

Original Paper

The muscle-bone relationship: methods and management - perspectives in glycogen storage disease

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Published online:

Abstract. Currently bone development is commonly presented as a process leading to the 'accumulation of peak bone mass'. Consequently, the usual approach to a suspected bone disorder in a child is to address the question are this child's bones as heavy as those of a healthy child of the same sex and age? However, from a functional perspective the aim of bone development should not be make bones as heavy as possible but to make them as stable as necessary. A functionally oriented approach should address two different questions: how strong are the bones? are they as strong as they need to be? It is clear that the bone has to be strong enough to withstand the mechanical forces to which it is exposed. *Conclusion:* since the main forces applied to bones are due to muscle action, the strength of a bone should be related to the force of the muscles attached to it.

Keywords. Bone mass - Bone mineral density - Children - Muscle

Abbreviations. *GSD* glycogen storage disease *pQCT* peripheral quantitative computed tomography

Introduction

Early observers noted a high incidence of secondary skeletal problems in glycogen storage disease (GSD) type 1 patients [8, 10, 14]. Apart from delayed bone growth and maturation, standard radiography showed decreased bone mass in a considerable proportion of patients [8, 10]. Quantitative evaluation of bone samples obtained at autopsy revealed a severely decreased amount of both trabecular and cortical bone, but there was no evidence for a mineralisation defect (osteomalacia) [14]. In a more recent survey of adults with GSD 1, osteopenia or pathological fractures were found in about 33% of patients [15].

Previous observers noted low muscle mass in a considerable proportion of patients with GSD 1 who were not continuously treated according to current protocols [8,15]. Thus, it is possible that low bone mass in such patients was the result of decreased mechanical stimulation.

The muscle-bone unit: theoretical basis

Bone development is one of the key processes of intrauterine and post-natal growth. A rapidly increasing number of factors, typically called 'regulators', have been implicated in this process, including molecular, cellular, environmental and behavioural factors. The problem is how to put the individual pieces back into place. This is an essential task when it comes to explaining bone development at the level which interests patients and physicians most - the organ level. One may try to devise simplifying models of the relationship between the known organ-level features of bone development and the known molecular, cellular and epidemiological factors implicated in this process.

A popular way of devising such a model is to present bone development as the cumulative effect of 'regulator' action. This could lead to a model, which, with more or less variations in detail, appears to be widely used in the current literature. Bone development results from the osteotropic action of a variety of contributors. While apparently straightforward, a weak point in this model is that it presents bone development as a process of blind steering. None of the proposed 'regulators' of bone development has any current information on how much bone has already accumulated and how much more is needed. It therefore must be argued that 'the genes know it all', i.e. the entire blueprint for constructing the skeleton is contained in the 'genes' box of the model.

This model may be applicable to some extent for skeletal patterning during embryonic development [4]. All participating cells can be coordinated through the diffusion of morphogens in soft tissue templates and the resulting structures have a relatively simple geometry [4,6]. However, it is more difficult to explain skeletal development on the basis of a similar process once mineralisation has occurred. Mineralised bone has an extremely complicated micro-architecture. The genome would have to harbour information on the final position of all structural elements (such as trabeculae and osteons) in the adult skeleton, and also on what each bone cell in the developing skeleton has to do to in order to assemble these structures at the correct position. This scenario is implausible, since it would require an astronomical amount of positional information.

Another basic flaw of these popular models of bone development is that they neglect bone function. In the current literature the hypothesis is often reiterated that the aim of bone development is to 'accumulate peak bone mass'. From a functional viewpoint this idea does not make much sense. Why should a bone be programmed to become as heavy as possible? Indeed, heavy bones may rather be a disadvantage for wild animals, since additional weight increases energy expenditure and decreases running speed. Obviously, the functionally most relevant property of a bone is not its weight, but its strength. Bone strength is critical for survival, since fracture of a major bone usually means death for an adult wild animal [9]. Thus, the aim of bone development should not be to make bones as heavy as possible but to make them as stable as necessary.

During growth, bone stability is continually threatened by two processes, the increase in bone length and the increase in muscle force. Longitudinal growth increases lever arms and bending moments and therefore leads to greater bone deformation [16]. Greater muscle force will also increase bone deformation during muscle contraction. Body weight alone puts relatively small loads on bones, but the effect of weight at many skeletal locations is amplified severalfold by muscle action [1,7]. Thus, growth of bone length, muscle force and body weight create the need for adaptational changes in bone mass and architecture in order to ensure bone stability. This is the essence of Frost's mechanostat model of bone physiology [5], which was devised more than three decades ago, but only recently has

gained widespread acceptance. This theoretical groundwork has practical consequences for the clinical assessment of bone development. The traditional way to analyse bone is to answer the question 'are this child's bones as heavy as those of a healthy child of the same sex and age?' In contrast, the mechanostat model urges the paediatrician to address more relevant questions.

Diagnostic question 1: how strong are this child's bones?

Obviously, for a bone of a given anatomical structure, mass generally correlates with strength. Bone mineral content (the mass of mineral in a bone) therefore still can be a useful parameter to assess bone development. The advantage of this parameter is that it can be determined with a variety of current densitometric techniques, such as single photon absorptiometry, dual energy X ray absorptiometry and peripheral quantitative computed tomography (pQCT). However, it is important to realise that a given amount of material will influence the strength of a structure differently, depending on where it is located. Specialised equipment such as pQCT is necessary to assess this architectural aspect of bone strength. Physicists and engineers have long used parameters which allow to calculate the strength of a structure from the amount and distribution of the raw material. Such 'size and shape' parameters include the polar moment of inertia, section modulus and derived parameters such as the Strength-Strain Index [13].

It must be noted that the use of areal bone mineral density is of little utility to answer the new questions. This is still the most widely used densitometric parameter. However it does not represent 'density' in its physical sense but rather reflects an ill-defined mixture of bone mass and size [11]. Smaller children will have low areal bone mineral density even if their bones are absolutely normal for their size. Neglect of this fundamental problem has led to many erroneous conclusions about bone involvement in a variety of paediatric disorders.

Diagnostic question 2: are this child's bones as strong as they need to be?

Regardless of whether bone mineral content or one of the architectural parameters is used to assess bone strength, a long overlooked key question remains: what level of bone strength is adequate for a given child? At present, bone parameters are typically compared to results in healthy children of the same sex and age. However, this is clearly inappropriate in many clinically relevant situations. Consider a child with growth retardation due to chronic disease, whose height and weight are three standard deviations below the mean for sex and age. Such a child inevitably has weaker bones than his healthy peers. In fact, this child's bones do not need to be as strong as those of an average sized child, because they are exposed to smaller mechanical forces. Nonetheless, it is a common experience in paediatric osteology to have such patients referred for evaluation of 'osteoporosis'. Similarly, the scientific literature abounds in reports on chronic paediatric disorders, which are all claimed to lead to 'osteoporosis' or 'increased fracture risk', simply because sick children tend to be small and therefore have smaller bones. Clearly, a more rational way is needed to interpret bone strength data in children.

We therefore propose to compare the strength of a bone with the mechanical challenges to which the bone is exposed. As stated above, the mechanical challenges on a bone mostly depend on muscle force, bone length, and body weight. Thus we should compare a measure of bone strength to these three parameters. Body weight and bone length are routine measurements in any paediatric consultation, since for most purposes body height can be substituted for bone length.

A 'new' parameter is muscle force, which until now has received little attention in paediatrics. In clinical practice, analysis of muscle force is typically limited to the subjective impression of the paediatrician. A more quantitative measure of muscle function can be gained by determining isometric grip force using a hand-held dynamometer. This is a simple, cheap and well established method to assess one aspect of muscle function. However, similar to other functional muscle tests, grip force depends on mood and motivation and therefore has a considerable variability even in adults. Another way to obtain a quantitative measure of the muscle system is to determine a muscle's cross-sectional area. This is traditionally done by measuring the circumference of a limb, which however is influenced by the amount of fat tissue. Muscle size can be evaluated more precisely by pQCT [12]. In the early years of CT, the radiation exposure was quite high, which prevented large scale studies in children. However, the radiation exposure of a measurement run with a modern system is well below that of a standard hand X-ray which makes this technique suitable for use in children.

As expected from the mechanostat model, there is a close correlation between grip force or forearm muscle cross-sectional area and bone mineral content at the distal radius. It should be feasible to use this close association for diagnostic purposes. When a child is diagnosed as having low bone mineral content even after body weight and height have been accounted for, this value can be compared to the corresponding grip force or muscle cross-sectional area. If muscle force or area is decreased as well, the 'decreased bone mass' is likely to be secondary to muscle weakness. If muscle force or area is decreased more than is expected from the muscle analysis (and thus the result is well below the regression line), a primary bone disorder is likely to be present. The validity of this concept will have to be tested in further studies.

Outlook for glycogen storage disease

Thin extremities have been described in untreated patients with GSD 1 and muscle atrophy has been demonstrated on plain radiographs [8]. In a study of adults, 8 out of 37 treated individuals with GSD 1a presented symptoms of muscle weakness [15]. Skeletal muscle does not express glucose-6-phosphatase activity; however, it is the major site for insulin-dependent glucose disposal in vivo [2]. A number of important muscle genes are under control of insulin [3]. In GSD 1, chronic hypoinsulinism due to impaired hepatic glucose output has been suggested [2] which could contribute to both disturbed energy supply and altered gene expression in skeletal muscle. Subclinical muscle weakness in adequately treated patients with GSD 1 has not been sufficiently explored. Reduced muscle strength and consequently a decreased mechanical stimulation could contribute to low bone mass. This relationship should be analysed more extensively in further studies.

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