Chapter

Musculoskeletal Abnormalities Caused by Cystic Fibrosis

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Abstract

Cystic Fibrosis (CF) can affect all organs of the human body including the musculoskeletal system. Although the musculoskeletal aspects of CF are less commonly studied, fractures (predominantly spinal), muscle injuries, and joint pain are more commonly seen in the CF population compared to the general public due to their lower bone mineral density, dysfunctional skeletal muscle, and elevated levels of pro-inflammatory cytokines. Additionally, due to elevated levels of inflammation in the CF population diagnosis of musculoskeletal injuries can be difficult to pinpoint. As treatment for CF evolves, an increased understanding of how CF affects the musculoskeletal system is imperative. We will discuss the orthopedic aspects of CF and provide potential insights into the future direction of orthopedic care in the CF population.

Keywords: cystic fibrosis, musculoskeletal, spine, arthropathy, fracture, bisphosphonates, allele specific drugs, cytokines, bone mineral density

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive disorder causing loss of function of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The most common gene alteration present in CF patients is a deletion of phenylalanine at position 508 (ΔF508). Fortunately, researchers and pharmaceutical companies have produced allele-specific drugs targeting CF genetic mutations. These work through multiple potential mechanisms, but allele potentiation (ivacaftor) and allele correction (tezacaftor) are some of the more promising therapeutics to date [1, 2].

Historically, patients with any combination of CFTR gene mutations could invariably expect a progressive course of worsening respiratory and endocrine function, resulting in irreversible and severe lung and pancreas damage. However, the introduction of allele-specific drugs has had a profound impact on improving both the length and quality of life in CF patients [3]. Given the improved life expectancy, orthopedic providers can expect to see a resultant increase in the proportion of patients with CF.

Throughout this chapter, we will discuss the three most likely scenarios for orthopedic consultation in the CF population: bone health/fracture, muscle and soft tissue dysfunction, and joint pain and arthralgia. In order to understand each of these topics appropriately, each subtopic will be prefaced by an in-depth introduction to the basic science causing the musculoskeletal pathology with subsequent detailed management of the disease.

1.1 Cystic fibrosis- related bone disease (CFBD): understanding the abnormal molecular pathway

Healthy bone undergoes continuous remodeling – bone resorption is mediated by osteoclasts through the RANK-RANKL (receptor activator of nuclear factor kappa-β ligand) pathway. Meanwhile, bone deposition occurs through activation of osteoblasts, which signal through the WNT-β-catenin pathway [4]. Osteoblasts also secrete osteoprotegrin, which binds to RANKL thus limiting activation of osteoclasts. In this manner, osteoblasts and osteoclasts are in delicate balance, and their goal is to optimize bone mineral density (BMD) while minimizing unnecessary storage of essential nutrients via reorganization of the boney trabecular microarchitecture. Bones under continual heavy loads (stress) or tension (strain) will adapt to the increase in forces imparted to the bone, while bones undergoing less frequent loading, will have a resultant leach of essential nutrients, thus allowing each bone to maximize its function (Wolff's Law) [5].

Mounting research is focused on improving our understanding of osteoblast and osteoclast function in CF patients. Emerging evidence indicates CF patients with pulmonary exacerbations caused by underlying indolent lung infections, have elevated cytokine levels [6]. The systemic increase in pro-inflammatory cytokines during these CF "flare-ups" leads to formation and activation of osteoclasts, resulting in bone resorption [7]. Additionally, the ΔF508 phenotype is known to promote RANKL production, which is normalized with the allele specific drug ivacaftor [8–10] and the drug miglustat [11].

Cystic Fibrosis not only increases osteoclast activity, but it also detrimentally affects osteoblast function and uncouples osteoblast–osteoclast homeostatsis leading to severe trabecular and cortical bone osteopenia through net bone mineral resorption [12]. Diminished ΔF508 osteoblast activity is thought to contribute to poor COX-2, PGE_2, and osteoprotegrin expression [13]. One potential therapeutic to mitigate poor bone quality and inhibited fracture healing is ivacaftor, which works through allele potentiation of the ΔF508-CFTR channel and channel optimization returns osteoblast function to 85% of normal [14]. This effectively increases systemic levels of cyclooxygenase-2 (COX-2) and PGE_2, which are integral for effective bone maturation and fracture healing [13].

Translational research performed in mouse models indicates that $Cftr^{-/-}$ mice have 50% less cortical bone width, thinner and less plentiful trabeculae and greater trabecular separation compared to normal mice [15]. Trabecular bone formation was also decreased by 92% in $Cftr^{-/-}$ mice likely due to the density of osteoclasts near the cortical surface [15]. Skeletal growth also appears to be hindered by 40% in $Cftr^{-/-}$ mice, due to a reduction in the hypertrophic zone of the growth plate [15]. The combination of these findings results in smaller bones that have decreased thickness and strength compared to normal bones [16]. This results in CF bones being able to tolerate less load to failure, which increases fracture risk [17]. It is believed that issues with poor BMD and increased fracture risk manifest prior to age six with no further significant worsening of BMD until after adolescence [18]. However, exercise programs in pre-adolescent children may increase BMD by 7% and these programs should be routinely implemented in all children with CF [19].

Aside from the poor bone quality imparted from phenotypic alterations by the CFTR gene, additional causes of lower BMD in CF patients include female sex, cystic fibrosis related diabetes (CFRD), vitamin D malabsorption, malnutrition, pancreatic insufficiency, exogenous corticosteroid use, chronic inflammation/chronic

pulmonary infections, and decreased activity levels (**Figure 1**). It should be noted that there is a paucity of well-designed studies demonstrating female sex [15, 20, 21], pancreatic [21, 22], CFRD [22, 23], and chronic inflammation/pulmonary infections [18, 24] have a significant effect on BMD. However, sufficient evidence does appear to suggest decreased activity levels, malnutrition, exogenous corticosteroid use, and vitamin D deficiency or malabsorption are potentially controllable risk factors that lead to a significant reduction in BMD [18, 21, 22, 25].

The net bone resorption in CF patients can be evaluated through serum or urinary analysis of type I collagen N-telopeptides, free deoxypyridinoline, and alkaline phosphatase. Increased levels of each of these molecular markers is common in CF patients, which may be further elevated by increased serum parathyroid hormone (PTH) levels and diminished serum 25-hydoxyvitamin D levels in these patients [26]. PTH and 25-hydoxyvitamin D create a positive feedback loop signaling the body to continue to resorb bone and increase serum calcium levels [27]. The combination of elevated osteoclast function and diminished osteoblast function results in early osteopenia or osteoporosis, which are diagnosed in 23.5% and 38% of the adult CF population, respectively [28].

1.2 Is there a role for bisphosphonates to improve bone health for CF patients?

Vitamin D deficiency affects up to 90% of patients with CF [29]. This is predominantly caused by poor systemic vitamin D absorption since CF patients absorb less than 50% of the dietary vitamin D absorbed by normal patients and 20% of CF patients have no measurable vitamin D absorption [30]. For this reason, the Cystic Fibrosis Foundation recommends each CF patient be given a daily prescription of vitamin D_3 to maintain baseline 25-hyroxyvitamin D levels at a minimum of 30 ng/ml [31]. However, even with sufficient vitamin D levels, patients with CF should undergo a dual energy X-ray absorptiometry (DEXA) scan at the age of 18 [26]. Repeat DEXA scans should occur every five years if the BMD is normal but repeat testing should occur every 2–4 years if the DEXA scan is between the ranges of <-1 and > -2 (osteopenia range) [26].

Current recommendations for initiation of bisphosphonate administration can be seen in **Table 1** [32]. In patients who are started on an oral or intravenous (IV) course of bisphosphonates, an approximate 3–6% increase in BMD can be expected at

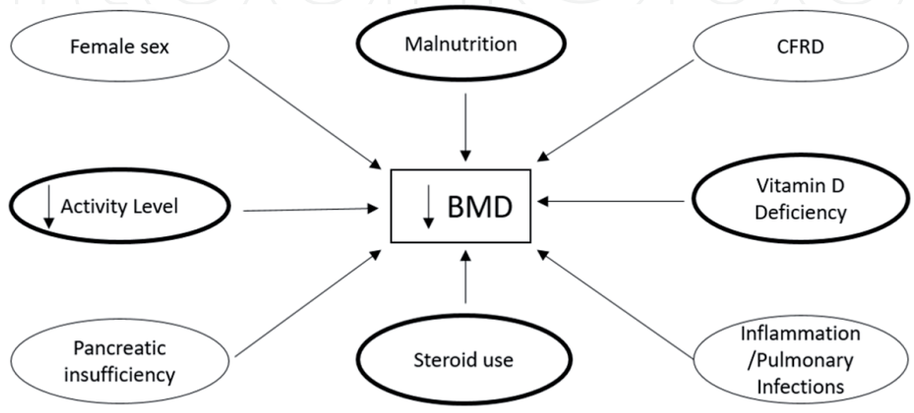

Figure 1.
*Risk factors for decreased bone mineral density (BMD) in patients with cystic fibrosis. * bold ovals indicate high quality evidence for risk factor contribution to decreased BMD in cystic fibrosis patients, while non-bolded ovals indicate poor quality evidence of contribution to diminished BMD.*

Adults	Children/Adolescents
Scheduled for or have previously had an organ transplant AND have a BMD Z or T score of ≤ −1.5	Scheduled for or have previously had an organ transplant AND have a BMD Z or T score of ≤ −2
Utilization of systemic glucocorticoids for longer than 3 months AND have a BMD Z or T score of ≤ −1.5	Utilization of systemic glucocorticoids for longer than 3 months AND have a BMD Z or T score of ≤ −2 OR have a low energy mechanism fracture
Sustain a low-energy mechanism fracture while on a course of systemic glucocorticoids	Sustain or have a history of fracture AND have a BMD Z or T score of ≤ −2
Sustain a low-energy mechanism fracture OR have a femoral neck BMD Z or T score of ≤ −2 AND have more than 4% BMD loss per year	About to start a prolonged course of systemic glucocorticoids AND have a BMD Z or T score of ≤ −2

Table 1.
Indications for initiation of oral or IV bisphosphonates in the adult or pediatric cystic fibrosis population.

1-year in the lumbar spine and femoral neck [33–35]. However, IV bisphosphonates are associated with severe bone pain and flu-like symptoms that should be discussed with patients prior to initiation [33, 36]. Additionally, atypical femur fractures and jaw osteonecrosis are risk factors for long-term treatment with bisphosphonates [37]. Clinicians should also keep in mind that BMD increases after bisphosphonate administration, but there is currently no evidence to support bisphosphonates ability to reduce the likelihood of sustaining a lower extremity or spine fracture [36].

Historically, there has been concern about fracture healing during bisphosphonate use. While there does appear to be a delay in fracture callus reorganization (immature woven bone is not replaced as quickly with mature lamellar bone), bisphosphonates do not inhibit fracture callus formation [38]. This type of fracture healing is referred to as secondary bone healing or endochondral ossification (examples of this type of healing include patients placed in a cast, surgery which involves an intramedullary nail/rod, or a bridge plate where the bone is not compressed together). While this type of fracture healing appears to be less affected by bisphosphonates, animal models suggest primary fracture healing (e.g. compression plating) is affected by bisphosphonates and causes lower BMD at the fracture site, decreases load to failure, and increases the presence of cartilaginous tissue at the fracture site [38]. However, clinical studies have not found any evidence to support a significant difference in fracture healing based on the administration of bisphosphonates, so at this time CF patients should be allowed to continue taking bisphosphonates even in the presence of a fracture [39, 40].

1.3 Predisposition to appendicular skeletal fractures: fracture management

Cystic Fibrosis predisposes patients to fracture even with minimal or no traumatic etiology due to their low BMD. Appendicular skeleton fractures occur at a rate of approximately 20% [28]. Notably, one case report described a femur fracture in an adolescent male baseball player who was running and had no associated trauma. In this instance, the femur fracture healed after treatment with an intramedullary nail; however, the patient then had an atraumatic contralateral femur fracture months later that was treated in the same manner [41]. There have also been reports of a unilateral femoral neck fracture in a 25-year-old male without associated trauma and bilateral femoral neck fractures in a 34-year-old male after a grand mal seizure [42, 43]. The 25-year-old patient had severe osteoporosis and was treated with internal fixation,

while the 34-year-old was treated with bilateral bipolar hemiarthroplasties [42, 43]. It should be noted that in non-CF patients, the femoral neck fractures would have been treated with fracture fixation instead of hip replacement. Since CF patients are now frequently treated with allele-specific drugs, there is no evidence to indicate CF patients should have fractures managed any different from patients without a diagnosis of Cystic Fibrosis. In instances of delayed fracture healing, subcutaneous teriparatide may be another effective tool to promote fracture healing, although there is poor quality evidence to support this management [44].

1.4 Spinal fractures and CF-related spine disease

Up to 94% of CF patients have back pain with potential etiologies often multifactorial, but they include muscle weakness, rib fracture, scoliosis, spinous process bursitis, and vertebral fracture [45–47]. A significantly higher rate of vertebral fractures are identified in CF patients with an incidence of approximately 14%, but interestingly BMD and the risk of vertebral fracture is not correlated [28, 48]. Vertebral fractures often result in vertebral wedging, which progresses to structural kyphosis if wedging is greater than 15% [45]. Since vertebral wedging is typically minimal, only 8% of pediatric patients develop structural kyphosis, with the rate nearly doubling in adult patients [45, 49]. This may be due to the increased rates of muscle weakness and osteopenia/osteoporosis as patients age [50].

Additional considerations for spinal pain include spinal process bursitis, which may be caused by improperly fitting high frequency chest wall oscillation devices (vest) [46]. In these instances, the bursitis should be managed expectantly as it will resolve without surgical intervention after appropriate vest adjustment [46]. Another consideration of spinal pain is idiopathic scoliosis, which is more prevalent in the CF population and typically manifests as a short mid thoracic curve [51]. Idiopathic scoliosis in CF patients is often treated non-surgically with bracing [47]. However, in skeletally immature patients with curve progression to 50 degrees the scoliosis should be managed with surgical correction [52].

1.5 Muscular/soft tissue dysfunction: is there a molecular basis for muscular dysfunction?

Diminished muscle mass and force is a common affliction of CF patients and lower extremity muscles are frequently affected to a greater degree than the upper extremity [53]. Theories abound as to the potential causes of muscle weakness and include elevated cytokine (IL-6) levels, low vitamin D levels, corticosteroids, presence of the ΔF508 phenotype, altered CFTR function in the sarcoplasmic reticulum, muscle disuse, and poor pulmonary function (**Figure 2**) [54–57]. The reality is the cumulative effect of each of these mechanisms contributes to decreased muscle mass since each theory is intertwined.

One of the more prominent theories for muscle dysfunction in CF patients includes abnormal function of the CFTR chloride channels in the sarcoplasmic reticulum, which results in inappropriate regulation of calcium homeostasis [57]. Since calcium is essential for muscle depolarization, dysregulation of these channels may lead to muscle mass loss, early fatigue, and generalized weakness. This mechanism was further evaluated in human and mice diaphragms, where intracellular calcium was significantly elevated after muscle depolarization in the presence of an inflammatory environment [54]. In the presence of *Pseudomonas aeruginosa*,

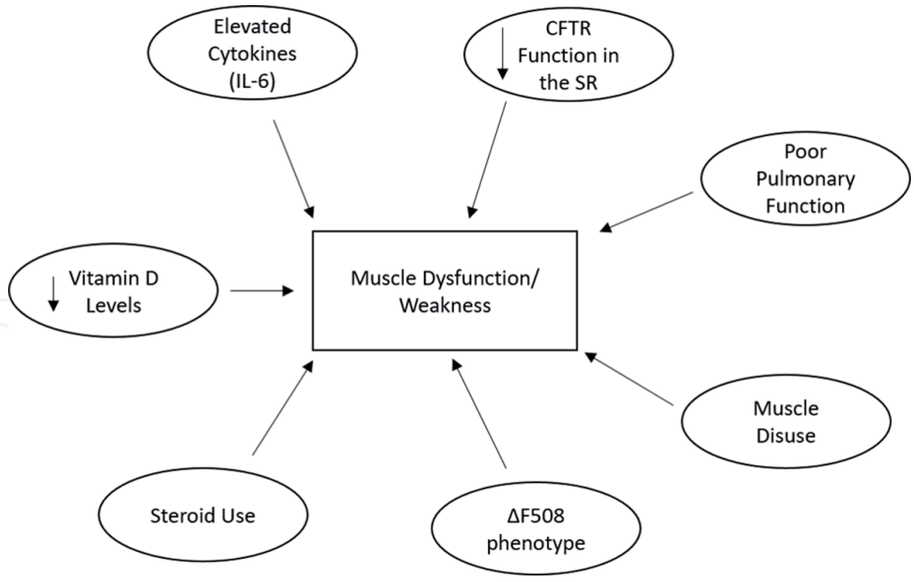

Figure 2.
*Potential contributors to muscle dysfunction and muscle weakness in cystic fibrosis patients. * CFTR = cystic fibrosis transmembrane conductance regulator; SR = sarcoplasmic reticulum.*

elevated pro-inflammatory cytokines were overexpressed and E3 ubiquitin ligases were upregulated (these are often identified in muscle atrophy) resulting in a significant decrease in muscle force generation [54]. Separate research has also identified elevated IL-6 levels and ΔF508 are correlated with diminished muscle mass [56].

The net loss of peripheral muscle strength has continuously been associated with poor pulmonary function [50, 58]. When decreased muscle strength is coupled with poor anaerobic capacity – evidenced by the decreased oxygenation of muscles due to the suboptimal V_O^2 max – [59, 60] early lactic acid accumulation may occur [58]. This can result in muscle disuse through early muscle fatigue. Additional contributing factors include low vitamin D levels, which have been linked to poor peripheral muscle strength although the exact mechanistic role linking vitamin D and muscle weakness is incompletely understood [61]. Luckily, muscle atrophy may not be permanent. Ivacaftor appears to independently increase fat free mass by one kilogram and significantly increases lung function, which may lead to significant long-term improvements in CF patients' health, endurance, and muscle function [62, 63].

Muscle dysfunction may also be linked to low-energy muscle injuries. A single case report identified an adolescent CF patient with an atraumatic mid-substance muscle rupture caused by running during a basketball game. Management of these injuries are typically non-surgical with gradual return to sport [46]. Similar to bony injuries, muscle injuries in the CF population should be treated comparably to muscle injuries in the general population. Future research is necessary to improve our understanding of muscle dysfunction in CF patients and to identify if allele specific drugs are effective at reducing CF patient's predisposition to muscle atrophy and subsequent muscle rupture.

1.6 Weight and aerobic training: improving quality of life

Baseline muscle weakness is present in CF patients, which is linked to decreased quality of life [64]. Therefore, multiple studies have explored the effect of exercise on improvements in strength, endurance, and quality of life [65–67]. An eight-week

resistance and aerobic training program demonstrated improved strength, pulmonary function, and % fat free mass [68]. Similar results were found comparing CF patients who participated versus those who did not in a six-month weight training program, which demonstrated effectiveness of the program at increasing muscle size, strength, and overall weight gain [66]. Further, a combined home exercise program including aerobic exercise and resistance training resulted in improved weight gain and quality of life [65]. Respiratory muscle endurance training has also been found to improve both respiratory endurance and exercise endurance [67]. Based on the overwhelming positive effects of exercise on lung and peripheral muscle endurance, consensus guidelines on aerobic activity and resistance training has been established [69]. These guidelines recommend that children and adolescents with CF should engage in at least moderate intensity exercise for 60 minutes per day, while adults should ideally participate in at least moderate intensity exercise for 300 minutes per week [69]. Adults should also participate in upper body, lower body, and trunk resistance training 3–5 times per week with 1–3 sets of 8–15 repetitions. The weight should be based on 70% of maximum weight. In fact, patients with severe CF may maximally benefit from resistance training since they may struggle to have the aerobic capacity for prolonged endurance training [69].

1.7 Joint pain: cytokines effect on the musculoskeletal system

Arthropathy is commonly identified in CF patients at a rate of ranging from 8.5 to 29% [70–72]. Two main forms of CF-related arthropathy exist: cystic fibrosis related arthropathy (CFA) and hypertrophic osteoarthropathy (HOA), although lesser forms of arthropathy have also been described including fluoroquinolone associated arthropathy and an elevated incidence of rheumatoid arthritis [72]. Although no definitive pathway has established the causality of arthropathy in the CF population, risk factors appear to include pulmonary exacerbations with *Pseudomonas* or *Aspergillus*, female gender, older age, serum levels of IgG, CFRD, pancreatic insufficiency, greater number of hospitalizations, and sinusitis (**Figure 3**) [71, 72]. One potential theory linking many of these risk factors with arthropathy is the associated increase in cytokines, especially IL-6, IL-8, and TNF-α [73]. A rapid increase in these cytokines is often associated with pulmonary exacerbations and joint pain is a common additional complaint during these CF "flare-ups" [72]. Further, these pro-inflammatory cytokines are also more prevalent in non-CF patients with radiographic evidence of osteoarthritis and are one potential mechanism that may potentiate joint degeneration [74]. Arthropathy can typically be managed with non-steroidal anti-inflammatory drugs (NSAIDs), which are the first line of treatment, but if corticosteroids are administered due to the underlying pulmonary exacerbation, they may be effective at treating the associated arthropathy [75].

Patients with CF commonly have elevated levels of inflammatory markers including CRP and ESR [76, 77]. The combination of elevated inflammatory markers and a propensity to develop joint pain makes consults for potential septic arthritis more likely for orthopedists. Therefore, physicians need to carefully evaluate the patient's cause of joint pain. Although arthrocentesis may be necessary to rule out septic arthritis for disabling joint pain, inflammatory markers are typically significantly elevated with septic arthritis while they may only be marginally elevated in cases of CFA or HOA [78]. A meticulous physical exam aimed at identifying limited passive range of motion and an inability to ambulate on the affected joint may further distinguish septic arthritis from either CFA or HOA.

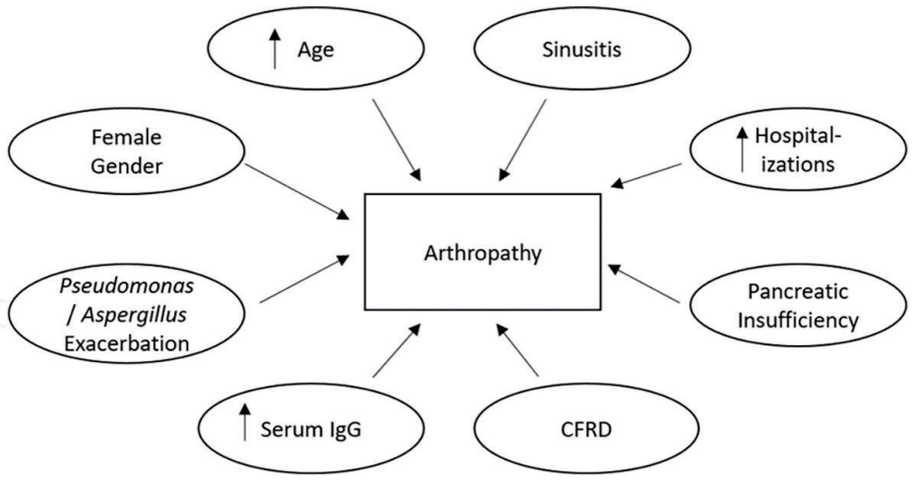

Figure 3.
Potential risk factors contributing to arthropathy episodes in cystic fibrosis patients.

1.8 Cystic fibrosis-related Arthropathy

CFA is the more common form of joint related pain with typical age of onset of approximately 13 years [79]. Although the incidence of CFA ranges from 8.5 to 29%, as the CF population continues to have a longer life span, the expected number of patients with CFA is expected to grow tremendously [71]. As such, practitioners should be cognizant of the symptoms of CFA and should systematically differentiate it from HOA and a septic joint.

CFA has distinct symptoms including, but not limited to, short bursts of recurring episodes of joint pain, fevers, joint swelling, and a rash that resembles erythema nodosum. However, pain and swelling are the most commonly identified forms of CFA and they typically present in the small joints of the hands, although knees and shoulders are also commonly affected [72, 80]. The combination of joint pain, joint swelling, overlying joint reddening, and severe pain causing loss of function is only present in around 13% of patients, allowing CFA to typically be easily differentiated from septic arthritis [72]. Further, CFA is often seen in the setting of oligo- or polyarthritis, which is uncommonly seen in patients with septic arthritis [72]. The onset of CFA symptoms occurs in less than 24 hours but the pain is often limited to four days after initiation of NSAIDs. After symptom resolution, the patient typically has no pain, but the arthropathy typically returns at variable, seemingly random time points. Further, there is often no evidence of radiographic abnormalities if x-rays are taken of the involved joint [79]. Although less commonly associated with pulmonary exacerbations, elevated systemic cytokines may exacerbate CFA [80].

1.9 Hypertrophic osteoarthropathy

HOA is characterized by a combination of medical conditions including periostitis of long bones, digital clubbing, and severe joint arthropathy with or without synovial effusions. Radiographs can help differentiate HOA from CFA due to characteristic periosteal elevation on the distal aspect of the tubular bones [81]. HPOA is also more commonly seen after initiation of a pulmonary exacerbation [82]. CF patients presenting with HOA also typically present with polyarthralgia, which may allow physicians to differentiate it from septic arthritis.

Two main pathways have been proposed for the underlying cause of HOA: humoral and vagal. The humoral pathway has two subtypes: (1) elevated cytokine levels and hypoxemia, which produces hypoxia-inducing factors including VEGF and PDGF or (2) lung arteriovenous [83]. VEGF and PDGF induce proliferation of the endothelial smooth muscle and vascular permeability resulting in angiogenesis. VEGF also stimulates osteoblast and osteoclast induction and the combination of these effects ultimately results in subperiosteal collagen deposition leading to periosteal elevation of the distal portion of the tubular bones [83]. The periosteal reaction seen in this condition results in the variable pain responses seen in these patients. From a mechanistic standpoint, this pathway has the most traction, especially amongst the CF population. The vagal pathway is not as well supported but includes stimulation of organs innervated by the vagal nerve resulting in peripheral vasodilation of the extremities [84]. However, to date, neither mechanism has been unequivocally supported with evidence.

2. Conclusion

Musculoskeletal manifestations are common in Cystic Fibrosis patients with most patients having arthropathy, muscular dysfunction or decreased bone quality at some point during their lifetime. The decrease in BMD in CF patients leads to an elevated risk of both appendicular and axial skeletal fractures, which can be mitigated with allele specific drugs due to their ability to return osteoblast function to near normal levels, while also significantly improving BMD. Vitamin D supplementation is also an important adjunct to maximize both bone health and muscular function. Although a combination of factors ultimately leads to skeletal and muscular dysfunction, targeted exercise and resistance programs have been shown to be effective at improving both BMD and muscular function (**Figure 4**).

As CF patients have improved life expectancies due to rapid improvements in pharmaceuticals and CF treatment protocols, the prevalence of arthropathy will continue to increase. Differentiating CFA and HOA from septic arthritis via non-invasive measures can help minimize unnecessary procedures including arthrocentesis, while optimizing outcomes. Additionally, both CFA and HOA can be treated with NSAIDs

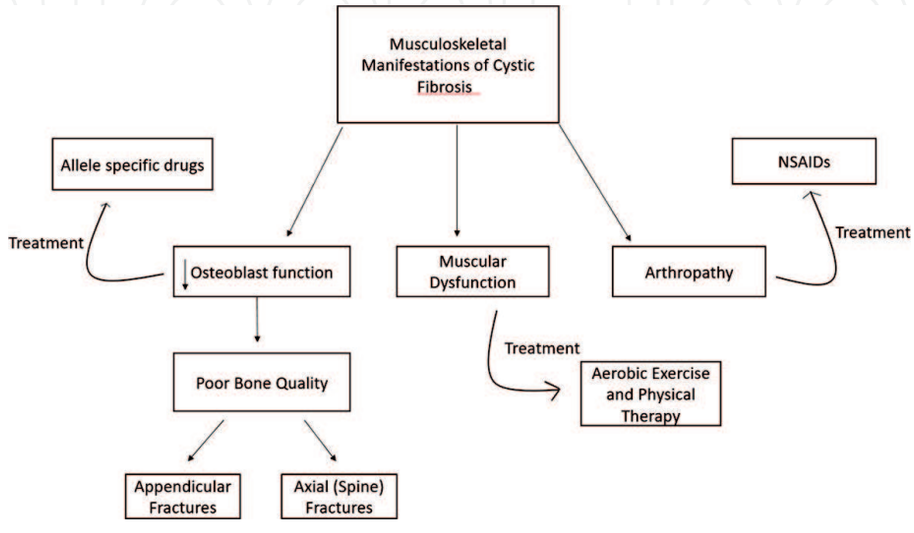

Figure 4.
Treatment algorithm for the varying presentations of the musculoskeletal manifestations of Cystic Fibrosis.

with abrupt minimization of symptoms. Future research is necessary to document the role of allele specific drugs in improving the musculoskeletal manifestations of Cystic Fibrosis.

Conflict of interest

The author declares no conflict of interest.

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