Regional Bone Density

Similar to the TB BMC analysis, Crabtree (14) also described a method to calculate z-scores for the lumbar spine (LS) BMC. Using these equations z-scores were derived for all the subjects in this study. The mean LSBMC z-score was -0.33 (*s.d.*=1.36, *range*=-3.46-2.81). The LS BMC z-score and the TB BMC z-score were positively correlated (r=0.614, (*95%CI:*0.493,0.735)). However in nine cases (21% of the sample) the LS BMC z-score did not agree with the total body BMC z-score and would have changed the classification of osteopenia. Furthermore, in the case of one child with FF in the primary osteopenia group, the LS BMC z-score fell in the normal range and thus the child would not have been called osteopenic. In this case the LS BMC z-score of -0.86 was not near the abnormal range of -2. The mean LS BMC z-score was -0.92 in those

with scoliosis, and –0.15 in those without scoliosis, a difference that was not statistically significant (p=0.24). Due to the inaccuracy for classifying FF, the large proportion of subjects with differing osteopenic categories, the lack of low bone mass in scoliotic subjects, and the fact that no vertebral FF's were noted in this sample the LS BMC z-score appears unhelpful in this sample. No further analyses were completed with the LS BMC z-score.

At this time no normative data is available for the femur in children so a similar approach could not be taken with the femoral neck BMC.

Discussion

Understanding the limitations of interpreting bone densitometry in children, a new paradigm for examining bone mass is being adopted by those who deal with bone density measurements and bone health in pediatric populations. This study has used this paradigm, the mechanostat theory, to examine bone health in a sample of children with cerebral palsy. As predicted by this theory, we demonstrated lean body mass to be the greatest predictor of bone mineral content, and in this sample of children with CP we were able to accurately classify fragility fractures. The results of this study reveal that in a cross section of children with CP most children had a normal bone profile. Contrary to the expected hypothesis, the next largest group of children was those with primary osteopenia followed by secondary osteopenia, and then mixed osteopenia. More severe CP, male gender and decreasing age, appear to be the greatest factors predicting low bone mass in children with CP. Although clinically important differences were seen in orthopedic complications, pain and HRQL between those children with and without

osteopenia many of these did not reach a statistical significance, which may be related to the small sample size.

Sample

Several issues hampered enrolment in the study, reducing the sample size below that which was originally intended. First, during the first week following the announcements being mailed out the phone line was inadvertently disconnected by the communications department at CHEO during hospital moves. It was not until a family contacted OCTC determined to participate that we realized that outside calls were not making it through. We were able to check the answering machine throughout this time but did not realize why we were not getting phone calls. After recognizing this error we re-mailed letters of apology about the phone line and urged people to call again. The second issue that caused recruitment problems is that in March of 2002 the SARS epidemic began, with stringent local and public health measures that caused us to stop booking subjects for their baseline interviews for a four-week period. We also did not encourage hospital visits for blood work and x-rays during this time. Finally, it was clarified that these visits held little risk for the clients and so we re-initiated visits but at that point we felt that significant momentum had been lost. There were many patients both within and outside the study who expressed considerable anxiety regarding hospital visits from that point onward. In January of 2003 we sent out another round of letters to all those subjects that had not contacted us initially. Following this, sample recruitment was closed.

This sample of children is similar to other cross-sectional samples of children with CP (30, 39, 40, 56). There was a wide range of severity and types of CP represented,

as well as representative complications that usually accompany CP. Because our sample was derived through mail invitation, and was smaller than anticipated, in order to feel comfortable generalizing to the greater population of children with CP we compared those who participated in the study with a sample from the same mailing list who did not participate and found the samples to be similar in age, type of CP and severity of CP. In the randomly selected comparison group the only obvious difference was a higher proportion of males than in the study sample (74% vs. 49% respectively). Although research in the area has not linked male gender to an increased risk of CP there is a slight increase in male: female ratio in several population based studies (56, 62, 63). In support of this, when the whole original mailing list is counted there is actually 56% males in the population from which these samples are derived. Given this, the finding of 74% boys in the control sample is likely a sampling phenomenon.

The fact that a family would enter their child into such a study may mean they have some potential interest in bone health and may be more apt to be aware of bone complications or to be attempting to manage bone mass through dietary manipulation, etc. This could lead to a sample with greater orthopedic issues than a random sample, however, the results show that only about half of the sample had an orthopedic complication and fragility fractures were slightly lower than expected from previous literature.

Comparing this sample to previously reported pediatric bone density studies in CP is difficult for several reasons. First, few studies have chosen to examine a cross-section of all children with CP; second, few studies use the same machinery to examine bone mineral density; and third, no one has yet used the mechanostat theory to define

osteopenia. In only three previous studies does the sample appear cross-sectional, however none of the studies actually described the recruitment methods. One of studies used quantitative CT and ultrasound to measure bone density, but the other two used DEXA measurements making a comparison between their samples and this study possible. So far this paper has avoided reporting on the areal bone mineral density for our study sample (as would be given compared to age matched controls on a Lunar DEXA machine) because of the previously stated theoretical problems with this approach. However, for the sake of comparison to other studies, the mean femoral and lumbar bone mineral density and corresponding z-scores are 0.38 g/cm squared and -1.2, and 0.69 g/cm squared and -1.1, respectively. These bone mineral density z-scores are quite similar to the mean scores reported in the study by Henderson et al. (30) of -0.92 for femoral, and -0.80 for lumbar sites. The mean age and range, type and severity of CP, as well as the distribution of ambulation, anti-convulsant use and calcium intake were comparable in the Henderson sample as well. Fractures were noted in 13% of that sample (compared to fragility fractures in 9% in this study), but no attempt was made to classify them as to whether or not they were fragility fractures. Although Unay et al., (40) also had approximately half ambulant children in their study the number of children with spastic quadriparesis was nearly 70% which is much higher than the sample presented in this paper, and may be why their sample had a lower lumbar bone mineral density measurement of 0.393 g/cm^2.

In summary, the external validity of the study appears sound, given that the sample of children in this study appear similar to a comparison group from the study base and other published samples of children with CP.

Issues of measurement and analyses

The participants were assessed in two phases in the study, a baseline interview and a follow-up x-ray and bone density assessment. The assessors of each of these phases were blind to the information from the other phase. This methodology minimizes the interpretation of baseline characteristics with regard to bone characteristics and visa versa, thus avoiding a classification bias or recall bias. Additionally, an experienced pediatric neurology nurse performed all the measurements on standard clinic equipment which reduced the chances of measurement error in the physical examination process as children with CP are not easy to position or may be less cooperative. This may involve a loss of precision, however represents a pragmatic, clinical reality. For this reason many of the results are presented with confidence intervals to reflect the degree of confidence in the point estimate.

In addition to the blinded assessments the study variables were primarily objective measures that would not be open to manipulation by the researchers or parents. Only the family history of osteoporosis, pain, HRQL and dietary questionnaires were potential sources of mis-information based on parent/caregivers responses especially in cases were the child was known, or perceived to have, many orthopedic complications. Similarly the researchers could have placed children in higher GMFCS levels if they knew of their fracture histories, etc. Most of the time, however, these levels had been previously assigned by a treating physiotherapist, and the interview was set up to determine the GMFCS and type of CP before the history of orthopedic problems. Despite these precautions it is possible that known orthopedic complications could alter parent or

researcher responses to create a significant relation between subjective variables and orthopedic complications.

Only one significant issue arose with the laboratory and x-ray testing and that was related to the urinary cross-linked N-telopeptides (NTX) which were strikingly high in every patient tested. The laboratory maintains that the testing was done correctly although at the time of the study this was a test that was referred out to a different laboratory. An elevated NTX level is interpreted as a marker of bone breakdown and in this sample, an elevated level does not seem appropriate in every single child, as many of the children with very elevated levels of NTX were of mild CP with few motor limitations and had no other laboratory or radiological evidence of bone disturbance. At this point we are investigating this but a resolution is not available at this time.

Given that the osteopenia classification system using the mechanostat conceptualization is relatively new, we chose to examine the results of our sample in two very different ways, both based on the mechanostat theory: using the system described by Crabtree (14) and the using the system described by Hogler (15). Our study found a similarity in results using the two classification systems. Essentially the similarity in results allowed us to verify our findings against two sets of normal control groups one published by each of these authors. The BMC z-scores and the BMC/LBM ratio even had identical significant predictor variables when linear regression analyses were performed, and similar relations to the outcome variables.

Risk factors and bone mineral content

The potential predictors of bone mineral content were examined in two stages in this study in keeping with the mechanostat theory of principle determinants of bone

strength and modulators of this relationship as seen in Figure 1. For the first stage, it was determined that lean body mass (and other intrinsic body variables) was the main predictor variable for bone mineral content. In the second stage, the contribution of other extrinsic variables, or potential modulators, both specific to CP and general ones, were examined. To date, no known previous research in children with CP has used the mechanostat theory of bone mass to analyze DEXA data.

The findings that lean body mass was a major contributor to bone mass helps to put previous research findings in perspective, and helps to provide a foundation for future research. The finding in this study that the lean body mass was normal (compared to control children when accounting for height) in many children with CP, even of a severe type, was contrary to previous anthropomorphic studies of children with CP (25, 26) on which our original hypothesis was based. Examination of these studies however, reveals that lean body mass was measured indirectly from fat mass and total body weight and not corrected for height. Comparisons were made directly to age matched controls and height was not used in regression equations as a determinant of lean muscle mass (26). Thus the literature was explored to find reports of body mass composition measured by DEXA in children with CP to determine if other samples had had normal lean body mass relative to peers. Surprisingly, few other studies appear to have dealt with this issue and the most relevant data comes from a study by Liu et al. (27). This study examined 10 children with CP (all spastic diplegia or quadriplegia) and reported data on fat and muscle mass (but not bone mass) as determined by a Hologic DEXA machine. This study was interested in correlating different methods of calculating body composition in children with CP for nutritional reasons (27). Using the data in this study z-scores were calculated

based on the study by Crabtree and there was also no significant decrease in LBM for height compared to normal controls. Mean z-score = 0.8 (range -1.5 to 3.7). What is somewhat reassuring in the Liu et al. study is that even children with severe CP all had LBM z-scores greater than -2. Ideally though, a larger sample of children with DEXA measurements on the same type of machine used in this study would be helpful in clarifying this finding.

Other modifying variables were analyzed to see which influenced the bone mass over and above lean body mass. Of note, age and gender were also considered in this stage of the analysis because bone mineral content values have been shown to be higher in females and increase with age in normal child populations even when accounting for lean body mass (15, 23). These variables seemed to be important in this CP sample as well with females and older children having higher bone mineral content z-scores.

Several previous studies in children with CP, using different methods and sites of bone density testing, have found that the major risk factor for low bone mineral density has been poor ambulatory or weight bearing status (30, 35, 39, 42) whereas others have found that ambulation is not significantly related to bone density (29, 31, 40). In the studies showing increasing mobility level to be related to increased bone density, the amount of variance this explains in multivariate models has generally been low (30, 33, 35). One attempt to improve bone density through an RCT of increased standing time found an increase in lumbar spine areal bone mineral density of 6% in the treated group over controls, but a non-significant decrease at the tibial site (42). Type of CP has been shown to be related to bone density albeit less strongly (30, 40), but again few studies have used a wide cross section of CP types. Both CP type and ambulatory status are often

related to weight bearing status. Our results support these previous observations that weight bearing plays some role in bone mass accrual because GMFCS appeared to be the only significant CP specific predictor variable once lean body mass, age and gender have been accounted for. With lean body mass controlled for, GMFCS, in this study, is likely a surrogate for amount of time weight bearing and accounts for the gravitational force on bone. It is possible that in this study the type of CP is not a risk factor because it is highly related to lean body mass that once this is controlled it becomes insignificant. In future it will be important to account for lean body mass in the interpretation of bone mineral content especially in children with CP to avoid confounding bias in the interpretation of results.

Other variables, such as nutritional scores (30), feeding difficulties (33, 35) and anticonvulsant use (33), which in various studies have been associated with low bone mass, are also apt to have some associated confounding with lean body mass in the CP population. All are more typically compromised in those with severe CP, which is the population that appears to have the greatest risk for small body size. Only one previous study found low calcium intake to be an important risk factor for low bone mineral density (30) whereas several others have not found this to be the case (29, 31, 40). Our results support the idea that calcium intake plays no substantial role in bone mineral content in the typical child with CP. Of course calcium deficiency may occur in individual patients and should always be checked as in any child with fragility fracture. This is not to discount calcium and vitamin D as potential modulators in the mechanostat theory of bone mineral content accrual. In fact in both normal child populations (64, 65) and those with CP (37) trials have demonstrated that supplements with calcium and

vitamin D do increase areal bone mineral density, but it has also been shown that the bone mineral density returns to a similar level as control values once calcium is stopped (66).

The finding in this study that anti-convulsant use was not shown to be a risk factor for low bone mass was not surprising, as we viewed this as a potential confounder to lean body mass. This association, however, has remained a source of controversy in the literature. In previous studies of bone density in children with CP anti-convulsant use has not been an important factor (30) and recent work examining it in other populations (i.e., epilepsy patients) using the mechanostat theory have not found carbamazepine or valproic acid to be a cause of low bone mass (24). In contrast, other studies in CP have found anticonvulsant use to be detrimental to bone density (33); and in a recent study in adult patients treated with anticonvulsants and their sibling controls, duration of anti-convulsant use greater than two years, and age over 40 years, did appear to have a detrimental impact on bone density, even when sibships were matched on lean body mass (67). There remains more to investigate in the CP population regarding bone mineral content and anti-convulsants, however it will need to be done with lean body mass accounted for. Our sample may have been too small to appreciate what may be, perhaps, only a marginal impact of anti-convulsants on bone mass.

The results of this study have demonstrated that those children with CP frequently have primary osteopenia, meaning that their bone density is lower than one would expect for their degree of muscle mass, yet beyond GMFCS, age and gender, there is no other CP specific factor that contributes to the regression model. What other alternative variables could account for the explanation for low bone mineral content in children with

CP? Several possibilities arise. First, this study has too few children with primary osteopenia to adequately address this issue. Because of the small numbers (n=11) it was inappropriate to run regression equations or even correlations on the primary osteopenia group alone to understand the relations to factors such as GMFCS, calcium intake, family history of osteoporosis, etc. In lieu of examining the primary osteopenic group alone, the whole sample was examined which might have led to a dilution of some of the relations between variables. Even including all the subjects in regression models the study was possibly underpowered to find significant relations between the above noted variables and bone mineral content.

The second reason is that there may be an unknown factor that we have not measured in this study that accounts for the unexplained variance in the model. To address this we should return to the mechanostat theory and examine again the major driver of bone mineral content, lean body mass. We propose here that one possible reason that children with CP have more frequently a pattern of primary osteopenia is that even though the lean body mass appears in the normal range for this group, the forces the muscle generates on the bone are abnormal resulting in abnormal bone mineral accrual. In contrast to normal children who have relatively balanced agonist/antagonist muscle movement around a bone with periods of rest, children with CP often have an imbalance between agonist and antagonist muscle, resulting in sustained agonist muscle action on a bone with little or no contraction of agonist muscle. It is quite possible that this imbalance leads to a state of bone architectural dysfunction that can be identified in measures of bone mineral content. Currently we are unaware of data to support this hypothesis and discuss it further in the section on future research.

Notwithstanding the preceding discussion, it may be that GMFCS level is a major risk factor for low bone mass because this is also related to orthopedic complications. In fact we may be missing a confounding variable in the interpretation of GMFCS that is also important for understanding the relationship between the presumed outcome variables and bone mass. Although we have presented background information about the risk factors for low bone content and the possible outcomes, it is quite possible that the outcome measures used here are in fact more predictors of low bone mass than consequences of it. Fragility fractures in the adult osteoporosis literature specifically have both a status as strong predictors of future fragility fracture, as well as being an adverse outcome of main concern (68). The same conclusions can not yet be made for children although intuitively it seems generalizable to pediatrics. Some findings do however support the conceptualization used in this study. First, there are many more subjects in this sample with osteopenia then fractures and other bone complications, which might be the opposite if the bone complications preceded osteopenia. Second, those with younger age actually tended to have worse bone mineral content z-scores than older children. With the average age of fracture and other bone complications being over seven years of age, this would suggest bone content changes happen earlier than the complications. Caution needs to be highlighted in regards to the assumption made in this sample about the directionality of the relation between the predictor variables, bone mineral content and the outcome variables (see Figure 3). Ultimately though, this will only be resolved through prospective studies.

In summary, once the lean body mass is controlled for in children with CP there are few other variables measured in this study that explain much of the variation in the

bone mineral content. This may be due to small sample size, or because we have not measured an unknown variable, such as a more dynamic measure of muscle force on bone.

Outcomes and bone mineral content

Joint subluxation, scoliosis and fragility fractures all appear to be increased in those with low bone mass and in those classified as having osteopenia. This has not been demonstrated before and will provide a basis for future research. Fragility fractures are more intuitively an outcome of low bone mass than either scoliosis or joint dislocation. Several lines of evidence, however, exist to support the possibility that low bone mass could predate scoliosis and joint subluxation. First, using data from this study it is evident that scoliosis happens at an older age (mean age of 11.2 years) than bone density change which was evident by a mean of 6 years and 10.7 years in the primary and secondary osteopenia groups respectively. Also noted in this study is that those with scoliosis tended to have lower lumber spine bone mineral content compared to those children without scoliosis although this was not statistically significant. Second, populations that have only low bone density for various reasons all experience high rates of scoliosis, for example: low muscle mass (Duchenne muscular dystrophy), irregular muscle forces (CP) and primary osteopenia (osteogenesis imperfecta). The common denominator is low bone mass. Finally, in idiopathic scoliosis, which affects otherwise healthy young females, there appears to be evidence of osteopenia which has led investigators to hypothesize that part of the pathophysiology is low bone mass. In a study of 81 females with newly diagnosed idiopathic scoliosis there was reduced bone density at the lumbar spine and femur compared to the 220 control subjects (69). The authors felt that low bone mass was

an inciting factor in the pathophysiology of scoliosis based on the findings that low bone mass was seen in the hips, that low bone mass was present in those with newly diagnosed scoliosis, and that the degree of osteopenia was similar regardless of age or degree of scoliosis.

Hip joint subluxation is perhaps more difficult to rationalize as an outcome of low bone mass and certainly many of the arguments above do not fully apply to joint subluxations. For example, children with joint subluxation in our study had a similar mean age (9 years) to those with osteopenia. Also hip subluxations are uncommonly seen in those with low bone mass for other reasons such as osteogenesis imperfecta or Duchenne muscular dystrophy. Although the strength, direction, and exact pathophysiologic mechanism of low bone mass as a cause of scoliosis, or joint subluxation, remains to be elucidated, this study raises important concerns that these may be potential outcomes of low bone mass. These complications need to be examined in future studies of bone mass as they are vastly more common than fragility fracture and create substantially greater morbidity. If these were felt to be problems that could be altered by improving bone strength this would be an important finding in the CP population that would dramatically improve lives on a magnitude much greater than that realized by simply preventing fragility fractures.

All children with fragility fractures, in this sample, were appropriately assigned to an osteopenia group, however, in contrast, this system has assigned many children to osteopenia groups who did not have fragility fractures. Three reasons may account for this finding. First is that it is possible many such children may go on to have fractures because our sample was generally young. Second, the cut off value of -2 may not be low

enough to provide an acceptable specificity. The third reason is that these children are in fact at risk but due to their lack of movement and perhaps gentle care-giving they have avoided fracture. Until further research is done a more accurate or clinically meaningful cut off value may not be defined and may be different for different types of osteopenia and different clinical conditions.

The group of children with mixed osteopenia appear to be at the greatest risk of bone complications. In that group of three children there was one child with a fragility fracture. As well, the child with fragility fracture in the primary osteopenia group was actually very close to being in the mixed group with a LBM z-score close to the -2 level.

Regional bone density

Henderson's group (45) have indeed made an important assertion that investigation of bone density in children with CP should focus on the distal femur as this appears to be the most frequent site of fracture. At this point though, their data does not support the use of lateral femoral scan with comparison to age match control as a reasonable way to predict fragility fracture (33). It is our presumption that this is due to both the conceptual inaccuracies in comparing CP children to normal age-matched controls and the empirical reason that their studies have not clearly defined those with osteopenia. At present, the use of the lateral femoral areal bone density scan proposed by Henderson is not helpful, but if re-analyzed using the bone mineral content and lean body mass relationship from the corresponding leg, this site may be a very important predictor of fracture.

For the subjects in this study the use of lumbar BMC z-scores did not improve the accuracy of classification of fragility fracture in this sample. We contacted Dr. N Shaw, a

member of the Crabtree group, to see if reference ranges for leg or proximal femur bone mineral content were available to calculate z-scores, but at present these are not available. When these become available it would be important to re-examine the sample presented here to see if regional femur BMC z-scores are a more accurate way to predict fracture than total body bone mineral content. Methods of evaluating regional bone density need to evolve as different populations of children appear to have different areas of fragility fracture predilection. For example those with Duchenne muscular dystrophy, especially with chronic steroid use (70), appear to have a high incidence of vertebral compression fractures.

Secondary objectives

Using the emerging conceptualization of osteopenia in the CP population shows that about half of the children would be expected to have some form of osteopenia. This is based on using cut-off values as described by Hogler and Crabtree and is based on total body measurements. As we have demonstrated here, and has been clearly stated by these authors, the use of specific cut-off values in children at this point is somewhat arbitrary. As shown in Table 10, if the cut-off values are lowered in this sample, we reduce by 40% the number of children called osteopenic while maintaining an excellent sensitivity for fragility fractures. Defining osteopenia will continue to be a difficult process in children until greater numbers of studies are done in those with disease states and until longitudinal studies determine the long term risks of having low bone mass.

Orthopedic complications are extremely common, even in a cross-sectional sample of children with all types and severity of CP. Fully 51% of children had at least one form of bone complication, with 15% of the sample having up to three complications.

Nearly a quarter of the children had an element of joint subluxation which is similar to one previous study with a rate of 21% (71). Also, 15% had significant scoliosis, which is lower than rates of 23% typically quoted for scoliosis (60), but this is from more severely affected, institutionalized children. Fragility fracture occurred in 9% of this sample which is similar to other studies of fracture in children with CP (30). Based on the chart review and parents descriptions it would appear that fragility fracture in this population is likely to consume considerably more time and resources to diagnose than would fractures occurring in other populations. Although a control group of fractures in other populations was not actually taken for this study, in three of the six fractures hospitalization was needed to diagnose or treat the fracture, which would seem unlikely to happen in a more verbal population. Also of interest was the relatively low rating of the degree of difficulty that the child experienced as a result of the fracture compared to other medical difficulties they had to go through. Perhaps this is falsely reassuring as these children experience considerable medical morbidity.

Despite the potential bias in parent/caregiver reporting of pain and HRQL information, only the HUI2 and 3 measures were related to low bone mass or osteopenic categories consistently in bivariate analyses. However this relation was not significant in multivariate analyses once GMFCS was incorporated. This finding is understandable given that those with lower GMFCS were over represented in the low osteopenic categories and that GMFCS is correlated with HRQL measures in this sample (72). Only one other study has examined the relation between areal bone mineral density and a standardized HRQL measure, the Child Health Status Questionnaire, in 117 children with CP (33). In this study no relation was noted between these variables.

Pain scores were consistently worse in those with low bone mass. Examination of the results shows 3-4 fold differences in mean pain scores between normal and various osteopenic groups, although not reaching statistical significance. This finding is important clinically. In other populations with low bone mass, many have considerable pain which is felt to represent micro-fracture and this improves with treatment of their osteopenia (73). Although this possibility is intriguing as a cause for pain in those with CP it is possible that the reason for the findings of high pain scores in those with osteopenia are mediated through the severity of CP, much like the HRQL data described above. Clearly if other studies identified a relationship between pain and low bone mass in children with CP several other factors, such as severity of CP, presence of dystonic spasms, etc., will need to be controlled for in determining the importance osteopenia alone.

Few conclusions can be drawn from the biochemical parameters used in this study, due to the poor compliance of the subjects in completing these investigations. Less than half the children had complete results and none of these had a profile that would independently raise concerns about bone fragility. For example, no child had a low calcium, phosphate or vitamin D serum levels; no one had an elevated serum alkaline phosphatase; and only two had low parathyroid hormone levels. The difficulty in obtaining the NTX levels has already been mentioned. Fortunately, few studies have found either blood or urine markers of great relevance in the clinical evaluation of bone health in children with CP (33) or other neuromuscular conditions (74), and recent commentary from experts highlights this (13, 20).

Future Research Directions

With this study being the first to examine children with CP using the mechanostat theory, using DEXA generated information, the next obvious research would be a validation of our study findings in another sample of children with CP. Two possible samples could be examined to determine if the conceptualization of osteopenia is appropriate. First would be a cross sectional study much like ours with a much greater sample size in order to obtain more fragility fractures and other orthopedic complications. A second approach would be to enroll a high risk group such as those with a severe (GMFCS III-V) spastic quadriparetic type of CP. The former sample would lead to a better understanding of how sensitive this classification is, and the latter would better define the specificity.

A compelling reason to complete long term temporal studies of bone density in children with CP would be to determine the directionality of the variables of low bone mass, fracture, and other bone complications. Ideally a new sample of children would be enrolled in a longitudinal study to help determine if bone density changes precede bone complications. In the same manner the association of pain and HRQL changes over time in reference to bone mineral content will provide valuable insight into whether these variables are related at all to bone, whether they are only related through orthopedic complications, or if they are independently related.

The findings in this study are intriguing in that many children had primary osteopenia, which was not expected. Perhaps even more surprising was the fact that few of the variables expected to contribute to poor bone mass actually did so. This led to the hypothesis that there is an abnormal bone mass accumulation or organization in children

with CP, due to aberrant muscle forces, even though the absolute muscle mass is near normal. Assessing this possibility in future studies would be difficult; one would need to quantify the abnormal muscle forces on the bone through three possible methods. One would be including a measure of strength or power around the bone being studied, such as grip strength or medical research counsel (MRC) measurements of muscle force in opposing muscle groups. It would be difficult to get accurate measurements in children with CP given the cognitive limitations of many as well as the poor motor control. Measuring the degree of contracture around a bone, or the passive Ashworth score of spasticity in opposing muscle groups, and quantitative electromyography of antagonistic muscles are other potential ways of expressing the degree of muscle imbalance.

Another possible way to determine the difference in agonist/antagonist muscle groups would be through quantitative CT scanning which has been used as another method of bone density testing especially using the mechanostat theory. In this method one can measure muscle cross sectional area around a bone of interest. It may be possible then to quantify the agonist and antagonist muscle groups and see if larger imbalances between the two are related to decreasing bone mineral content. Finally, one wonders if examining bone biopsy samples in children with CP, principally those with primary osteopenia, would be helpful in determining if their bone architecture is abnormal. No study of bone biopsy in children with CP could be identified in the literature at the time of this investigation.

A major requirement in future studies that use the mechanostat theory to describe osteopenia would be the determination of a cutoff value to describe osteopenia and those at risk for fracture. This study used cutoff values proposed by Crabtree and Hogler which

were arbitrary values. We have shown here that by lowering the cutoff value the definition of osteopenia becomes more specific. A similar approach should be taken to examine other orthopedic conditions.

For clinical trials the data presented here will provide another method for determining a high risk groups for entry criteria. At this point trials of bisphosphonates have started, using high risk groups defined as those with low age-matched bone mineral density changes and/or fractures with minimal trauma. This study should help to refine the definitions of those enrolled in clinical trials, and to understand the response to bisphosphonates in those with different pathophysiologic mechanisms for their osteopenia (i.e. primary vs. secondary osteopenia).

Clinical Implications

At this point a cautious approach to the findings in this study should guide the clinical application of the findings of this study. Routine bone mineral density testing is frequently done in clinics managing children with CP despite the lack of a physiologic way of interpreting the data. The findings of this study will be useful in giving reporting radiologists and ordering physicians a different way to interpret the results. The ease of determining LBM z-scores and BMC z-scores, or a BMC/LBM ratio lends itself to busy clinical practice and will fill a void in the interpretation of bone mineral density reports. Many physicians are provided only with results based on adult normal values (i.e. the T-score) with interpretations guided by radiologists with principally adult bone density experience. Greater clinical experience using the mechanostat osteopenic classification is important as it will lead to observations that will again guide research.

Limitations

The most significant limitation to the current study is the small sample size. As mentioned previously, a number of circumstantial factors led to difficulty in recruiting and/or a lower response rate than expected. The lower than expected sample size limited the viability of some analyses which would have been helpful in better disentangling the relation between bone complications and low bone mass and osteopenic states. Despite this we have demonstrated both from an examination of an internal data base and from other published studies of children with CP that the sample is generalizable to the general CP population.

A second limiting factor in this study, similar to other such studies was the lack of complete data for each subject, particularly DEXA measurements. The greatest issue was getting subjects to come back for a second visit to have the x-ray investigations and DEXA done despite offering some minor incentives. This is particularly evident in the group of subjects with FF where two children out of five did not have bone mineral density testing. If both of these subjects had DEXA that showed they were not osteopenic the conclusions of the study would be vastly different. Similarly, poor return of dietary questionnaires made analyses involving diet more difficult. It is possible that those with a poor diet in calcium and vitamin D did not return the questionnaire more often than those with an excellent diet which would minimize our conclusions that diet does not substantially impact on bone mass accrual. However we have no bases to expect such a bias. Overall, the amount of missing data is a concern and reviewing the methodology in order to help reduce this problem in future is important to consider. For example,

offering incentives to patients for completing all aspects of the study and offering frequent reminders for completion of the varying aspects of the study may be helpful.

The control data from the Crabtree study (14) came from white European children age 5-18 years old. No black or younger children were included and so no account for race was made during the analysis in this study. Most studies have found differences in BMD between races (21). At present not enough information has been accumulated to determine if race remains an important influence on bone mass even once lean body mass is accounted for. In the Crabtree and Hogler studies, as well as others (75), only white subjects were studied, and in other studies using the mechanostat concept, where multi-racial samples were used, race has not been mentioned as a factor (23, 24). Even though race does not appear in this sample to be associated with bone mass it needs to be examined in a larger sample.

The Hogler study used only white children but had a wider range of ages from 3 years to 30 years; our data fit well with the methods they described. Even though the data set of normals that we used to generate z-scores had children who were at the youngest 5 years of age (14), we have evidence that in a population of 778 Argentinean children ranging from 2-20 years old the relationship between LBM and total body BMC is constant even down to 10 kilograms of weight (23). None of our children were less than 10 kg providing some reassurance about drawing conclusions in our younger children. Finding a control group is a difficult task in studies of bone mineral density as age range, weight ranges, height ranges, gender, race, type of DEXA machine used (or other method of measuring bone density), and location of bone mineral density testing (i.e. total body vs. lumbar spine vs. leg) are all factors that need to be considered. At this point as well

there is a paucity of normal control values to use, especially based on the mechanostat theory, so one has to choose from the best of a limited selection. Thus, in this study we chose two different methods of examining BMC in children with the same theoretical basis. The best technique, and one that would have added value to the current study, is to have a control group or diseased or normal children, using the same DEXA machine as the study sample.

Conclusions

The findings from this thesis demonstrate an important shift in the conceptualization of bone density testing in children with CP, both in the areas of research and clinical care. Although the findings are modest and the study limitations need to be borne in mind, the study has achieved the objectives set out by defining osteopenia in a group of children with CP and demonstrating that orthopedic complications are increased in osteopenic subjects. This study is the first to systematically include quality assessments of pain and HRQL in relation to pediatric CP bone health.

The introduction of the mechanostat theory to the field of bone health in CP, and the specific findings of this investigation would appear to be a viable catalyst for further research. Moreover the study will add to the growing body of literature using lean body mass as the major parameter to explain bone mineral content in pediatric disease states.

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Table 1. Equations used to generate TB BMC z-scores and LS BMC z scores. From Crabtree et al. (14).

	Pre-puberty (Tanner 1)	Early (Tanner 2 and 3)	Late (Tanner 4 and 5)
Predicted equations and z score calculations for girls			
Predicted LBM (g) for height (cm)	LBM=0.237x Height$^{2.33}$	LBM=0.248x Height$^{2.33}$	LBM=0.256x Height$^{2.33}$
z-score	Measured LBM- Predicted LBM/ (0.07125x Predicted)		
Predicted TBBMC (g) for LBM (g)	TBBMC=0.0142x (LBM$^{0.887}$) x (Height$^{0.494}$)	TBBMC=0.0142x (LBM$^{0.887}$) x (Height$^{0.494}$)	TBBMC=0.0152x (LBM$^{0.887}$) x (Height$^{0.494}$)
z-score	Measured TBBMC- Predicted TBBMC/ (0.09108x Predicted)		
Predicted LSBMC (g) for LBM (g)	LSBMC=0.0001363x (LBM$^{1.181}$)	LSBMC=0.0001483x (LBM$^{1.181}$)	LSBMC=0.0001699x (LBM$^{1.181}$)
z-score	Measured LSBMC- Predicted LSBMC/ (0.14856x Predicted)		
Predicted equations and z score calculations for boys			
Predicted LBM (g) for height (cm)	LBM=0.160x Height$^{2.423}$	LBM=0.165x Height$^{2.423}$	LBM=0.186x Height$^{2.423}$
z-score	Measured LBM- Predicted LBM/ (0.07115x Predicted)		
Predicted TBBMC (g) for LBM (g)	TBBMC=0.0347x (LBM$^{0.829}$) x (Height$^{0.426}$)	TBBMC=0.0347x (LBM$^{0.829}$) x (Height$^{0.426}$)	TBBMC=0.0372x (LBM$^{0.829}$) x (Height$^{0.426}$)
z-score	Measured TBBMC- Predicted TBBMC/ (0.08636x Predicted)		
Predicted LSBMC (g) for LBM (g)	LSBMC=0.0002515x (LBM$^{1.112}$)	LSBMC=0.0002522x (LBM$^{1.112}$)	LSBMC=0.0002764x (LBM$^{1.112}$)
z-score	Measured LSBMC- Predicted LSBMC/ (0.13220x Predicted)		

Note: BMC: bone mineral content; LBM: Lean body mass; LS: Lumbar spine; TB: total body.

Table 2. Demographic characteristics.

Characteristic	Total Sample (N=53)
Mean age years (*s.d.*, range)	9.0 (3.8, 2.5-15.8)
Number of females (%)	29 (55)
GMFCS number and (%) I	23 (46)
II	2 (4)
III	5 (10)
IV	6 (12)
V	14 (28)
Associated cognitive impairment	22 (45)
Associated visual impairment	22 (45)
Associated hearing impairment	3 (4)
Associated GI problems	12 (26)
Associated feeding problems	10 (21)
Associated seizure disorder	19 (38)
Mean percent weight for age	46th percentile (32, 0-100)
Mean percent height for age	28th percentile (29,0-93)
Mean HUI2 score (*s.d.*, range)	0.567 (0.295, 0.070-1.000)
Mean HUI3 score (*s.d.*, range)	0.328 (0.444, -0.340-0.973)
Mean Caregiver Questionnaire (*s.d.*, range)	3.0 (1.8, 0.1-7.1)

Note: Category number totals may be less than 53 due to missing information. Percentages are based on valid percents. GMFCS: Gross Motor Function Classification System; HUI: Health Utilities Index.

Table 3. Characteristics of control group compared to total sample.

Characteristic	Total Sample (N=53)	Comparison Group (N=43)	
Mean age years (*s.d.*, range)	9.0 (3.8, 2.5-15.8)	9.9 (4.0, 2.2-16.1)	p=0.26
Number of females (%)	29 (51)	11 (26)	p=0.004
GMFCS number and (%) I	23 (47)	12 (29)	Chi Square p>0.05
II	2 (4)	7 (17)	
III	5 (6)	3 (7)	
IV	6 (13)	4 (10)	
V	14 (30)	16 (38)	
Type of CP Dystonic or other	3 (6)	4 (9)	Chi Square p>0.05
Spastic Hemiplegia	25 (48)	17 (40)	
Spastic Diplegia	3 (6)	1 (2)	
Spastic Quadriplegia	21 (40)	21 (49)	

Note: GMFCS: Gross Motor Function Classification System.

Table 4. Tanner stages.

Tanner stage	Male genitalia (n=22)	Male pubic hair (n=22)	Female pubic hair (n=21)	Female breast (n=21)
I	10	14	10	10
II	5	2	4	2
III	3	3	3	3
IV	2	1	2	3
V	2	2	2	3

Table 5. Causes of pain and severity of pain associated with each cause.

Cause of pain	Rating of severity Least severe				Most Severe	
	1	2	3	4	5	Total number of responses
Spasticity	2	4	1			7
Constipation	3	4	5	2	2	16
Medical procedures	3	3	1		1	8
Transferring or positioning	6	4	2			12
Dressing or toileting	2	4	1			7
Ambulating	2	4	1			7
Reflux	2	3	2		2	9
Joint problems/scoliosis		2	6		3	11
Seizures	2	1				3
Fractures			1	2	2	5
Unsure	1	2		1	2	5
Other: headaches	1	1	1	2	1	6

Table 6. Multiple correlations for total body bone mineral content, lumbar spine bone mineral content and femoral neck bone mineral content with predictor variables: Lean body mass, fat body mass, weight, height, age. Pearson r shown with confidence interval and p value.

Body parameter	Total body BMC	Lumbar spine BMC	Femoral neck BMC
Lean body mass	0.922 (0.863,0.981) p<0.001	0.838 (0.755,0.921) p<0.001	0.391 (0.250,0.532) p=0.01
Weight	0.912 (0.849,0.975), p<0.001	0.827 (0.742,0.905) p<0.001	0.382 (0.241,0.523) p=0.012
Height	0.873 (0.798,0.948) p<0.001	0.820 (0.733,0.907) p<0.001	0.422 (0.283,0.561) p=0.005
Age	0.873 (0.798,0.948) p<0.001	0.788 (0.695,0.881) p<0.001	0.317 (0.172,0.462) p=0.039
Fat body mass	r=0.757 (0.657,0.857) p<0.001	0.574 (0.448,0.700) p<0.001	0.339 (0.195,0.483) p=0.026
Leg lean body mass	Not applicable	Not applicable	0.448 (0.311,0.585) p=0.003

Note: BMC: bone mineral content

Table 7. Multiple regression analyses of TB BMC and predictor variables.

Model building stepwise	Variables entered	R square	R square change	Significance (p value)
1	TB LBM	0.849	0.849	0.000
2	TB LBM Weight	0.909	0.060	0.000
3	TB LBM Weight TB Fat mass	0.925	0.016	0.007
4	TB LBM Weight TB Fat mass Gender	0.938	0.013	0.007
Variables: height and age were not significant factors with an entry criteria of $p<0.1$				
Final model	TB LBM Weight TB Fat mass Gender	0.938		
		Beta coefficient	t value	Significance
	TB LBM TB Fat mass Weight Gender	0.622 0.173 0.236 -0.126	7.510 2.843 2.504 -2.841	0.000 0.007 0.017 0.007

Note: BMC: bone mineral content; LBM: Lean body mass; TB: total body.

Table 8. Osteopenia groups.

Characteristic	Normal	Primary	Secondary	Mixed
Number	24	11	5	3
Age (*s.d.*, range)	10.2 (3.4, 3.3-15.8)	6.0 (3.5, 2.5-13.2)	10.7 (4.0, 4.7-15.5)	9,10 and 13
Gender (female: male ratio)	15:9	3:8	4:1	1:2
Type of CP	Hemi-15 Quad-7 Di-1	Hemi-6 Quad-3	Quad- 3 Hemi-2 Di -2	Quad-3
GMFCS Level I	16	5	1	0
III	4	3	3	0
V	1	3	1	3
Past or current anti-convulsant use	5	2	2	2
Family history of osteopenia	5	4	1	0
Any bone complication	9	7	3	3
Fragility fracture	none	1	1	1

Note: GMFCS: Gross Motor Function Classification System

Table 9. Comparison of osteopenia classification by Crabtree and Hogler.

Osteopenia category	Crabtree system	Hogler system	Difference and explanation
Normal	24	24	3 children classified in the Crabtree system as normal moved to primary osteopenia in the Hogler system.
Primary	11	11	3 children classified as having primary osteopenia in Crabtree system moved to normal in the Hogler system.
Secondary	5	5	None
Mixed	3	3	None

Table 10. Tables for different cut off values of total body BMC z-score for defining osteopenia. (a) Cut off of -2 *s.d.* (b) cut off of -2.5 *s.d.*

(a)

	Fragility Fracture	No Fragility Fracture	Total	
Osteopenic	3	16	19	Positive predictive value= 3/19 =16%
Not Osteopenic	0	24	24	Negative predictive value= 24/24 =100%
Total	3	40	43	
	Sensitivity = 3/3 = 100%	Specificity= 24/40 = 60%		

(b)

	Fragility Fracture	No Fragility Fracture	Total	
Osteopenic	3	8	11	Positive predictive value= 3/11 =27%
Not Osteopenic	0	32	32	Negative predictive value= 32/32 =100%
Total	3	40	43	
	Sensitivity = 3/3 = 100%	Specificity= 32/40 = 80%		

Table 11. Univariate analysis of independent variables on total body BMC z-score and BMC/LBM ratio.

Factor	BMC z-score		Ratio BMC/LBM	
	Statistical Test	p value	Statistical test	p value
Type of CP (Comparison of spastic quadriparetics to all others or to spastic hemiplegia)	t-test	p=0.737	t-test	P=0.313
GMFCS Kendall's non-parametric correlation	tau b= -0.35	p=0.006	tau b= -0.29	p=0.025
Calcium intake (Low intake vs. normal intake)	t-test	p=0.900	t-test	p=0.669
Vit D intake (Low intake vs. normal intake)	t-test	p=0.125	t-test	p=0.205
Average daily calcium intake, Pearson r (CI)	r =0.202 (-0.02,0.424)	p=0.354	r =0.139 (-0.086,0.364)	p=0.526
Average daily vit D intake, Pearson r (CI)	r =0.293 (0.076,0.510)	p=0.175	r=0.217 (-0.005,0.439)	p=0.321
Family history (No family history vs. family history)	t-test	p=0.512	t-test	p=0.655
Anti-convulsant use (Never vs. current or past; current vs. past or never)	t-test	p=0.934	t-test	p=0.785
Age, Pearson r (CI)	r =0.505 (0.373,0.637)	p=0.001	r =0.638 (0.520,0.756)	p<0.001
Gender	t-test = 3.171	p=0.002	t-test=3.49	p=0.002
Race (Caucasian vs. others)	t-test = 0.493	p=0.634	t-test = 0.308	P=0.765

Note: BMC: bone mineral content; GMFCS: Gross Motor Function Classification System; LBM: lean body mass; NS: Not significant.

Table 12. Multiple regression equation for total body BMC z-score and GMFCS, age, and gender.

Model building	Variables entered	R square	R square change	Significance (p value)
1	GMFCS	0.181	0.181	0.006
2	GMFCS Age	0.517	0.336	0.000
3	GMFCS Age Gender	0.639	0.123	0.001
4	GMFCS Age Gender Age x Gender	0.650	0.011	0.305
Final model		Beta coefficient	t value	Significance
3	GMFCS Age Gender	-0.479 0.521 -0.357	-4.712 5.062 -3.499	0.000 0.000 0.001

Note: GMFCS: Gross Motor Function Classification

Table 13. Univariate and bivariate analyses of total body BMC and potential outcome variables.

Factor		BMC z-score			Ratio BMC/LBM		
		Mean Value	Statistical Test	p value	Mean Value	Statistical Test	p value
Any bone complication	At least one bone complication	-1.5	t-test	p=0.285	0.045	t-test	p=0.505
	No bone complication	-0.9			0.047		
Scoliosis	Scoliosis	-1.1	t-test	p=0.873	0.049	t-test	p=0.582
	no scoliosis	-1.3			0.045		
Joint complications (similar for both right and left hip)	Joint subluxation	-2.8	t = -3.8	p=0.012	0.039	t= -3.4	p=0.05
	no subluxation	-0.9			0.047		
Pain, Pearson r (CI)		r = -0.283 (-0.444,-0.122)		p=0.094	r = -0.276 (-0.438,-0.114)		p=0.103
HRQL Pearson r (CI)	CQ	r =-0.299 (-0.455,-0.143)		p=0.069	r =-0.220 (-0.383,-0.057)		p=0.184
	HUI2	r =0.376 (0.225,0.527)		p=0.02	r =0.294 (0.135,0.453)		p=0.073
	HUI3	r =0.330 (0.176,0.484)		p=0.043	r =0.246 (0.084,0.408)		p=0.137

Note: BMC: bone mineral content; GMFCS: Gross Motor Function Classification System; HRQL: Health related quality of life; HUI: Health Utilities Index; LBM: lean body mass; NS: Not significant.

Table 14. Comparisons between normal and primary osteopenia groups on potential outcome variables.

Characteristic	Normal vs. Primary		Normal vs. Primary plus mixed	
	Normal (n=24)	Primary (n=11)	Normal (n=24)	Primary plus mixed (n=14)
Any bone complications	9	7	9	10
No bone complications	15	4	15	4
Statistical test and significance	Chi square=2.076, p=0.15 Fisher's exact test , p=0.273		Chi square=4.071, p=0.044 Fisher's exact test , p=0.091	
Scoliosis	2	1	2	3
No scoliosis	22	10	22	10
Statistical test and significance	Fisher's exact test, p=0.691		Fisher's exact test, p=0.321	
Joint subluxation	2	5	2	6
No joint subluxation	21	6	21	7
Statistical test and significance	Fisher's exact test, p=0.024		Fisher's exact test, p=0.016	
Pain	4.95	12.0	4.95	14.0
Statistical test and significance	t-test, p=0.232		t-test, p=0.090	
HRQL	HUI 2=0.69 HUI 3=0.56 CQ=2.4	HUI 2=0.54 HUI 3=0.31 CQ=2.8	HUI 2=0.69 HUI 3=0.56 CQ=2.4	HUI 2=0.47 HUI 3=0.20 CQ=3.4
Statistical test and significance	HUI 2, t-test, p=0.174 HUI 3, t-test, p=0.142 CQ, p=0.65		HUI 2, t-test, p=0.028 HUI 3, t-test, p=0.020 CQ, p=0.201	
Number of bone complications	1.22	1.71	1.22	1.8
Statistical test and significance	t-test, p=0.304		t-test, p=0.132	

Note: CQ: Caregiver Questionnaire; HUI: Health Utilities Index; NS: Not significant.

Table 15. Comparisons between normal and secondary osteopenia groups on potential outcome variables.

Characteristic	Normal vs. Secondary		Normal vs. Secondary plus mixed	
	Normal (n=24)	Secondary (n=5)	Normal (n=24)	Secondary plus mixed (n=8)
Any bone complications	9	3	9	6
No bone complications	15	2	15	2
Statistical test and significance	Fisher's exact test, p=0.622		Fisher's exact test, p=0.106	
Scoliosis	2	2	2	4
No scoliosis	22	3	22	3
Statistical test and significance	Fisher's exact test, p=0.127		Fisher's exact test, p=0.014	
Joint subluxation	2	1	2	2
No joint subluxation	21	3	21	4
Statistical test and significance	Fisher's exact test, p=0.395		Fisher's exact test, p=0.180	
Pain	4.95	20.67	4.95	21.00
Statistical test and significance	t-test, p=0.527		t-test, p=0.187	
HRQL	HUI 2=0.69 HUI 3=0.56 CQ=2.4	HUI 2=0.52 HUI 3=0.22 CQ=3.9	HUI 2=0.69 HUI 3=0.56 CQ=2.4	HUI 2=0.38 HUI 3=0.03 CQ=4.5
Statistical test and significance	HUI 2, t-test, p=0.427 HUI 3, t-test, p=0.293 CQ, t-test, p=0.174		HUI 2, t-test, p=0.042 HUI 3, t-test, p=0.019 CQ, t-test, p=0.016	
Number of bone complications	1.22	1.67	1.22	1.83
Statistical test and significance	t-test, p=0.577		t-test, p=0.200	

Note: CQ: Caregiver Questionnaire; HUI: Health Utilities Index; NS: Not significant.

Table 16. Comparison of normal to all osteopenic subjects.

Characteristic	Normal vs. All osteopenic	
	Normal (n=24)	All osteopenic (n=19)
Any bone complications	9	13
No bone complications	15	6
Statistical test and significance	Chi square= 4.058, p=0.044	
Scoliosis	2	5
No scoliosis	22	13
Statistical test and significance	Chi square=2.800, p=0.094 Fisher's Exact test, p=0.118	
Joint subluxation	2	7
No joint subluxation	21	10
Statistical test and significance	Chi-Square=5.914, p=0.015 Fisher's exact test, p=0.023	
Pain	4.95	15.18
Statistical test and significance	t-test, p=0.067	
HRQL	HUI 2=0.69 HUI 3=0.56 CQ=2.4	HUI 2=0.48 HUI 3=0.29 CQ=3.5
Statistical test and significance	HUI 2, t-test, p=0.020 HUI 3, t-test, p=0.010 CQ, t-test, p=0.093	
Number of bone complications	1.22	1.77
Statistical test and significance	t-test, p=0.102	

Note: CQ: Caregiver Questionnaire; HUI: Health Utilities Index; NS: Not significant.

Table 17. Regression equation for HRQL and TB BMC z-score and GMFCS (a) HUI 2 and (b) HUI 3.

(a) HUI 2

Model building	Variables entered	R square	R square change	Significance (p value)
1	GMFCS	0.631	0.631	0.000
2	GMFCS BMC z-score	0.634	0.003	0.625
Final model		Beta coefficient	t value	Significance
2	GMFCS BMC z-score	-0.771 0.055	-6.859 0.493	0.000 0.625

(b) HUI 3

Model building	Variables entered	R square	R square change	Significance (p value)
1	GMFCS	0.714	0.714	0.000
2	GMFCS BMC z-score	0.715	0.001	0.796
Final model		Beta coefficient	t value	Significance
2	GMFCS BMC z-score	-0.856 -0.026	-8.62 -0.26	0.000 0.796

Note: BMC: bone mineral content; GMFCS: Gross Motor Function Classification System; HRQL: Health related quality of life; HUI: Health Utilities Index.

Figure 1. The mechanostat theory. Used with permission from Dr. F Rauch (16)

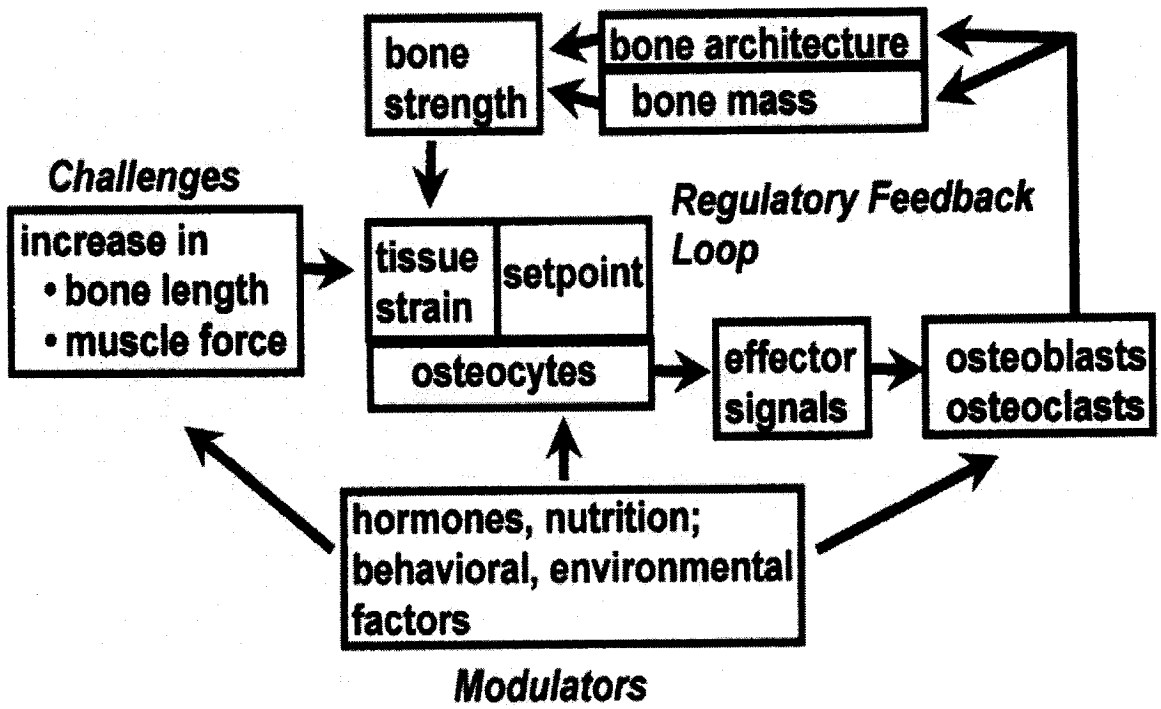
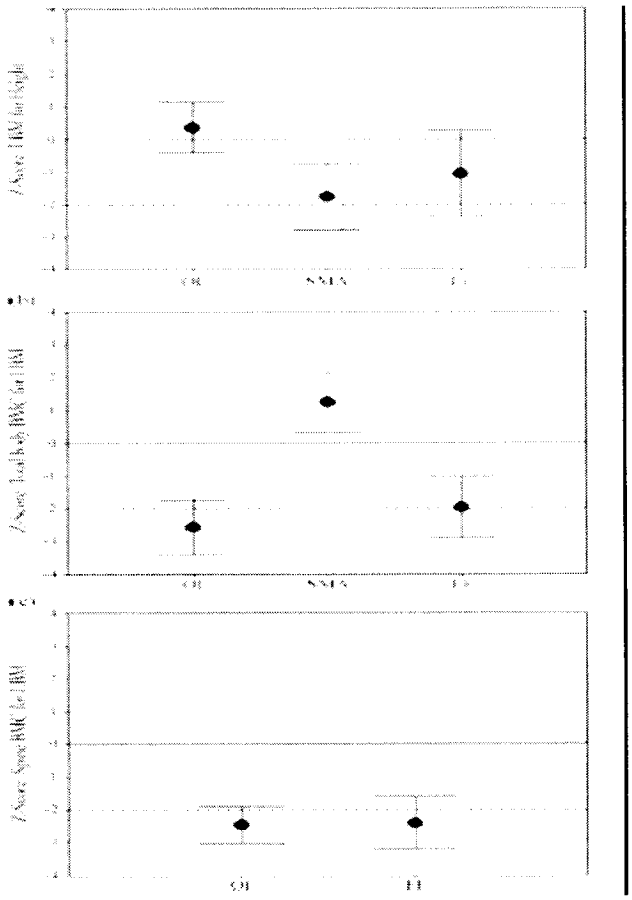
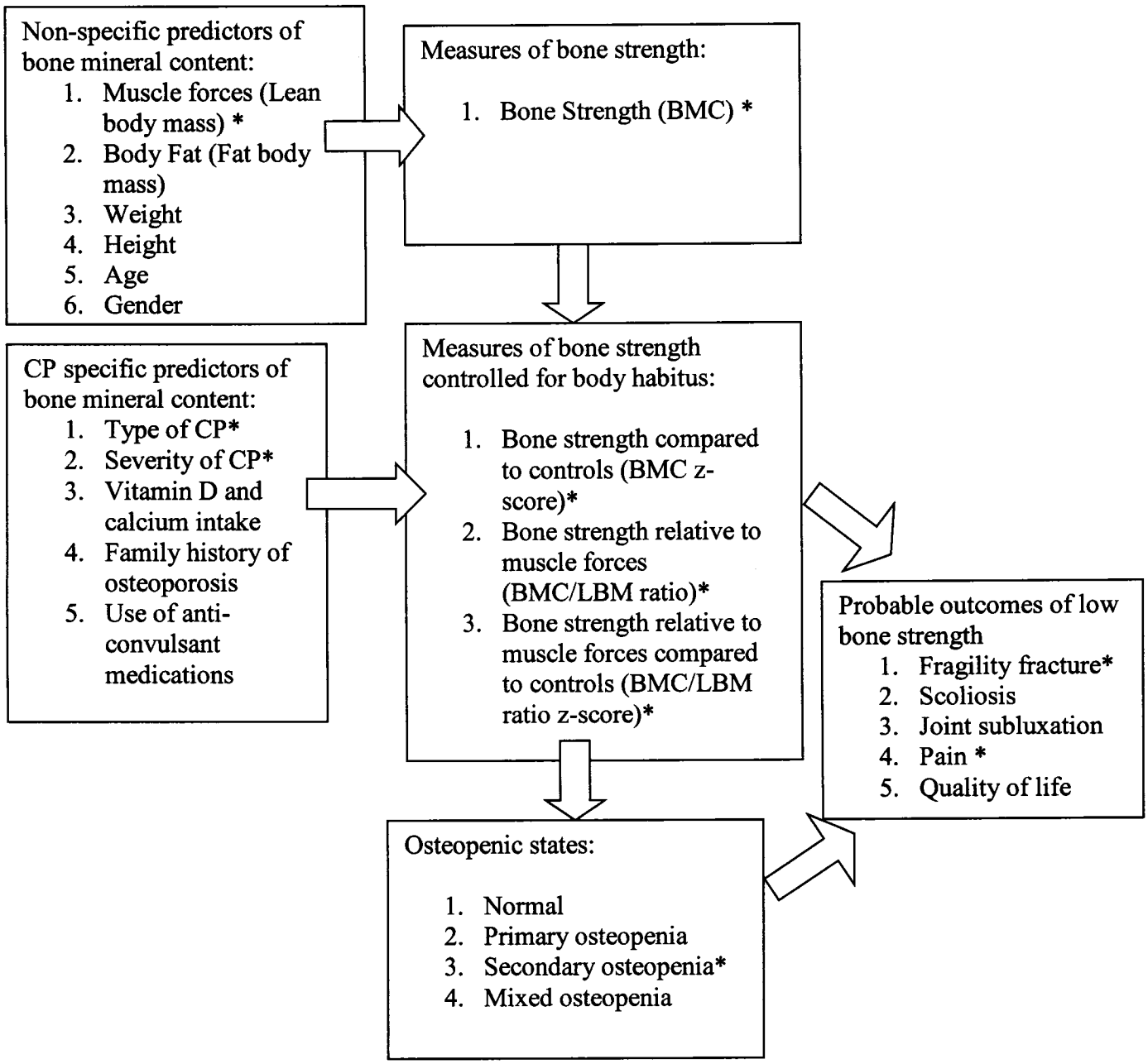


Figure 2. Diagram defining primary, secondary and mixed osteopenia using the mechanostat theory as outlined by Crabtree 2004.Classification applied to various patient groups. Used with permission from Dr. N Shaw (14). (OI=Osteogenesis imperfecta, SMA=Spinal muscular atrophy, FF= frequent fractures)



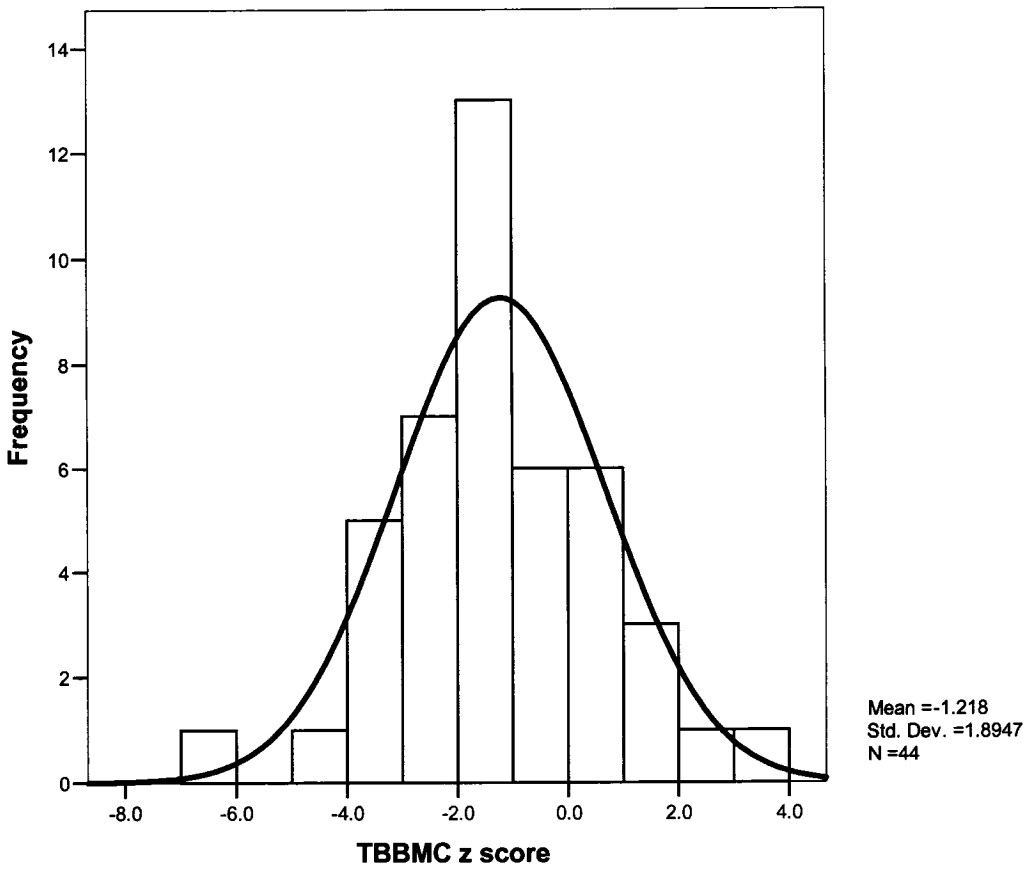
	Normal	Primary muscle defect	Primary bone defect	Mixed muscle and bone defect
OI	4	1	14	2
SMA	4	6	0	0
FF	2	2	5	3

Figure 3. Conceptual diagram of study objectives and hypotheses.



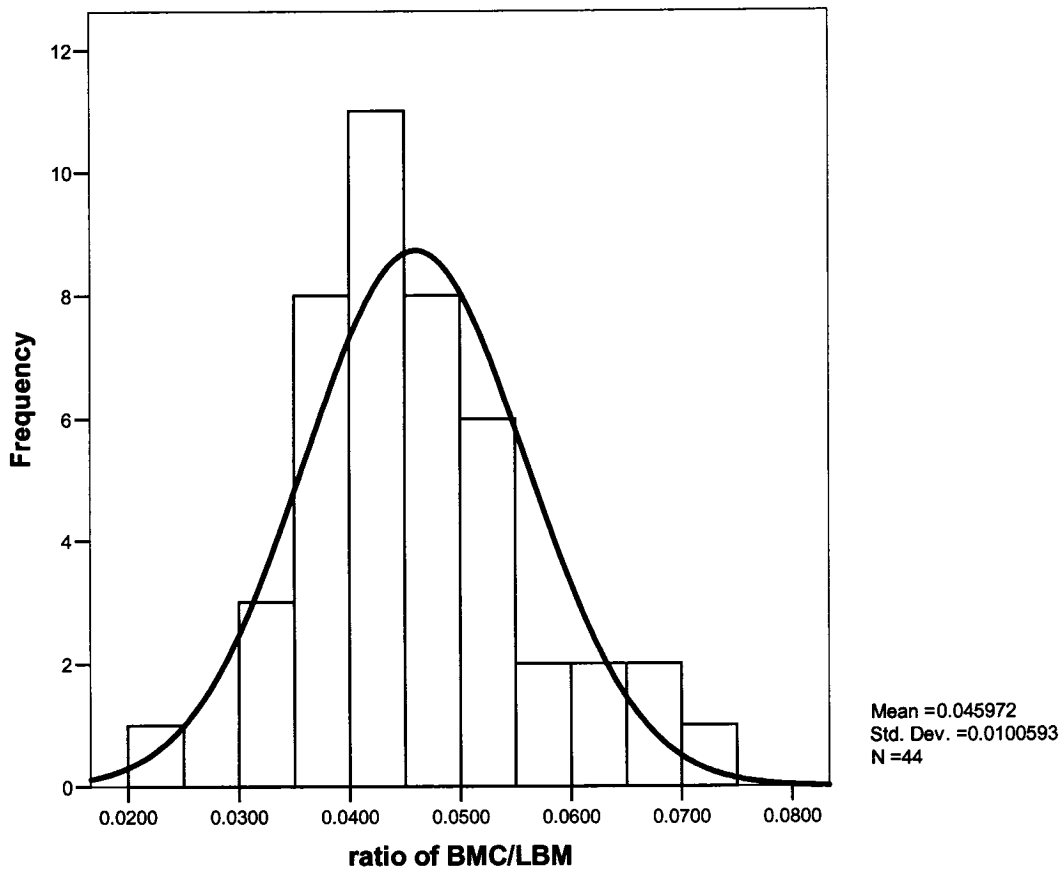
Note: * denotes those variables hypothesized to be significant or important factors (see hypotheses). BMC: bone mineral content; CP: Cerebral palsy; GMFCS: Gross Motor Function Classification System; LBM: lean body mass.

Figure 4. Histogram demonstrating normal distribution of total body BMC z-score.



Note: BMC: bone mineral content; TB: total body.

Figure 5. Histogram demonstrating normal distribution of ratio of BMC/LBM.



Note: BMC: bone mineral content; LBM: lean body mass.

Figure 6. Flow diagram of subjects in this study.

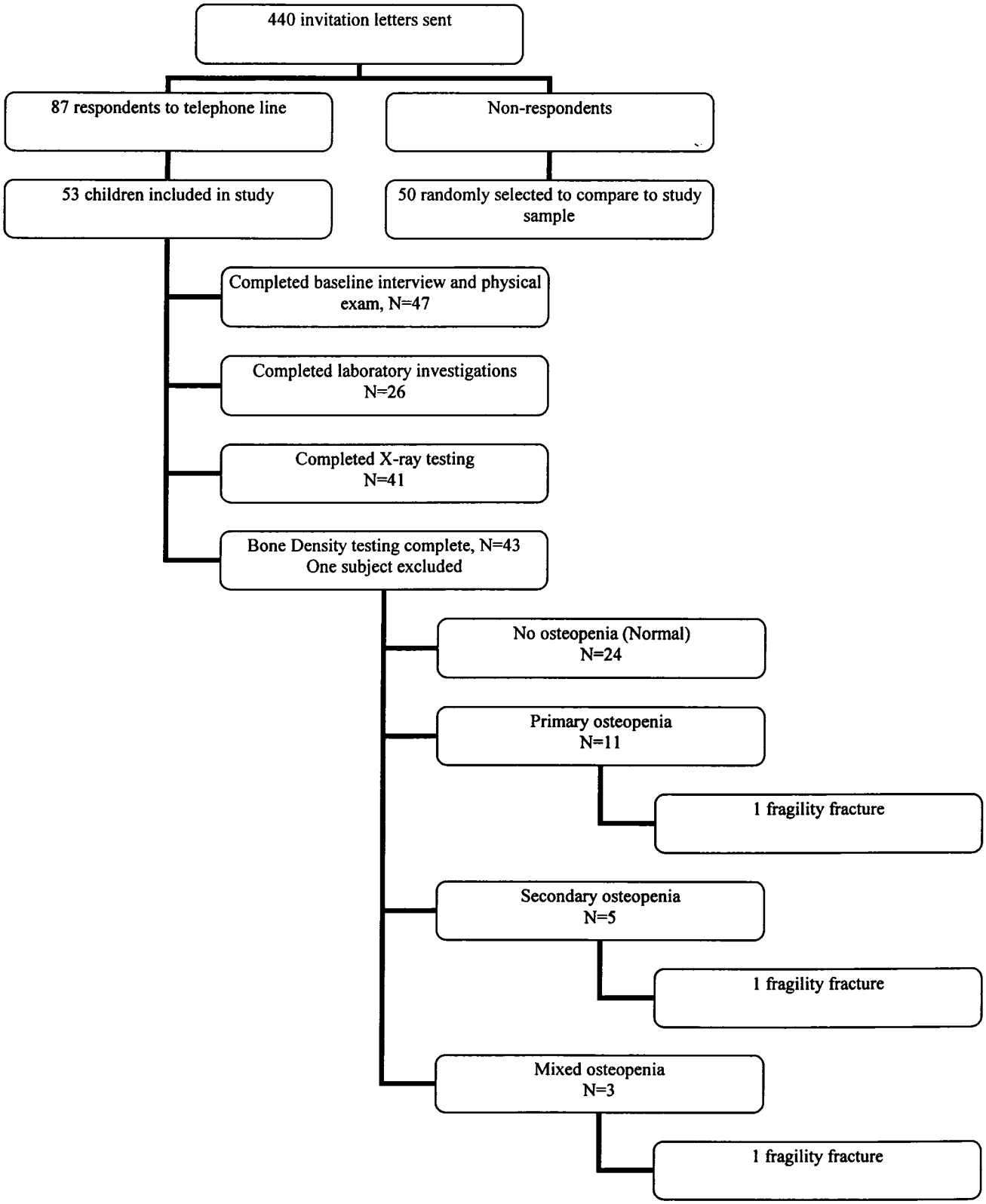


Figure 7. Height and weight distributions.

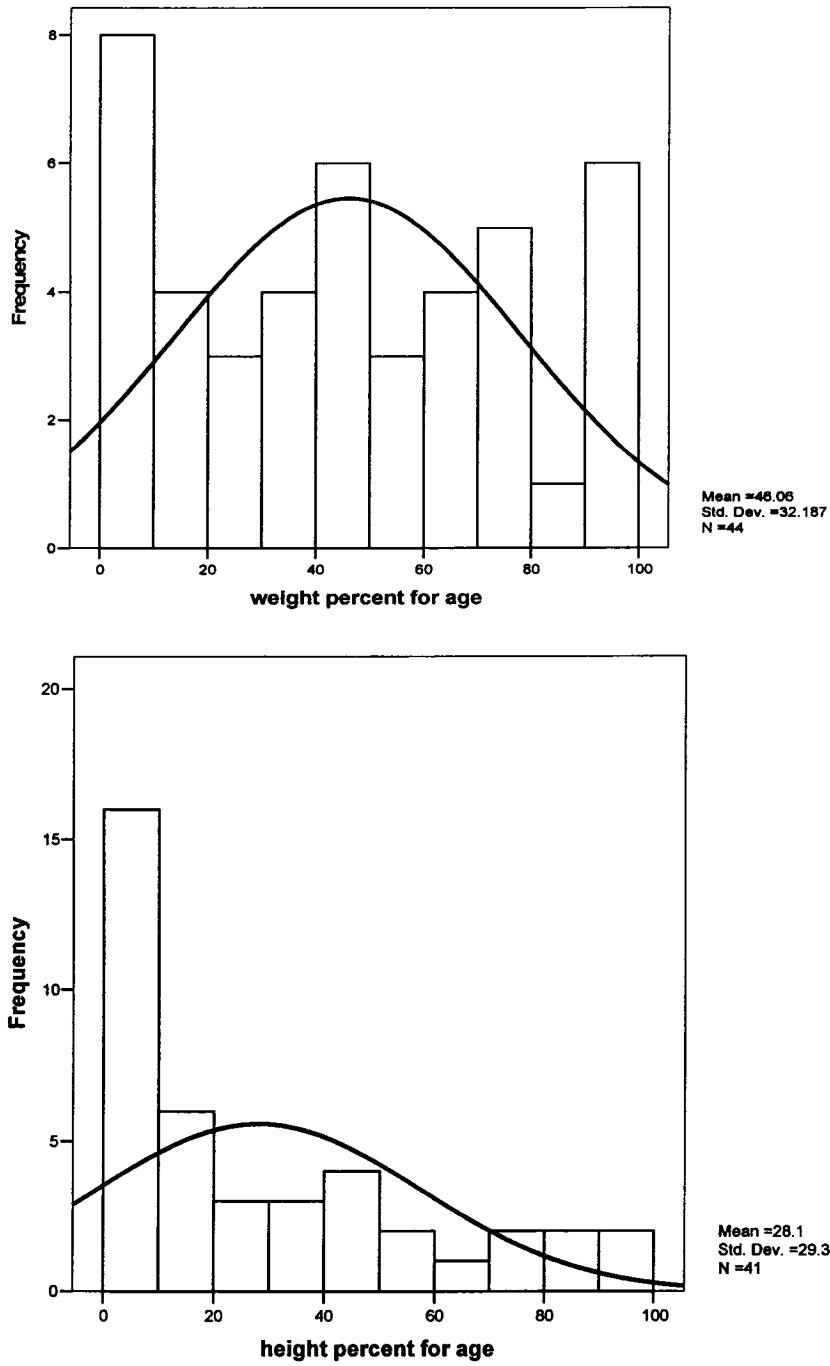
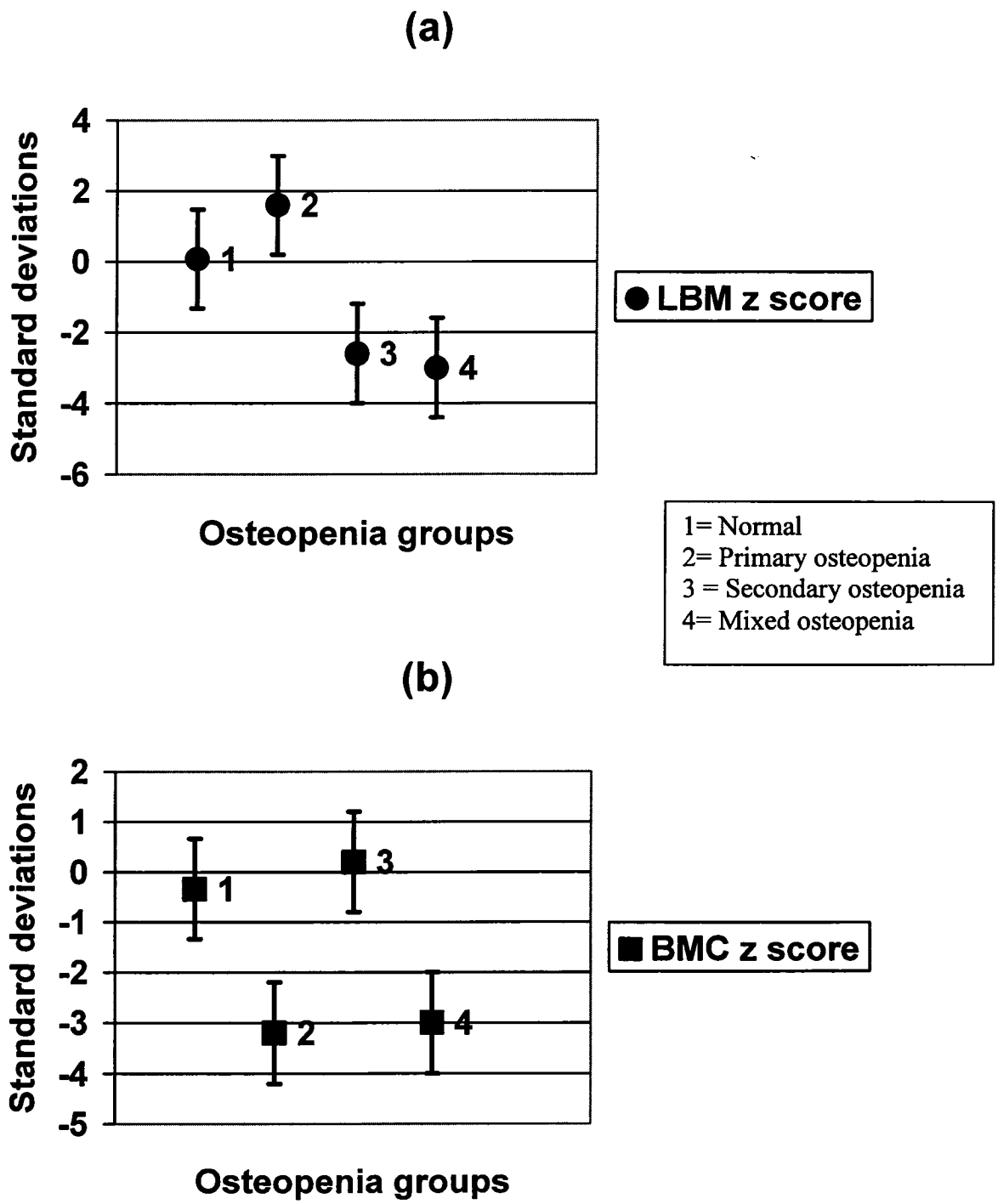


Figure 8. Graphs of (a) LBM z scores and (b) BMC z-scores for each osteopenia group.



Note: BMC: bone mineral content; LBM: lean body mass.

Appendix A. Ethics letter of approval (see attached page)
Appendix B. OCTC letter of approval (see attached page)
Appendix C. Grant letters of approval- CHEO RI (see attached page)
Appendix D. Grant letter- OFCP (see attached page)

Children's Hospital of Eastern Ontario
Hôpital pour enfants de l'est de l'Ontario
401 SMYTH, OTTAWA, ONT. K1H 8L1 TELEPHONE (613) 737-7600

June 24, 2002

Dr. Craig Campbell
Neurology
CHEO INTRA

Re: Proposal 02/28E - Bone Mass in Children with Cerebral Palsy

Dear Dr. Campbell:

Thank you for your letter of June 14, 2002, outlining the modifications to the above-mentioned proposal as requested by CHEO Research Ethics Committee in our letter of May 6, 2002.

Please accept this letter as written approval to proceed with the above-mentioned proposal .

Kindly refer to the above-mentioned **Proposal Number** in all correspondence.

It is your obligation to notify the Research Ethics Committee prior to the institution of any modifications to this study, or any adverse events which may occur during the course of this study.

To ensure that the REC is kept informed of the progress of clinical studies, we request a yearly progress report from each investigator.

Sincerely,

David Palfreyman, F.R.C.P. (C)
Chair
Research Ethics Committee

CHEO Research Institute
Institut de recherche

November 25, 2002

Alex MacKenzie, MD, PhD
Director / Directeur
(613) 737-2772

Ian Manion, PhD, C.Psych
Associate Director /
Directeur-Associé
(613) 737-2259

Mr. Serge Taillon
CHEO Trustee /
membre du conseil
d'administration de CHEO

Mr. D. Moher
Director,
Clinical Research Unit
Directeur/
recherches cliniques
(613) 738-3956

Ms. P. Brazeau
Office Manager /
Gérant du bureau
(613) 737-2686

Dr. Craig Campbell
Pediatric Neurology Fellow
Division of Neurology
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario
K1H 8L1

Award Notification

Principal Applicant: **Dr. Craig Campbell**
Research Project Title: ***Bone Health in Children with Cerebral Palsy***

Dear Dr. Campbell:

Congratulations! The above-mentioned grant application, you submitted as principal investigator has been rated highly by the Research Institute review panels. Funds have been allocated for this project as noted below:

Amount Awarded:	
Salaries & Benefits	$ 5,688.00
Supplies & Services	24,172.00
Total	$29,860.00
Type of Award:	Feasibility/Start-up Grant
Funding Period:	Dec. 1, 2002 – Nov. 30, 2003

CRITICAL FUNDING INFORMATION

1) The budget review was detailed and if you had requested funds for travel to meetings, statistician services from the Chalmers Research Group, or more than incidental administrative costs, these were removed. The CHEO Research Institute financially supports a Statistician in the Chalmers Research Group

2) This grant is not renewable under normal circumstances and will be paid on a cost recoverable basis. An account will be established in your name from which you may draw funds. Should you not be successful in publishing your results, funds encumbered for reprints will be returned to the Research Institute. *Any departures from the items specified in your approved budget will require review prior to approval of expenditure.*

.../2

Principal Applicant: **Dr. Craig Campbell**
Research Project Title: ***Bone Health in Children with Cerebral Palsy***

CRITICAL FUNDING INFORMATION **(cont'd)**

3) Please advise us if you are successful in securing funds for the same project from outside agencies. Should this occur, the above-mentioned funds will be returned to the CHEO Research Institute.

4) The CHEO Research Institute funds projects for a **1 year period**. A final report is to be submitted upon completion of this study. The final report should list the original objectives of the study and state whether these objectives have been met. The report should be no longer than 10 pages. Abstracts and/or publications will be accepted as final reports.

5) If at the end of 1 year, you have not utilized all of the funding, you may apply for a time extension. *Such requests will be accompanied by a progress report, and reviewed on an individual basis.*

6) It is the policy of the CHEO Research Institute to consider freezing funds if final/interim reports are not submitted in a timely fashion.

7) **No funds will be released until:**
   a) Ethics approval (human/and or animal, if required) is received in the CHEO R.I. Admin. Office.
   b) **A signed (by principal investigator) copy of this Award Notification is received in the CHEO R.I. Admin. Office.**
   c) Clarification is received and approved by the Director of the Research Institute regarding who will be leading this study to conclusion after your departure from CHEO in 2003.

Thank you for your submission to the Research Institute. It was most satisfying to review this scientific proposal. Once again, congratulations for your successful competition.

Sincerely,

Alex MacKenzie, M.D., Ph.D.
Director
Children's Hospital of Eastern Ontario
Research Institute

Cc: Chalmers Research Group

I have read and noted the Critical Funding Information section.

_____ _____
Dr. C. Campbell Date

Ottawa Children's Treatment Centre
Centre de traitement pour enfants d'Ottawa
Founded in 1951 Fondé en 1951

Serving children and youth with physical disabilities and associated developmental and learning difficulties

Au service des enfants et des adolescents ayant une incapacité physique ainsi que des difficultés associées au niveau du développement et de l'apprentissage

October 16, 2002

Craig Campbell, M.D., F.R.C.P. (C)
Principal Investigator,
Study of Bone Health in Cerebral Palsy
CHEO

Dear Dr. Cambell:

I am writing this letter on behalf of the OCTC Research and Review Committee. The committee has given its approval for your project: Bone Mass in Children with Cerebral Palsy. Please forward to the committee a copy of the client recruitment notice that will be used at OCTC, if possible by next Tuesday October 22, 2002. The committee would like to see the announcement prior to distribution.

The committee wishes you success in conducting this study. Please send a brief report to the committee upon the completion of your study. If the study will go beyond one year, please send an interim report at the end of October 2003.

Sincerely,

Mary Lysyk, MA., OT Reg. (Ont.)
Chair
Research and Review Committee
OCTC

cc. Jennifer McLean, M.D., F.R.C.P. (C)
Medical Director,
OCTC

ONTARIO FEDERATION FOR CEREBRAL PALSY

June 18, 2002

Craig Campbell MD FRCPC
Division of Neurology
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, Ontario
K1H 8L1

Dear Dr. Campbell:

In response to your request for funding of *Bone Mass in Children with Cerebral Palsy* research, to be done at Children's Hospital of Eastern Ontario, the following motion was presented and carries.

Motion # 5 - "That the recommendation to the Board of Directors be approved, that the proposal from Children's Hospital Eastern Ontario and Dr. Craig Campbell be approved for funding in the amount of $20,000.00 (twenty thousand dollars) as a first instalment."

The Board would like to be kept abreast of the progress made with this research and are prepared to consider further funding. We wish you success with your endeavors.

Yours very sincerely,

Clarence Meyers
Executive Director

/vr

Enclosure: Cheque

1630 Lawrence Ave. West, Suite 104, Toronto, Ontario M6L 1C5 Ph: 416-244-9686 Fax: 416-244-6543, Long Distance: 1-877-244-9686
Email ofcp@ofcp.on.ca Net www.ofcp.on.ca Charitable Registration Number 10779-7722

Appendix E. Poster

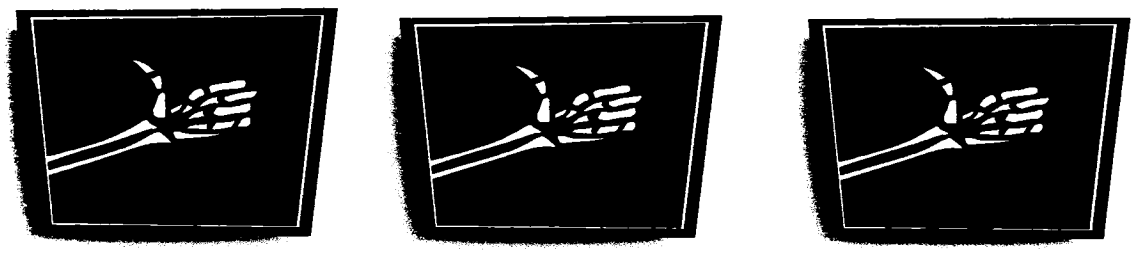
CHEO

Ottawa Children's Treatment Centre
Centre de traitement pour enfants d'Ottawa
Founded in 1951 Fondé en 1951

A STUDY OF

BONE HEALTH IN CHILDREN

WITH CEREBRAL PALSY



THIS IS AN OPPORTUNITY TO FIND OUT MORE ABOUT YOUR CHILD'S BONE HEALTH AND TO HELP OTHER CHILDREN WITH CEREBRAL PALSY!

IF YOU HAVE A CHILD WITH CEREBRAL PALSY BETWEEN THE AGES OF 2-15 YEARS PLEASE CONTACT US AT THE NUMBER BELOW!

A Study on Bone Health in Children with Cerebral Palsy

738-3233

Appendix F. Letter of invitation

(CHEO Letter Head)
(Date)

Dear Parent:

Bone health in children with Cerebral Palsy is important! As a parent of a child with Cerebral Palsy, you may be aware of this already. Problems caused by poor bone health may have even affected your child already. Unhealthy bones may cause spine curvature (scoliosis) and joint problems to become worse and even lead to pain and broken bones.

At this time, doctors have not completely sorted out all the risks for poor bone health in children with Cerebral Palsy (CP). A group of concerned doctors who take care of children with CP at the Children's Hospital of Eastern Ontario (CHEO) and the Ottawa Children's Treatment Centre (OCTC) would like your help in finding out more about bone health in children with CP. We are sending this note to all parents of children with Cerebral Palsy age 2-15 years who receive care at CHEO or OCTC to participate in a study designed to gather information only (no treatments will be given). We are hoping that you call us whether your child has already had lots of bone problems and/or bone strength testing or even if your child has never had bone problems.

The study would include two visits to CHEO. First, we would see you and your child in clinic, at your convenience, to discuss the study and details about your child's bone health. Next, we would measure your child's bone strength using a special radiology test called a bone densitometer. Using this information we will be able to talk to you about your own child's bone health and also we will be able to help many children with cerebral palsy who suffer from bone problems. Please call us at 738-3233 to find out how your child can be involved in the study. We are excited about answering any questions or concerns you have when we speak to you.

Again, the study phone number is 738-3233. We look forward to speaking with you.

Craig Campbell, MD, Pediatric Neurology Fellow

(signature) Jennifer McLean, MD, Medical Director OCTC

(signature) Peter Humphreys, MD, Head Pediatric Neurology

(signature) Louis Lawton, MD, Orthopedic Surgeon OCTC

(signature) Leanne Ward, MD, Pediatric Bone Specialist

(signature) Renee Brannan, RN, Research Coordinator

Appendix G. Dietary Questionnaire

Dear Parent/Caregiver,

Enclosed you will find a three-day food diary form which is part of the "Bone Health in Children with Cerebral Palsy Study". The diary is for you to record your child's usual food intake for three consecutive days so that we can assess your child's nutritional status. Please bring in the completed food diary

_____

_____.

Instructions

1. Choose either a Thursday, Friday and Saturday or a Sunday, Monday and Tuesday as the three days for completing the food diary.

2. Record your child's food intake, on the enclosed forms, as soon as possible after the meal or snack is taken. Please be sure to include all the foods and beverages eaten throughout the day.

3. Record accurately the amount of food or beverages taken using the following measures:
   - liquids in fluid ounces (oz) or millilitres (mL) *8 fluid ounces = 1 cup = 250 mL*
   - meats/fish in ounces (oz) after cooking (see attached guide for details)
   - gravy, sauces, salad dressing, mayonnaise, butter, and margarine in teaspoons (tsp) or tablespoons (Tbsp)
   - cooked pasta, dry or cooked cereal, vegetables and cooked rice in cups (c) or millilitres (mL)

4. Record the method of cooking - fried, baked or broiled, for example.

5. Record the type of milk, yogurt or cheese. For example, 2% milk, creamed 2% b.f. cottage cheese, etc.

6. If the item is homemade, please include a copy of the recipe and indicate the portion size taken by your child. For example, homemade shepherd's pie, lasagna, spaghetti, cakes, cookies, etc.

7. If the main course item is a commercial product indicate the portion the child has taken and the brand name of the product. For example, McCain's Three-Cheese Mini Pizza – one mini pizza out of a package of six.

8. If your child takes a commercial meal replacement or supplement such as Pediasure, Nutren/Nutren Junior, Ensure, etc. record the volume taken per meal/feed.

Please call your dietitian, as indicated below, if you have any questions about the food diary.

- Debbie Gomez (613) 737-7600 ext.3638
- Charlene Anderson (613)737-7600 ext.3045

Thank you for taking the time to complete this food diary as part of the research project.

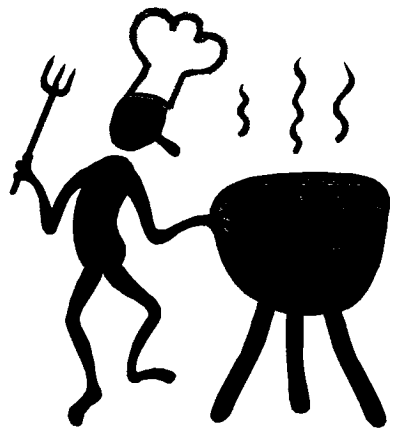
Yours truly,

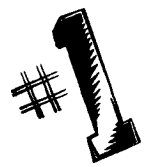
Debbie Gomez, Registered Dietitian

Charlene Anderson, Registered Dietitian

Meat Portion Size Guide

Meat and Poultry	Amount Equivalent to 1 Ounce
Cold cuts, beef, veal, lamb, pork, ham, poultry, liver	1 slice 4" x 2" x 1/4" (cooked)
Minced beef, veal, lamb, pork, ham, poultry, liver	2 tbsp or a small patty (cooked) 3 tbsp raw
Chops - lamb - pork or veal	1 small chop, 3 oz raw with bone 1/2 medium chop, 4 oz raw with bone
Bacon	3 slices
Hot Dog	specify regular size or jumbo
Fish	
Fillets and steaks: haddock, halibut, cod, sole, whitefish, salmon	1 piece 2" x 1" x 1" (cooked)
Canned tuna, salmon	1/4 cup
Cheese	
Cheddar or hard cheese	1 cube, 1 1/2" x 1" x 1"
Processed cheese (cheese slices)	1 slice (indicate package size and number of slices in a package)
Dried, grated (Parmasan)	4 level tbsp
Cottage Cheese	1/4 cup





ID#_____

Date_____

Food Diary Day 1			
Meal	**Amount**	**Food/Beverage**	**Method of Cooking**
Breakfast			
Snack			
Lunch			
Snack			
Dinner			

Snack			
Vitamin/Mineral Supplements			
Additional Comments			

ID#_____

Date_____

Food Diary Day 2			
Meal	**Amount**	**Food/Beverage**	**Method of Cooking**
Breakfast			
Snack			
Lunch			
Snack			
Dinner			

Snack			
Vitamin/Mineral Supplements			
Additional Comments			

ID#_____

Date_____

Food Diary Day 3			
Meal	**Amount**	**Food/Beverage**	**Method of Cooking**
Breakfast			
Snack			
Lunch			
Snack			
Dinner			

Snack			
Vitamin/Mineral Supplements			
Additional Comments			

Appendix H. Letter of Information and Consent

[CHEO LETTER HEAD]
INFORMED CONSENT STATEMENT
Bone Mass in Children with Cerebral Palsy
Investigators: C. Campbell, L. Ward, P. Humphreys, R. Nair, M. Matzinger, L. Lawton, J. McLean

INTRODUCTION:

Your child has been invited to participate in a study called "Bone Mass in Children with Cerebral Palsy". Your child has been selected for this study because she/he was between age 2 and 15 years and has a diagnosis of cerebral palsy. If you choose to enter your child in the study they will be one of approximately 150 children participating. As you can see from the list of investigators this study has been planned and is being run by physicians at the Children's Hospital of Eastern Ontario (CHEO) and the Ottawa Children's Treatment Centre (OCTC) that have worked for many years with your children and are concerned about the health and well-being of children with CP and their families. The study is being supported through research funds from the Ontario Federation for Cerebral Palsy.

The following information will describe the study and your role as a participant. We will answer any questions you may have about this form and about the study. Please read carefully and do not hesitate to ask anything about the information provided below.

STUDY PURPOSE:

As you are aware, cerebral palsy (CP) is a common disorder caused by brain damage during early development that affects a child's strength and movement. Many children with CP have other problems including learning difficulties, seizures and bone problems. Bone problems include broken bones, scoliosis (curvature of the spine) and joint dislocations. These problems all cause significant suffering for affected children and their families when they occur. Also a great deal of health care resources is frequently required to diagnose and treat these problems. The causes of the bone problems in children with CP are due partly to abnormal muscle tension but may also be due to low bone strength as well.

Researchers in previous studies have felt that poor nutrition, inability to walk and the use of epilepsy medication are all factors that may make bones weaker. These studies on bone strength in children with CP have been done on small groups of children and so a clear picture of the extent of the problem and the risk factors that may cause low bone density are similarly not fully known. As well, the potential impact of low bone strength on pain and on quality of life in children with CP has never been examined.

The purpose of the study that we are inviting your child to participate in is to help find out more about the risks for low bone strength and the relationship to bone complications in children with CP. By interviewing families and reviewing medical histories of children with CP and then testing bone strength using a bone densitometer these questions will be better understood. Information on children with low and normal

bone strength will be compared to find differences that represent risk factors and also complications that arise from poor bone health.

PROCEDURE FOR THE STUDY:

The study involves three visits to CHEO. The first visit is at the time of the entry into the study and is probably the visit you are attending right now. The second visit is to gather information on bone strength and the final visit is to give you feedback on the study results. Each day throughout the study period there is a person who can be reached at the following number 737.3233 to answer any questions or concerns that you may have.

First Visit

At the first visit a study coordinator will meet with you and your child to review the criteria for entry to the study and then to provide you with this document to read privately. If you need clarification on any part of the consent form please ask the co-ordinator as it is very important that you feel informed of all parts of the study. After reading the consent form and addressing any questions if you choose to enroll your child this document will be signed by you and the study coordinator. The first visit is the longest and a number of things are required. Because of your time commitment we will be paying for your parking and providing a meal ticket for use in our cafeteria.

The study coordinator will then spend approximately 30 minutes with you and your child asking about information important to bone health. The coordinator will examine your child for growth measurements and puberty status if applicable. Following this, the coordinator will ask you to fill out several questionnaires that will help us to understand how your child functions and feels on a daily basis. Also we will ask for a record of some of the foods your child regularly eats. *Please remember you have a right to withdraw your child from the study at anytime as well you can refuse to answer any questions, withdraw any answer, stop the interview and refuse any physical examination at any point in the process.*

Following this the coordinator will decide on a set of seven laboratory tests that may be required. Three tests are from the urine and four from the blood. These tests all measure different parts of bone health. If your child has had any of these tests in the past three months then those tests will not be done, but the others will be necessary. The amount of blood to be taken is not dangerous to your child's health. Your child will be offered EMLA cream, a mild topical anaesthetic, to be placed on the skin in anticipation of the blood test to help reduce pain. *This blood will only be used for this examination and will not be tested for any other purpose.*

Following the laboratory tests three x-rays will be taken. These include an x-ray of the spine to look for scoliosis and spine fractures, a hip x-ray to look for dislocations and a wrist x-ray to look at bone age. Again, if any of these have been done in the last 3 months those will not be done.

After these tests are complete we ask you to return to the clinic, as we will have an appointment time for your second appointment and a ticket for reimbursement of your parking expenses.

Second Visit

The second visit will be for the purposes of testing your child's bone density (thickness). This test is completed in the radiology department at CHEO on a machine called a Lunar bone densitometer. The machine used to measure bone density is called dual energy x-ray absorptiometry (DEXA). Your child will lie on an x-ray type table while a scanning arm moves over them. The procedure is entirely painless. This machine measures the content of bone tissue throughout the whole body as well as measures of bone tissue at certain body points. In this study we will be testing the lower back and the hips. The machine also gives an estimate of the amount of muscle your child has which is important because muscle and bone work together to help with body movement. These bone tests take approximately 10 minutes with short breaks in-between. Proper positioning is important and if your child is having difficulty holding still or being positioned properly than the test will be rescheduled and the study coordinator will talk further to you about the possibility of using a sedative treatment before the test to help your child continue in the study.

After the second visit we would again ask you to report to the clinic as a parking ticket will be available and we will clarify any missing information from the first visit. This is the completion of the information needed for the study. An appointment for the final follow-up visit will be scheduled. The final visit is simply to give feedback on your child's test results.

Final Visit

At this visit the results of your child's tests will be given to you. Depending on how many children have completed the study we may or may not be able at this time to give the results for the whole study. If this is the case you will receive the study results at a later date if you wish. Several possibilities exist for your child once they have completed this phase of the study. If your child has normal bone density then you have a choice between two options:

1) You can continue with the regular medical care you have been receiving and you do not need to worry more about bone health.
2) You can enroll your child in a follow-up study that is to look at bone health each year in the same way as it was done in this study. This will help us to find the causes of poor bone health in a way that is even better than the current study.

If your child is found to have low bone density then you have two options:

1) You can be referred to a bone specialist at CHEO for advice regarding your child's test results.
2) You can enroll your child in a follow-up study to see if treatment of low bone density helps to improve your child's scoliosis, joint problems and pain, and possibly prevent broken bones. If you choose to enter in this follow-up study

then similar testing to what will happen during this study will take place, but in addition your child would take some treatment to improve bone health.

Following our discussions at the last visit you will have completed the study and there is no obligation to choose any of the options listed above. You may simply return to your child's health care providers. You will be given a phone number to contact at any time should you change your mind or need further information.

RISKS OF PARTICIPATING IN THE STUDY:

The potential risks of the study are related to laboratory assessments and radiation exposure. The risks of drawing blood include, pain, bruising, and rarely, infection. To minimize these risks, the experienced staff at CHEO will draw all blood.

Radiation risk: Participation in this research study does involve exposure to radiation. The three x-rays (if needed) and the bone densitometry all have some radiation associated with them. We are exposed to radiation every day from both natural and human-made sources. The average affective dose to people from these sources is about 360 millirem per year. By comparison, the effective dose that your child will receive when participating in this research study equivalent to approximately 10 days of normal background exposure. The approximate dose of radiation from the study procedures is 75 mR. This dose is well below the levels that are thought to result in a significant risk of harmful effects. The calculated effective dose resulting from your participation in this study is available upon request. The study has been reviewed by the Radiation Protection Committee of the hospital and has been determined to be safe for your child's participation.

BENEFITS OF PARTICIPATING IN THE STUDY:

Some studies have suggested that children with CP have poor bone health for a number of reasons but these studies have been small and have not fully examined the factors that this study intends to examine. Volunteering for this study will help to complete a large study that may give health care providers who work with children with CP more answers about bone health. Also by participating in this study your child's bone health will be determined. If your child's bone density is poor then we may also be able to help determine the factors that have led to this. Also by being a part of this study opportunities for further studies of bone health at CHEO in children with CP will be more easily open to your child.

There is no direct monetary compensation for patients enrolled in the study, however, we will cover parking expenses and provide a meal coupon on your longest visit.

ALTERNATIVES TO PARTICIPATING IN THE STUDY:

Participation in this research is entirely voluntary. You may choose not to participate at any time. Your choice will not at any time affect the commitment of the health care providers to administer care to your child.

COSTS OF PARTICIPATING IN THE STUDY:

In the unlikely event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you. Costs not covered by OHIP or by your private health care insurer will be your responsibility. There is no program in place for other monetary compensation for such injuries. *However, By signing this consent form you are in no way waiving your legal rights or releasing the investigator from their legal and professional responsibilities.*

CONFIDENTIALITY:

Your child's identity and participation are confidential to the extent permitted by law. Any information that we learn about your child that can be individually traced will be used responsibly and be protected against release to unauthorized people. Your child's identity will not be revealed in any publication that may result from this study, although statistical reports of this research study may be disclosed in scientific forums.

If the investigator feels that you have not followed directions for hospital tests, outpatient follow-up visits we will contact you to discuss the possible obstacles to your child's participation but may need to exclude your child if necessary information is not obtained during the study period.

You may terminate participation in this study at any time by contacting Dr. Craig Campbell or any of the other investigators involved in the study.

PEOPLE TO CONTACT:

If you have questions regarding the study you can reach **Dr. Craig Campbell or the study coordinator** at 613 737 3233. In the event of an emergency related to the study, you may call the hospital operator at the 24 hour number **613 737 7600** and ask for **Dr. Campbell or the study coordinator** to be paged.

A patient representative who is not associated with this research study to whom you may address complaints about this study, as well as questions about your rights as a research participant, may be reached at 613 738 3272 (the Chair of the Research Ethics Committee). However, this person cannot provide any medical information with regard to this study.

NEW FINDINGS IN THE STUDY:

You will be informed of any new findings either from this study or from other research for patients with CP that may affect your willingness to have your child continue to participate.

SUBJECT'S CONSENT:

In consideration of all of the above, I give my consent for my child (me) to participate in this research study. I may withdraw my child (myself) from the study without fear of changing the investigator's interest or the quality of medical care which my child (I) may seek or receive in the future from the doctors participating in the study. I acknowledge that I have been provided enough time to reflect on my decision to participate in this study.

I acknowledge receipt of a copy of this informed consent statement.

PARTICIPANT'S SIGNATURE _____ DATE: _____

(Or person authorized to sign on behalf of the participant e.g. parent or guardian)

SIGNATURE OF WITNESS _____ DATE: _____

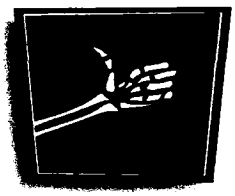
I HAVE EXPLAINED THIS STUDY TO THE PERSON AUTHORIZED TO SIGN ABOVE AND I AM SATISTFIED THAT IT IS UNDERSTOOD.

SIGNATURE OF INVESTIGATOR: _____ DATE: _____
(OR DESIGNEE)

IF YOU SHOULD HAVE ANY CONCERNS OR QUESTIONS REGARDING THE STUDY PLEASE CONTACT DR. CRAIG CAMPBELL AT 738.3233.

Dated July 2002

Appendix I. Data Collection Sheet



CASE REPORT FORM

PATIENT ID # _____ **DATE STARTED:**_____ **DATE COMPLETE:**_____

SECTION 1: DEMOGRAPHICS

Date of birth: Day_____ Month_____ Year_____.

Gender: ☐ Female ☐ Male

Race: ☐ Caucasion ☐ Black Other:_____

GA at birth: _____ weeks ☐ N/À

Family hx of osteoporosis: ☐ Maternal ☐ Paternal ☐ Both

Type: ☐ Spastic ☐ Dyskinetic ☐ Ataxic ☐ Mixed ☐ Unspecified ☐
Other:_____

Distribution: ☐ Quadriparetic ☐ Diplegic ☐ Hemiplegic ☐ Monoplegic ☐
Other:_____

Etiology of CP: _____

Associated Problems: ☐ Hearing Impairment☐ Visual Impairment
☐ Cognitive Impairment Est Mental Age:_____
☐ Seizures Frequecy (per month) _____
☐ Feeding Difficulty g-tube oral other:
☐ Reflux drugs fundo other:
☐ Constipation

GMFCS: 1 2 3 4 5

Hoffer: 1 2 3 4

Anticonvulsant Use: ☐ Never ☐ Past ☐ Current
Medication / Duration of Use (months)

1. _____

2._____ (Use back if needed)

SECTION 3: ORTHOPEDIC HISTORY

Diagnosis of Scoliosis☐ Yes ☐ No ☐ N/A

Scoliosis Surgery: ☐ Yes ☐ No ☐ N/À Date (d/m/y):

Diagnosis of hip joint sub/dislocation☐ Yes ☐ No ☐ N/À

Hip Joint Surgery: ☐ Yes ☐ No ☐ N/À Date (d/m/y):

Diagnosis of femoral torsion ☐ Yes ☐ No ☐ N/À

DeRotational Surgery: ☐ Yes ☐ No ☐ N/À Date (d/m/y):

Diagnosis of fracture ☐ Yes ☐ No ☐ N/À

Number of Fractures: _____

FOR EACH FRACTURE PLEASE FILL OUT À FRACTURE HISTORY FORM AND ATTACH TO BACK OF ORIGINAL FORM ☐

SECTION 4: ANTHROPOMETRY

Weight:_____ kg Height: _____ cm Head Circ. _____ cm

% wt for age:_____% Ht for age:_____

wt/ht centile:_____ knee ht:_____ cm

est ht: _____ cm

Tanner Stage:

Male genitalia stage_____ Male pubic hair stage:_____
Testicular Volume _____cm3

Female breast stage _____ Female pubic hair stage:_____

SECTION 5: DIETARY INFORMATION

Average Daily Calcium Intake: _____ units?

Average Daily Vitamin D Intake: _____ units?

Average Daily Caloric Intake: _____ units?

ATTACH A COPY OF THE 3-DAY FOOD HISTORY TO BACK OF ORIGINAL FORM ☐

[redacted]

HUI III CODE: _____

HUI III UTILITY: _____

Care Giver Questionnaire Score: _____

Non-Communicating Child Pain Checklist Score: _____

FOR EACH MEASURE PLEASE FILL OUT CORRESPONDING FORM AND ATTACH TO BACK OF ORIGINAL FORM ☐

[redacted]

Blood: Calcium _____ units

Phosphate _____ units

Alk Phos _____ units

PTH _____ units

Vit D _____ units

1,25 Vit D _____ units

Urine: Ca/ Cr ratio _____ units

Ntx _____ units

Phosphate _____ units

PLEASE ATTACH LAB REPORTS TO BACK OF ORIGINAL FORM ☐

SECTION 3: RADIOLOGY

Degree of Scoliosis (greatest curve): _____ degrees
Date (d/m/y):_____

Number of Vertebral Compression Fractures: _____ Location: _____
Date (d/m/y):_____

Percent of Hip Dislocation: Right_____ % Left_____ %
Date (d/m/y):_____

Bone Age: _____
Date (d/m/y):_____

PLEASE ATTACH REPORTS TO BACK OF ORIGINAL FORM ☐

[illegible]

Done at Outside Facility: Y N Location: _____
Date (d/m/y):_____

Reason: _____

IF DONE AT AN OUTSIDE FACILITY GET CONSENT FOR RELEASE OF INFORMATION. ☐

Bone Densitometry Results

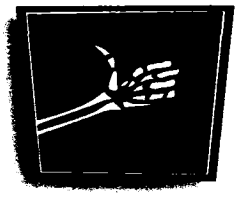
Location		aBMD (g/ cm^2)	Z-Score	vBMD (g/cm3)	% age match	BMC (g)	Area (cm^2)	LBM (g)	Fat (g)	N/A (why)
L2-L4										
HIP (TOTAL)										
TOTAL BODY										
LEG	R									
	L									
	B									
AR M	R									
	L									
	B									
DISTAL FEMUR										

PLEASE ATTACH REPORTS TO BACK OF ORIGINAL FORM □

COMMENTS:

COPY SENT TO CHALMERS: (date) _____

Appendix J. Fracture Data Collection Sheet



CASE REPORT FORM

PATIENT ID # _____ DATE:_____

SECTION 1 - FRACTURE HISTORY

Date of Fracture: Day_____ Month_____ Year_____.

Date of Last Immobilization: Day_____ Month_____ Year_____.

Cause of Last Immobilization: ☐ Surgical procedure
☐ Illness
☐ Other

Location of Fracture: ☐ Radius/Ulna distal mid proximal

☐ Humerus distal mid proximal
☐ Clavical distal mid proximal
☐ Rib _____
☐ Vertebra _____
☐ Femoral Neck

☐ Femor distal mid proximal
☐ Tibia/Fibula distal mid proximal
☐ Other _____

How long to realize fracture was present?

☐ same day ☐ next day ☐ <7 days ☐ 8-14 days ☐ 15-30 days ☐ longer

SECTION 2: FRACTURE MECHANISM

SECTION C: FRACTURE TREATMENT

Did the fracture require hospitalization to diagnose? ☐ Yes ☐ No ☐ N/A

Length of hospitalization: _____ days

Did the fracture require hospitalization to treat? ☐ Yes ☐ No ☐ N/A

Length of hospitalization: _____ days

What treatment was needed? ☐ Observation only duration_____
☐ Removable splint or sling duration_____
☐ Casting duration_____
☐ Traction duration_____
☐ Open reduction
☐ Surgery
☐ Other _____

SECTION D: COMPLICATIONS

During the course of the diagnosis or treatment of the fracture did any complications occur?

☐ Infection ☐ UTI
☐ Pneumonia
☐ Wound
☐ Other
☐ DVT
☐ Loss of seizure control
☐ Feeding intolerance
☐ Skin breakdown/ulceration
☐ Other

How much pain did your child experience?

None 1 2 3 4 5 Worst Ever

Was analgesic medication able to control the pain? ☐ Yes ☐ No

How much analgesic medication was required to control the pain?

☐ None ☐ 1 dose/day ☐ Several doses/day ☐ Every time it was available

Compared to other medical difficulties your child has experienced please rank the impact of this fracture on your child.
(not difficult) 1 2 3 4 5 (most difficult)

Compared to other medical difficulties your child has experienced please rank the impact of this fracture on you (parent).
(not difficult) 1 2 3 4 5 (most difficult)

Compared to other medical difficulties your child has experienced please rank the financial impact of this fracture on you (parent).
(did not cost much) 1 2 3 4 5 (most expensive)

What dollar figure would you have been willing to pay out of your own pocket to avoid this fracture in your child? _____ *[need to look at this more]*

Did your child return to her/his prior health? ☐ Yes ☐ No ☐ N/A

How long did it take for your child to return to prior health?_____

If not what is different about your child following the fracture?

_____
_____
_____
_____

_____
_____
_____
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_____

Appendix K. Gross Motor Function Classification System

Gross Motor Function Classification System for Cerebral Palsy

Robert Palisano, Peter Rosenbaum, Stephen Walter, Dianne Russell, Ellen Wood, Barbara Galuppi

Introduction & User Instructions

The Gross Motor Function Classification System for cerebral palsy is based on self-initiated movement with particular emphasis on sitting (truncal control) and walking. When defining a 5 level Classification System, our primary criterion was that the distinctions in motor function between levels must be clinically meaningful. Distinctions between levels of motor function are based on functional limitations, the need for assistive technology, including mobility devices (such as walkers, crutches, and canes) and wheeled mobility, and to much lesser extent quality of movement. Level I includes children with neuromotor impairments whose functional limitations are less than what is typically associated with cerebral palsy, and children who have traditionally been diagnosed as having "minimal brain dysfunction" or "cerebral palsy of minimal severity". The distinctions between Levels I and II therefore are not as pronounced as the distinctions between the other Levels, particularly for infants less than 2 years of age.

The focus is on determining which level best represents the child's present abilities and limitations in motor function. Emphasis is on the child's usual performance in home, school, and community settings. It is therefore important to classify on ordinary performance (not best capacity), and not to include judgments about prognosis. Remember the purpose is to classify a child's present gross motor function, not to judge quality of movement or potential for improvement.

The descriptions of the 5 levels are broad and are not intended to describe all aspects of the function of individual children. For example, an infant with hemiplegia who is unable to crawl on hands and knees, but otherwise fits the description of Level I, would be classified in Level I. The scale is ordinal, with no intent that the distances between levels be considered equal or that children with cerebral palsy are equally distributed among the 5 levels. A summary of the distinctions between each pair of levels is provided to assist in determining the level that most closely resembles a child's current gross motor function.

The title for each level represents the highest level of mobility that a child is expected to achieve between 6-12 years of age. We recognize that classification of motor function is dependent on age, especially during infancy and early childhood. For each level, therefore, separate descriptions are provided for children in several age bands. The functional abilities and limitations for each age interval are intended to serve as guidelines, are not comprehensive, and are not norms. Children below age 2 should be considered at their corrected age if they were premature. An effort has been made to emphasize children's function rather than their limitations. Thus as a general principle, the gross motor function of children who are able to perform the functions described in any particular level will probably be classified at or above that level; in contrast the gross

motor functions of children who cannot perform the functions of a particular level will likely be classified below that level.

Reference: Dev Med Child Neurol 1997;39:214-223

Gross Motor Function Classification System for Cerebral Palsy (GMFCS)

Before 2nd Birthday

Level I Infants move in and out of sitting and floor sit with both hands free to manipulate objects. Infants crawl on hands and knees, pull to stand and take steps holding on to furniture. Infants walk between 18 months and 2 years of age without the need for any assistive mobility device.

Level II Infants maintain floor sitting but may need to use their hands for support to maintain balance. Infants creep on their stomach or crawl on hands and knees. Infants may pull to stand and take steps holding on to furniture.

Level III Infants maintain floor sitting when the low back is supported. Infants roll and creep forward on their stomachs.

Level IV Infants have head control but trunk support is required for floor sitting. Infants can roll to supine and may roll to prone.

Level V Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll.

Between 2nd and 4th Birthday

Level I Children floor sit with both hands free to manipulate objects. Movements in and out of floor sitting and standing are performed without adult assistance. Children walk as the preferred method of mobility without the need for any assistive mobility device.

Level II Children floor sit but may have difficulty with balance when both hands are free to manipulate objects. Movements in and out of sitting are performed without adult assistance. Children pull to stand on a stable surface. Children crawl on hands and knees with a reciprocal pattern, cruise holding onto furniture and walk using an assistive mobility device as preferred methods of mobility.

Level III Children maintain floor sitting often by "W-sitting" (sitting between flexed and internally rotated hips and knees) and may require adult assistance to assume sitting. Children creep on their stomach or crawl on hands and knees (often without reciprocal leg movements) as their primary methods of selfmobility. Children may pull to stand on a stable surface and cruise short distances. Children may walk short distances indoors using an assistive mobility device and adult assistance for steering and turning.

Level IV Children floor sit when placed, but are unable to maintain alignment and balance without use of their hands for support. Children frequently require adaptive equipment for sitting and standing. Selfmobility for short distances

(within a room) is achieved through rolling, creeping on stomach, or crawling on hands and knees without reciprocal leg movement.
Level V Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent mobility and are transported. Some children achieve self-mobility using a power wheelchair with extensive adaptations.
Between 4th and 6th Birthday
Level I Children get into and out of, and sit in, a chair without the need for hand support. Children move from the floor and from chair sitting to standing without the need for objects for support. Children walk indoors and outdoors, and climb stairs. Emerging ability to run and jump.
Level II Children sit in a chair with both hands free to manipulate objects. Children move from the floor to standing and from chair sitting to standing but often require a stable surface to push or pull up on with their arms. Children walk without the need for any assistive mobility device indoors and for short distances on level surfaces outdoors. Children climb stairs holding onto a railing but are unable to run or jump.
Level III Children sit on a regular chair but may require pelvic or trunk support to maximize hand function. Children move in and out of chair sitting using a stable surface to push on or pull up with their arms. Children walk with an assistive mobility device on level surfaces and climb stairs with assistance from an adult. Children frequently are transported when travelling for long distances or outdoors on uneven terrain.
Level IV Children sit on a chair but need adaptive seating for trunk control and to maximize hand function. Children move in and out of chair sitting with assistance from an adult or a stable surface to push or pull up on with their arms. Children may at best walk short distances with a walker and adult supervision but have difficulty turning and maintaining balance on uneven surfaces. Children are transported in the community. Children may achieve self-mobility using a power wheelchair.
Level V Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent mobility and are transported. Some children achieve self-mobility using a power wheelchair with extensive adaptations.
Between 6th and 12th Birthday
Level I Children walk indoors and outdoors, and climb stairs without limitations. Children perform gross motor skills including running and jumping but speed, balance, and coordination are reduced.
Level II Children walk indoors and outdoors, and climb stairs holding onto a railing but experience limitations walking on uneven surfaces and inclines, and

walking in crowds or confined spaces. Children have at best only minimal ability to perform gross motor skills such as running and jumping.
Level III Children walk indoors or outdoors on a level surface with an assistive mobility device. Children may climb stairs holding onto a railing. Depending on upper limb function, children propel a wheelchair manually or are transported when travelling for long distances or outdoors on uneven terrain.
Level IV Children may maintain levels of function achieved before age 6 or rely more on wheeled mobility at home, school, and in the community. Children may achieve self-mobility using a power wheelchair.
Level V Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At level V, children have no means of independent mobility and are transported. Some children achieve self-mobility using a power wheelchair with extensive adaptations.

Distinctions Between Levels I and II

Compared with children in Level I, children in Level II have limitations in the ease of performing movement transitions; walking outdoors and in the community; the need for assistive mobility devices when beginning to walk; quality of movement; and the ability to perform gross motor skills such as running and jumping.

Distinctions Between Levels II and III

Differences are seen in the degree of achievement of functional mobility. Children in Level III need assistive mobility devices and frequently orthoses to walk, while children in Level II do not require assistive mobility devices after age 4.

Distinctions Between Level III and IV

Differences in sitting ability and mobility exist, even allowing for extensive use of assistive technology. Children in Level III sit independently, have independent floor mobility, and walk with assistive mobility devices. Children in Level IV function in sitting (usually supported) but independent mobility is very limited. Children in Level IV are more likely to be transported or use power mobility.

Distinctions Between Levels IV and V

Children in Level V lack independence even in basic antigravity postural control. Self-mobility is achieved only if the child can learn how to operate an electrically powered wheelchair.

This work has been supported in part by the Easter Seal Research Institute and the National Health Research and Development Program.
Distribution of the Gross Motor Function Classification System for Cerebral Palsy has been made possible by a grant from the United Cerebral Palsy Research and Educational Foundation, USA.

Want to know more? Contact:
Institute for Applied Health Sciences, McMaster University
1400 Main Street West, Rm. 408, Hamilton, ON, Canada L8S 1C7
Tel: 905-525-9140 Ext. 27850 ! Fax: 905-522-6095
E-mail: canchild@mcmaster.ca
Website: www.fhs.mcmaster.ca/canchild

Appendix L. Hoffer Scale

1. **Community Ambulators**: These patients walk indoors and outdoors for most of their activities and may need crutches or braces, or both. They use à wheel chair only for long trips out in the community.

2. **Household ambulators**: These patients walk only indoors and with apparatus. They are able to get in and out of the chair and bed with little if any assistance. They may use the wheel chair for some indoor activities at home and school, and for all activities in the community.

3. **Non-functional ambulators**: Walking for these patients is à therapy session at home, in school, or in the hospital. Afterward they use their wheel chairs to get from place to place and to satisfy all their needs for transportation.

4. **Non-ambulatory**: These patients are wheel chair bound but usually can transfer from chair to bed.

Appendix M. Tanner Staging System

Male Genital

- Stage 1 testes small in size with childlike penis
- Stage 2 testes reddened, thinner and larger (1.6-6cc) with childlike penis
- Stage 3 testes larger (6cc-12cc) and scrotum enlarging. Increase in penile length
- Stage 4 testes larger (12cc-20cc) with greater enlargement and darkening of the scrotum. Increase in length and circumference of penis
- Stage 5 testes over 20cc with adult scrotum and penis

Female Breast

- Stage 1 no breast tissue with flat areola
- Stage 2 breast budding with widening of the areola
- Stage 3 larger and more elevated breast extending beyond the areola.
- Stage 4 larger and even more elevated breast. Areola and nipple projecting from the breast contours
- Stage 5 Adult size with nipple projecting above areola

Male and female pubic hair

- Stage 1 none
- Stage 2 small amount of long hair at base of male scrotum or female labia majora
- Stage 3 moderate amount of curly and coarser hair extending outwards
- Stage 4 resembles adult hair but does not extend to inner surface of thigh
- Stage 5 adult type and quantity extending to the medical thigh surface

Appendix N. Non-Communicating Child Behavior Checklist and related questions.

PAIN QUESTIONNAIRE

ID#:_____

Date(d/m/y):_____

Completed by: M F

Please complete the following questions.

If you have any help completing the form please ask the research coordinator for assistance rather than leaving questions incomplete.

1. On average, how often does your child have pain?

   ☐ never
   ☐ less than once per month
   ☐ one time per month
   ☐ one time per week
   ☐ one time per day
   ☐ several times per day
   ☐ almost constantly

2. What are the causes of your child's pain?
   Please only check the causes of pain your child has experienced and then rate how severe the pain is that goes with that cause. Circle a number between 1 and 5 to show the severity of the pain.

Cause	Severity					
☐ medical procedures (eg IV's)	mild	1	2	3	4	5 severe
☐ transferring or positioning	mild	1	2	3	4	5 severe
☐ constipation	mild	1	2	3	4	5 severe
☐ dressing or toileting	mild	1	2	3	4	5 severe
☐ ambulating (walking, crawling)	mild	1	2	3	4	5 severe
☐ spasticity (muscle tightness)	mild	1	2	3	4	5 severe
☐ reflux (heartburn)	mild	1	2	3	4	5 severe
☐ joint problems	mild	1	2	3	4	5 severe
☐ scoliosis	mild	1	2	3	4	5 severe
☐ seizures	mild	1	2	3	4	5 severe
☐ broken bones	mild	1	2	3	4	5 severe
☐ not sure?	mild	1	2	3	4	5 severe
☐ other:_____	mild	1	2	3	4	5 severe

3. Have you discussed pain with any of your health care providers?
   ☐ Yes ☐ No ☐ Unsure
   If yes, who?

☐ Nurse ☐ Family physician ☐ Specialist ☐ Other:_____

4. Did you receive an adequate answer to your concerns?
   ☐ Yes ☐ No ☐ Unsure

5. Has your child ever been admitted to hospital due only to pain or irritability?
   ☐ Yes ☐ No ☐ Unsure

6. If you answered yes what was the presumed cause of the pain?

_____

7. On average, how often does your child take pain medication?

   ☐ never
   ☐ less than once per month
   ☐ one time per month
   ☐ one time per week
   ☐ one time per day
   ☐ several times per day

8. Compared to other problems your child has to deal with how significant are problems with pain?

   Not significant 1 2 3 4 5 most significant

Please continue on the next page.....

Past Pain Behaviour

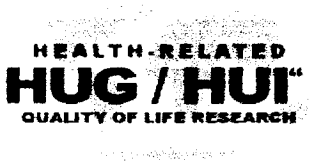
How often has your child usually shown these behaviours when they have been in pain in the past 2 weeks? Please circle a number for each behaviour. If your child has not had an episode of pain in the last two weeks please check this circle μ and do not complete this section.

	Not at all	Just a little	Fairly often	Very often
Moaning , whining, whimpering (Fairly soft)	1	2	3	4
Crying (Moderately loud)	1	2	3	4
Screaming/yelling (Very loud)	1	2	3	4
A specific sound or word for pain (for example: a word, cry, or type of laugh)	1	2	3	4
Eating less, not interested in food	1	2	3	4
Increase in sleep	1	2	3	4
Decrease in sleep	1	2	3	4
Not co-operating, cranky, irritable, unhappy	1	2	3	4
Less interaction with others, withdrawn	1	2	3	4
Seeking comfort or physical closeness	1	2	3	4
Being difficult to distract, not able to satisfy or pacify	1	2	3	4
A furrowed brow	1	2	3	4
A change in eyes, including: squinching of eyes, eyes opened wide; eyes frowning	1	2	3	4
Turning down of mouth, not smiling	1	2	3	4
Lips puckering up, tight, pouting or quivering	1	2	3	4

Clenching or grinding teeth, chewing or thrusting tongue out	1	2	3	4
Not moving, less active, quiet	1	2	3	4
Jumping around, agitated, fidgety	1	2	3	4
Floppy	1	2	3	4
Stiff, spastic, tense, rigid	1	2	3	4
Gesturing to or touching part of the body that hurt	1	2	3	4
Protecting, favouring or guarding part of the body that hurts	1	2	3	4
Flinching or moving the body part away, being sensitive to touch	1	2	3	4
Moving the body in specific way to show pain (e.g. head back, arms down, curls up etc.)	1	2	3	4
Shivering	1	2	3	4
Change in colour, pallor	1	2	3	4
Sweating, perspiring	1	2	3	4
Tears	1	2	3	4
Sharp intake of breath, gasping	1	2	3	4
Breath holding	1	2	3	4

The Non-Communicating Child Pain Checklist was developed by L. Breau and colleagues. This instrument was used with their permission.

Appendix O. The Health Utilities Index Mark 2 and 3.



HEALTH UTILITIES INDEX:

Multi-Attribute Health Status Classification System: Health Utilities Index Mark 2 (HUI2)

Attribute	Level	Description
SENSATION	1	Able to see, hear, and speak normally for age.
	2	Requires equipment to see or hear or speak.
	3	Sees, hears, or speaks with limitations even with equipment.
	4	Blind, deaf, or mute.
MOBILITY	1	Able to walk, bend, lift, jump, and run normally for age.
	2	Walks, bends, lifts, jumps, or runs with some limitations but does not require help.
	3	Requires mechanical equipment (such as canes, crutches, braces, or wheelchair) to walk or get around independently.
	4	Requires the help of another person to walk or get around and requires mechanical equipment as well.
	5	Unable to control or use arms and legs.
EMOTION	1	Generally happy and free from worry.
	2	Occasionally fretful, angry, irritable, anxious, depressed, or suffering "night terrors".
	3	Often fretful, angry, irritable, anxious, depressed, or suffering "night terrors".
	4	Almost always fretful, angry, irritable, anxious, depressed.
	5	Extremely fretful, angry, irritable, anxious, or depressed usually requiring hospitalization or psychiatric institutional care.
COGNITIVE	1	Learns and remembers school work normally

		for age.
	2	Learns and remembers school work more slowly than classmates as judged by parents and/or teachers.
	3	Learns and remembers very slowly and usually requires special educational assistance.
	4	Unable to learn and remember.
SELF-CARE	1	Eats, bathes, dresses, and uses the toilet normally for age
	2	Eats, bathes, dresses, or uses the toilet independently with difficulty.
	3	Requires mechanical equipment to eat, bathe, dress, or use the toilet independently.
	4	Requires the help of another person to eat, bathe, dress, or use the toilet.
PAIN	1	Free of pain and discomfort.
	2	Occasional pain. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
	3	Frequent pain. Discomfort relieved by oral medicines with occasional disruption of normal activities.
	4	Frequent pain; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief.
	5	Severe pain. Pain not relieved by drugs and constantly disrupts normal activities.
FERTILITY	1	Able to have children with a fertile spouse.
	2	Difficulty in having children with a fertile spouse.
	3	Unable to have children with a fertile spouse.

NOTE: The above level descriptions are worded here exactly as they were presented to interview subjects in the HUI2 preference survey.

HUI2 Single-Attribute Utility Functions*

Level	Sensation	Mobility	Emotion	Cognition	Self-Care	Pain	Fertility
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.87	0.92	0.86	0.86	0.85	0.95	0.75
3	0.65	0.61	0.60	0.66	0.55	0.75	0.00
4	0.00	0.34	0.37	0.00	0.00	0.42	
5		0.00	0.00			0.00	

*Torrance et al. *Medical Care* 1996, Table 7, page 715.

HUI2 Multi-Attribute Utility Function*
on Dead-Health Scale

Sensation x_1 b_1	Mobility x_2 b_2	Emotion x_3 b_3	Cognition x_4 b_4	Self-Care x_5 b_5	Pain x_6 b_6	Fertility x_7 b_7
1 1.00	1 1.00	1 1.00	1 1.00	1 1.00	1 1.00	1 1.00
2 0.95	2 0.97	2 0.93	2 0.95	2 0.97	2 0.97	2 0.97
3 0.86	3 0.84	3 0.81	3 0.88	3 0.91	3 0.85	3 0.88
4 0.61	4 0.73	4 0.70	4 0.65	4 0.80	4 0.64	
	5 0.58	5 0.53			5 0.38	

*Torrance et al. *Medical Care* 1996, Table 8, page 716.
Where x_n is the attribute level and b_n is the attribute utility score
Formula (Dead - Perfect Health scale) $u^* = 1.06 (b_1 * b_2 * b_3 * b_4 * b_5 * b_6 * b_7) - 0.06$
where u* is the utility of a chronic health state on a utility scale where dead has a utility of 0.00 and healthy has a utility of 1.00. Because the worst possible health state was judged by respondents as worse than death, it has a negative utility of -0.03. The standard error of u* is 0.015 for measurement error and sampling error, and 0.06 if model error is also included.

Sources

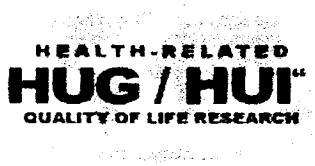
Feeny, David, William Furlong, Michael Boyle, and George W. Torrance, "Multi-Attribute Health Status Classification Systems: Health Utilities Index." PharmacoEconomics, Vol 7, No 6, June, 1995, pp 490-502.

Feeny, David H., George W. Torrance, and William J. Furlong, "Health Utilities Index," Chapter 26 In Bert Spilker, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. Second Edition. Philadelphia: Lippincott-Raven Press, 1996, pp 239-252.

Torrance, George W., David H. Feeny, William J. Furlong, Ronald D. Barr, Yueming Zhang, and Qinan Wang, "Multi-Attribute Preference Functions for A Comprehensive Health Status Classification System: Health Utilities Index Mark 2." Medical Care, Vol. 34, No. 7, July 1996, pp 702-722.

HUG/HUI *Health Related Quality of Life Research*

HUG / HUI "HUI2 Classification" updated - April 7, 2003
HUG Webpages designed and maintained by John R. HorsmanCE&B



HEALTH UTILITIES INDEX:

Multi-Attribute Health Status Classification System: Health Utilities Index Mark 3 (HUI3)

Attribute	Level	Description
VISION	1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
	2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
	3	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses.
	4	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses.
	5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
	6	Unable to see at all.
HEARING	1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.
	3	Able to hear what is said in a conversation with one other person in a quiet room with a

		hearing aid, and able to hear what is said in a group conversation with at least three other people, with a hearing aid.
	4	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	6	Unable to hear at all.
SPEECH	1	Able to be understood completely when speaking with strangers or friends.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well.
	3	Able to be understood partially when speaking with strangers or people who know me well.
	4	Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
	5	Unable to be understood when speaking to other people (or unable to speak at all).
AMBULATION	1	Able to walk around the neighbourhood without difficulty, and without walking equipment.
	2	Able to walk around the neighbourhood with difficulty; but does not require walking equipment or the help of another person.
	3	Able to walk around the neighbourhood with walking equipment, but without the help of another person.
	4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood.
	5	Unable to walk alone, even with walking

		equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood.
	6	Cannot walk at all.
DEXTERITY	1	Full use of two hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
	5	Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools).
	6	Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).
EMOTION	1	Happy and interested in life.
	2	Somewhat happy.
	3	Somewhat unhappy.
	4	Very unhappy.
	5	So unhappy that life is not worthwhile.
COGNITION	1	Able to remember most things, think clearly and solve day to day problems.
	2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems.
	3	Somewhat forgetful, but able to think clearly and solve day to day problems.
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.
	5	Very forgetful, and have great difficulty

		when trying to think or solve day to day problems.
	6	Unable to remember anything at all, and unable to think or solve day to day problems.
PAIN	1	Free of pain and discomfort.
	2	Mild to moderate pain that prevents no activities.
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.

NOTE: The above level descriptions are worded here exactly as they were presented to interview subjects in the HUI3 preference survey.

HUI3 Single-Attribute Utility Functions*

Level	Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.95	0.86	0.82	0.83	0.88	0.91	0.86	0.92
3	0.73	0.71	0.67	0.67	0.73	0.73	0.92	0.77
4	0.59	0.48	0.41	0.36	0.45	0.33	0.70	0.48
5	0.38	0.32	0.00	0.16	0.20	0.00	0.32	0.00
6	0.00	0.00		0.00	0.00		0.00	

*Furlong et al. CEHPA WP#98-11, Appendix B, Table 2, page 97.
NOTE: the mean single-attribute utility score for level 3 cognition is greater than the mean single-attribute utility score for level 2 cognition.

HUI3 Multi-Attribute Utility Function* on Dead-Health Scale

Vision		Hearing		Speech		Ambulation		Dexterity		Emotion		Cognition		Pain	
x_1	b_1	x_2	b_2	x_3	b_3	x_4	b_4	x_5	b_5	x_6	b_6	x_7	b_7	x_8	b_8
1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00
2	0.98	2	0.95	2	0.94	2	0.93	2	0.95	2	0.95	2	0.92	2	0.96
3	0.89	3	0.89	3	0.89	3	0.86	3	0.88	3	0.85	3	0.95	3	0.90
4	0.84	4	0.80	4	0.81	4	0.73	4	0.76	4	0.64	4	0.83	4	0.77
5	0.75	5	0.74	5	0.68	5	0.65	5	0.65	5	0.46	5	0.60	5	0.55

6	0.61	6	0.61	6	0.58	6	0.56	6	0.42	

*Furlong et al. CEHPA WP#98-11, Table 11, page 76 and Appendix B, Table 1, page 96.
Where x_n is the attribute level and b_n is the attribute utility score
Formula (Dead - Perfect Health scale) $u^* = 1.371 (b_1 * b_2 * b_3 * b_4 * b_5 * b_6 * b_7 * b_8) - 0.371$
where u* is the utility of a chronic health state[1] on a utility scale where dead[2] has a utility of 0.00 and healthy has a utility of 1.00.
Notes:
1. Chronic states, and healthy states, are here defined as lasting for a lifetime.
2. Dead is defined as immediate.
Example: For subject "A" whose HUI3 comprehensive health status is classified as follows:

	VISION	HEARING	SPEECH	AMBULATION	DEXTERITY	EMOTION	COGNITION	PAIN
Level	2	1	1	2	1	2	1	3

Referring to the Multi-attribute Utility Function Table above, substitue the appropriate scores for b_n for each attribute as follows:
u* = 1.371 (0.98 * 1.00 * 1.00 * 0.93 * 1.00 * 0.95 * 1.00 * 0.90) - 0.371 = **0.70,**
the utility score for individual "A" on the Dead=0.00 to Perfect Health=1.00 scale.

Sources

Feeny, David, William Furlong, Michael Boyle, and George W. Torrance, "Multi-Attribute Health Status Classification Systems: Health Utilities Index." PharmacoEconomics, Vol 7, No 6, June, 1995, pp 490-502.

Feeny, David H., George W. Torrance, and William J. Furlong, "Health Utilities Index," Chapter 26 In Bert Spilker, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. Second Edition. Philadelphia: Lippincott-Raven Press, 1996, pp 239-252.

Furlong, William, David Feeny, George W. Torrance, Charles Goldsmith, Sonja DePauw, Michael Boyle, Margaret Denton, and Zenglong Zhu, "Multiplicative Multi-Attribute Utility Function for the Health Utilities Index Mark 3 (HUI3) System: A Technical Report," McMaster University Centre for Health Economics and Policy Analysis Working Paper No. 98-11.

Appendix P. The Caregiver Questionnaire

Participant ID# _____

Caregiver Questionnaire

Date (d/m/y):_____

Completed by: M F

Please rate how easy it is for you or your child to perform each of the following tasks by drawing a slash (/) across the line at the point that represents the difficulty you experience. If an item is not appropriate, circle NA.

Personal Care

1. Putting on pants?

Not Difficult I ——————————————— I Most Difficult
NA

2. Taking off pants?

Not Difficult I ——————————————— I Most Difficult
NA

3. Changing diapers?

Not Difficult I ——————————————— I Most Difficult
NA

4. Cleaning child's bottom?

Not Difficult I ——————————————— I Most Difficult
NA

5. Ease of toileting?

Not Difficult I ——————————————— I Most Difficult
NA

6. Ease of bathing?

Not Difficult I ——————————————— I Most Difficult
NA

7. Ease of feeding?

Not Difficult I ——————————————— I Most Difficult
NA

8. How satisfied are you with your child's progress in the personal care area?

Very satisfied I ——————————————— I Not at all satisfied
NA

Positioning/Transferring

9. Ease of positioning in a wheelchair?

Not Difficult I ——————————————— I Most Difficult
NA

10. Ease of positioning out of a wheelchair?

Not Difficult I ——————————————— I Most Difficult
NA

11. Ease of transferring in and out of a wheelchair?

Not Difficult I ——————————————— I Most Difficult
NA

12. Ease of getting down on the floor?

Not Difficult I ——————————————— I Most Difficult
NA

13. Ease of getting up from the floor?

Not Difficult I ——————————————— I Most Difficult
NA

14. Ease of putting on braces or positioning devices?

Not Difficult I ——————————————— I Most Difficult
NA

15. Ease of getting out of a car?

Not Difficult I ——————————————— I Most Difficult
NA

16. How satisfied are you with your child's progress in the positioning/transferring area?

Very satisfied I ——————————————— I Not at all satisfied
NA

Comfort

17. My child is usually healthy and active?

Agree I ——————————————— I Disagree

Does your child have pain? Circle one. Yes No
If No go to Question 22.

18. Is there pain or discomfort during position changes?

Never I ——————————————— I Always

19. Is there pain or discomfort during diaper changes?

Never I ——————————————— I Always
NA

20. Does the pain or discomfort prevent your child from participating in school, various programs, or other activities?

Never I ——————————————— I Always

21. Is your child using pain control medicine?

Never I ——————————————————— I
Always

22. How important are these questions on health and comfort to your child's quality of life?

Not Important I ——————————————————— I Very Important

Interaction/Communication

23. How easy is it for your child to play alone?

Very Easy I ——————————————————— I
Impossible

24. How easy is it for your child to play with other children?

Very Easy I ——————————————————— I
Impossible

25. How easy is it for your child to keep up with other children during play?

Very Easy I ——————————————————— I
Impossible

26. How easy is it for your child to be completely understood by those who know your child well?

Very Easy I ——————————————————— I
Impossible

27. How easy is it for your child to be completely understood by someone who is a stranger?

Very Easy I ——————————————————— I
Impossible

28. How satisfied are you with your child's abilities in the interaction/communication area?

Very satisfied I ——————————————————— I Not at all satisfied

29. Describe your child?

Very Happy I ——————————————————— I Very Unhappy

The Caregiver Questionnaire was developed by Deborah Geabler-Spira MD, and adapted by Jane W Schneider PhD PT, Linda M Gurucharri MPT, and Allison L Gutierreq MPT.

Appendix Q. Description of each fracture

Bone Health in Children with Cerebral Palsy
Fracture History: January 25 2005

Please review the following clinical scenarios that led to a fracture and indicate if you feel it was a fragility fracture or not. Please fax back to me at 519.685.8350 or email.

1. 5 year old child fell forward out of a chair and twisted right leg. Was found to have a fracture of the tibia/fibula
   ☐ Fragility fracture ☐ fracture ☐ unsure

2. 10 year old girl was playing soccer and her left arm was struck by the ball causing it to bend backward. She was found to have a left distal radial/ulnar fracture.
   ☐ Fragility fracture ☐ fracture ☐ unsure

3. 10 year old girl was roller bladding without wrist guards. She fell forward on hands and was found to have a right radial/ulnar fracture.
   ☐ Fragility fracture ☐ fracture ☐ unsure

4. 5 year old girl pushed off a trampoline by another child and fell on the stairs leading to the trampoline. She was found to have a left radius/ulnar fracture.
   ☐ Fragility fracture ☐ fracture ☐ unsure

5. 9 year old girl got her foot caught while getting on a bus. The foot was caught in between the seat and foot rest of her chair. She was found to have a fracture of one of the bones of her foot.
   ☐ Fragility fracture ☐ fracture ☐ unsure

6. 11 year old boy was wrestling with brother and fell to the floor. He tried to break his fall with his hands and one thumb was bent backwards. The thumb appeared injured immediately and he was found to have a fracture of one of the right hand thumb bones.
   ☐ Fragility fracture ☐ fracture ☐ unsure

7. 10 year old female with no clear reason for fracture. Parents felt it might have occurred during a seizure. She was later diagnosed with a fracture of the femur.
   ☐ Fragility fracture ☐ fracture ☐ unsure

8. 11 year old boy came home from school and when mother felt leg she thought she could feel a bone moving. No one at school was aware of an event that caused

this problem. He was assessed in the emergency and found to have a left proximal femoral shaft fracture.

☐ Fragility fracture ☐ fracture ☐ unsure

9. 9 year old boy was having his caregiver move his leg when they heard a crack. The child was assessed in the emergency and found to have a fracture of the proximal femur.

☐ Fragility fracture ☐ fracture ☐ unsure

10. 8 year old female. No obvious cause for fracture and was noted to have a left femur fracture.

☐ Fragility fracture ☐ fracture ☐ unsure