Mini Review

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Osteoporosis due to Glucocorticoid Use in Children with Chronic Illness

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Abstract
Osteoporosis is increasingly recognized as a complication of chronic childhood illnesses, particularly when glucocorticoids (GCs) are necessary for treatment. Elucidation of the mechanisms leading to bone fragility in these settings requires disentanglement of the relative contributions of myriad risk factors, including disease activity, muscle weakness, immobilization, delayed growth and puberty, compromised nutrition, and osteotoxic medications. Over the years, bone mass and density evaluations by dual energy X-ray absorptiometry (DXA) have become popular for assessing bone health in children; however, such measurements are difficult to interpret because of the confounding effect of bone size and the lack of DXA-based densitometric criteria for defining osteoporosis in childhood. Recently, a new diagnostic approach for evaluation of densitometric data in children has been suggested, driven by Frost’s mechanostat theory. A diagnostic algorithm based on the mechanostat theory of bone-muscle development is proposed for the characterization of bone disease in children with chronic illness. In addition to DXA-based assessments, techniques such as peripheral quantitative computerized tomography and ilial histomorphometry, for which there are pediatric reference data, are gaining ground in the characterization of skeletal changes due to chronic illness. Although these diagnostic techniques expand our understanding of osteoporosis in children, they do not replace clinical assessment. Concrete clinical evidence for GC-induced bone fragility can be seen in spinal changes due to vertebral compression, with spinal morphometry emerging as an essential, but frequently overlooked, tool in the evaluation of children’s bone health. Presently, osteoporosis treatment in the chronic illness setting remains experimental and should be restricted to clinical studies. Following an understanding of the natural history of GC-induced osteoporosis in children, randomized, placebo-controlled prevention and intervention trials will be the next step toward the development of clinical practice guidelines.

Introduction

Osteoporosis, defined as atraumatic fractures associated with low bone mass and microarchitectural deterioration, is the most common metabolic bone disorder in adults, and remains a major public health problem worldwide [1, 2]. While osteoporosis has typically been considered a disease of the aging, there is increasing awareness that children are not exempt from developing the disease. Threats to bone health that are operative during the pediatric years may be particularly costly long-term, since growth and development of the skeletal system play a critical role in determining bone strength and stability in later years [3].

Key Words
Glucocorticoids · Osteoporosis
Scope of the Problem

There is a growing list of pediatric osteoporotic conditions associated with chronic disease, and studies suggest that glucocorticoid (GC) treatment plays a pivotal role in the pathogenesis of osteoporosis secondary to childhood illness [4–6]. The skeletal morbidity associated with GCs has been studied for over 70 years, since Cushing’s [7] first report of endogenous cortisol excess and spontaneous vertebral compression fractures. While endogenous hypercortisolism is a rare entity in children, exogenous GCs are commonly prescribed for their anti-inflammatory and immunosuppressive properties in the treatment of a variety of pediatric conditions, including rheumatic conditions, leukemia, and organ transplantation, to name a few. In adults, it has been estimated that up to 50% of patients on long-term (>1 year) GCs demonstrate decrements in bone mineral density (BMD) that are measurable during the first 6 months of treatment [8]. The risk of fractures increases as much as 5-fold at the spine, with a doubling of the risk at nonvertebral sites [9]. Bone morbidity among children treated with GCs has been studied less extensively; however, a number of smaller studies attest to the potentially deleterious effects of GCs on bone health [4, 10].

The largest study to evaluate the incidence of fractures among pediatric GC users was a case-control study involving over 37,000 children treated with four or more courses of oral GCs for a mean duration of 6.4 days [11]. Compared to controls, GC-treated children had an adjusted odds ratio for fracture of 1.32 (95% confidence interval, 1.03–1.69). The purpose of this review is to provide a general overview of pediatric osteoporosis due to GC use, as a detailed description of GC-induced osteoporosis for each of the specific chronic illnesses (such as pediatric asthma and inhaled GC use) is beyond this article’s scope.

Pathogenesis of GC-Induced Osteoporosis

There are myriad osteotoxic GC effects on bone and mineral metabolism that may lead to osteoporosis. Our understanding of GC-induced osteoporosis is further complicated by challenges in disentangling the relative contributions of associated risk factors for skeletal morbidity in chronic illness, including underlying disease activity, muscle weakness and immobilization, compromised nutrition and intestinal absorption, associated endocrinopathies, and the deleterious impact of other osteotoxic medications (table 1). Leong et al. [12] provided insight into the isolated effect of hypercortisolism on the maturing skeleton in a report of a female, monozygotic twin who presented with Cushing’s disease at 10 years of age. This study highlights both the direct and indirect impact of cortisol excess on various aspects of skeletal development and is discussed in the ensuing sections on pathogenesis.

GC Effects on Bone Metabolism

It is now widely held that the cardinal feature of the bone disease caused by GCs is decreased bone formation [13]. Leong et al. [12] provided clinical evidence for reduced bone formation due to chronic cortisol excess, with the Cushingoid twin manifesting complete suppression of osteocalcin during an overnight profile. Furthermore, the signature histological features of GC toxicity support a diminished effort on the part of osteoblasts, including a decrease in the bone formation rate, in the number of osteoid seams, and in trabecular wall thickness [14]. GCs are associated with a reduction in osteoblast protein synthesis, likely mediated by direct GC receptor regulation of a number of important osteoblast genes, including type I collagen, osteocalcin, osteopontin, alkaline phosphatase, and collagenase [8]. While GCs at physiological doses appear to be essential for normal osteoblast differentiation [15], at high doses GCs diminish the number of osteoblasts by promoting apoptosis [16]. Osteocytes have also been shown to undergo premature cell death, and accumulation of such cells is thought to result in osteonecrosis, another serious consequence of GC use.

While it is recognized that the major deleterious effect of GCs is on bone formation, the impact of GCs on osteoclast function has been more controversial due to conflicting findings. Clinical support for inhibition of osteoclastogenesis with long-term cortisol excess among children stems from reports of reduced bone resorption markers in Cushing’s disease, with a rise in resorption indices following resolution of hypercortisolism [12]. Furthermore, ilial histomorphometric evaluations in children with fractures due to chronic GC exposure show a significant reduction in osteoclast surface/bone surface with low bone turnover [17] (table 2). Weinstein et al. [16] also reported that high-dose prednisolone was associated with impaired osteoclastogenesis in mice. On the other hand, the discovery and characterization of the osteoprotegerin (OPG)/RANK-ligand/RANK paracrine triad in skeletal biology has expanded our concepts of the GC effect on bone. RANK-ligand binds to RANK with high affinity and together with macrophage colony-stimulating factor, stimulates osteoclastogenesis. The third molecule, OPG, exerts a strong inhibitory effect on osteoclas-
togenesis and skeletal resorption by acting as a decoy receptor for RANK-ligand. In vitro studies have shown a profound inhibition of OPG by GCs, with subsequent stimulation of RANK-ligand expression by human osteoblasts [18]. It is suggested that this may be the mechanism by which GCs stimulate osteoclastogenesis, leading to a hyper-resorptive state. In some clinical studies of exogenous GC excess, serum levels of OPG have been shown to be reduced, in concert with the in vitro observations [19, 20]. However, OPG levels were found to be elevated in a report of patients with Cushing’s syndrome [21]. To reconcile these conflicting findings, it has been suggested that the OPG response may be different in exogenous versus endogenous cortisol excess. It has also been hypothesized that osteoclast stimulation may occur during an early, transient phase of GC-induced skeletal toxicity, followed by inhibition of bone resorption if GC use is prolonged [13]. This process may represent a compensatory response to prevent further bone loss in long-standing cortisol excess, an explanation which fits with the biphasic pattern of bone loss observed in adults on long-

### Table 1. Medical therapies which may be administered at the time of glucocorticoid treatment, compounding the deleterious effect on bone health

<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed osteotoxic effect (direct or indirect)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Uncertain. Proposed mechanisms include impaired protein synthesis by osteoblasts, interference with vitamin C metabolism</td>
<td>43, 100</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Uncertain. High-turnover state with increased resorption has been observed</td>
<td>101</td>
</tr>
<tr>
<td>Heparin</td>
<td>Uncertain. Proposed mechanisms include inhibition of renal 1-α-hydroxylase activity with reductions in circulating levels of 1,25-dihydroxyvitamin D and concomitant increases in PTH; direct drug effect on bone tissue with increased resorption and decreased formation, affecting primarily cancellous bone</td>
<td>102</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Hormonal deficiencies (growth hormone, central or peripheral hypogonadism), avascular necrosis, muscle atrophy</td>
<td>103</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>Central hypogonadism</td>
<td>104</td>
</tr>
<tr>
<td>GnRH analogs</td>
<td>Central hypogonadism</td>
<td></td>
</tr>
<tr>
<td>L-thyroxine suppressive therapy</td>
<td>Osteoblast-mediated T3 activation of osteoclasts, resulting in bone resorption</td>
<td>106–108</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Reduced trabecular bone, but compensatory increased cortical bone, with preservation of the absolute bone mass</td>
<td>109</td>
</tr>
</tbody>
</table>

GnRH = Gonadotropin-releasing hormone; PTH = parathyroid hormone.

### Table 2. Quantitative ilial histomorphometry in children* with glucocorticoid-induced osteoporosis secondary to chronic illness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results** (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural</td>
<td></td>
</tr>
<tr>
<td>Core width, mm</td>
<td>6.8 (79%)</td>
</tr>
<tr>
<td>Cortical width, μm</td>
<td>618.0 (62%)</td>
</tr>
<tr>
<td>Bone volume per tissue volume, %</td>
<td>17.9 (70%)</td>
</tr>
<tr>
<td>Formation</td>
<td></td>
</tr>
<tr>
<td>Osteoid thickness, μm</td>
<td>4.5 (68%)</td>
</tr>
<tr>
<td>Osteoid surface per bone surface, %</td>
<td>12.0 (60%)</td>
</tr>
<tr>
<td>Mineralizing surface per bone surface, %</td>
<td>8.7 (74%)</td>
</tr>
<tr>
<td>Mineral apposition rate, μm/day</td>
<td>0.9 (94%)</td>
</tr>
<tr>
<td>Resorption</td>
<td></td>
</tr>
<tr>
<td>Osteoclast surface per bone surface, %</td>
<td>0.5 (44%)</td>
</tr>
</tbody>
</table>

* Subjects presented with the following diagnoses: nephrotic syndrome (n = 2); systemic lupus erythematosus (n = 2), Duchenne’s muscular dystrophy (n = 2), leukemia (n = 1), Wegener’s granulomatosis (n = 1).
** Expressed as the median of the raw values and as the percent of the healthy average for age (normative data taken from [105]).
term steroids (characterized by a rapid, initial phase of loss in the first few months of GC use, followed by a slower rate of loss thereafter). Further studies are needed to determine the validity of these proposed mechanisms.

**GC Effects on Vitamin and Mineral Metabolism**

GC administration is associated with diminished intestinal calcium absorption and increased renal tubular calcium excretion, resulting in a negative calcium balance [8]. If the degree of hypercalcuria is marked, nephrocalcinosis may result [12]. Mild, secondary hyperparathyroidism has been demonstrated in some [12, 22], but not all [23], studies of patients exposed to chronic cortisol excess. To date, the relative contribution of hyperparathyroidism in the development of GC-induced osteoporosis remains controversial, but a recent review of the issue in adults has concluded that the effects are likely to be minor [24]. There has been no convincing indication of clinically relevant changes in vitamin D metabolism during GC administration [25]. When 25-hydroxyvitamin D levels are low in GC-treated patients, this finding likely reflects decreased vitamin D intake and lack of sun exposure.

**GC Effects on Growth, Muscle Development, and Puberty**

The growth-retarding effect of GCs is well known in children, due to a direct effect of GCs on chondrocyte function [26] and an indirect effect on growth through inhibition of the growth hormone/insulin growth factor 1 axis [12, 27]. Long-term GC administration may also result in myopathy [28]. Therefore, GCs reduce two critical mechanical challenges (muscle forces and changes in bone length) that normally stimulate bone mineral accrual during development [29].

Children with chronic illness may experience delays in pubertal maturation even in the absence of GCs [30, 31], implicating the underlying systemic condition. The patient with Cushing's disease described by Leong et al. [12] provided support for a direct effect of GCs on pubertal progression. This patient manifested a delay in bone age and pubertal signs, with hormonal evidence of central hypogonadism. In addition to inhibition of gonadotrophins, adrenal and gonadal sex steroid production may also be blunted by GCs [32, 33]. In girls, when sexual development proceeds normally, estrogen serves to enhance bone tissue response to mechanical strain by lowering the bone's 'mechanostat set-point' at the endosteal bone surface [34]. With rising estrogen concentrations, the endosteum is sensitized to mechanical strain, leading to endocortical apposition at many skeletal sites (thought to represent an estrogen-dependent bone reservoir to be tapped during pregnancy and lactation). In boys, testosterone plays a critical role in muscle development, which in turn is a potent stimulus for mineral accrual [29]. The hypogonadal effect of GCs may interfere with these adaptive processes of puberty to foster bone strength.

**Skeletal Manifestations of GC Toxicity and the Potential for Recovery**

GCs toxicity appears to have a predilection for trabecular bone, which has a higher metabolic activity than cortical bone, and thus may be more sensitive to the deleterious effect of steroids [35]. This is supported by the propensity of GCs to affect the spine (fig. 1).
The temporal pattern of bone mass changes in adults with GC-induced osteoporosis appears to be biphasic, with a precipitous drop observed in the first 6–12 months of therapy, followed by a gradual, but sustained, loss in subsequent years [36, 37]. Among adults, there is potential for restitution of bone mass following discontinuation of GC therapy, with a concomitant reduction in fracture risk [38, 39]. Studies have shown that the greatest reduction in bone mineral content (BMC) and BMD among children with leukemia occurred during the first 6–8 months of chemotherapy [4, 10], similar to the potent GC effect on bone seen in the adult population. Furthermore, these findings were associated with an increased fracture risk both during [4] and following [10] leukemia treatment.

The effect of age and duration of the insult on the potential for bone mass recovery in young subjects raises an important issue for clinical care. This was recently explored by Gafni et al. [40], who showed that short-term, high-dose dexamethasone administration to 5-week-old rabbits resulted in greatly reduced tibial bone mass. Complete recovery through endochondral bone formation was then achieved by 16 weeks, following cessation of dexamethasone. These data suggest that significant, but temporary, insults to the skeleton early in life may not ultimately affect bone strength because much of the young skeleton is replaced entirely through bone growth. On the other hand, insults that affect skeletal health in the long term, or during the later pediatric years when growth potential is less, may be associated with persistent skeletal disease [5, 41]. Studies of GC-treated children with systemic lupus erythematosus and nephrotic syndrome [42] suggest that if a full recovery from underlying disease is achieved prior to puberty, obviating the need for ongoing GC use, normalization of BMD may be possible. On the other hand, patients who continue to receive long-term steroids, or whose GC threat to bone health persisted into the pubertal years, may not have similar potential for recovery [4]. Halton et al. [4] showed, among children who were prepubertal at diagnosis with leukemia, that changes in spinal BMC and BMD were not significantly different from the age- and gender-matched mean after 2 years of leukemia therapy, while pubertal children did show significant decrements in these parameters. On the other hand, Mandel et al. [43] reported that for patients with a history of childhood leukemia, a low femoral neck BMD at a mean of 10.1 years from diagnosis was not related to chronological age or age at diagnosis, but to higher doses of GCs and also to methotrexate. The age or pubertal stage after which potential for restitution of bone mass is lost in the various childhood illnesses, and the relative contribution of associated risk factors, requires further study through longitudinal research programs.

In clinical care, it is useful to know the fracture risk associated with a given BMD, a fact which has been worked out for some adult populations. For example, a 6-fold increase in the risk of vertebral fracture was associated with a decrement of ≤ 1 standard deviation (SD) in lumbar spine BMD among GC-treated postmenopausal women with rheumatoid arthritis [44], compared to a 2- to 3-fold increased risk among women with postmenopausal osteoporosis alone [45]. It has been proposed that alterations in bone quality independent of BMD may explain these observations. Epidemiological studies to determine fracture risk for a given BMD (or change in BMD) among children receiving GCs are not available, although such data are emerging among children without medical diagnoses or treatments. Jones et al. [46] showed in healthy girls that a 1 SD reduction in areal BMD compared to the age-matched mean was associated with an almost 2-fold increased risk of forearm fractures. The fracture risk associated with a given BMD in children with various chronic illnesses remains an important area for further study.

Since BMD determination by dual energy X-ray absorptiometry (DXA) in children poses additional challenges in interpretation, largely due to the effects of changes in bone size and body composition (fat mass), and since bone strength is determined not by bone mass/density but by bone geometry and quality, recent attention has turned to the exploration of alternative methods for characterization of bone health and disease among children receiving GCs. For example, Leonard et al. [47] reported peripheral quantitative computerized tomography (pQCT) results at the distal tibia in 68 patients with incident Crohn’s disease, 31 of whom were re-evaluated 12 months later. At diagnosis, significant reductions were observed in cortical cross-sectional area, stress-strain index and muscle cross-sectional area. After 12 months of Crohn’s therapy, muscle cross-sectional area increased, while further deterioration in cortical cross-sectional area and stress-strain index were noted.

Insight into the mechanisms of bone fragility in children with GC-induced osteoporosis can also be gleaned from ilial bone histomorphometric studies (table 2; fig. 2). Eight pediatric patients with chronic systemic illness (mean age 13.3 years, range 7.4–17.6), all of whom developed painful vertebral compression due to chronic GC use, underwent ilial sampling following dual tetracycline labeling [17]. Histomorphometry revealed low bone turnover with reduced formation and resorption indices, reduced cancellous bone volume and thinning of the corti-
ces as potential mechanisms for bone fragility in these advanced cases. At the same time, the average size-corrected (volumetric) BMD at the lumbar spine was −1.8 SD below the mean (range −3.0–0), highlighting that children with bone tissue abnormalities associated with GC-induced skeletal fragility may have BMD values within what would typically be considered the ‘normal range’ according to a Gaussian curve.

Impact of Dose, Frequency, and Route of GC Treatment on Bone Health

Studies in adults have shown that the magnitude of the GC effect on bone appears to be dose dependent [9]. However, it remains unsettled whether low doses cause bone loss in all patients. The concept of a threshold dose is controversial in the adult field, as even low doses of GCs affect skeletal metabolism [48]. In adults with rheumatoid arthritis, it appears from a clinical perspective that a dose of prednisone <5 mg/day is relatively safe [49, 50]. Alternate day steroid use does not appear to reduce the skeletal effect compared to daily administration, at higher doses [51]. The lowest-dose threshold for children, if it exists, has not been determined. Deflazacort, an oral steroid derivative, has a bone-sparing effect when compared to prednisone or methylprednisone in the short term [52, 53]. However, a report of 46 boys with Duchenne’s muscular dystrophy who received deflazacort over a 4-year period showed that 26/46 (52%) of the boys suffered 37 fracture events [54]. Of the 37 fractures, 39% were vertebral compression fractures, while the rest were long bone fractures. Significant decrements in bone mass were also observed over the study period in these boys who were on deflazacort. Among boys with Duchenne’s who did not receive steroids, Larson and Henderson [55] observed that 44% of patients had sustained fractures, the majority of which occurred in the lower extremities. None of these patients were noted to have vertebral compression. These results suggest that the osteotoxic effect of deflazacort appears to exacerbate the underlying predisposition for osteoporosis in boys with Duchenne’s muscular dystrophy, and has a predilection for the spine. Inhaled GCs have fewer systemic, including skeletal, effects compared to oral or intravenous therapy [56–58], unless they are administered at high doses [59, 60].

While studies support reductions in BMD and BMC during GC treatment for children [61–63], not all studies are consistent with a definite GC effect on bone health. It has been reported that despite receiving an average prednisone dose of 23,000 mg administered over a mean of 4.4 years (almost triple the adult GC threshold dose of prednisone 5 mg daily), children with GC-sensitive nephrotic syndrome did not demonstrate deficits in BMC of the spine or whole body relative to age, bone size, sex, or degree of maturation [64]. The study patients had a lower BMC than controls only after correction for body mass index, and only at the lumbar spine. The investigators hypothesized that the intermittent nature of the pulse GC therapy in this disease allowed the growing skeleton

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Fig. 2. Qualitative ilial histomorphometry in children with glucocorticoid-induced osteoporosis, with results compared to healthy controls. T-cell ALL = T-cell acute lymphoblastic leukemia.
to tolerate transient reductions in bone formation through recovery during periods of disease remission and GC withdrawal. It should be noted that these results may be unique to nephrotic syndrome, where children are typically well-nourished, ambulatory, and exempt from the bone tissue effects of inflammatory mediators [64]. Despite these reassuring results, the limitations of the study’s design leave a number of issues unsettled. Since these data are cross-sectional, they do not address the pattern of bone mass and density development in individual patients. Furthermore, bone mass and density by DXA were the only indices assessed, with further studies needed to evaluate bone strength more comprehensively.

**Approach to Diagnosis and Treatment**

The characterization of bone health in children has traditionally been based on DXA measurement of BMD or BMC. However, this approach is fraught with difficulties, given that BMD criteria for the diagnosis of osteoporosis in children do not exist (i.e., the fracture threshold for a given BMD in this setting is unknown presently). The simple use of Gaussian curve cutoffs for defining bone health and disease in GC-treated patients is sometimes used but is not sensible, since children with BMD values that are within 2 SD of the age- and gender-matched mean may still develop vertebral compression, and children at the limits of the Gaussian curve may not have a bone health abnormality. BMD evaluations by DXA are further complicated by the need to consider bone size, the stage of maturation, and the effect of changes in fat mass on the DXA results, all of which can be significantly abnormal in GC-treated children. Given these issues, an understanding of the relationship between skeletal morbidity due to GC use and DXA parameters of bone health must be further delineated in children before treatment decisions based solely on DXA-based parameters will be justified.

Recently, a new diagnostic approach to evaluation of densitometric data in children has been suggested [65] and subsequently applied to DXA parameters [66]. This approach is driven by Frost’s mechanostat theory [67], and proposes that the skeleton continuously adapts its strength in order to maintain the strains that result from physiological loads close to a set-point. Since muscle contractions provide the largest physiological load, a close relationship between bone strength and muscle force/size is expected, and indeed has been corroborated in pediatric clinical studies [65]. A diagnostic algorithm based on the mechanostat theory of bone-muscle development is proposed for the characterization of bone disease in children with chronic illness, and could be implemented for children taking GCs. Measures of height, muscle force/size (such as muscle cross-sectional area by pQCT or lean body mass by DXA) and BMC at a corresponding location are required. If BMC is lower than expected for muscle force/size, a ‘primary bone defect’ is diagnosed. If muscle force or size is too low for height, even if BMC is adapted adequately to the decreased mechanical challenge, this means that bone mass and presumably strength are still too low for body height, and therefore a ‘secondary bone defect’ is diagnosed. If muscle force/size is abnormally low and BMC is lower than expected for a normal muscle-bone relationship, a ‘mixed (primary and secondary) bone defect’ is present (fig. 3). This algorithm is useful in the clinical

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**Fig. 3.** Algorithm for assessment of pediatric osteoporosis in the context of chronic illness (proposed by Schoenau et al. [65] for pQCT, and adapted to DXA by Crabtree et al. [66]; © American Society for Bone and Mineral Research). BMC = Bone mineral content.
setting and will facilitate understanding of the relative contribution of various risk factors for compromised bone health in the GC-treated patient.

Biochemical markers of bone metabolism do not facilitate the diagnosis of osteoporosis, but may be useful to monitor responses to GC-induced osteoporosis treatment. pQCT and ilial histomorphometry, while highly informative, are typically reserved for research settings. As such, to date, the diagnosis of GC-induced osteoporosis remains largely a clinical one, and will be said to exist when the child’s skeleton has not been able to withstand its mechanical challenges, resulting in fragility fractures. Recently, it has been shown that quantification of vertebral dimensions (morphometry) has clinical utility for monitoring of osteoporosis treatment response [68]. Given that vertebral changes due to compression fractures may be present before significant alterations in BMD by DXA are evident in GC-treated children [69], evaluation of spinal changes during GC treatment can be useful for early identification of osteoporosis.

A comprehensive assessment of all risk factors should be undertaken before initiating a treatment plan for pediatric patients with GC-induced osteoporosis. As a general principle for patients with GC-responsive diseases, the minimally effective dose to treat disease activity should be prescribed, and topical or inhaled therapies should be offered when appropriate. Hypogonadism, inadequate nutrition (including calcium and vitamin D intake), growth hormone deficiency, malabsorption, and impaired mobility should also be addressed as part of the overall management plan.

With established osteoporosis (i.e., fragility fractures), these treatment measures are frequently inadequate, and pediatric GC-induced osteoporosis patients often have persistent pain and vertebral fractures, despite attempts to quell disease activity and restore nutrition, mobility, and the hormonal milieu. Trials of rescue therapy (secondary prevention) in adults, once osteoporosis is established, have led to the study of calcium, vitamin D (calciferol), vitamin D analogs (calcitriol and alphacalcidiol), calcitonin, hormone replacement, and bisphosphonates. Calcium and vitamin D have not been shown to be effective in reducing fracture rates among adults on long-term GCs [70]. Studies of sex hormones, vitamin D analogs and calcitonin have not been sufficiently powered to address fracture incidence, though BMD has been positively affected in a number of studies [71–74]. Among adults, none of these agents appear to be as effective as bisphosphonates, where evidence of benefit has been more consistently documented [75, 76].

Unlike in adults, medical intervention for GC-induced osteoporosis in children remains virtually uncharted in the literature to date, with studies of calcitonin [77], alendronate [78], pamidronate [79–81], and growth hormone [82] restricted to small numbers of patients, observational studies, and case-control trials. The greatest experience with osteoporosis treatment in children comes from the use of intravenous, cyclical pamidronate in children with osteogenesis imperfecta (OI, a congenital bone fragility condition). Pamidronate is a member of the bisphosphonate group and a potent inhibitor of bone resorption through inhibition of protein prenylation [83, 84], a process which renders the osteoclast inactive. Intravenous pamidronate has been shown in a number of observational and case-control studies to benefit children with moderate-to-severe OI by improving pain, mobility, grip force, bone mass, and by decreasing the number of fractures [85–90]. The beneficial effect of pamidronate at the bone tissue level appears to be due to expansion of cortical width through selective inhibition of resorption during the modeling process [91].

Common adverse effects observed in the majority of pediatric patients who have received intravenous pamidronate have been a transient low-grade fever and flu-like symptoms (known as the ‘acute phase reaction’) [92]. Bisphosphonates suppress bone resorption and turnover, leading to reduced levels of serum alkaline phosphatase with decreased production of collagen breakdown products (due to a reduction in bone turnover). Asymptomatic hypocalcemia and hypophosphatemia are also typical findings. Anterior uveitis and scleritis are rare complications, and transient decreases in lymphocyte counts have also been observed [93].

Theoretical concerns about the effect of bisphosphonate therapy on the growing skeleton have not been confirmed after a decade of clinical and histological observation [93, 94]. Zeitlin et al. [95] found that long-term, cyclical intravenous pamidronate therapy was associated with significant height gain in OI types I, III, and IV. When treatment is given before closure of the epiphyses, sclerotic lines appear at the distal metaphyses of long bones. Despite this finding, skeletal maturation proceeds at a normal rate [93]. The importance of judicious use of pamidronate for patients with confirmed diagnosis of bisphosphonate-response disease and of adherence to published protocols for dosing of the drug and scrutiny of bone development and metabolism [96] is highlighted in the recent case published by Whyte et al. [97]. In this report, high doses of intravenous pamidronate were given over a short interval to a young boy with an unclearly defined condition characterized predominantly by hyperphosphatasemia.
This patient, who received excessive doses of pamidronate between the ages of 7 and 10 years, not surprisingly developed an osteopetrotic phenotype including ‘cartilage bars’ on transiliac bone biopsy. These findings were due to delayed removal of calcified primary spongiosa by osteoclasts resulting from excessive doses of pamidronate over a short interval, which was administered without close monitoring of the patient’s bone development and metabolism.

Positive reports of intravenous pamidronate in children with OI have led to interest in the more convenient oral bisphosphonates. A pharmacokinetics study of oral, weekly alendronate in children with mild OI recently showed that the absorption was <1%, comparable to adult studies [98], and that there were documented side effects similar to the acute phase reaction observed with intravenous pamidronate. Alparadronate, administered as weekly tablets to children with severe OI, was shown to positively impact on bone mass, density, and fracture rates, although reshaping of compressed vertebrae and mobility were unchanged after 2 years’ treatment in this randomized, controlled trial of 34 patients [99].

The clinical benefit and safety profile of pamidronate for the treatment of OI, and preliminary reports of oral and intravenous bisphosphonates in children with other osteoporotic conditions, support the development of randomized, controlled trials in children with GC-induced osteoporosis to determine their efficacy and safety in this population. However, any such treatment with bisphosphonates should be recognized as experimental at the present time, administered within the context of research programs, and restricted to specialized centers with expertise in the diagnosis and treatment of pediatric osteoporosis. Furthermore, informed consent should be obtained in all patients prior to therapy. The safety and efficacy of newer compounds on the horizon, such as parathyroid hormone and vitamin D analogs, have not been determined in children.

Table 3. Practice points

<table>
<thead>
<tr>
<th>Practice points</th>
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<tbody>
<tr>
<td>Osteoporosis is increasingly recognized as a complication of chronic childhood illness, particularly when GCs are necessary for treatment.</td>
</tr>
<tr>
<td>GCs exert their deleterious effect on bone through a direct impact on osteoblast (and possibly osteoclast) function, and by disturbing mineral metabolism, growth, muscle development, and progression through puberty.</td>
</tr>
<tr>
<td>At present, the diagnosis of osteoporosis in children with chronic illness remains a clinical one, existing when low-trauma fractures are present in association with reduced bone mass. Vertebral morphology is an important (and frequently overlooked) tool for assessment of such fragility fractures, particularly since steroids have a predilection for the spine.</td>
</tr>
<tr>
<td>BMD (by DXA) criteria for the diagnosis of osteoporosis in children do not currently exist. However, DXA-based parameters can be useful to understand the patient’s bone health status. By applying an algorithm that is based on Frost’s mechanostat theory, a primary, secondary, or mixed bone defect can be determined [65, 66].</td>
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<tr>
<td>Spontaneous recovery from GC-induced osteoporosis may be possible, depending upon the timing and duration of the steroid insult, and on the status of associated risk factors.</td>
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<td>Before consideration is given to experimental therapies in the treatment of GC-induced osteoporosis, a comprehensive assessment and treatment of all associated risk factors needs to be carried out. Such risk factors include inadequate nutrition, impaired mobility, and endocrine disorders (delayed growth and puberty).</td>
</tr>
<tr>
<td>Bisphosphonates hold promise for the prevention and treatment of GC-induced osteoporosis in children; however, their use should be restricted to research programs in centers which are specialized in the diagnosis and treatment of pediatric osteoporosis due to chronic illness.</td>
</tr>
</tbody>
</table>

GC = Glucocorticoid; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry.

GC-Induced Osteoporosis in Children

Table 4. Research directions

<table>
<thead>
<tr>
<th>Research directions</th>
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<tbody>
<tr>
<td>There is a need for prospective, natural history studies which determine the pattern and frequency of fractures among children receiving GCs, and which evaluate the relative contributions of associated risk factors. Such studies are also required to determine the relationship between DXA parameters and fractures, with long-term follow-up of children who start, and subsequently cease, steroids.</td>
</tr>
<tr>
<td>Establishment of collaborative health registries would facilitate the natural history study of patients with steroid-requiring diseases, and would be of particular benefit for rarer illnesses, where patient numbers are small.</td>
</tr>
<tr>
<td>Studies of techniques beyond DXA-determined BMD for the characterization of bone health in children are needed to further our understanding of pathogenetic mechanisms. To this end, ilial histomorphometry, vertebral morphometry, and pQCT are emerging as useful tools.</td>
</tr>
<tr>
<td>Following an understanding of the natural history of GC-induced osteoporosis in children, randomized, placebo-controlled prevention and intervention studies on large numbers of patients will be the next step toward development of comprehensive clinical practice guidelines.</td>
</tr>
</tbody>
</table>

GC = Glucocorticoid; DXA = dual-energy X-ray absorptiometry; BMD = bone mineral density; pQCT = peripheral quantitative computerized tomography.
Summary and Future Horizons (tables 3, 4)

The study and treatment of children with GC-induced osteoporosis presents a particular challenge to pediatric researchers and clinicians. The investigative hurdles to overcome, for the design and execution of effective observation and treatment studies, stem from the tremendous heterogeneity and complexity of the underlying conditions associated with GC use, from the fact that children with GC-induced osteoporosis are often unwell, and from the loss of statistical power due to potentially small patient numbers for certain disease categories. At present, there is considerable need for prospective studies of fracture pattern and incidence and for charting of additional bone health indices (pain, mobility, bone strength, and geometry) in the various disease categories, both during and after GC use. At the same time, there is a persistent need for the use of techniques beyond BMD to characterize bone health and disease in children with chronic illness, including spinal morphometry, pQCT, and ilial histomorphometry. Following an understanding of the natural history of GC-induced osteoporosis in children, randomized, placebo-controlled prevention and intervention trials on large numbers of patients will be the next step toward the development of comprehensive practice guidelines.

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