Chapter 11
Osteoporosis in Patients with Peripheral Neuropathies

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Peripheral neuropathy, characterized by damage or destruction of neurons that determines how they communicate with each other, affects three types of nerves: sensory, motor, and autonomic (nerves that control involuntary or semi-voluntary function such as heart rate, blood pressure, and digestion) [1]. Damage to only one nerve is termed a mononeuropathy; mononeuritis multiplex neuropathy occurs when two or more isolated nerves in different part of the body are damaged; polyneuropathy implies the involvement of multiple nerves simultaneously. As opposed to hereditary neuropathy, acquired neuropathy has a number of causal factors including systemic diseases, medications and toxins, trauma, infections, autoimmune disorders, and vitamin imbalances. Its symptoms include numbness and tingling in the hands and feet, severe pain or the inability to feel pain at all, loss of coordination and reflexes, and muscle weakness [2, 3]. Diabetes, the primary cause of peripheral neuropathy, will be considered in this chapter together with critical illness polymyopathy and polyneuropathy and their association with immobility and medications. Two autoimmune disorders, Guillain–Barre syndrome and inflammatory demyelinating polyradiculoneuropathy, will also be discussed.

Diabetes Mellitus

Epidemiology

Diabetes mellitus (DM) is a disease of pandemic proportions in both the developed and developing nations. The International Diabetes Foundation reports that, as of 2014, some 387 million people worldwide were living with diabetes, with an estimated increase to 592 million by 2035 [4]. If the current trend persists, diabetes

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prevalence in the United States will likely increase from 14 % in 2010 to 21 %, and, possibly, 33 % by 2050, depending upon the health of an aging population, the longevity of diabetic patients, and the survival of increasing numbers of high-risk minority groups [5].

Diabetes is divided into type 1 and type 2 variants, previously known as insulin- and non-insulin-dependent diabetes mellitus; the potential for hyperglycemia is present in both [6]. Type 1 diabetes (T1DM), affecting approximately 5–10 % of all diabetic individuals, is related to a rheumatoid-like autoimmune reaction that destroys the beta cells of the pancreas, leading to decreased production of insulin and, within a short time, total cessation of production. Formerly known as juvenile diabetes, it commonly begins in childhood but can develop in older adults as well. Type 1 diabetes cannot be prevented but can be controlled with daily insulin injections or an insulin pump [6].

In type 2 diabetes (T2DM), occurring in 90–95 % of diabetic patients, the pancreas continues to produce insulin but encounters peripheral receptor resistance/insulin resistance which occurs when fat, muscle, and liver cells fail to respond to insulin, preventing blood sugar from entering these cells as stored energy and leading to a buildup of sugar in the blood, resulting in hyperglycemia. Although the pancreas responds initially by producing more insulin, in time it cannot create a sufficient amount to meet the body's needs. Some 37 % of adults over the age of 20 have early signs of developing insulin resistance (prediabetes) and are at high risk for developing T2DM [7, 8], a condition that particularly targets the overweight and obese population. T2DM can be effectively treated with lifestyle changes including loss of weight, improved diet, and increased levels of physical activity. In addition, metformin, (Glucophage) used alone or with insulin, increases insulin sensitivity and reduces glucose levels without risk of hypoglycemia and weight gain.

Diabetes is associated with a number of health complications including cardiovascular diseases such as heart attack and stroke, kidney disease, blindness and other vision problems, and, the most common complication, peripheral neuropathy. The symptoms of peripheral neuropathy are related to the types of nerves involved, be they sensory, motor, autonomic, or a combination. The longer the duration of diabetes, the greater the risk of diabetic neuropathy. Caused by a number of factors, principally high glucose levels and high lipid levels, diabetic neuropathies are diagnosed on the basis of signs and symptoms including tingling, burning, numbness, and muscle weakness in the extremities as well as problems with coordination, balance, and walking; laboratory tests and electrodiagnostic findings are also employed [9].

The most common diabetic neuropathy, known as chronic distal sensorimotor symmetrical polyneuropathy (DSPN), impacts up to 50 % of diabetes patients; it is commonly manifested by burning and a deep aching pain in the feet and lower limbs and occurs in a relatively symmetrical manner on both sides of the body. DSPN contributes to an increased risk of foot ulceration and Charcot osteoarthropathy, the progressive destruction of bone and joint integrity, and it remains the leading cause of lower leg amputation [10].

Etiology and Pathophysiology of Osteoporosis in Diabetes

Both T1DM and T2DM have serious effects on the skeleton, with bone formation, bone microarchitecture, and bone quality altered in both forms. In terms of bone density, evidence shows a decrease in BMD in T1DM and an increase in T2DM. An increased risk of bone fractures has been found in both but to a lesser degree in T2DM. Given the different pathogenesis of T1DM and T2DM, no uniform entity of diabetic osteopathy exists [11]. Nearly 70 years ago, before the development of dual x-ray absorptiometry, Albright and Reifenstein first demonstrated an association between reduced bone mass and poor glycemic control in childhood diabetes. In the years since, numerous trials have been conducted to examine the nature and extent of bone mineral density and fractures in both types of diabetes; some generalizations have emerged but, to a considerable extent, the results remain inconclusive.

Mechanisms of Diabetic Bone Disease

Diabetes mellitus affects bone through the following mechanisms [12]:

1. Direct metabolic influence of insulin insufficiency on osteoblastic and osteoclastic function
2. Alterations in endocrine secretagogues by pancreatic beta cells, particularly amylin, causing decreased bone integrity (particularly in T1DM)
3. Impact of peripheral neuropathy on proprioception and activity levels
4. Relation between bone loss and both vascular dysfunction and impaired bone microcirculation evident in hyperglycemia
5. Contribution to diabetic retinopathy, resulting in decreased function and disuse osteopenia and osteoporosis from reduced immobility in setting of visual impairment
6. Effect of diabetes medications on bone pathology

Whereas T1DM is widely associated with bone loss and decreased osteoblast activity, T2DM is characterized by preserved-to-increased bone mineral density. As Vestergaard has determined [13], bone mineral density is reduced by 0.2 *Z*- scores in the hip and spine in T1DM, while it is increased by 0.3–0.4 *Z*- scores in T2DM. Yet, in spite of this data, the fracture rate in T2DM is increased over that of the normal population, indicating that the structural strength of bone is impaired.

In this section we will review the mechanisms associated with diabetic bone loss. Given the complex relationship between bone density and fracture risk, it should be emphasized that BMD is only one of the variables responsible for bone strength and quality. Understanding the mechanisms underlying the diabetes–bone relationship and advancing studies of this interaction are critical to the development of new therapies to restore bone loss, particularly as the human life span increases, with a concomitant rise in diabetes complications associated with aging. The following discussion focuses on the effect of diabetes on bone primarily in T1DM with references to T2DM as applicable.

Insulin and Insulin Secretagogues

Historically, as well as in recent years, the majority of studies focusing on the state of bone in T1DM have found decreased BMD in both the spine and hip. Osteopenia is present in about 50–60 % of people with T1DM with osteoporosis occurring in 14–20 % of cases [14]. Both osteopenia and osteoporosis are more prevalent in men than in women. One investigation reported that 14 % of the male patients and none of the females met the criteria for osteoporosis [15]. Similar trends for osteopenia have also been reported for diabetic men versus women [16]. Estrogen may also exert a protective effect on women.

Patients who develop T1DM in childhood and adolescence experience frequent episodes of prolonged bone loss, negatively affecting their ability to attain peak bone mass. Insulin is thought to exert an anabolic effect on bone formation based on data indicating that decreased adolescent growth velocity leads to insulin sufficiency which, in turn, impairs osteoblastic function and produces abnormalities of bone microarchitecture [17]. A 7-year prospective study of BMD in T1DM found that intensive insulin therapy significantly increased body mass index and stabilized BMD at all sites, although patients with retinopathy continued to lose body mass [18].

In addition to insulin, T1DM patients are unable to produce the insulin secretagogue, amylin—a peptide hormone co-secreted with insulin by the beta cells in the pancreas. Amylin enables blood glucose levels to remain relatively stable by slowing digestion, inhibiting secretion of glucagon (a pancreatic hormone that raises blood glucose levels), and enhancing satiety, thereby limiting the possibility of blood glucose "spikes" [19]. In fact, in animal models, supplementation of amylin maintained bone-mass-inhibited biochemical markers of bone reabsorption, and stimulated elevated bone formation [20]. Other secretagogues involved in bone regulation but inhibited in T1DM are glucagon-like polypeptide 2 (GLP2) and gastric inhibitory peptide (GIP). GLP2 receptors have been found on osteoclasts, and their activation is associated with reduced bone reabsorption. GIP receptors are present on osteoblasts, and their activation results in increased secretion of type 1 collagen [21]. It is unclear if the underlying autoimmune process that causes T1DM plays a role in bone metabolism. Table 1 [15, 18, 22–26] describes bone changes in patients with T1DM.

Hyperglycemia

Hyperglycemia exerts adverse effects on both T1DM and T2DM [19]. It leads to nonenzymatic glycosylation of various bone proteins including type 1 collagen, a condition that may impair bone quality [27]. On a cellular level, diabetes is believed to stimulate bone reabsorption by increasing both the number of osteoclasts and their activity through functions involving tumor necrosis factor alpha (TNF-α),

Table 1 Bone changes in patients with type I diabetes mellitus

Sources	*n*	Age (range in years)	Age (mean in years)	Mean duration follow-up (years)	Gender (F/M)	Major findings
Hamilton et al. [22] (2008)	102	20–71	–	Cohort study	52/50	When compared with age-matched control subjects, adult males with T1DM had lower BMD (hip, femoral neck, spine) ($P \leq 0.048$). No significant difference in terms of BMD between females with T1DM versus age-matched control subjects
Lumachi et al. [23] (2009)	18	36–51	–	Cohort study	8/10	~60 % lower BMD was found in patients with T1DM when compared to age-matched control subjects
Rozadilla et al. [24] (2000)	88	–	29	11	43/45	Retinopathy found to be associated with low BMD. Osteoporosis present in 3 %. Decreased lumbar spine BMD. No significant decreased of BMD in the femoral neck of patients with T1DM
Munoz-Torres et al. [25] (1996)	88	–	30	12	49/45	Decreased lumbar spine and femoral neck BMD in patients with T1DM. Osteoporosis present in 19 %. Retinopathy, active smoking, and neuropathy were also associated with decreased BMD
Campos Pastor et al. [18] (2000)	57	–	35	17	30/27	Retinopathy and poor glycemic control were associated with higher rates of osteopenia and osteoporosis (72 % vs. 53 % without retinopathy); benefits of intensive insulin therapy
Kemink et al. [15] (2000)	35	–	38	9	14/21	Decreased lumbar spine and femoral neck BMD in patients with T1DM. Osteopenia associated with decreased serum levels of IGF-1 and bone formation markers
Tuominen et al. [26] (1999)	56	–	61 (F) 62 (M)	18	27/29	Decreased (6.8 in females and 7.6 % in males) femoral neck BMD when compared with age-matched control subjects

macrophage colony-stimulating factor (M-CSF), and the receptor activator of nuclear factor-kB ligand (RANKL). These cytokines activate osteoclast proliferation and differentiation. As described in earlier chapters of this text, hyperglycemia also suppresses osteoblastic function by decreasing runt-related transcription factor 2 (RUNX2), decreasing osteocalcin and osteopontin expression, and reducing osteoblast proliferation. Due to an adverse effect on bone microcirculation, hyperglycemia reduces neurovascularization, thereby decreasing bone formation and impeding bone repair. The cumulative effect of these actions is a net decrease in bone formation.

Indicators of Bone Health

The sympathetic nervous system is thought to have a positive effect on maintenance of bone density but is impaired in the setting of neuropathy, common in both T1DM and T2DM. Research by Rix et al. shows that peripheral neuropathy in T1DM is associated with a greater risk of reduced bone mass in the spine, femur, and distal forearm, indicating that it may be an independent risk factor for reduced BMD not only as a localized process in the affected limbs but in the skeleton more generally [28]. Both diabetic neuropathy and retinopathy may also lower BMD by reducing physical activity needed to build bone and muscle strength as well as by increasing fall risk and resulting fractures.

At the same time, a meta-analysis of studies examining the relation between neuropathy and indicators of bone health in diabetes found no significant association with poor peripheral bone health in seven of the ten studies reviewed [29]. However, four of the ten studies did find an association between poor bone health in patients with neuropathy compared to those without neuropathy. Moreover, the authors acknowledge that methodological limitations in the studies reviewed (e.g., different methods to quantify and classify neuropathy) as well as limitations in the analysis itself (conflation of studies involving both T1DM and T2DM patients and the exclusion of relevant findings from studies that did not meet the review's criteria) point to the need for further investigation.

Adipokines: Leptin and Adiponectin

Adipokines including leptin and adiponectin are strongly associated with T1DM. Serum levels of leptin, a hormone produced by the anterior pituitary, are positively correlated with bone mineral density but are decreased in the setting of T1DM [30, 31]. Leptin increases cortical bone but decreases trabecular bone formation. By acting on the hypothalamus, it works through the sympathetic portion of the central nervous system (CNS) to upregulate bone formation. Whereas diabetic neuropathy exerts its effects on the peripheral nervous system, leptin is more often associated with CNS-related bone metabolism; consequently other mechanisms of

leptin may be relevant to DM. Leptin exerts a direct effect on bone through actions on insulin-like growth factor-1 (IGF-I) [32]. Evidence further indicates that leptin may be the key to understanding the link between energy intake and bone metabolism [33].

In contrast, serum levels of adiponectin are negatively correlated with bone mineral density [34]. T1DM is associated with increased adiponectin which is related to insulin sensitivity. Studies indicate that adiponectin is a potent insulin enhancer linking adipose tissue and glucose metabolism throughout the body [35] and that it may influence immune response in T1DM just as leptin affects autoimmune diabetes [36].

To an extent, however, the role of these adipokines remains unclear. Leptin contributes to systemic inflammatory changes and is associated with atherosclerosis, hypertension, and neointimal thickening with vascular disease [35]. Adiponectin, which is present at lower levels in diabetic individuals, has anti-inflammatory properties [37], protects endothelial and vascular smooth muscle cells, and exerts a positive effect in myocardial remodeling [35, 38]. In terms of fractures, the positive effects of adipokines are countered by their negative effect on the cardiovascular system, predisposing diabetes patients to falls and increasing the risk for osteoporosis [19].

Glycation End Products

While the influences on both osteoblast and osteoclast formation and function significantly affect overall BMD, bone quality in individuals with DM is also reduced through several other metabolic processes. The production of advanced glycation end products (AGE) reduces levels of type 1 collagen which, in turn, increases bone flexibility. In stressful circumstances, a less rigid bone is more likely to fracture even under conditions of lower force and lower energy, such as falling or stumbling from a seated or stationary position. Table 2 summarizes the adverse effects of impaired glucose metabolism on bone.

Microvascular Disease

A recent report by Shanbhogue and colleagues considers yet another mechanism [39]. Comparing patients with T1DM against age-matched, healthy controls, they propose that the presence of microvascular disease may be a factor in bone loss for patients with T1DM. Specifically there were no differences between patients *without* microvascular disease and controls. However, T1DM patients *with* microvascular disease demonstrated lower total, trabecular, and cortical volumetric bone mineral density as well as microarchitectural changes in the form of thinner bone cortices at the radius, lower trabecular bone strength, and greater trabecular separation at both radius and tibia which could partially explain the higher level of

Table 2 Adverse effects of impaired glucose metabolism on bone

Factors that decrease BMD	Cause	Solution
Increased urinary calcium excretion	Poor glycemic control	Evaluate and monitor Hg A1c
		Improve dietary control
		Alter antidiabetic medications
Functional hyperparathyroidism	Low bone turnover resulting in decreased osteoblast function (advanced T1DM)	Correct thyroid levels
		Follow thyroid stimulating hormone [TSH] levels
		Optimize vitamin D
		Monitor renal function
Hyperparathyroidism	Excess cortisol seen in early stages of T1DM	Optimize/supplement vitamin D and monitor serum vitamin D 25OH and parathyroid hormone [PTH] levels
Altered vitamin D metabolism	Diabetic nephropathy	Supplement vitamin D possibly with calcitriol rather than cholecalciferol
		Consider renal consultation
Adverse effects of insulin and insulin-like growth factors	Poor glycemic control that may increase need for insulin	Consider endocrine consultation
		Encourage improving glycemic control through nutritional therapy
		Follow growth hormone [GH] levels
		Follow insulin-like growth factor-1 [IGF-1] levels
Estrogen deficiency	Early menopause	Monitor BMD, obtain levels of key pituitary hormones (gonadotropins such as follicle-stimulating hormone [FSH], luteinizing hormone [LH]; as well as growth hormone [GH] and prolactin); in addition, consider pharmacologic interventions during perimenopausal phase

skeletal fragility evident in these subjects. Differences between microvascular positive and negative T1DM remained significant after controlling for age, years of DM, and average glycated hemoglobin over the prior 3-year period. Vitamin D insufficiency and celiac disease are still other causal factors in diabetes-induced osteoporosis.

Fracture Risk

Type 1 Diabetes

Vestergaard et al. have reported a trend toward an increased fracture risk at most skeletal sites in type 1 diabetes as well as a marked trend toward higher fracture risk in the presence of complications; most of the studies examined in his analysis focused on

hip fracture [13]. For example, Nicodemus et al. [40] reported that postmenopausal women were 12.25 times more likely to experience a hip fracture—a finding confirmed by subsequent studies of diabetic men and women in the relevant age groups [41] and in a different study, specifically in women ages 34–59 [42]. A recent study by Weber et al. [43] was the first to report that an increase in fracture risk begins in childhood and adolescence and extends over the life span of T1DM patients. Men ages 60–69 and women ages 40–49 have double the fracture risk of those without diabetes. Moreover, people with retinopathy and neuropathy have a higher fracture risk in the lower extremities with falls being a major contributing factor.

Type 2 Diabetes

In recent years, increased fracture risk, formerly associated primarily with T1DM, has become a growing concern in T2DM patients, although they are still affected to a lesser degree. In terms of hip fractures, Nicodemus et al. found a 1.7-fold increased risk of hip fractures in postmenopausal women with T2DM than in those without diabetes [40]. An association between higher fracture incidence and such factors as longer disease duration, decreased bone quality, diabetic complications, inadequate glycemic control, the use of insulin or oral diabetes medications, and increased fall risk has also been identified and reported. Despite the paradox of higher bone density coexistent with increased fracture risk in T2DM, Schwartz et al. determined [44] that women ages 65 and older were at greater risk of developing hip, proximal humerus, and foot fractures than nondiabetic women, in part because of associated comorbidities including decreased bone quality and impaired balance and gait due to neuropathy, and visual impairment resulting from diabetic retinopathy and cataracts.

The recognition that diabetes compromises bone health, particularly in an aging population, strengthens the need to incorporate bone assessment together with possible treatment options as an integral part of long-term diabetes care. A 2015 International Osteoporosis Foundation review of bone fragility in T1DM [45] strongly recommends early and regular evaluation of fracture risk in T1DM coupled with the implementation of fracture prevention strategies; in addition, it advocates intensified efforts to evaluate the efficacy of anti-osteoporotic agents in the context of diabetes.

Complications of Diabetes Mellitus Related to Bone and Physical Function

Charcot Osteoarthropathy

Diabetes mellitus and its neuropathies are regarded as the most common cause of Charcot osteoarthropathy (COA), also known as Charcot foot. A chronic, progressive, potentially limb-threatening disease, it is relatively rare, occurring in an

estimated 0.08–7.5 % of patients with both T1DM and T2DM [46]. Characterized by destruction of bone and joint integrity, it initially presents with redness, swelling, and increased warmth, progressing to severe deformities including collapse of the midfoot and ulcers that could predispose to amputation.

COA is associated with vascular calcification which includes abnormal calcified deposits in the smooth muscle of blood vessels of all sizes and with atherosclerosis that results in vascular stiffness and increases systolic blood pressure [47]. The primary underlying etiology of the disease is thought to be increased trauma resulting from impaired sensory feedback of the joint under conditions of both peripheral and autonomic neuropathy. This trauma, often minimal in nature, causes excess production of pro-inflammatory cytokines including TNF-α which, in turn, leads to an increase in RANKL-mediated osteoclast activation, causing bone fracture and destruction [47, 48].

The first step in treating COA is to control the heat and swelling and stabilize the foot to prevent disease progression and minimize deformity. Nonoperative treatment generally includes the use of a total contact cast or a bivalved cast (Aircast walker) followed by bracing and the use of footwear designed to accommodate preexisting deformities, relieve pressure, and ensure joint stability [48]. Surgical treatment, reserved for patients with recurrent joint instability and ulceration, may entail removal of a bony prominence, midfoot fusion, and realignment osteotomy. Pharmacological therapies including bisphosphonates and calcitonin as well as anabolic agents such as human parathyroid hormones are being investigated as treatment options with some early success [49].

Diabetes Medications Detrimental to Bone

The link between fracture risk and diabetes medication is most clearly established in the class of drugs called thiazolidinediones (rosiglitazone/Avandia and pioglitazone/Actos). Although their efficacy in controlling diabetic hyperglycemia has been demonstrated, their prolonged use negatively impacts osteoblastogenesis by decreasing activity of both osteoblast transcription factors (e.g., RUNX2) and osteoblast signaling pathways (e.g., ICF-1) [50]. As a result, thiazolidinediones decrease bone formation and bone mineral density while increasing bone reabsorption, leading to greater fracture risk. A large, population-based case–control analysis demonstrated that the use of rosiglitazone and pioglitazone in men and women with T2DM for 12 or more months may be linked to a two to threefold increased risk of hip and nonvertebral osteoporotic fractures [51]. Both drugs are now in limited use as a result of FDA warnings about the adverse heart-related side effects of rosiglitazone and the heightened risk of bladder cancer of pioglitazone [52].

Recently, canagliflozin (Invokana, Invokamet), a sodium–glucose cotransporter-2 (SGLT2), has been used in combination with a sulfoylurea, pioglitazone, or short acting insulins to lower blood sugar in T2DM by stimulating the kidneys to remove sugar through the urine. In 2015 the FDA issued two warnings regarding

the use of canagliflozin, one dealing with bone fracture risk and decreased BMD [53] and the other with the presence of too much acid in the blood (acidosis) due to the production of high levels of ketones [54]. Drawing on the results of several clinical trials, the first warning was based on findings that fractures occur more frequently with canagliflozin than with placebos and within a time span of 12 weeks after initiating treatment. It is not FDA approved for patients with T1DM.

Antiepileptic medications such as gabapentin and pregabalin are commonly used as therapy for the pain associated with diabetic peripheral polyneuropathy. As a class, they affect balance and coordination, increasing fall and fracture risk; moreover, they also lead to vitamin D25(OH) insufficiency and deficiency [55]. Large-scale RCTs as well as long-term follow-ups are needed to elucidate the efficacy of antiepileptic drugs in neuropathic pain [56]. Patients with diabetic polyneuropathy may also receive selective serotonin–norepinephrine reuptake inhibitors (SNRIs), a class of antidepressant medications that is associated with decreased bone mineral density, increased falls, and a greater risk of nonspine fracture including hip fractures [57].

Prevention and Treatment of Diabetes Mellitus-Related Bone Disease

Treatment of bone disease in diabetes requires a multipronged approach. Several of the following therapies apply to osteoporosis in general. Others are related to conditions specific to diabetes.

Nonpharmacologic Interventions

The first step is to minimize any inciting events that adversely affect bone demineralization and increase fracture risk including poor glycemic control, harmful medications, and falls. Patients with T1DM are at particularly high risk of osteoporotic fractures, with T2DM patients affected to a lesser degree; however, both groups of patients should be made aware of the principal causes of osteoporosis in diabetes, particularly insulin deficiency and the impact of peripheral neuropathy and retinopathy. As Brown et al. emphasize, no osteoporosis screening recommendations have been adopted for patients with diabetes, but it is deemed prudent to provide screening for both men and women (particularly thin women), with T1DM complications [58]. In T2DM, conventional dual-emission x-ray absorptiometry scans may be misleading given that, in this condition, higher BMD coexists with increased fracture risk due primarily to falls [19].

Poor nutrition and a compromised lifestyle are factors contributing to the development of osteoporosis in diabetes. Diets with adequate amounts of calcium and vitamin D or supplements if needed should be maintained in order to help ensure

Table 3 Factors that increase falls in diabetic patients

Factor	Cause	Solution
Diabetic neuropathy	Altered sensation and proprioception and balance Foot ulcers that alter weight-bearing	Proper footwear PT evaluation Use of assistive devices (cane, walker) if appropriate Improve glucose control
Diabetic retinopathy and cataracts	Retinal vascular changes that impair visual acuity caused by years of poor glucose control	Routine optical evaluation
Orthostatic hypotension	New medications, excessive doses of antihypertensive medications, or dehydration	Educate patient on getting up from seated position Avoid drastic dose alternations in antihypertensive medications
Hypoglycemia	May cause syncope or dizziness	Close monitoring of glucose levels throughout day

bone health and optimal glucose control. Smoking and excessive alcohol intake should be avoided. Weight management is an issue for both excessively thin women with T1DM and obese and overweight women with T2DM. Risk factors for falls including advanced age, household hazards, and impaired balance should also be minimized (Table 3).

The next factor in both prevention of further decline and ongoing treatment is regular physical therapy to develop proprioceptive and balance skills and to increase and maintain bone and muscle strength. With the assistance of a physical therapist, if needed, diabetic patients should be encouraged to walk, jog, dance as well as practice yoga and engage in weight-bearing and resistance exercises. As predicated in Wolff's law (bone adapts to the loads placed upon it), bone strength is directly correlated with use. Given painful peripheral polyneuropathy, retinopathy, and poor proprioception as well as possible cardiac deconditioning and a propensity for coronary vascular accidents, diabetic patients experience a decline in activity. In contrast, maintaining appropriate activity levels not only contributes to healthy bone remodeling as well as muscle coordination and balance, but it also exerts beneficial effects on glycemic control, atherosclerosis risk, and weight control [58].

Pharmacologic Treatment

A number of medications that positively alter the bone formation and reabsorption balance have proved effective in treating diabetic osteoporosis. In the first instance, recombinant insulin therapy, acting through its osteoblast receptors, exerts an osteogenic effect on osteoblasts [12]. As Gopalakrishnan et al. [59] have shown, insulin in combination with estradiol counters the deleterious effect of high concentrations of glucose on osteoblast proliferation and function.

The antidiabetic drug, metformin, positively influences bone turnover and is associated with a decrease in risk fracture. It not only has a direct osteogenic effect at all glucose concentrations [60] but in animal studies, it has been shown to exert a positive impact on osteoblast differentiation and function both in vivo and in vitro [61]. Long used in T2DM, metformin has recently assumed new importance as the focus of a proposed study examining its efficacy in treating several age-related ailments including cardiovascular disease, cancer, and cognitive impairment—a significant departure from studies addressing treatments for only a single disease [62].

A study of ovariectomized and non-ovariectomized rats demonstrates that glimepiride, a first-line drug in the treatment of T2DM, inhibits the deleterious bone changes caused by estrogen deficiency in ovariectomized rats and heightens bone formation, indicating that it may reduce the risk of osteoporosis, particularly in postmenopausal women [63].

In terms of prescription agents for osteoporosis, the bisphosphonates—specifically alendronate, risedronate, and pamidronate—have become a significant addition to the therapeutic armamentarium for osteoporosis. By reducing osteoclast activity, they inhibit bone resorption, thereby preventing bone loss and inducing increased BMD. Interestingly, recent studies have indicated a possible correlation between the use of alendronate and both a decrease in daily insulin requirements as well as a possible decrease in T2DM itself. As a treatment for senile T1DM alendronate produced an increase in BMD accompanied by a reduction in the required daily consumption of insulin, perhaps because it alleviated some of the pain, rigidity, and restricted movement in osteoporosis, enabling patients to improve their physical activity [64].

An examination of the use of alendronate in patients with T2DM revealed a reduced risk of T2DM in users of alendronate as opposed to a 21 % increased risk of developing the disease in those not receiving the drug. Increased physical activity may also be a factor in this analysis [65]. Similarly, a British study found that the long-term use of bisphosphonates reduced the chance of developing T2DM by one-half with a greater risk reduction in women (51 %) than in men (23 %); a slight increase in risk occurred in the period from 1 to 2.5 years of exposure, followed by a sustained decrease thereafter [66]. These findings await confirmation. Few if any bisphosphonate treatments have been studied in patients with both diabetes and osteoporosis, although small studies have shown the efficacy of pamidronate in COA [58].

Compared with bisphosphonates, the selective estrogen receptor modulator, raloxifene, exhibits relatively modest BMD gains but causes reductions in vertebral fractures similar to those of bisphosphonates. A randomized clinical trial involving 40 postmenopausal women with T2DM found that raloxifene did not affect either glycemic control or insulin sensitivity [67]. Although approved by the FDA for treatment of postmenopausal women with osteoporosis, the androgynous peptide, calcitonin, is regarded as a second-tier therapy because of the availability of more effective drugs, the lack of definitive evidence on calcitonin's

efficacy in preventing fracture, and recent studies indicating a possible causal relationship with cancer [68].

Also approved by the FDA but with a 2-year limitation, parathyroid hormone (PTH) is generally reserved for patients at greatest risk of fracture, not only because of its cost but also because of its possible relation to increased risk of osteosarcoma [58]. This risk has only been observed in laboratory animals, but individuals with high-risk conditions such as Paget's disease of the bone or prior radiation should avoid PTH [69].

Future Treatments

The protein PPAR-γ, currently the focus of efforts to develop insulin sensitivity in T2DM, shows highly preliminary but promising results as a new therapeutic approach to bone formation. PPAR-γ is known to inhibit the production of stem cells in bone marrow, preventing the cells from developing into bone, cartilage, and connective tissue. In a laboratory trial involving mice and human tissue, Marciano et al. found that when stem cells were treated with a compound that represses PPAR-γ activity, a statistically significant increase occurred in osteoclast formation leading to increased bone formation. The next step is to test the compound in animal models of bone loss, aging, obesity, and diabetes [70]. These and other investigations related to PPAR-γ, together with the development of new medications, are forthcoming.

Critical Illness Polyneuropathy and Polymyopathy

Critical illness polyneuropathy (CIP), particularly when associated with sepsis and systematic inflammatory response syndrome (SIRS), is one of the most common neuromuscular complications of critical illness. An axonal degenerative polyneuropathy presenting as both limb and respiratory muscle weakness, CIP affects primarily distal motor fibers as opposed to proximal ones [71]. It is often cited as an underlying factor in a patient's difficulty in weaning from a mechanical ventilator, thereby increasing the risk of intensive care morbidity; greater susceptibility to infection and organ failure are also likely to result [72]. CIP and an overlapping syndrome, critical illness myopathy (CIM), are thought to occur in approximately 25–50 % of patients admitted to the intensive care unit with SIRS or sepsis [73].

The etiology of critical illness polyneuropathy is unclear. Observations of its clinical course have led to speculation that it may be caused by a defect in the transportation of nutrients through the axon—a process that requires significant energy expenditure which may be deficient due to the sepsis and various interleukins and cytokines that affect cellular respiration. Further, microcirculation to peripheral nerves may be impaired by sepsis and its cardiovascular consequences as well as by elevated glucose levels associated with diabetic polyneuropathy [74].

In terms of diagnosis, the following criteria for critical illness polyneuropathy have been put forward by Latronico and Bolton [75]:

1. Patient is critically ill with multi-organ dysfunction.
2. Patient has limb weakness or difficulty in weaning after non-neuromuscular etiologies have been ruled out.
3. Electrophysiological evidence of axonal motor and sensory polyneuropathy exists.
4. Detrimental response on repetitive nerve stimulation is absent, thus excluding neuromuscular junction pathology.

A diagnosis of CIP is established if all four of these criteria are met. In the absence of limb weakness or difficulty in weaning from a ventilator but in the presence of other criteria, critical illness polyneuropathy is considered probable but cannot be confirmed.

Medical care for CIP emphasizes intensive insulin treatment (IIT), early mobilization through physiotherapy, and electrical muscle stimulation. Studies indicate that CIP and its accompanying hyperglycemia may be mitigated with strict glucose control [76]. A 2001 RCT enrolling 1,548 surgical ICU patients demonstrated that IIT to maintain blood glucose level at or below 110 mg per deciliters reduced overall in-hospital mortality by 34 % and CIP by 44 %, with patients less likely to require prolonged mechanical ventilation and intensive care [76]. On the basis of these results, IIT was widely prescribed. However, a subsequent 2009 trial involving 3,054 patients on IIT and 3,054 on conventional glucose control reported that IIT increased the absolute risk of death at 90 days by 2.6 % and recommended that a blood glucose level of 180 mg or less per deciliter be adopted. IIT is also known to increase the risk of hypoglycemia [77].

Early treatment with immunoglobulin M-enriched intravenous immunoglobulin (IVIG) initially seemed promising but ultimately has not been efficacious in the prevention and treatment of critical illness polyneuropathy in patients with multiple organ failure and sepsis/SIRS nor does it influence the length of ICU stay or mortality in these patients [78]. Early mobilization combined with physiotherapy in the ICU shows limited but promising results in terms of improved functional independence as well as reduced inflammation and disability. A progressive four-step mobility and walking program, conducted by a multidisciplinary team, is among the potential interventions designed to reduce the duration of mechanical ventilation and the length of hospital stays [79].

It should be noted, however, that two recent systematic reviews—one dealing with the effect of physical rehabilitation on activities of daily living and quality of life [80] and the other with the impact of exercised-based intervention following ICU discharge [81]—produced inconclusive results, largely attributable to marked differences between studies, variability in the way they were performed and presented, failure to meet inclusion criteria, and insufficient methodological rigor. Further research is needed to elucidate the benefits of physical therapy in various critical illnesses as well as the intensity and frequency of physical activity required to produce optimal results [82].

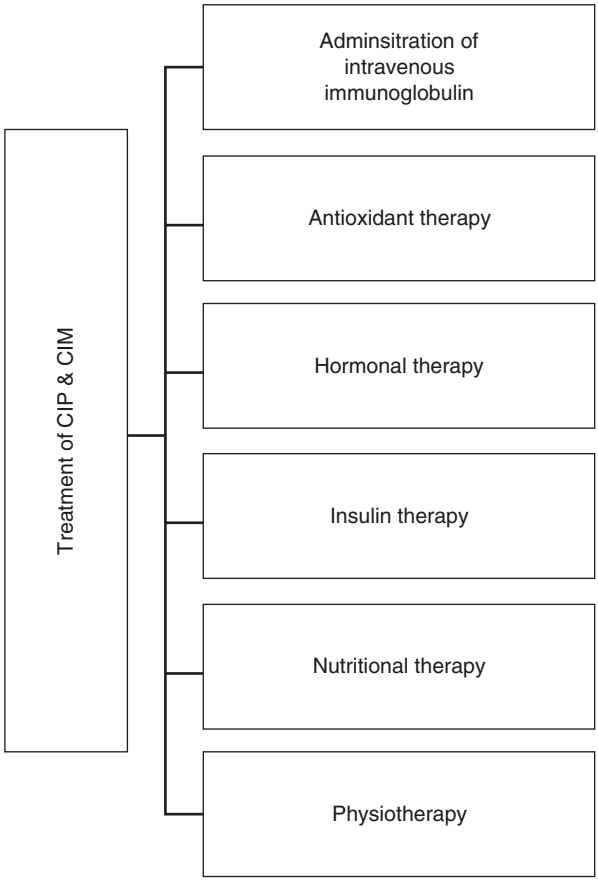

Fig. 1 Approaches to treatment of CIP and CIM. The figure illustrates many approaches to treatment with the more aggressive treatments at the top and less aggressive approaches below. While initial studies on IVIG indicated it might be a possible treatment, later, more robust investigations found it conferred substantially less benefit. The figure is not meant to imply a stepwise progression of treatment; in fact, nutritional therapy and physiotherapy should be done in all patients with CIP and CIM (*Source*: Zhou et al. [72]. Adapted with permission)

As an alternative to active exercise, electrical muscle stimulation (ESTIM) is emerging as a safe and effective therapy for ICU patients, particularly those with heart failure and chronic obstructive pulmonary disease (COPD). In their study of the effects of ESTIM on muscle strength, Karatzanos et al. indicated that ESTIM had a beneficial effect on the muscle strength of ICU patients primarily in terms of the muscle groups stimulated but also in those not involved, indicating its potential ability to improve overall muscle strength and to promote early mobilization [83]. Approaches to treatment for CIM and CIP are illustrated in Fig. 1 [72].

Complications Related to Bone

Critical illness and ICU care may be associated with decreased bone mineralization in part because of the immobility associated with this condition. Immobilization is a long-established but seldom-recognized cause of recurrent hypercalcemia which, in turn, can lead to multiple organ dysfunction, impaired renal function,

gastrointestinal disorders, and neurological symptoms including weakness and depression [84]. In the presence of sepsis, hypercalcemia of immobility may be worsened due to pro-inflammatory cytokines such as IL1, IL6, and TNF-α that accelerate osteoclastic resorption.

Medications for Treatment of Hypercalcemia

Treatment options for hypercalcemia exist, principally in the form of bisphosphonates, specifically pamidronate and zoledronic acid, and in the form of and the human monoclonal antibody, denosumab.

Gallacher et al. demonstrated that pamidronate at doses as low as 10 mg is safe and effective in immobilization-related hypercalcemia and proposed that sepsis be added to the list of risk factors for developing the disorder [85]. In cases of severe renal insufficiency, bisphosphonates may cause renal toxicity; thus denosumab, which is not excreted by the kidneys, has been introduced as an alternative medication to reduce serum calcium concentration, with demonstrated success [86]. Unlike an IV infusion of bisphosphonates, denosumab is given as a two-yearly subcutaneous injection, meaning that it can be easily administered in a skilled nursing facility without monitoring; it remains in the blood stream for months and could eventually have wider applicability for those with immobilization hypercalcemia [87]. Both bisphosphonates and the monoclonal antibody denusomab are also given for treatment of osteoporosis.

Like bisphosphonates, denosumab has been associated with atypical femur fractures [88]; however, such fractures are uncommon and both medications are likely to prevent more fractures than they cause [89]. In its primary use as an FDA-approved medication for postmenopausal osteoporosis, denosumab treatment, sustained over a period of six years, remained well tolerated, reduced bone turnover, increased bone mineral density, and reduced the risk of vertebral and nonvertebral fractures while maintaining a low fracture rate, even below that projected for a virtual placebo group [90].

Medications Causing Bone Loss

In addition to immobility, medications commonly administered to critically ill patients affect bone mineral density and fracture risk. The benefits and risk of prescribing these drugs, particularly for the long term, should be considered in the context of the severity of the disease and its complications as well as the evidence supporting the drug's efficacy.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are regarded as the leading therapy for gastroesophageal reflux disease. In contrast to their less potent counterpart, histamine-2 receptor antagonists (H2RAs) which work by inhibiting histamine action in the parietal cells of the stomach, PPIs including omeprazole, pantoprazole, esomeprazole, and

lansoprazole block the site of acid production in these cells, while H2RAs such as famotidine and ranitidine inhibit the action of histamine on parietal cells in the stomach, reducing the secretion of stomach acid. Numerous studies on the possible effect of PPIs on fracture risk have been undertaken with conflicting results; no association or a small decrease in fracture risk has been detected with H2RAs.

Whereas the PPI, omeprazole, has been found to decrease bone resorption in vitro [91], proton pump inhibition has been associated with the reduction in calcium absorption [92]. It has been postulated that a decrease in gastric pH inhibits calcium absorption since patients who have undergone gastrectomy (surgical removal of all or part of the stomach) and those with hypochlorhydria (inability of the stomach to produce hydrochloric acid) evidence decreased calcium absorption. Countering these results is the finding that patients with vagotomy (surgical severance of part of, or a resection of, the vagus nerve) but without gastrectomy do not experience bone density loss [93].

A trial involving postmenopausal women indicated that 30 days of continuous PPI therapy did not alter functional calcium absorption [94]. In addition, a recent study using the Manitoba Bone Mineral Density Database [95, 96] found no association between PPIs and either osteoporosis or accelerated BMD loss, independent of a link with fracture risk. The Manitoba study matched 2,193 subjects evidencing osteoporosis of the hip with 5,527 normal controls and 3,596 subjects with osteoporosis of the lumbar spine with 10,257 normal controls. Proton pump inhibitor use was defined as greater than 1,500 standard proton pump inhibitor doses over a 5-year period of time. In both a cross-sectional and a longitudinal analysis, results indicated that chronic use of PPIs inhibition was not associated with increased likelihood of BMD loss or osteoporosis (as determined by bone mineral densitometry), at either the hip or lumbar spine. The majority of patients with CIP do not require long-term GI prophylaxis but rather use these agents to get through the current hospital course and potentially a short duration after hospitalization to protect against stress ulcers, particularly in a setting where blood thinners for deep vein thrombosis prophylaxis are prescribed. This situation lies in contrast to that experienced by patients with more chronic conditions of severe gastrointestinal reflux, or valvular heart disease where high dose anticoagulation is required for the patient's remaining life.

Just as the studies relating to BMD loss are contradictory, so too are studies examining the link between PPIs and fracture risk. Two large trials published in 2006 reported evidence of an association between the two. Vestergaard et al. [97] demonstrated that PPIs produce a limited increase in fracture risk for use within one year in contrast to H2RAs that appeared to produce a small decrease fracture risk over the same period. In a nested case–control study, Yang et al. corroborated the Vestergaard et al. results by determining that PPIs, when taken for more than one year, led to increased fracture risk and that the risk was significantly greater with PPI use than with H2RAs; moreover the adjusted rate of fractures was significantly higher in patients taking a long-term high dose of PPIs [98].

At a time when PPI use was still relatively low, a trial examining its relationship to hip fracture found no increase in fracture risk in patients in the absence of other medical risk factors, such as alcohol dependence and neurologic disease.

A subsequent study of more than 130,000 postmenopausal women enrolled in the Women's Health Initiative revealed no connection between PPIs and hip fracture at a 7-year follow-up but did identify a 47 % increased risk for spine fracture and a 26 % increased risk for forearm/wrist fracture. A marginal effect on 3-year BMD change was present at the hip but not at other sites [99].

On the basis of these and other epidemiological studies, in 2010, the FDA instituted a product label change on both prescription and over-the-counter PPIs including a warning that "PPI therapy may be associated with an increased risk for osteoporosis-related fracture of the hip, wrist or spine with the risk of fracture increased in patients who received high-dose, long–term PPI therapy for a year or longer." A year later, the FDA rescinded the ruling on over-the-counter PPIs, citing the unlikelihood of fracture risk based on their lower doses and recommended short-term use [100].

In the years since the FDA ruling, researchers have continued to indicate a link between PPIs and fracture risk, but the magnitude of the risk still remains uncertain. In contrast to earlier studies, the newer trials indicate a lower risk of osteoporosis at the lumbar spine and hip as well as a more modest increase in spine, forearm/wrist, and total fractures [101]. Yet findings remain contradictory. A Canadian study found no correlation between PPI use over 10 years and accelerated bone mineral density loss [102]. However, a large American trial involving nearly 80,000 postmenopausal women [103] reported that, compared with nonusers, women who took PPIs regularly for at least two years evidenced a 35 % higher risk of hip fracture, with longer use associated with greater risk. The relationship was sustained after adjusting for body mass index, physical activity, calcium intake, and the use of drugs (bisphosphonates, corticosteroids) that affect fracture risk. After other factors contributing to hip fractures were taken into account, only one, smoking, was found to independently contribute to the association: in current and former smokers, the risk of hip fracture increased to greater than 50 %.

While postmenopausal women remain a focus of PPI studies, men and younger adults have also been studied. In a trial involving men taking omeprazole and pantoprazole, PPI consumption was associated with an increasing risk of fractures in long-term PPI users, in the most adherent users, and in most recent users [104]. This association, together with a dose-responsive effect, is also evident in young adults but not in children [105].

Thus far, some 35 studies of PPIs and fractures involving two million participants [106] have been conducted. In assessing the results, several analyses have pointed out that these are nearly all retrospective, observational studies which have a greater potential for bias and produce less accurate estimates [107]. Nonetheless, given the marked increase in PPI use—an estimated 113 million prescriptions, excluding over-the-counter medications, are filled globally each year [108]— concerns over PPI use appear to be warranted. Again the risks and benefits of therapy should be taken into account, especially at a time when PPIs are considered to be overprescribed. In general, PPIs are indicated in cases of severe acid peptic disorders including gastroesophageal reflux disease (GERD), peptic ulcers, and dyspepsia with an indication that they not be used in higher doses or for a longer period than needed [101]. High-risk patients such as postmenopausal women, the elderly, the nutritionally deficient, and those with osteoporosis who are at a high risk of falling should be monitored

regularly. Most patients with upper GI symptoms can be treated with the lowest effective dose or with far less expensive H2RAs which have little or no association with increased fracture risk.

Large prospective RCTs are needed to confirm or refute the results of past observational studies on PPIs as well as to determine causality and magnitude of risk. The most widely "assumed" mechanism [92] underlying the relation between PPIs and bone fractures involves long-term use leading to increased calcium absorption which, in turn, results in a negative calcium balance and increased risk of osteoporosis, bone loss, and fractures. However, a clearly defined, noncontroversial mechanism awaits further investigation.

Loop Diuretics

Although not directly associated with sepsis, loop diuretics are another class of medications commonly used in the ICU environment to manage congestive heart disease and anasarca (extreme generalized edema). In a 2006 trial with postmenopausal women, Rejnmark et al. reported that the loop diuretic, bumetanide, inhibits sodium and chloride reabsorption, thereby blocking calcium reabsorption, increasing renal excretion and bone turnover, and significantly decreasing bone mineral density by 2% at the total hip and forearm [109].

By contrast, a large, prospective study of postmenopausal women enrolled in the Women's Health Initiative [110] found no significant association between ever-use of loop diuretics and changes in BMD, fall occurrence, and total and clinical vertebral fractures. The study did confirm a link between prolonged use (over three years) and increased fracture risk. Whether it was sufficiently empowered to address the relation between loop diuretics and bone fracture has been questioned on the basis that the data documented only long-term use [111].

Conflicting findings emerge from two other studies of hip bone loss in older women and men. Lim et al. reported a small but significantly higher rate of bone loss in female loop diuretic users compared with nonusers after a mean duration of 4.4 years [112]. In men, the adjusted rates of loss were twofold greater among intermittent loop diuretic users and 2.5-fold greater among continuous users. These inconclusive results may be attributable, in part, to potential bias, heterogeneity, residual confounding, lack of relevant data, and other methodological issues, leaving open the question of whether and to what extent the association can be confirmed. A 2015 meta-analysis of 113 studies indicates that users of loop diuretics had a significant positive association with overall risk of total and hip fractures [113].

Anticoagulants

Deep vein thrombosis (DVT) prophylaxis is often administered to patients in the form of unfractionated or low-molecular-weight heparin, both of which are associated with impaired bone metabolism. Intravenous heparin has been found to not

only decrease cancellous bone volume in a dose and time-dependent manner but also to produce a dose-dependent decrease in alkaline phosphatase, a marker of bone formation, and a dose-dependent increase in urinary type 1 collagen cross-linked pyridinoline (PYD), a marker of bone resorption. It is also postulated that effects of heparin upon bone are long lasting with deficits seen for many years after intense heparin therapy [114].

A derivative of heparin, low-molecular-weight heparin, is a commonly used alternative to unfractionated heparin and is linked with fewer hematologic side effects. Whereas standard heparin is known to cause spontaneous fracture of the rib and vertebrae, studies have borne out the fact that low-molecular-weight heparin is linked to decreased risk for developing osteoporosis [115]. Monreal et al. found that 15 % of nonpregnant women treated with unfractionated heparin reported vertebral fractures within six months of initiating therapy, while only 2.5 % treated with the low-molecular-weight heparin, dalteparin, reported similar fractures [116]. Fondaparinux, a synthetically produced anticoagulant used in similar fashion to low-molecular-weight heparin but often reserved for those with heparin-induced thrombocytopenia, has not been associated with changes in bone metabolism or integrity [114].

Guillain–Barre Syndrome (GBS)/Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Epidemiology

Guillain–Barre syndrome (GBS) is defined as an acute inflammatory disease of the peripheral nerves caused by damage to the myelin, the insulation surrounding sensory, motor, or autonomic nerve fibers. It is also termed acute demyelinating polyneuropathy (AIDP). Symptoms, including numbness, weakness and cramping in the limbs, and difficulty breathing, develop rapidly and progress within a 2–4-week period, followed by a plateau and eventual improvement in the majority of cases; there is no recurrence and little if any further deterioration. Because of its acute onset and rapid decline, GBS can be confused with critical illness polyneuropathy. Table 4 compares features of CIP and Guillain–Barre [72].

Chronic inflammatory demyelinating polyneuropathy (CIDP) is regarded as the chronic form of GBS (AIDP). While both AIDP and CIDP are caused by an attack on myelin, they differ in terms of onset and progression. Unlike GBS, CIDP develops more slowly and may progress for as long as eight weeks with a possibility of recurrence; without treatment, some 30 % of CIDP patients mobilize predominantly by wheelchair [117]. Although CIDP exists in several different phenotypic variants, it is primarily characterized by loss of sensation or abnormal sensation such as tingling and pain and weakness associated with loss of reflexes and manifested by difficulty in walking. Just as recognition of different types of GBS has led to advances in treatment, so greater understanding of

Table 4 Comparison of critical illness polyneuropathy (CIP) and Guillain–Barre syndrome (GBS)

	CIP	GBS
Prodromal indications	Sepsis and multiple organ failure	Respiratory or gastrointestinal infection
Clinical presentation	Typically the onset follows an intensive care unit admission	Typically the onset precedes an intensive care unit admission
Electrophysiology	Axonal motor and sensory polyneuropathy	Unresponsive nerves or demyelinating polyneuropathy; spontaneous neuronal activity; Axonal motor and sensory polyneuropathy
Cerebrospinal fluid	Typically normal	Albuminocytologic dissociation
Magnetic resonance imaging	Absent of any significant findings	On occasion, there will be indications involving the enhancement of spinal nerve roots
Biopsy	Primarily axonal degeneration of the distal peripheral nerves without inflammation	Primarily demyelinating process with inflammation, or motor axonal degeneration only, or motor and sensory axonal degeneration
Treatment	Typically antiseptic treatment is appropriate, but no specific therapy is indicated	Plasmapheresis, intravenous immunoglobulin
Outcome	Patient may have spontaneous recovery with variable timing; 50 % of patients with full recovery	Usually more than 75 % of patients with full recovery

Source: Zhou et al. [72]. Used with permission

these phenotypes should help guide diagnostic and treatment strategies for CIDP [118]. Table 5 illustrates the comparison of CIDP and GBS [117, 119–121].

Treatment of GBS

Distinguishing between GBS and CIDP is important in terms of determining optimal therapies. To hasten improvement, Guillain–Barre is generally treated with either plasma exchange or high-dose intravenous immunoglobulin (IVIG), both of which are equally effective. Because it is easier to administer, IVIG is the treatment of choice beginning as soon as possible after diagnosis. Accelerated recovery occurs in some patients but others experience residual deficits [122]. In a Cochrane review of the use of corticosteroids in GBS, moderate quality evidence revealed that, when given alone, corticosteroids do not significantly

Table 5 Differentiation between CIDP and GBS

	CIDP	GBS
What is it?	A neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. Considered the chronic counterpart of Guillain–Barre	An acute inflammatory disease of the peripheral nerves that causes an autoimmune attack on the myelin leading to a loss of myelin
How to differentiate	Considered when a patient thought to have Guillain–Barre syndrome deteriorates again after eight weeks from onset or when deterioration occurs three times or more	Symptoms include paresthesia in toes and fingers on both sides of the body, loss of reflexes (such as knee jerk), slowed nerve conduction velocity, high protein in cerebrospinal fluid
Likelihood of osteoporosis	Unlikely; risk increases with intake of steroids; more likely in elder patients	Unlikely; fracture risk increases with pain treatment
Likelihood of neuropathy	More likely; polyneuropathy	Less likely; may develop in some cases

Sources:
National Institute of Neurological Disorders and Stroke [119]
National Institute of Neurological Disorders and Stroke [120]
Center for Peripheral Neuropathy [121]
John Hopkins Medicine. Guillain–Barre and CIDP. http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/peripheral_nerve/conditions/guillain_barre_and_cidp.html. Accessed 17 Jan 2016

hasten recovery or affect the long-term outcome [123]. New clinical trials are underway to test the hypothesis that complement inhibitors such as eculizumab may control inflammation, reduce nerve injury, and prevent progression of weakness in GBS [124].

Patients with GBS often need aggressive rehabilitation to maintain body functioning during recovery. Mechanical ventilation is required by 20–30% of those with the disorder, and other machines may be needed to assist body function. Manual manipulation of patient's limbs is employed as a first step, followed by physical therapy including training in safe transfers and balance, passive range of motion exercises, the use of partial body weight support systems, airway clearance techniques, and hydrotherapy [125].

Like GBS, CIDP responds to IVIG, to plasma exchange, and, to a limited extent, to corticosteroids, all administered on a short-term basis with similar effectiveness. IVIG improves disability for at least 2–6 weeks and up to 48 and possibly even 48 weeks, a similar efficacy to plasma exchange and oral prednisone; however, long-term benefits are unknown [126]. Moderate to high-quality evidence indicates that plasma exchange leads to short-term improvements in disability, but rapid deterioration occurs shortly after treatment cessation [127]. Corticosteroids are commonly used in practice with one study showing no significant difference between monthly dexamethasone and daily prednisone.

As Gorson has observed, IVIG is time-consuming and expensive; plasma exchange is invasive and can be administered only by highly trained personnel in specialized centers with hematologic testing imperative throughout the infusion process; corticosteroids have several serious side effects and are poorly tolerated in the long term [128]. There is no consensus on the best long-term strategy for CIDP. In considering new medications, the benefits of the relatively safe IVIG/plasma exchange therapies must be balanced against as yet undetermined risks of drugs currently under investigation [129].

GBS/CIDP Complications Related to Bone

Vitamin D deficiency has been associated with autoimmune-related neurologic diseases including both Guillain–Barre and CIDP. Although impaired serum levels of vitamin D deficiency may cause an abnormally regulated immune response, the link to bone involvement is unclear because the active form of vitamin D, specifically vitamin 1,25 $(OH)_2D_3$, may not fluctuate in autoimmune disease. A study by Elf et al. found that patients with primary immune-mediated peripheral neuropathies were deficient in vitamin D and had significantly lower serum vitamin D25-OH levels values than healthy controls [130], suggesting the need to monitor vitamin D status, ensuring that immune cells respond to the ameliorative effect of vitamin D. As previously indicated, corticosteroid use is ineffective and possibly deleterious in the treatment of GBS but is employed in CIDP, independently reducing already diminished levels of vitamin D25-OH to severe levels [131].

Glucocorticoid-induced osteoporosis, the most common form of secondary osteoporosis, occurs in 50 % of patients taking glucocorticoid medications and has a profound effect on bone formation by impairing osteoblastic differentiation and function and increasing bone resorption even in the early treatment phase [132]. Thus far, glucocorticoids appear to affect bone regardless of their dosage [133]. Fractures seen in patients with glucocorticoid-induced osteoporosis occur at a higher BMD level than in postmenopausal osteoporosis [134]. As a consequence, guidelines for treatment of postmenopausal osteoporosis should not be applied to patients taking glucocorticoid steroids. Instead, vitamin D and calcium, along with bisphosphonates, are administered to patients who anticipate exposure to glucocorticoids for 3–6 months [133]. The combination of all three agents has been shown to increase BMD by as much as twice the increase produced by vitamin D alone. Moreover, the efficacy of bisphosphonates is further enhanced with concomitant use of vitamin D [135].

GBS, in itself, evidences no independent association with any fracture risk. The only exception occurs in patients undergoing pain treatment which doubles the risk of fracture—a finding also apparent in controls being treated for pain [136]. Patients with GBS that later presents as CIDP may suffer from prolonged periods of immobilization which increases bone resorption and results in hypercalcemia [87]. The proposed mechanism is an increase in osteoclast-driven reabsorption manifested in

reduced bone formation and decreased osteoblastic activity, offsetting the balance of bone metabolism toward reabsorption. The most direct treatment of hypercalcemic immobility consists of ambulation, passive and active range of motion exercises, and other forms of physical therapy. In situations where mobilization of the patient is not feasible, bisphosphonates, as well as denosumab, are the preferred pharmacologic treatment. However, caution must be exercised in those with renal insufficiency if selecting a bisphosphonate [86].

There are over 100 different types of peripheral neuropathy, each with its own set of causes, symptoms, and therapies. The prognosis depends on the underlying causes and the extent of the nerve damage; the earlier the diagnosis, the greater the chance of slowing or reversing the process. In some cases, nerve damage is permanent, and pain can persist for a lifetime. Research is focusing on a broad spectrum of contributing factors ranging from the biological mechanisms involved and the role of genetic mutations to the impact of neurotropic factors and new strategies for relieving neuropathic pain.

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