Chapter 18
Secondary Osteoporosis in Conditions of Pediatric Onset

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Continuing the themes set forth in the prior chapter, secondary osteoporosis can result from disorders of the central nervous system or directly from the muscles. This chapter will discuss two of the most common pediatric disorders seen in pediatric units, transitional care clinics, and "young adult" programs in rehabilitation hospitals: cerebral palsy and Duchenne muscular dystrophy. Other forms of muscular dystrophy, such as Becker's muscular dystrophy, produce significantly less disability and are not considered here.

Cerebral Palsy in Children

The classic definition of cerebral palsy (CP), developed by Risenbaum et al., is a "group of permanent disorders of the development of movement and posture, causing activity limitations that are attributable to nonprogressive disturbances that occur in the developing fetal or infant brain" [1]. It is the most common motor disability in children and the childhood disease most associated with osteoporosis. CP is characterized as *congenital* when brain damage occurs before or during birth as it does in 85–90 % of CP cases or *acquired* when damage occurs more than 28 days after birth, generally associated with an infection or a head injury [2].

Types of Cerebral Palsy

Several different *classification systems* are currently in use for CP, sometimes leading to a confused diagnosis especially if different specialists are involved. Severity level, body control: spastic (increased muscle tone) or nonspastic (decreased or

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Table 1 The four types of cerebral palsy and their features

	Predominance	Damaged area	Diagnostic groups
Spastic	70–80 %	Aspects of the brain which control movement	Divided into three groups, *hemiplegia*, *diplegia*, and *quadriplegia*, reflecting the parts of the body affected and the level of severity
Hemiplegia	Principal characteristics defined by exaggerated reflexes and stiff muscles. Specifically defined by unilateral stiffness which typically affects the upper extremity as opposed to the lower extremity; almost all children can walk		
Diplegia	Principal characteristics of exaggerated reflexes and stiff muscles. Specifically defined by stiffness which typically affects the lower extremities as opposed to the upper extremities, which are typically unaffected; three in four children can walk		
Quadriplegia	Principal characteristics of exaggerated reflexes and stiff muscles. Specifically defined by stiffness which typically affects all four extremities, the trunk, and face. Quadriplegia is identified as the most severe form of spasticity; generally includes other associated conditions (e.g., vision and hearing loss, seizures, and intellectual disabilities); one in four children can walk		
Dyskinetic	10–20 %	Basal ganglia	Two basic subcategories: *athetoid* and *dystonic*
Athetoid	Abnormal muscle contractions resulting in slow, involuntary writhing movements of the arms, hands, feet, and legs which may result in a disruption of the normal abilities to sit straight, hold or grasp objects; dysfunctional gait		
Dystonic	Abnormal muscle contractions resulting in a twisted position caused by trunk movements that are affected more than limb muscles; general uncontrollable muscle spasms		
Ataxic	5–10 %	Cerebellum	
	Ataxic muscles are generally floppy, which may result in coordination impairments, unsteady or shaky movements, hand tremors, and other balance problems; functional standing, walking, and depth perception are all typically impaired. Ataxia is identified as the least severe form of cerebral palsy		
Mixed	A combination of several of the impediments characteristic of the other three forms		

Sources: Fairhurst [3]
National Institute of Neurological Disorders and Stroke [4]
Center for Disease Control and Prevention [5]

flexible muscle tone), gross motor function (impairment level), and topographical distribution (body parts affected) are the four principal categories as applied to four different *types* of CP (Table 1) [3–5].

Causes and Symptoms

The causes of CP stem from problems occurring at three different stages [6, 7]:

1. *Prenatal*: genetic and environmental factors; damaged nerve cell fibers in the white matter of the brain, hemorrhage, and brain malfunction; and maternal infections such as rubella
2. *Perinatal*: problems in birthing process leading to ruptured blood vessels or oxygen deprivation to the brain and maternal infections
3. *Postnatal*: trauma (accidental injuries), infection (meningitis), and asphyxia that disrupt synapses between brain cells

Risk factors that may lead to an increased chance of a child being born with CP include birth conditions, medical conditions, and unforeseen trauma (Fig. 1) [6, 7]. In an Australian study of four risk factors for CP—asphyxiated birth events, inflammation or other signs of infection, birth defects, and poor fetal growth including low birth weight—McIntyre et al. [8] reported that birth defects and poor fetal growth, seen in almost half of the children studied, were the most common contributing factors. Babies with severe cerebral palsy show symptoms of the disease (notably a weak or shrill cry, problems sucking and swallowing, and seizures) at or shortly after birth. However, most children are diagnosed between the ages of six months and two years. The first sign is generally a delay in developmental milestones such as crawling, walking, rolling over, controlling head movements, sitting without support, and rocking with one hand.

The primary symptoms of CP [9, 10] and their influence on fracture risk are:

1. Poor muscle tone
2. Impaired muscle coordination and control
3. Persistence of primitive reflexes
4. Damaged gross and fine motor skills
5. Diminished oral motor functions
6. Compromised posture and balance

Descriptions of each of the six features listed above are given in Table 2 [9].

Secondary conditions associated with CP include epilepsy (up to 36% of children with CP experience these seizures by 12 months), visual and cognitive impairment, joint contractures, foot deformities, hip dysplasia, incontinence, and constipation, among others [4].

Diagnosis and Prognosis

Because there is no single medical test that definitively confirms cerebral palsy, the diagnosis is necessarily complex and can extend over a period of time, on occasion as many as 2–5 years. The parental stress brought about by this lengthy process, a concern that doctors may be overly cautious in undertaking the necessary diagnostic procedures, and recognition of the importance of early detection and intervention have led the American Academy of Pediatrics to issue a 12-step program focused on developmental surveillance and screening of motor skills at ages 9, 18, and, 30 months [11]. In addition, diagnosis should include a parental interview with family history, physical examination, laboratory tests, and imaging studies. Physicians

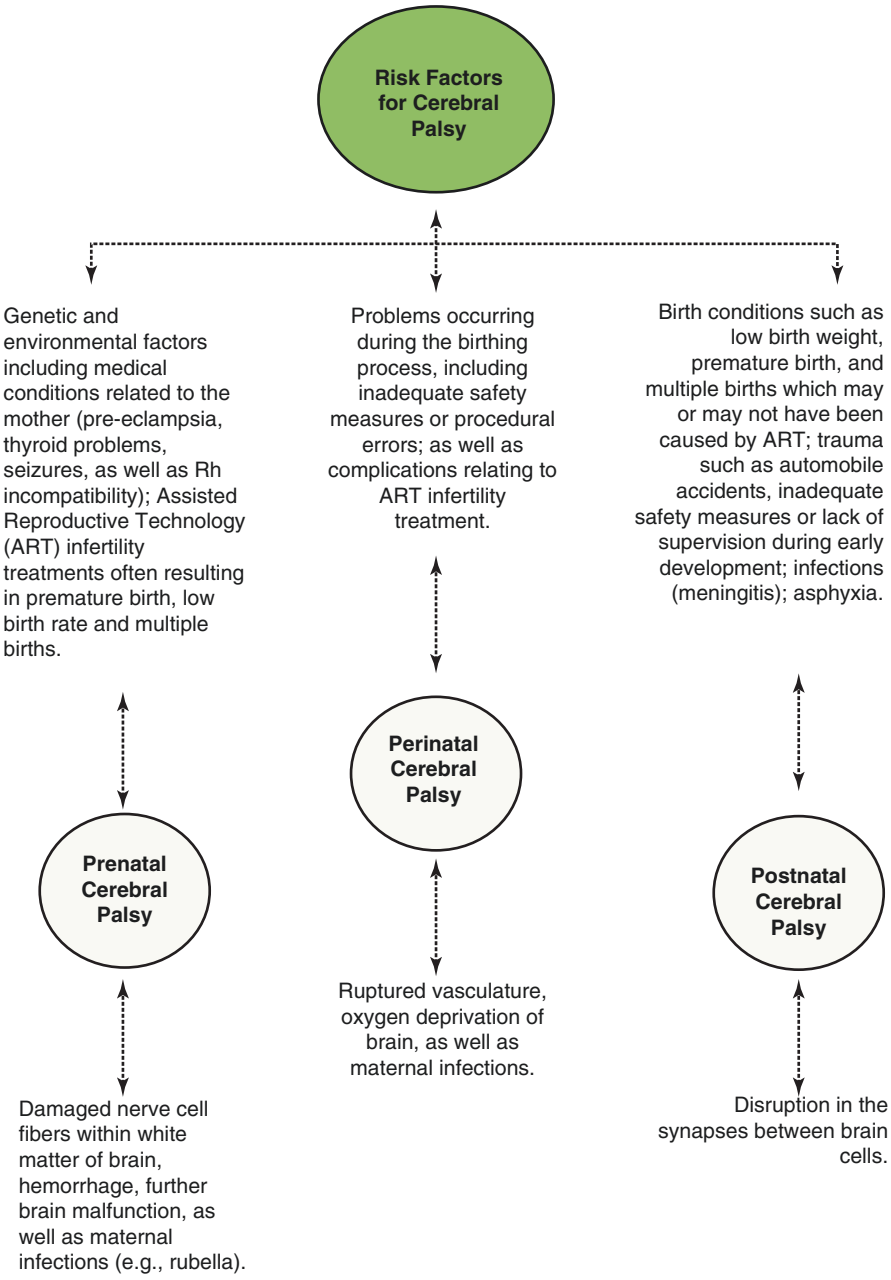

Fig. 1 Risk factors contributing to CP: Genetic, environmental factors and physiologic causes of CP, according to timing of onset (*Sources*: Nelson and Grether [6] and Reddihough and Collins [7])

Table 2 Primary symptoms associated with cerebral palsy

Primary symptom	Clinical description	Effect on bone
Poor muscle tone	The inability of muscles to work together with respect to both contracting and relaxing muscle fibers as needed is the most frequently observed symptom of CP. Exemplified by hypotonia: the floppy, rag doll appearance signifying decreased muscle resistance to passive movement or, more likely, by hypertonia, the stiffness or rigidity of muscles indicating increased resistance to passive movement	Compromised ability to reach peak bone density in the setting of weakened muscles limiting activities
Persistence of primitive reflexes	Reflexes such as sucking or grasping and holding an object persist beyond the typical and predictable time frame; in addition, a preference for use of the right or left hand is manifest before the normal age of 18 months	–
Damaged gross and fine motor skills	Abnormal muscle tone impairs crawling, standing, and walking; in addition it also affects the fine motor fibers necessary for precise movements such as picking up small objects and placing them in designated containers, turning book pages, or using a variety of writing and coloring instruments	–
Diminished oral motor functions	Difficulty conducting movement of the lips, jaw, and other facial muscles can result in feeding difficulties [117]. With respect to speech impediments, poor muscle control impedes air flow and posture; as well as negatively affecting the articulation of words and syllables [118]	Nutritional compromise may limit intake of calcium and other key vitamins and minerals
Compromised posture and balance	In contrast to the typical symmetrical posture, the asymmetrical posture characteristic of CP occurs because the right and left limbs do not mirror each other. Use of both hands for support in sitting, swaying when standing, and walking abnormally are all indications of balance abnormalities	Increase risk of fractures secondary to an increased fall risk

Sources: Jones et al. [9]
Reilly and Skuse [117]
Parkes et al. [118]

may use an assessment tool such as the Gross Motor Functional Classification System, an age-specific, five-level classification system, with five indicating total dependence [12]. Recently expanded to encompass a 12–18-year-old age group, it emphasizes functional abilities including movement and mobility, sitting, walking, and the need for assistive devices.

To establish an etiology and prognosis for children with CP, magnetic resonance imaging with its greater sensitivity is preferable to non-contrast computerized tomography (CT) as evidenced in studies showing that the yield of finding an abnormal MRI scan in a child is high (average of age 88 %) and greater than that reported using CT (77 %) [13].

Approaches to Management of CP in Children

Nonpharmacologic Management in Children

A multidisciplinary team of physicians, specialists, and therapists are needed to meet the complex needs of children with CP with a goal of increasing functional abilities, sustaining cognitive development, and achieving a sense of independence [3, 14, 15].

Physical therapy to improve muscle strength, balance, flexibility, and motor skills as well as to prevent contractures is one of the cornerstones of CP treatment. Resistance exercise has been shown to be effective in muscle strengthening, with no increase in spasticity [16]. Aqua exercises are also recommended. Braces, splints, casts, and ankle foot orthoses can help strengthen weak muscles and enhance joint motion, while gait function is improved with muscle strength training and orthoses. In a study of children with spastic diplegia, eight weeks of muscle strength training produced stronger muscles, higher GMFM scores, an increase in both stride length and hip extensor movement, and improved gait function [17]. Occupational therapy assists children in eating, grooming, dressing, attending school, and using a computer with a voice synthesizer; speech and language therapy enables them to gain greater control of jaw and mouth muscles, making their speech clearer and building their language skills.

Pharmacologic Management in Children

The most commonly prescribed medications for management of CP in children are oral and intrathecal baclofen (ITB), botulinum toxin (BT-A), diazepam, and tizanidine. Infused into the spinal canal with an inflatable pump, baclofen is a muscle relaxant that reduces muscle spasticity throughout the body. Administered by local injection, botulinum toxin is regarded as a standard treatment to reduce localized, segmental spasticity in the upper and lower extremities; it is most effective in children who have some control over their movements and when used in conjunction with a stretching program. Diazepam may be considered as a short-term treatment for generalized spasticity, while tizanidine has been found to be "possibly effective," recognizing that its impact on motor function has yet to be determined [18]. These medications may be important to improve the overall functional mobility of these patients, without which transfers and ambulation may be impossible. Maximizing mobility is an essential component of preventing osteoporosis.

Although surgery is rarely needed, it is recommended in some cases to reduce spasticity in legs, improve muscle development, lengthen or release tendons to increase mobility, and improve gait function. In addition, the insertion of spinal rods may be warranted to avoid the risk of musculoskeletal scoliosis [15].

Osteoporosis in Children with CP

Causes

In a frequently cited study, Houlihan and Stevenson observe that given their decreased bone density and bone mass, CP children suffer painful pathogenic fractures that are caused by poor bone mineralization. When inflicted with minimal trauma, such fractures result in compromised motor function and quality of life [19]. In the absence of mechanical loading by muscle force, the periosteal circumference of bone fails to expand; the long, narrow lever arms become weaker and more susceptible to fracture, and stiffness increases in the major joints, particularly in the hips and knees [20]. Other contributing causes of osteoporosis in CP are calcium and vitamin D deficiency, nutritional disorders associated with feeding and swallowing problems, anticonvulsant therapy, and delayed pubertal development that affects longitudinal bone growth and bone mineral accrual.

Diagnosis

As stipulated by the International Society for Clinical Densitometry (ISCD), DXA findings must be combined with evidence of a clinically significant fracture history to constitute a diagnosis of osteoporosis [21]. DXA scans in themselves pose special difficulties for children with CP [22]. Their smaller, thinner bones may lead to a false appearance of low BMD in these scans; abnormally shaped bones, prior surgeries, and surgical implants may also distort the results. Positioning the child in the scanner poses its own challenges. Excessive motion means that it is difficult to replicate positions from one scan to another, and these constantly changing positions can lead to a false BMD reading.

Adaptations in the use of conventional scanners are being made including supporting the extremities with splints and allowing the child to remain in a wheelchair, reducing or eliminating the need for sedation [23]. In addition, new, wider fan-beam scanners with their shorter span time minimize the effects of involuntary body movement [24]. Of particular significance, Henderson et al. have sought to counteract the effects of hip and knee contractures and scoliosis on the standard proximal femur testing site by developing an effective alternative: the measurement of BMD in the distal femur with the child in a lateral position [25].

Improved assessment tools are needed to increase understanding of the factors that promote bone quality in CP, including geometry and microarchitecture. Peripheral quantitative computed tomography (pQCT) is a more effective measure of the structural and material properties of bone, but it is not yet widely used in CP children, in part because of its lack of precision and high radiation doses [19]. It should be noted, however, that when used as a research tool, pQCT has demonstrated that bone strength in children with CP is due not to low cortical bone density

but to the presence of smaller and thinner bone. Moreover, a recent assessment of the potential of high-resolution pQCT demonstrates what the authors term its "unprecedented ability" to measure bone microarchitecture in a clinical setting, providing much-needed insight into changes in bone quality as well as the impact of anti-osteoporosis treatment on bone quality. However, before it is generally accepted in routine clinical practice, researchers will need to demonstrate its utility for fracture prediction [26].

Treatment

In order of their increasing efficacy, the three basic categories of treatment for osteoporosis in children with CP are (1) weight-bearing interventions, (2) calcium and vitamin D supplementation, and (3) bisphosphonate medication [27]. Before treatment is initiated, consideration should be given to eliminating the risk factors for osteoporosis in CP children, specifically the anticonvulsant medications that reduce BMD and increase fracture risk.

Weight-Bearing Activities

Studies on the efficacy of weight-bearing interventions in improving BMD and preventing fractures have produced inconclusive, sometimes conflicting, results, which can be attributed to the small number of subjects involved, the short duration of the studies, their limited number, and the inadequate rigor of their research designs [28]. In an examination of 18 children (nine with cerebral palsy and nine controls), Chad et al. found that after eight months of physical activity, volumetric BMD increased 5.6 % in the cerebral palsy group compared with −6.3 % in controls, with femoral neck bone mineral content at 9.6 % in the cerebral palsy group and −5.8 % in controls [29]. However, interpreting the results may be problematic because the extent of the increase in BMD needed to affect fracture risk has yet to be determined for children with CP [19].

In a pilot trial to determine whether a 50 % longer standing time (with or without assistive devices) could increase BMD in nonambulatory children with CP, Caulton et al. found a significant 6 % mean increase in the vertebral trabecular BMD (vTBMD), but no change in the proximal tibial BMD (pTBMD) over a 9-month period. They conclude that while this result may reduce the risk of vertebral fractures, it is unlikely to reduce the risk of lower limb bone fractures: the most common site of trauma fracture in children with CP [30]. By contrast, in a 6-month trial involving short duration, low-magnitude, high-frequency mechanical stimuli, Ward et al. [31] demonstrated a 6.3 % mean increase in vTBMD in disabled children who stood on active devices as opposed to an 11.9 % decrease in those on placebo devices, representing a total net benefit of 17.7. On the basis of these findings, they conclude that low-magnitude mechanical loading may provide

a surrogate for suppressed muscular activity in children with disabilities, representing a potential nonpharmacologic, noninvasive treatment. Although an analysis of the effect of stepping while standing revealed no added benefit to bone compared with passive standing [32], repetitive locomotor training with an electromechanical gait trainer led to improvements in 10 and 6-minutes walk tests, gait speed, and stride length [33]. Further research and stronger evidence are needed to justify an overall recommendation on weight training for osteoporosis treatment in cerebral palsy.

Nutrition

Children with limited exposure to sunlight and inadequate dietary intake, as in the case of those with cerebral palsy, are likely to experience vitamin D deficiency. The recommended daily requirement is 600 IU daily; however, a study by Kilpinen-Loisa et al. found that administration of 1,000 IU of vitamin D_3 daily five days a week for 10 weeks resulted in a significant increase in vitamin D concentration, without producing hypercalciuria or other adverse effects [34]. Calcium intake can be enhanced through diet or calcium supplementation, with diet as the preferred alternative, because it is more soluble and is associated with greater patient compliance [27]. Jekovec-Vrhovsek et al. conducted a study of 20 children ($n = 13$, 7 controls) with spastic quadriplegia and epilepsy, before and after vitamin D and calcium supplementation. Their results showed that in the treated group, BMD increased significantly, while the untreated group continued to experience bone loss [35].

Pharmacologic Intervention

Of the treatments currently in use, bisphosphonate therapy appears to be the most effective in increasing BMD and, to an extent, in reducing fragility fractures [27]. Despite concerns about long-term efficacy and safety in children, studies report generally favorable findings, specifically for the drug, intravenous pamidronate. In an evaluation of the effect of IV pamidronate on osteopenia in nonambulatory children with quadriplegic cerebral palsy [36], Henderson focused on six pairs of subjects with each pair matched by age, sex, and race. One subject in each group received a placebo; the other was administered with IV pamidronate for three consecutive days, repeated at 3-month intervals for one year, with continued evaluations for six months after the final treatment. The result was an $89\% \pm 21$ increase in BMD at the distal femur for the pamidronate group as opposed to a $9 \pm 6\%$ increase for the controls. Age-normalized *Z*-scores also increased for the pamidronate group, while controls showed no significant change.

Subsequent research on the effect of pamidronate has confirmed increases in BMD for femoral neck and lumbar spine, with increased *Z*-scores at both sites [37]. When used in combination with vitamin D, another bisphosphonate, risedronate,

improved BMD in cerebral palsy patients for greater than one year [38]. Bisphosphonate intervention is generally recommended only after a child has sustained at least one fragility fracture and not as a preventative measure. Fehlings et al. further propose that treatments be initiated only if fractures continue after vitamin D and calcium have been optimized [27].

Another potential treatment for CP children with osteoporosis is growth hormone (GH) replacement therapy. In a study of 46 children (ages 3–11 years), Devesa et al. found that 70 % of the children had impaired GH secretion, making it the most common anterior pituitary abnormality in children with CP. Their analysis of other studies relating to GH (generally carried out in adults or rodents) emphasized that not only did GH increase the possibility of achieving normal height, but when combined with the insulin-like growth factor-1 (IGF-1), it also increased cell proliferation and survival in both the central and peripheral nervous system. Given these findings they propose that GH therapy be initiated as early as possible [39].

Cerebral Palsy in Adults

The number of adults living with cerebral palsy in the United States is estimated at about 400,000 and that number is expected to grow due to the heighted survival rate of low birth-weight infants as well as the increased longevity of the generalized adult population including those with CP. The initial challenge is the transition from pediatric to adult health care that offers more limited interdisciplinary care and rehabilitation services. Not only must a thorough and accurate medical history be provided to the adult facility, but provision should be made for initial overlap and continued communication, if needed, between pediatric care providers and adult health care professionals to ensure continuity of care. An interdisciplinary care center is the optimal adult facility given the needed to detect, monitor, and treat the multiple consequences of aging with cerebral palsy [40, 41].

Only within the last two decades have individuals with cerebral palsy lived long enough to encounter the effects of aging imposed upon their lifelong disability. Adults with CP experience early-onset aging in their 40s as developmental delays in childhood, continual spasms, and additional stress and strain result in deterioration of the cardiovascular and pulmonary systems as well as muscle groups. They may also have acute or chronic pain, generally situated in the hips, knees, ankles, and upper and lower back. Those with spastic cerebral palsy indicate pain at a greater number of sites and to a more intense degree than patients with other forms of CP [4]. In a study of 93 adults recruited from the University of Washington area, 67 % reported one or more areas of pain of a minimum of three months duration, most commonly in the lower extremities and back, with 56 % reporting pain on a daily basis [42]. In an analysis of the frequency and severity of several symptoms of cerebral palsy in 83 adults, Hirsh et al. [43] confirmed Schwartz et al.'s earlier findings that moderate-to-severe pain persisted in a cohort of 50 CP adults followed over a 2-year period.

Among the causes of pain in adult CP are osteoarthritis, contractures, spasticity, orthopedic deformity, fractures, poor nutrition, weakness, and fatigue [44]. The National Institute of Neurological Disorders and Stroke has reported that CP patients require three to five times the amount of energy to walk and move about than do normal persons [4].

An examination of 101 adults (aged 19–74) with cerebral palsy revealed that 76 % had multiple musculoskeletal problems; in 63 %, these occurred under the age of 50, suggesting that abnormal biomechanical forces and immobility led to excessive physical stress overuse syndromes and possibly early joint deterioration [45]. In a survey of 221 Swedish subjects (ages 25–58) [46], 35 % of the subjects reported decreased walking ability before age 35, with participants citing increased spasticity, balance problems, and musculoskeletal deterioration as the causes; researchers pointed to contractures in weight-bearing joints, immobility, knee pain, and the lack of physiotherapy as additional causal factors. One of the predictors of sustained walking is childhood experience: those better able to walk as a child persisted walking into adulthood for a longer period than those who used gait aids [47]. Other challenges facing adults with CP include communication, hearing and vision impairments, osteoarthritis, and depression which is three to four times greater in patients with such disabilities as CP, resulting primarily not from the disease itself but from the ability to cope with its consequences.

Medical Management and Symptom Control in Adult CP

The most critical need of patients with adult cerebral palsy is pain management. In a study of chronic pain in this population, Jensen et al. followed 50 patients (half women/half men) over the course of two years, finding that pain intensity did not change significantly over that period despite the use of several forms of treatment; although participants characterized a number of treatments as "moderately helpful," in their view, only three—whirlpool, ultrasound, and transcutaneous electrical nerve stimulation—were associated with decreased pain [48]. In a descriptive study of 64 adults (ages 18–76), Engel et al. reported that more than half of the participants used non-steroidal anti-inflammatory medications (i.e. acetaminophen, aspirin, ibuprofen) to treat pain, while one-third turned to anti-spasticity medications or opioids; all were reported to have limited success [49].

Intravenous botulinum toxin (BT-A) and intrathecal baclofen (ITB) have also been used in adults with limited success. Injected into muscles, BT-A is primarily directed at managing spasticity; its effect on pain is not fully understood and remains primarily anecdotal [44]. One of the most significant new advances in cerebral palsy, ITB, has been shown to be a safe and effective treatment for muscle spasticity in cerebral palsy, with demonstrated functional improvement and pain relief [50].

The positive effect of exercise in reducing pain has been examined in a number of disabilities including cerebral palsy. Patients themselves have indicated that physical therapy and strengthening exercises are beneficial. In an analysis of pain

treatments in adults with CP [51], physical therapy, mobility/ROM exercises, and strengthening exercises were among the most common treatments, used with a rating of "moderately effective." However, more extensive studies are needed to demonstrate the effectiveness of various types of exercise and their direct relation to specific sites of pain and specific types of CP.

Beyond pain management, traditional physical therapy has long been one of the cornerstones of CP treatment and rehabilitation, with anticipated improvement in lung and heart efficiency, mobility, and bone strength as well as a reduction in the risk of complicating diseases such as osteoporosis. However, evidence on the actual effect of physical therapy remains limited. In a systematic review of 13 trials on the impact of physiotherapy on adults with CP, Jeglinsky et al. found that none met the criteria for high methodological quality and pointed up the need for new, well-designed studies [52].

At the same time, newer forms of exercise, notably strength training, have become prominent in both able-bodied and disabled individuals and have secured a place in the CP population. In previous decades, strength training was avoided because of the unfounded belief that it led to increased spasticity; even today, despite some evidence that it can improve strength and possibly improve motor function, strength training remains controversial, particularly in children and adolescents [53]. However, several studies of strength training in adults have shown promising results. In a study of the impact of a 10-week progressive strength training program focused on the lower extremities of a small group of adults with CP, Andersson et al. reported significantly improved muscle strength in hip extensors, resulting in improved walking ability, walking velocity, and gross motor function with no increase in spasticity [54]. A small study conducted at a community gymnasium demonstrated that during another 10-week intervention period, participants increased leg strength by 22.0 % and arm strength by 17.2 % [55]. Participating in a strength training program can have psychological and social benefits as well, even increasing adherence to the programs themselves. Participants in a trial involving adults aged 40+ cited enjoyment and social interaction as the principal benefits, leading to perceptions that their strength and ability to carry out everyday activities had improved [56]. Aquatic exercise, functional electrical stimulation, and whole body vibration in a community setting are other new techniques currently being studied for their efficacy in increasing muscle strength and motor performance, fostering social interaction without negatively affecting spasticity.

The adoption of new therapeutic approaches, coupled with a growing appreciation of the value of social involvement, is leading to a rethinking of how to assess physical interventions [57]. Instead of attempting to undertake and evaluate a multifaceted therapy program, researchers increasingly focus on assessing the value of a specific well-defined treatment. This is the goal of strength training evaluations. Other activity-based programs such as cycling and treadmill training aimed at increasing endurance and coordination require similar evaluations.

The extended life span of patients with CP and the fact that many lose their walking ability by the age of 35 have even led to questioning the value of the "symbolic"

goal of independent walking for children and adolescents, resulting in significant implications for adults with the disease. As Bottos et al. emphasize [58], the need to plan for an entire life span, rather than focus on the childhood experience, has taken on a new importance. When walking is upheld as the ultimate achievement and is subsequently lost, frustration and disappointment are the inevitable result. In contrast, Damiano demonstrates that mobility, whether achieved independently or with motor devices, has positive effects in terms of the emotional and social development of the child and ultimately the adult. Children with increased motor ability are more likely to develop a "can do" attitude rather than retreat into a "help me" mode [57]. Independence achieved through the use of advanced assistive devices coupled with the benefits derived from social participation in the community should be among the altered and achievable goals of adults with CP who seek an improved quality of life [58]. Unfortunately, it must be noted that a number of "external" impediments impose limitations on access to exercise facilities. They range from the costs involved and the need for transportation to accessible fitness centers and for personal assistance at the centers themselves to the very existence of centers willing to accept adults with CP as well as lack of motivation on the part of some CP patients to engage in physical exercise [59].

Medications to Improve Functional Mobility

Botulinum toxin A (BoNT-A) is used to manage spasticity that interferes with motor control and function in CP adults, whereas ITB, injected in the spinal cord, has been reported to reduce dystonic and spastic tonal abnormalities, improve mobility and self-care, and increase stride length and walking speed [44].

Surgical Interventions

Orthopedic surgery is generally recommended to increase range of motion in CP patients with severe spasticity and stiffness [60]. Surgeons can lengthen or cut through muscles and tendons as well as attach a tendon to a different bone. Contracture release involving the cutting of an overly tight muscle is one of the most common procedures, often used to lengthen the Achilles tendon in an effort to correct contracture of the calf muscles. Foot deformities and hip displacement resulting in painful weight-bearing can also be corrected through a procedure called osteotomy, the selective removal of a small piece of bone which is then repositioned or reshaped. Hip arthrodeses, which fuse together bones that normally move independently, limit spastic muscles from pulling ankle and foot bones as well as hips out of position. Hip dislocation also responds to interposition arthroplasty which involves the use of muscles or tendons to separate inflamed bone surfaces in arthritic joints [44].

In terms of neurosurgery, selective dorsal rhizotomy (SDR), a procedure recommended only after more conservative treatments such as physical therapy and

medications have been employed, involves cutting up to 50–70 % of the sensory nerve roots at the base of the spinal column to reduce muscle contractures and spasticity; the motor roots are left intact. It is most often used in cases of spastic diplegia to decrease chronic pain in the lower and upper extremities. In a trial involving 21 ambulatory adults with CP, Reynolds et al. reported that patients experienced significant improvements in lower extremity passive joint range of motion as well as decreased spasticity in all measured lower extremity muscles groups. Patients observed improvements in ambulatory ability, coordination, and overall quality of life, leading to the conclusion that SDR can be an effective treatment for adults with spastic diplegia [61].

Osteoporosis in Adults with Cerebral Palsy

By the time patients with CP reach adulthood, the bone and muscle impairment that adversely affected their earlier years has already been manifested in low bone mineral density (BMD), greater fracture risk, and increased number of fractures themselves, often occurring with minimal trauma. The neuromuscular impairments that affect the reliability of the standard DXA scans have been overcome, in large part, by the adaptation of the new lateral distal femur DXA scan to adults. Although administration of these scans requires special training and expertise, they promise to produce reliable, reproducible, and clinically relevant assessments of BMD in adults [62].

Several trials have documented low BMD in adults with cerebral palsy. In an examination of 48 premenopausal women and adults (age range: 25–46 years) [63], the mean BMD *Z*-scores were −1.40 for the lumbar spine, −1.36 for the total hip, and −1.02 for the femoral neck, with nonambulatory patients exhibiting significantly lower scores at all three sites. There was also a correlation between low BMD and low body mass index (BMI), reflecting the lower body fat generally observed in patients with cerebral palsy and confirming similar results for children and young adults reported by Henderson et al.

Causes

Among the principal causal factors for osteoporosis in adults are the degree of physical disability, prolonged immobilization or limited ambulatory status, nutritional deficits particularly in terms of calcium and vitamin D, and use of anticonvulsant drugs. A Japanese study of 123 institutionalized adults (51 men, aged 21–41, and 39 nonambulatory; 72 premenopausal women, aged 24–47, 54 nonambulatory) [64] examined the effect of mobility level, calcium status, and anticonvulsant drugs. Women who were nonambulatory had significantly lower BMD than those who

were ambulatory; for nonambulatory men, BMD was also reduced, but it did not reach statistical significance. The use of anticonvulsant drugs (reported by 50 % of the patients) was significantly associated with lower BMD in both sexes. Anticonvulsants are known to be related to low levels of vitamin D as well as to hypocalcemia and higher serum alkaline phosphate levels. Twenty-nine percent of the patients in the study had abnormal calcium metabolism, while higher alkaline phosphate levels in the male participants were significantly associated with their low BMD. Patients in the study also evidenced shorter stature and lower weight than a comparable sample with normal height and weight values. Falls and resulting fractures are another risk factor for the development of osteoporosis. In a sample with a mean age of 44 years, one study found that 40 % of adults with CP fell monthly and that 75 % fell bimonthly [65, 66].

As in the normal population, osteoporosis may not be detected until a bone fracture actually occurs; in the case of cerebral palsy patients, the pain associated with fracture may not even be communicated by patients with cognitive or speech disabilities. Sheridan [67] observes that given the small number of studies on the prevalence and incidence of fractures in adults with CP, information must be extrapolated from pediatric studies to provide insight into the likelihood of fractures in adults. Specifically, he proposes that because adults have had a much longer exposure to bone deformities, joint surgeries, nutritional deficiencies, and the like, clinicians must assume a greater risk of fractures in adults than in children—a risk that will increase as the already compromised bone strength is compounded by the age-related decline in bone mass.

Nonpharmacologic Treatment

Physical Exercise

Osteoporotic patients are known to benefit from a regimen of physical activity that can increase bone mass through weight-bearing exercises and decrease fall risk by improving balance and coordination. However, the defining characteristics of adult cerebral palsy, including spasticity, degenerative arthritis, sarcopenia contractures, and pain, make such activity extremely difficult if not impossible in many cases. Assistive equipment including standers, standing frames, and standing on a vibrating platform are among the new approaches to osteoporosis treatment, but studies in adults are sparse. In several animal studies, low-magnitude, high-frequency whole body vibration (WBV) stimulation has produced an increase in trabecular bone mineral content and strength; investigations of the effect of WBV on postmenopausal women indicate an attenuation of the decline of BMD at the hip [68]. A recent trial involving older adults on vibration therapy demonstrated a significant improvement in all fall risk factors including a significant increase in the range of motion of ankle joints [69]. However, despite the beneficial effects shown in broader

studies, little is known about the specific effect of WBV on CP patients faced with developing new motor skills and normal movement patterns. Moreover, WBV raises safety concerns about broken bones, musculoskeletal problems, and low back pain [70]—issues that may be especially problematic in adults with CP.

Nutrition

Bone quality in adults with CP, as in the broader population, is dependent on an adequate intake of calcium and vitamin D. In accordance with Institute of Medicine recommendations, the level for calcium is 1,000 mg/day for ages 19–50 and 1,200 mg/day for over age 50 up to a maximal limit of 2,500 mg/day. Because patients with CP are unlikely to be exposed to sunlight for a sufficient time period, vitamin D supplementation is needed in specified amounts for three different age categories: 200 IU/day for ages 50 and below; 400 IU/day for ages 50–70, and 600 IU/day for over age 70. Serum phosphate and parathyroid hormone (PTH) may also be recommended for patients with CP. Studies demonstrate that PTH, in its synthetic form, teriparatide, increases bone formation on all bone surfaces (trabecular, endosteal bone, and periosteal bone) and decreases the risk of vertebral and nonvertebral fractures [71].

Caloric intake for CP patients must be assessed on an individual basis. Muscular deformities, the inability to chew and swallow, gastroesophageal reflux disease, and malabsorption restrict caloric intake, while the specific form of paralysis can affect the energy needs of the CP individuals [67].

Pharmacologic Treatment

Estrogen replacement therapy and selective estrogen receptor modulators (SERMS) are known to increase BMD, but they are plagued with safety concerns and potentially harmful side effects including blood clots in the legs and lungs, particularly in patients who are inactive or immobile. Trials involving another option, growth hormone replacement therapy, indicate that after an initial 6–12 month period of bone resorption, GH results in both an improvement in balance and an increase in BMD that continues for 18–24 months after discontinuation of therapy. Moreover, concern persists as to whether long-term use of GH may promote tumor initiation or recurrence [72].

For the most part, the interventions outlined above have not been examined in adults with CP who face different and more complex challenges than those encountered by more able-bodied individuals with osteoporosis. In addition to further epidemiological research, trials focused on the impact of physical, nutritional, and pharmacologic therapies—both established and emerging—must be targeted *specifically* to these adults to better understand, possibly prevent, and more effectively treat osteoporosis in individuals with severely compromised bone strength and function [67].

Duchenne Muscular Dystrophy in Children

The most common form of muscular dystrophy, Duchenne muscular dystrophy (DMD), accounts for approximately half of muscular dystrophy cases and affects primarily young boys at an incidence of 1 in 3,500–6,000 male births in the United States [73].

Causes and Symptoms

Duchenne muscular dystrophy is caused by a mutation in the gene, dystrophin, which can be inherited in an X-linked recessive pattern; alternatively it can occur in individuals with no family history of the disease [74]. Dystrophin ensures muscle strength and health by maintaining the structure of muscle cells. Without it, profound muscle weakness and wasting caused by degenerating muscle fibers appear generally before the age of 6. The principal symptoms include frequent falls, a waddling gait, difficulty rising from a lying or sitting position, and enlarged calf muscles resulting from an accumulation of fat and connective tissue (pseudohypertrophy). As shown in Fig. 2, equinus of the feet and a hyperlordotic posture of the spine can compensate for balance loss temporarily, but a significant fall risk accompanies attempts to remain ambulatory using compensatory measures [75]. As the diseases progresses, the heart muscle weakens, scoliosis may develop, and the muscles associated with breathing and swallowing deteriorate to the point where ventilators must be used, initially at night but subsequently extending into the day. The thin, demineralized bone becomes osteoporotic and fractures occur easily. By early adolescence, children with DMD generally lose their ability to walk. Without the care of specialists from a number of disciplines and the use of advancing technologies and medication, these children die in their late teens or early 20s as a result of cardiac or respiratory failure; however, such interventions are now leading to survival rates in the 30s and even 40s [76, 77].

Diagnosis

Given the many complications of DMD, physicians may need to undertake a plethora of laboratory tests to confirm a diagnosis [78]. Among the most important are creatine kinase (CK) blood tests, genetic tests, and muscle biopsies. Following a thorough medical history and physical examination, one of the first tests to be conducted for DMD focuses on the identification of defective genes and neuromuscular disorders. Damaged muscles release the enzyme, CK, into the blood. Elevated CK levels including those found early in Duchenne indicate

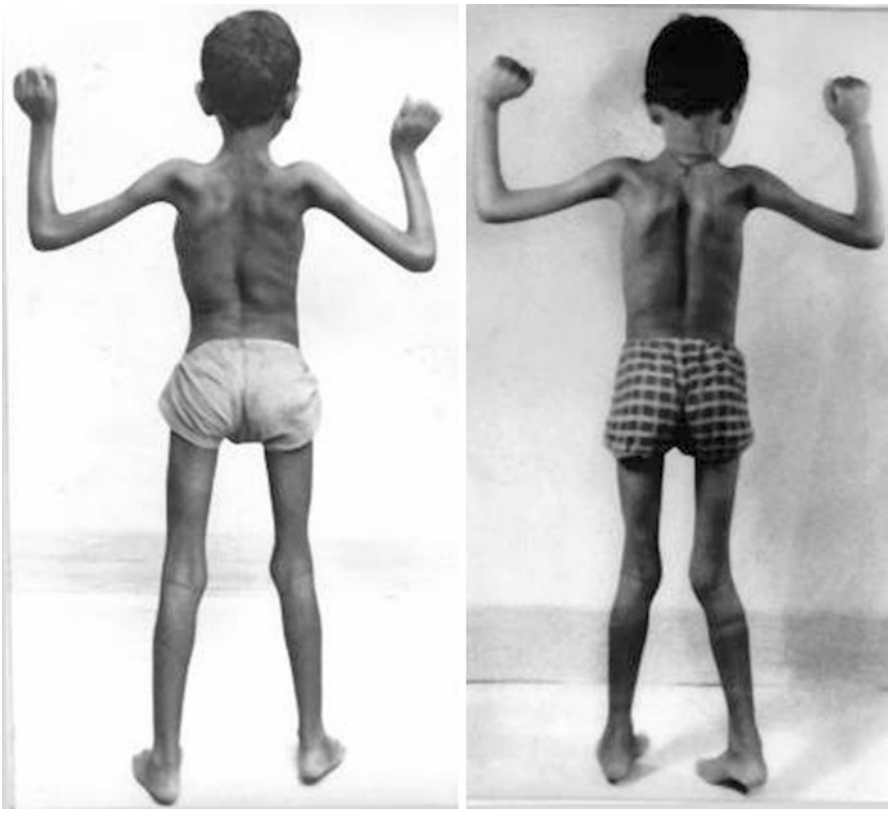

Fig. 2 Hyperlordotic posture and proximal muscle wasting of DMD. The photograph demonstrates muscle wasting in periscapular region, humerus, and thigh muscles but shows calf hypertrophy. In order to maintain balance, a hyperlordotic posture of spine can be adopted as a compensatory measure (*Source*: Wikipedia Public Domain (WPD) 1.0. Accessed 20 Dec 2015)

that muscles are being destroyed even before physical symptoms appear; however, the test may not indicate precisely what muscle disorder is involved.

Genetic testing, specifically single condition amplification/internal primer (SCAIP) sequencing [79], is increasingly recognized as the gold standard of diagnosis in inherited muscular dystrophy. Analysis of cell DNA can determine whether and where a mutation in the dystrophin gene has occurred and can identify women DMD carriers who are likely to pass the disease on to their sons and their carrier status on to their daughters. Knowledge of an individual's precise genetic mutation is essential not only for diagnosis but for the development of new therapies. Moreover, it provides the clinical information for genetic counseling that can identify whether mothers are carrying a mutated gene and thereby assist parents in planning for a family.

If these tests confirm a DMD diagnosis, no further testing is required. However, if the results show a high CK level and symptoms of DMD but no genetic mutation, a muscle

biopsy is needed to determine whether dystrophin is present and, if so, in what amount and molecular size. The absence of dystrophin confirms a Duchenne diagnosis [78].

Treatment Approaches

Established forms of treatment for DMD encompass physical therapy and assistive devices, corrective surgery, medication, and dietary supplementation of calcium and vitamin D. Some newer approaches, as yet experimental but with implications for the severity of osteoporosis, are also in development.

Physical Therapy

Range-of-motion and stretching exercises, particularly those involving upper extremity muscles, are important for keeping muscles and joints as flexible and strong as possible; they may help patients maintain the ability to use a computer keyboard or control a wheelchair as well as delay contractures by preventing tendons from shortening prematurely. Passive stretching, carried out by a therapist and often used in conjunction with night splints, is also effective against contractures, whereas braces and standing frames enable DMD patients to stand for several hours a day, improving circulation and aiding bone strength. Therapy can help correct postural stance when a child is younger by strengthening those muscles with remaining function and using other modalities and supports to minimize lordosis (see Fig. 2). Aquatic exercises are examples of low-impact activities that use the buoyancy of the water to alleviate undue stress on muscles [80].

Surgical Intervention

Spinal fusion or the attachment of metal rods to the spine to correct posture and increase strength ease the adverse effects of scoliosis on sitting, sleeping, and even breathing. If severe contractures seriously impair movement, tendons or muscles can be lengthened to restore or improve range of motion. In terms of new surgical techniques, Forst et al. have reported that prophylactic surgery performed on the lower limbs and spine when patients are still ambulatory can delay the point at which they become wheelchair-bound by as much as two years; by enabling the patient to stand for a much longer period, it stimulates circulation and prevents or delays the onset of contractures, scoliosis, and osteoporosis. The long-term results may be a life expectancy of over 30 years and an improved quality of life [81]. End-stage dilated cardiomyopathy is recognized as an adverse outcome of DMD in patients who cannot tolerate cardiac transplantation. In such cases, a surgical technique involving the implantation of a ventricular assist device has been developed as a new therapeutic option [82].

Medications

The most widely used medications for DMD are corticosteroids, specifically prednisone (dose = 0.75 mg/kg) and deflazacort (dose = 0.9 mg/kg). Corticosteroids have been shown to attenuate muscle weakness, thereby prolonging ambulation and preserving cardiac and respiratory function. A 2008 Cochrane meta-analysis of four RCTs demonstrated that these drugs improved muscle strength and function in the short term—six months to two years [83]. However, this and subsequent studies have also shown that corticosteroids produce serious side effects ranging from rapid weight gain and myopathy to bone fragility and osteoporosis, with deflazacort having more bone-sparing qualities than prednisone [84].

In terms of new treatments, researchers using gene therapy are now developing strategies to replace the dystrophin gene or to bypass dystrophin mutations [85]. The skipping of sections of the genetic code called exons (exon skipping) is being investigated to determine if it would create partially functional dystrophin to lessen severe muscular weakness and atrophy [86]. If such treatment is successful and ambulation is extended for more years, the onset of osteoporosis would be proportionately delayed, potentially at a time when linear growth is occurring. Such measures would enable DMD patients to come closer to reaching peak bone density during puberty, an essential measure to limit future osteoporosis.

Osteoporosis in Children with DMD

Causes and Symptoms

The development of osteoporosis in DMD is generally attributed to decreased weight-bearing, progressive muscle weakness affecting bone loading, reduced mobility, and long-term use of corticosteroids. Side effects of corticosteroids include impaired osteoblast formation and mineralization, delayed puberty, and poor calcium absorption from the intestine [87]. Although long bone osteoporosis can occur in patients who are still ambulatory, vertebral bone osteoporosis, which is more susceptible to the effects of steroids, is generally not evident until boys are wheelchair-dependent [88].

Several studies have demonstrated the existence and effects of low BMD in this disease. An analysis of the interaction of bone density, mobility, and fracture in 41 DMD patients (31 nonambulatory) who had received no steroid treatment revealed that bone density in the lumbar spine and, to an even greater extent, in the proximal femur decreased, while the boys were still ambulatory. Moreover, 44 % of the boys sustained a fracture, with 66 % of the fractures involving the lower extremities; 44 % of nine boys who were walking with some support prior to the fracture never resumed walking [89]. In a subsequent study, a weakness in hip flexors as well as proximal femur and spine osteoporosis were apparent, despite continued ambulation [88].

When DMD patients are treated with corticosteroids, the incidence of both decreased BMD and fracture occurrence is even more pronounced. Bianchi et al. [90] evaluated bone mass and metabolism in 22 children on long-term prednisone therapy compared with 10 who had not been treated. Results indicated a correlation between corticosteroid dosage and decreased BMD at the spinal level as well as reduced BMD in the trunk and lower limbs, although the authors observed that the latter could be due to decreased weight-bearing on bone. Reduced intestinal calcium absorption was also observed. King et al. reported that not only did long bone fractures occur 2.6 times more frequently in steroid-treated DMD patients than in those untreated but also that 32 % of the steroid group experienced vertebral fractures compared with no fracture occurrence in the untreated group [91].

An analysis of the length of time between the initiation of corticosteroids and fracture occurrence indicated a latency period of 40 months before the first vertebral fracture appeared and predicted that 75 % of boys with DMD would experience a vertebral fracture following 100 months of steroid treatment [92]. In addition, a study of 408 steroid-treated patients reported that fracture prevalence, together with worsening motor function, progressively increases throughout the pediatric age span: 16.5 %, 37.45 %, and 83.3 % at ages 5, 10, and 15, respectively, with prevalence of vertebral fractures rising 4.4, 19.1, and 58.3 % for the same ages [93].

Diagnosis

The use of size-adjusted and subcranial analysis in DXA provides the most effective assessment of BMD in boys with DMD, indicating a deficit in total body BMD-for-age (*Z*-score of −1.2) that increases with age [94]. An international conference on corticosteroid treatment in DMD (2009) recommended that a baseline lumbar spine DXA be performed before such treatment is initiated and repeated at 12–24 month intervals while the patient continues on treatment [95]. Spinal screening for vertebral fractures in steroid-treated patients should also be performed to determine if fractures had occurred previously, an indication that bisphosphonates should be prescribed [87].

Treatment

Nutrition

With long-term corticosteroid treatment becoming the standard of care in DMD, the need for adequate calcium and vitamin D in this population assumes increasing importance. In a 2-year study of 33 DMD patients on corticosteroid therapy, first-line treatment with calcifediol (25-OH vitamin D_3), coupled with an adjustment in dietary calcium to the recommended dose, resulted in a significant increase in BMD in over 65 % of the patients, while bone resorption declined and bone mass increased in 78.8 % [96]. Bianchi et al. further recommend that when calcifediol

levels are low, vitamin D metabolite, rather than vitamin D standard supplements, should be administered. Patients should adhere to at least the FDA recommended dose of calcium per age group in order to avoid hypocalcemia and an increase in bone turnover [90].

Exercise

The role of exercise in optimizing bone health is subject to conflicting reports. Light to moderate exercise appears to be beneficial in some forms of muscular dystrophy, but increased risk of muscle damage remains a serious concern. Some researchers point to the limited positive effect of standing programs and vibration therapy in cerebral palsy. However, the few studies focused specifically on muscular dystrophy demonstrate that although whole body vibration therapy (WBVT) was well tolerated and muscle damage did not occur, no improvements in bone density and muscle strength were observed [97, 98]. Further studies on larger cohorts are needed to evaluate the efficacy and safety of WBVT with attention to the duration and dose of exposure.

Medications

Thus far, the small number of trials involving bisphosphonate treatment and DMD patients on steroids has shown promising but limited results with respect to BMD and *Z*-scores. A study of boys (mean age = 10.2 years) using daily deflazacort [99] and treated with alendronate showed a positive effect on BMD, specifically maintenance of BMD *Z*-scores and the absence of symptomatic fractures, in contrast to the anticipated age-related decline in bone mass and increased fracture risk. During a 2-year follow-up period, the improvement in *Z*-scores was greatest in the youngest boys who received alendronate early in the course of the disease; the older boys were given a more conservative dose because of the prevailing concerns about a possible negative effect of bisphosphonates on longitudinal bone growth.

A more recent study indicated that *Z*-scores at the hip trended downward without alendronate and upward (stabilized) with alendronate, but the trends were not statistically significant [100]. In an analysis of the effect of intravenous bisphosphonates (pamidronate: 9 mg/kg/year or zoledronic acid: (0.1 mg/kg/year) on vertebral fractures caused by osteoporosis, back pain decreased or resolved completely and height ratios of previously fractured vertebrae stabilized or improved. However, such therapy did not completely prevent the development of new vertebral fractures [101]. Again, further research is needed to determine the long-term effects of bisphosphonate treatment, the most effective dose, frequency of treatment, optimal age to begin treatment, and relative efficacy of oral versus intravenous administration. Quinlivan et al. question the routine use of bisphosphonates to prevent fractures until these issues are addressed [95], while Hawker et al. indicate that they have been using daily deflazacort as a standard treatment [99]. Looking to the

future, Buckner et al. recommended that the effect of such drugs as denosumab, recombinant parathyroid hormone (teriparatide), and melatonin on BMD and fracture risk be investigated [87].

Duchenne Muscular Dystrophy in Adults

Without intervention, progressive muscle degeneration, loss of ambulation, and other respiratory, cardiac, and orthopedic complications associated with DMD can lead to death at a mean age of 19 years [102]. However, significant advances in the management of DMD have now extended life expectancy into the late 20s and 30s [103]. Key to this improved prognosis has been the development of multidisciplinary teams incorporating physicians, therapists, psychologists, and other specialists to meet the complex challenges of DMD. The benefits of coordinated care underline the importance of an effective transition from childhood to adult facilities which can provide not only integrated medical therapy but also guidance about education, careers, living arrangements, social interaction, and, taken together, the demands of independent living [102].

Among the most critical issues in adult DMD are the complications caused by weakened breathing muscles or chest infections. At the onset of muscle weakness, lung function tests are conducted to monitor both muscle strength and oxygen levels in the blood. To counter breathing difficulties, "noninvasive ventilation," the use of a mask over the nose or mouth to deliver pressurized air, has emerged as a highly effective therapy, leading to higher survival rates. Initially used only overnight or from time to time, ventilation can be extended if muscle weakness progresses. In a study of the impact of nocturnal ventilation over the period 1967–2002, Eagle et al. demonstrated that the mean age of death in the 1960s was 14.4 compared with 25.3 years for patients ventilated since 1990. Although they acknowledged that the advent of more effective coordinated care has helped to advance life expectancy to 25 years (from 0 % in the 1960s to 4 % in the 1970s to 12 % in the 1980s), they emphasized that nocturnal ventilation improved the likelihood of survival to 53 % for those ventilated since 1990. These findings have been confirmed by subsequent trials [104, 105]; in addition, a later study, also led by Eagle, reported that ventilation combined with spinal surgery improved median survival to 30 years [106]. In the period since the original Eagle study, survival rates into the 30s with a few cases in the 40s and 50s have been reported [107]. Cough-assisted devices and manually assisted coughing may also be used in the early stages of breathing problems.

Whereas respiratory issues were the major cause of death in adult DMD until the 1980s–1990s, advances in respiratory treatments have focused attention on cardiac failure as an increasingly significant factor in morbidity and mortality. Caused by dilated cardiomyopathy (alone or in combination with infections and abdominal problems) and/or by cardiac arrhythmia [108], cardiac complications affect nearly all adults with DMD [103].

Diagnosis

The standard diagnostic tests to screen for cardiac abnormalities include electrocardiography (ECG), echocardiography, and cardiac magnetic resonance (CMR) imaging. ECGs are effective in determining cardiac arrhythmias such as atrial fibrillation but lack the sensitivity to assess structural cardiac disease. Echocardiography is used to assess left ventricular (LV) size, wall thickness, and valve function; it can be administered to patients in a wheelchair and offers cost and convenience benefits for DMD patients [103]. In addition to providing a more reliable assessment of LV size and function, CMR promises to provide insight into early cardiac involvement so that heart failure therapy may be initiated at a younger age, thereby delaying the onset and progression of left ventricular dysfunction [109]. However, its high cost and the blurred, ghostly images resulting from heart motion restrict greater use [103].

Medications

The most commonly used therapies for cardiac dysfunction in DMD are angiotensin-converting enzyme (ACE) inhibitors and beta (β) blockers. In some cases, evaluations of the efficacy of these drugs have been carried out in related disease populations, with applicable findings extended to those with DMD. For example, the effect of the ACE inhibitor, captopril, was analyzed in 2,231 patients (mean age = 59); they had no symptoms of heart failure but had experienced left ventricular dysfunction following myocardial infarction and had an ejection fraction (the amount of blood being pumped out of the left ventricle) of less than 40%. The results showed not only an improvement in survival but also reduced morbidity and mortality resulting from major cardiovascular events [110]. In a more recent study, focused specifically on DMD, Duboc et al. reported that another ACE inhibitor, perindopril, administered between the ages of 9–13, delayed the onset of LV dysfunction and mortality, leading to their recommendation that ACE inhibitor treatment begin as early as nine years of age [111]. Now regarded as "first-line therapy," ACE inhibitors are customarily given to adult DMD patients who had never received this therapy, even if cardiac function is normal [103]. Studies supporting the use of β blockers point to their benefits in treating arrhythmia and improving LV ejection fraction when administered after the initiation of ACE inhibitor and in cases of symptomatic heart failure. A trial focusing on the effect of ACE inhibitors on cardiomyopathy in DMD, administered alone and in combination with β blockers, revealed no significant difference between the treatment groups [112].

Although corticosteroids are known to prolong ambulation in childhood, their continued use into adulthood remains controversial in terms of balancing the risks of long-term use against the potential benefits for cardiac and respiratory muscles. Whereas some trails in humans indicate improvement with steroid therapy, animal studies tend to indicate deleterious effects on myocardial function. These contradictory findings point up the need for further research on the impact of corticosteroid use in DMD [113].

Other Concerns and Challenges in Adult DMD

Given the limited motor abilities of adults with DMD, exercise must necessarily be restricted and studies of its efficacy are inconclusive. Stretching the upper extremity muscles, particularly finger flexors, may help minimize contractures and enable patients to use a computer keyboard or control a wheelchair joystick; stretching the lower extremity muscles, including hip and knee flexors, may relieve stiffness and pain [78]. Strenuous exercise is contraindicated in adult DMD because it can permanently damage already compromised muscle fibers and generate cardiac and respiratory problems. Hydrotherapy defined as moving in the water but not actually swimming may be beneficial. A recent systematic review of several trials on the effect of muscle exercise in DMD and other muscular dystrophies produced inconclusive results: given the absence of controls and the conflagration of different diseases in a single study, Gianola et al. could only conclude that "exercise might be useful, not useful, or even detrimental" while recommending that multicenter trials, focusing on muscle strength, fatigue, functional limitation, and pain, be undertaken as a next critical step [114].

Gastrointestinal problems in the form of constipation and gastroesophageal reflex are among other issues in adult DMD. Constipation responds to hydration, a balanced diet, stimulant laxatives, and stool softeners, whereas gastroesophageal reflex can be treated with proton pump inhibitors. With a multidisciplinary approach, dietitians can provide guidance on both undernutrition and obesity concerns, while swallowing/speech therapists deal with dysphagia and difficulties with oral expression and language comprehension [103].

Osteoporosis in Adult DMD

Maintenance of bone health is critical in patients with DMD, regardless of their age. Low bone mineral density in adults is attributed primarily to decreased weight-bearing, with the loss of ambulation occurring in the mid-teen years, and to the extended use of corticosteroids. At present, data on bone mineral density and fracture occurrence in this group are scarce. An analysis of one group of patients with neuromuscular disorders revealed fracture prevalence of 42 % with 72.5 % of the subjects experiencing a fall once a year [115]. Other causes of fractures, particularly in the lower limbs, include falls from wheelchairs resulting from tipping in transfers and sudden changes in wheelchair positions as well as accidents in the course of routine daily activities.

Although corticosteroids are effective in protecting cardiac and respiratory function and in delaying the onset of scoliosis in DMD, they lead to the development of vertebral compression fractures in what is known as "steroid-induced osteoporosis." Thus, annual DXA assessment is recommended to monitor bone density.

Treatment options for osteoporosis in adult DMD are much the same as those advocated in other childhood disorders, with necessary restrictions imposed by the

progression of the disease. Because calcium and vitamin D deficiency contribute to bone resorption and osteoporosis, particularly in patients treated with corticosteroids, levels must be continually monitored with supplementation prescribed as needed. Whereas the impact of calcium alone is limited, research indicates that calcium in combination with vitamin D can improve bone mineral content and BMD. Bisphosphonates are known to increase BMD but their effect on vertebral fractures remains unclear [108].

For the first time, 60% of patients with DMD are surviving into their third decade, dictating the need to further refine and develop national and international standards of care that will incorporate information on the transition to adult care and the challenges facing adults as the disease progresses. In addition to information relating to cardiac and respiratory issues as well as other complications noted above, guidelines on bone health in long-term steroid-treated adults as well as data on BMD in DMD adults and the effect of bisphosphonates should be incorporated in these standards [108]. Moreover, a recent assessment of the quality of life in men with DMD (mean age = 28 years) [116] reveals that DMD adults have an overriding concern not with their physical health but with their psychosocial needs ranging from intimacy and work capability to such measures as the "meaningfulness of life." Greater opportunities for social participation, education, and employment coupled with provision for transportation and assistance in undertaking leisure activities are a vital component of DMD therapy and should be addressed in the management guidelines for the disease.

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