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Impact on Musculoskeletal after Spinal Cord Injury

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ABSTRACT

Spinal cord injury is the most disabling condition affecting an individual's life. Subjects who have severe spinal cord injury (SCI) can develop osteoporosis.SCI subjects are mostly immobilized, so they lack long bone loading; clinically, disuse is the primary factor for osteoporosis, characterized by multi-factorial disorders like low bone mass, impaired bone quality and increased risk of fragility fractures. Studies have demonstrated that bone loss in SCI Subjects begins shortly after injury, whereas bone resorption was at its high peak approximately three months after injury. Hormones such as parathyroid (PTH), vitamin D3, sex steroids, thyroid hormone and leptin may also be involved in bone loss after SCI. Many studies have shown that neuronal impairment and disability in SCI subjects may contribute to an upregulation of receptor activator of nuclear factor-κB ligand (RANKL), which mainly promotes bone absorption. The molecular mechanism is primarily involved in contributing to SCI-related Osteoporosis's pathogenesis, such as Wnt signalling pathway disruption and dysregulation of RANKL. In contrast, bones are protected from resorption due to Estrogenic effects as it helps decrease the upregulation of RANKL. Our review tries to cover all aspects of the current physiological and cellular mechanisms responsible for contributing to SCI-related osteoporosis.

Introduction: Spinal cord injury(SCI) is a life-threatening process; it greatly impacts subjects' quality of life and families. Around over 1million people in North America

are affected, with direct lifetime costs estimated at 1.1–4.6 million USD **[1,2],** whereas 8.0 to 246.0 cases per million inhabitants are affected by this life-threatening event annually **[3].** With improvement in rehabilitation services and nursing care, the number of tetraplegias and complete lesions patients gradually increased over 20 years [**4,5]**. After SCI, people mostly suffer from secondary complications, such as an extensive decrease in bone density, high-risk fragility fractures and associated morbidity and mortality**.[5,6,7,8].** The main reason for the fragility of bone after SCI is immobilization, which leads to a decrease in bone density, bone mass osteopenia, and sometimes osteoporosis, a condition leading to an increased risk of fractures. According to histomorphometric and biochemical reports, it happens due to uncoupling between bone formation and resorption. But the main cause is still unknown. It's an unavoidable complication after SCI, occurring mostly in the pelvis and lower extremities. It has been documented that fall in bone mineral density, and bone mineral content mostly happens in subjects with acute and chronic phase of SCI. In SCI subjects, the sub-lesional bones undergo deterioration in their trabecular micro-architecture. Many clinical studies have demonstrated a high incidence of fractures in the lower extremity in SCI subjects ranging from around 1% to 34%.

After SCI, the pathogenesis of osteoporosis is mostly considered disuse. At the same time, unloading is regarded as an essential factor in pathogenesis. After SCI, the neural lesion plays a significant role in developing osteoporosis, followed by denervation of the sublesional bones. In normal bone remodelling, an important role is played mainly by nerve innervation and neuropeptides. In subjects with paraplegia, bone loss also occurs in the upper extremity through upper limbs are innervated and typically loaded, which is an indication of the role of hormonal changes in the development of Osteoporosis after SCI by a different mechanism such as (1) reduced intestinal absorption of calcium and increased renal elimination leading a negative calcium balance; (2) Vitamin D deficiency; (3) SCI antagonizes gonadal function and inhibits the osteo-anabolic action of sex steroids; (4) After SCI higher level of serum leptin also plays a significant role in progressing of osteoporosis; (5) Suppression of TSH by the pituitary gland is another factor responsible for bone loss after SCI; (6) bone loss after SCI may be caused directly, at least in part, by insulin resistance and IGFs.

Aetiology of bone loss after SCI: A combination of factors is responsible for osteoporosis development after SCI, whereas the primary causal factor to be responsible is mechanical unloading(9). In addition, neuronal and hormonal changes also play a role in its pathogenesis(9). Studies also proved that bone loss after SCI also occurs due to space flight and bed rest (10,11).

Osteoblasts and osteoclasts: Bone remodelling is responsible for maintaining bone homeostasis, continuously replacing old and damaged bones with new ones to maintain bone strength and elasticity (12). Osteoclast and osteoblast are two types of cells normally responsible for bone remodelling. Former originating from haematopoietic cells, responsible for bone resorption and later originating from mesenchymal cells, responsible for bone formation(13). Unbalanced bone remodelling is the primary cause of SCI induced bone loss. So, excess supply of

osteoclast results in bone resorption and undersupply of osteoblast, needed for cavity repair, may be the crucial factors in SCI induced osteoporosis. Clinically it was shown that after the SCI process of bone resorption increases, therefore, In SCI subjects, there is an increased level of hydroxyproline, pyridinoline, deoxypyridinoline, and type I collagen C-telopeptide in their urine(14-17). All these findings reveal that ex vivo formation of osteoclast is promoted by SCI(18), and the key molecule responsible for its development is the receptor activator of the NF-κB ligand (RANKL) (19) which is expressed on the surface of bone marrow stromal/osteoblast precursor cells, T cells and also B cells. After binding to its cognate receptor RANK on osteoclast lineage cells(20), it is further neutralized by Decoy receptor osteoprotegerin (OPG), which is produced by osteoblastic lineage cells(21). Studies have shown that in cultured osteoblast-like cells from SCI rats, increased expression of RANKL mRNA and protein was observed. In contrast, a significant decrease in OPG expression was demonstrated, and an enhanced RANKL/OPG ratio might result in elevated osteoclastogenesis, hence promoting Osteoporosis after SCI(22).

Compared to osteoporosis that arises from disease, malnutrition or any pharmacological side effects, the mechanism of osteoporosis occurring after SCI is entirely different(23). Demulder et al.(24) demonstrated that SCI might promote the secretion of compounds enhancing osteoclastogenesis. In the iliac bone, the marrow culture increased the number of osteoclast-like cells, and a higher amount of interleukin 6 (IL-6) was seen compared to the sternal bone marrow culture of SCI subjects (25). Through the secretion of interleukin 1β (IL-1β) by local monocyte-macrophages in the marrow microenvironment, IL-6 also stimulates osteoclast-like cell formation[26]. These findings reveal that promoting osteoclasts like cells and progenitors is because of motor impairments due to SCI[24].

Unloading and the bone formation-resorption imbalance: SCI causes immediate disuse and continuous loss of biomechanical stress on bones, mainly responsible for the bone remodelling process controlled by osteocytes. So the absence of mechanical loading results in bone demineralization by inhibiting osteoblastic activity and promoting osteoclastic activity(27). In many cases, this imbalance of bone formation and resorption is so high and sustained that it leads to severe bone loss, and it is ubiquitous both in chronic and acute SCI. In the case of both chronic and acute SCI, it was found that bone resorption biochemical markers such as total deoxypyridinoline (DPD), N-telopeptide (NTx), serum and urinary type I collagen C-nicatelopeptide (CTx) and hydroxyproline significantly increases in blood and urine (28). But in comparison to acute SCI, their concentration is somewhat significantly lower than chronic SCI(33). After ten years or more of SCI injury, it was found that in 30% of subjects, there is an elevation in the level of DPD (29). There is a question that arises if the bone loss occurs due to unloading in the case of SCI. Can it be prevented through functional exercises, similar to osteopenia that appears from bed rest, or can it be reversed by ambulation or return to normal gravity (30). However, studies have shown that weight-bearing exercises with standing frames and bikes, using forms of functional electrical stimulation, are somewhat effective in preventing osteoporosis and restoring bone mineral density after SCI (31). Apart from unloading, other factors

are also responsible for SCI induced osteoporosis, Levasseur et al. demonstrated that the sympathetic nervous system (SNS) transmits mechanical loading on bones. In case of ineffectiveness of mechanical loading on bone in SCI subjects may lead to denervation of the SNS (32).

Hormonal changes: In subjects with paraplegia, mainly bone loss occurs in the upper extremities, though upper limbs are typically loaded and innervated. Hormones such as PTH, vitamin D3, sex steroids, thyroid hormone and leptin may also be involved in bone loss after SCI.

Calcium balance: In the case of SCI after injury, a negative calcium balance and hypercalciuria have been seen; the main reason behind hypercalciuria after SCI is increased osteoclastic bone resorption. In the acute phase of SCI, it has been found that there is a decrease in absorption of calcium in the gastrointestinal tract; in the case of SCI, in its early stage (less than six months post-injury), there is a significantly elevated level of serum phosphate and ionized calcium. It has been demonstrated that there is reduced renal function in acute SCI subjects. Hence, increased urinary calcium elimination in response to SCI may be related to diminished renal tubular reabsorption. However, ambulation and exercises may help decrease hypercalciuria and, to some instant, modify calcium balance positively, so it is clear that immobilization is the primary factor resulting in negative calcium balance.

In contrast, a normal range of serum calcium has also been observed. One of the cross-sectional studies demonstrated that acute SCI subjects (n=7) who had sustained an injury three months earlier than normal controls had elevated urinary calcium excretion, serum phosphorus, and ionized calcium. In contrast, a normal serum calcium level was found[33]. Identical results were found in two other longitudinal studies by Roberts et al. [34] and Bergmann et al. [35] in the case of acute SCI subjects. Thus, to prevent complications of hypercalciuria and suppress calcium excretion, it has been mostly recommended to reduce dietary calcium consumption, which may lead to negative calcium balance[36]. Negative calcium balance also causes complications in SCI subjects; thus, dietary calcium restriction cannot be applied to SCI subjects. 1600 mg daily calcium consumption is recommended for SCI subjects to modify their calcium balance[37]. Kohli et al., in their study, have shown that there is no correlation between serum calcium level and kidney stone formation in SCI subjects[38].

Adults SCI subjects with multiple fractures are at high risk for hypercalcemia. In contrast, children and adolescents with acute SCI may be particularly susceptible to hypercalcemia due to elevated bone resorption and increased bone turnover[39]. Prolonged immobilization, dehydration, complete neurological injury, high cervical cord injury, paralysis, and male gender are other risk factors for hypercalcemia[40]. One of the longitudinal studies has proved that a low dietary intake of calcium diet (400 mg/day) probably elevate urinary calcium level. In contrast, dietary uptake of calcium (to at least 1,160 mg/day) did not further increase either urinary or serum calcium concentrations in acute SCI subjects[41].

PTH and vitamin D: With depressed PTH and 1,25(OH)2 vitamin D in the case of

acute SCI subjects, the PTH–vitamin D axis is suppressed. In one of the longitudinal studies, a decrease in serum PTH level was demonstrated after three weeks in SCI subjects [42]. It was also proved by some of the cross-sectional studies that after three weeks of injury in SCI subjects, there are a decrease in serum PTH and 1,25(OH)2 vitamin D levels in comparison to controls[43,]. In SCI subjects, suppressed PTH hormone levels are primarily associated with the degree of neurological impairment. In one of the studies by Mechanick et al.in case of complete and incomplete SCI subjects, when they investigated the PTH and 1,25(OH)2 vitamin D levels in their serum at a mean of 76·5 days postinjury, they observed that there is a significant suppression of PTH–vitamin D axis in case of complete SCI subjects in comparison to incomplete subjects[44].In the case of acute SCI, the levels of PTH and 1,25(OH)2 vitamin D were suppressed by 80.6 and 66%, respectively [45]. Studies have shown that in the case of long-standing SCI subjects, there is a significant decrease in 1,25(OH)2 vitamin D and PTH concentrations [46].

In the case of chronic SCI subjects, persistent inhibition of PTH seems to indicate that for many years low, grade bone resorption occurs; this may be because of constant reduction in the mechanical stresses, the direct action of 1,25(OH)2 vitamin D at high concentrations on parathyroid tissue and changes in cytokine regulation. In contrast, one of the cross-sectional studies on 100 chronic SCI subjects observed no serum PTH level between SCI subjects and controls and higher serum 1,25(OH)2 vitamin D levels in SCI subjects [47]. This difference between the two studies cannot be easily explained; it may be because of the racial, sunlight exposure, diet, and duration variation. After acute SCI, the possibility of calcium nephrolithiasis is prevalent, so individuals in the chronic phase of SCI are advised to restrict their calcium uptake of most dairy products. There must be a possibility of vitamin D deficiency because of this dietary restriction, reduced exposure to sunlight due to non-ambulation or may receive anticonvulsants or other medications that induce hepatic microsomal enzymes, accelerating vitamin D metabolism[48,]. The main expected reason for lower calcium &vitamin concentration in serum is reduced uptake of calcium and vitamin D, which stimulates PTH, resulting in increased resorption of bone. Thus, this emphasizes osteopenia. One-third of chronic SCI subjects predominantly suffer from secondary hyperparathyroidism and vitamin D deficiency[49]. Some other studies on chronic SCI observed either suppressed PTH levels or no change in their PTH level[51]. Therefore we can say that this evidence does not support much to hyperparathyroidism as a causal mechanism in SCI induced osteoporosis.

In one study, higher calcitonin level was reported in SCI subjects [50]. This may represent a compensatory response to ongoing calcium efflux from the skeleton of the paralyzed structures. Because of elevated level of endogeneous calcitonin level might help to lessen the rate of bone resorption[50].

Growth hormone(GH): Bone metabolism is influenced by Insulin and Insulin growth factors(IGF), and their receptors are present on osteoblastic cells [52]. Both Insulin and IGF-1 prevent apoptosis and promote osteoblast differentiation and their survival[53]. The reduction in whole-body glucose transport in SCI subjects may be

due to a proportional decrease in muscle mass[54]. Insulin resistance in SCI subjects is because of skeletal muscle denervation [55].In the case of chronic SCI subjects, it has been reported that apart from Insulin resistance contributing to SCI-induced osteoporosis, growth factors and their secondary messengers, like IGF-1, also contribute as their level got depressed. In his study, Bauman et al. observed that lack of daily physical activity results in depressed growth hormone GH/IGF-I axis in younger individuals with SCI. It may be considered a state of premature ageing [56]. Compared to ambulatory controls, a depressed level of average plasma IGF-1 was reported in tetraplegia subjects[57]. In SCI subjects, depressed levels of GH and IGF-I might contribute to developing insulin resistance and probably bone loss in SCI subjects [58]. However, one study demonstrated that growth factors have no impact on accelerating bone resorption following SCI [59].

Sex Hormone: Sex hormone also plays an essential role in regulating the metabolism of bone. Both sex hormones, oestrogen and androgen, play a crucial role in inhibiting bone resorption and promoting bone formation through many mechanisms [60]. Thus after SCI, there is suppression in the production and secretion of sex hormones [61]. Subjects with acute SCI have significantly lower testosterone levels than controls [62]. These hormones also considerably inhibit the osteoblastic release of local stimulating osteoclastogenesis factors [63]. So if there is a decline in the concentration of the above hormones, then there is an elevation in osteoclast precursor formation in the bone marrow; thus, in cancellous bone, there is an increased number of mature osteoclast cells**[64].** The decline in the circulating concentration of sex steroids in females after menopause or ovariectomy and after orchidectomy in males leads to increased bone loss. Studies have demonstrated that FSH hormones play a vital role in increasing osteoclastogenesis and bone resorption[65]. So to prevent osteoporosis which is stimulated by reduced bone formation due to a decrease in sex hormones, sex steroid replacement therapy can stimulate bone formation[66]. Almost 80% of women with SCI have found an abnormality in at least one axis of the hypothalamus-pituitary-ovary and hypothalamus-pituitary-thyroid axes. Thus, there is a possibility of disrupting endocrine function in subjects with SCI, which contributes to bone loss after SCI [67].

Bone Biochemical Changes: In SCI subjects, it is observed from histo-morphometric data that in the first 16 weeks of immobilization, trabecular osteoclastic resorption surfaces increase, returning to normal at approximately 40 weeks. Over 40 weeks of immobilization, the thickness of iliac cortices and osteoblastic apposition rate decrease [68]. Bone formation markers remain normal or slightly higher than the average level after SCI. Several months after spinal injury, the osteocalcin level rises to a peak or marginally higher than the normal level[69]. Serum procollagen I carboxyterminal propeptide level remains normal until three months after SCI[70]. However, no difference was observed in the level of Bone alkaline phosphatase compared to controls when measured in SCI subjects after three months post injury[Maimoun L,et al 2002]. However, during the first year post-injury in SCI subjects, a high level of alkaline phosphatase was reported, showing high levels of overall bone turnover[Maimoun L,et al 2002].

Studies have demonstrated dramatic changes in bone resorption markers after spinal cord injury. Pietschmann et al.1992,has shown that in comparison to control SCI, subjects have a significantly higher urinary hydroxyproline/creatinine ratio, even within one month after injury. Similarly, another study has demonstrated that, approximately after three months of injury, elevated levels of urinary and serum type I collagen C-telopeptide (CTXu and CTXs) were elevated by a factor of 5 and 2.5, respectively, respectively observed in comparison to control[Maimoun L,et al 2002]. In contrast to bone resorption markers, a very different variation rate is shown by bone formation markers. One prospective study revealed that in subjects with acute SCI, there is a minor rise in serum osteocalcin concentration after injury in 6 months of follow-up [Roberts D,et al 1998]. As we know, osteocalcin is directly stimulated by 1,25(OH)2 vitamin D in osteoblasts, so elevation in serum osteocalcin can be easily explained by the low level of 25(OH)2 vitamin D concentration[Price PA,et al 1980]. In contrast, one of the cross-sectional studies reveals that in the case of SCI, subjects after three months of injury have a significantly high level of serum osteocalcin level compared to the control[Maimoun L,et al 2002]. Whereas in another one of the longitudinal study, the same result was found in the case of six acute spinal cord injury subjects where serum osteocalcin level was normal initially, but after six months, it continuously rose [Zehnder Yet al 2004]. One cross-sectional study showed that in the case of SCI subjects after injury for three months, no changes in the serum bone alkaline phosphatase (B-ALP) levels were observed[Maimoun L,et al 2002]. Both Osteocalcin and B-ALP showed different aspects in bone formation. The normal level of bone formation markers has been observed in most chronic SCI subjects[Zehnder Yet al 2004].The bone turnover markers demonstrate that an imbalance between increased bone resorption and normal (or minor elevated) bone formation after SCI plays a significant role in bone loss and fracture pathogenesis in SCI patients.

Effects on thyroid function: Any traumatic condition will affect serum thyroid hormone levels. Prescription of immediate administration of corticosteroids frequently after SCI may also affect the serum thyroid hormone levels (71). Studies have demonstrated that in the case of acute SCI subjects, levels of T3 and T4 remain depressed (72).

After acute stress, suppression in serum thyroid hormone level may occur because of changes in thyroid hormone-binding protein compared to controls (73); suppression in the level of serum T3 and T4 have been seen in subjects with chronic SCI[74]. Compared to paraplegia subjects, a lower level of serum T3 has been found in tetraplegia subjects[75]. Neuronal differentiation &proliferation, synaptic plasticity and myelination are promoted by TSH[76]. However, the normal plasma concentration of thyroid-stimulating hormone(TSH) has been reported in the case of chronic SCI subjects; this has been proven by several studies[67]. These studies determine the TSH concentration in the case of SCI subjects only by on relying a single morning sample. In contrast, it is not sufficient to assess the 24-h profile on a single time point sample. However, one study by Zeitzer et al. observed that the level of TSH was within the low end of than normal range in the case of chronic SCI when

they investigated their 24-h average and the circadian amplitude of the TSH rhythm[77]. Thus this study proves that after SCI, there might be pituitary suppression of TSH[78].TSH plays a crucial role in bone remodelling, independent of its effects on circulating thyroid hormone[79]. High turnover osteoporosis has been seen in TSHR knockout mice. These data suggest that a decline in TSH amplitude might contribute to the pathogenesis of osteoporosis in the case of chronic SCI subjects[79].

Leptin: leptin receptors are located in the hypothalamus, human osteoblasts and mesenchymal stem cells that undergo osteogenic differentiation. Leptin plays an essential role in bone metabolism regulation. Investigations have shown the positive effect of this hormone on bone mineral density; apart from promoting osteoblastic differentiation, it also suppresses osteoblast apoptosis and osteoclastogenesis[80]. Previous studies on mouse models have demonstrated that leptin helps in fracture healing and earlier osseous union seen in rats who underwent limb fracture with associated SCI[81]. It is thought that bone mass is regulated by leptin through alternate pathways; when it is administered peripherally, it involves a direct stimulatory effect on bones[82], and when it is centrally administered, it inhibits bone formation involving hypothalamic relay indirectly [83]. As SCI subjects are less physically active, they are characterized by obesity and disruption of mechanisms that link fat mass with BMD; in simple terms, we can say that greater BMD is related to greater body fat mass[84]. So, in general, it is true to say that the obesity gene product leptin provides a protective effect on bone and increases bone mineralization. Whereas some results are controversial, a positive correlation has been found in some studies between Serum leptin levels and BMD[85]. Some studies reported a negative correlation [86]. Still, no association between Serum leptin and BMD has been reported in some studies[86]. One of the recent studies by Lei Wang et al. [87] also reported no correlation between BMD and leptin levels; However, elevation in the serum Leptin level was found in the SCI group, and the protective effect of leptin on male patients was insignificant, the same outcome was observed by Sabour et al. [88]. The peripheral impact of leptin on the skeleton countervail over its central action may be because it's a systematic hormone[89].In SCI subjects, it seems that due to less physical activity and lower activity of SNS, there may be an escalation in the production and secretion of leptin hormone[90] due to an increase in plasma leptin concentration in SCI subjects and the accompanying augmented circadian variation may alter normal turnover of bone tissue, leading to osteoporosis[91].

Soft tissue changes after SCI changes in Muscle: Below the lesion level, there is a rapid and dramatic loss of muscle mass after SCI[92]. Compared to control, average muscle cross-sectional areas (CSAs) were 18% to 46% lower only after six weeks post-SCI[94]. Prospective study till 24 weeks post-SCI in these subjects showed declines in average gastrocnemius and soleus muscle CSAs of 24% and 12%, respectively[94].similarly average decreases in quadriceps, hamstrings and adductor muscle CSAs of 16%, 14%, and 16% were found. In the first year after SCI, it was demonstrated by one of the prospective studies using DXA that there is a loss of lower limb lean mass by 15%[93]less percentage lean mass after SCI is because of

advancing age and duration of injury[94]. Muscle atrophy may be limited to sublesional areas; One of the studies in monozygotic twins demonstrated that twins suffering from SCI have a significantly lower trunk and leg lean mass, whereas no significant difference was found in lean arm mass when both the twins were compared[95].SCI give rise to insignificant and rapid bone loss, predominantly in areas below the neurological level of injury. The significant finding of SCI on bones is that during the first year of injury there is heavy bone loss occurs[96]. Continuous demineralization occurs three years after trauma in the tibia, with a dynamic bone loss over 12 to 16 months before stabilizing[97].

In comparison to cortical bones, cancellous bones are more affected by SCI. In one prospective study, six subjects with acute tetraplegia were followed for 12 months; it was found that cancellous and cortical bone mineral density (BMD) of the tibia were decreased by 15 and 7%[98]. In the case of paraplegia subjects, the most affected sites are trabecular metaphysical-epiphyseal areas of the distal femur and the proximal tibia[99]. Another cross-sectional study by Dauty et al. demonstrated that in SCI subjects, a heavy demineralization at the distal femur (-52%) and the proximal tibia (-70%), respectively[100].In the upper limbs, no demineralization occurs in people with paraplegia. Some studies have reported a minor increase in BMD, whereas, compared to long bones cortical bone demineralization, the lumbar spine trabecular bone demineralization remains relatively low[100]. Of normal or even higher than normal values, a phenomenon is known as "dissociated hip and spine demineralization[101]. Bone mass preservation in the vertebral column may be because of the continuous weight-bearing function in paraplegics. But it is not always true; higher BMD of the lumbar spine sometimes may be because of lumbar spine arthrosis, bone callus, vertebral fracture, aortic calcification, osteosynthesis material, etc. These degenerative changes may be one reason for false BMD[100].

Bone mineral density: In the case of SCI, bone loss begins immediately after injury and is affected by age, immobilization, bed rest, and a lack of gravity environment[102]. During the first year after the injury, a reduction in bone mineral content has been seen at 4% and 2% per month in regions rich in cancellous and cortical bones, respectively[103]. One of the studies on 41 subjects with SCI showed that 25 of them met WHO's criteria for osteoporosis (61%), eight subjects were osteopenic (19.5%), whereas normal values were recorded only in 8 subjects(19.5%)[104]. In the case of SCI subjects, studies with the help of peripheral quantitative computed tomography (p QCT) have shown that bone loss in the epiphyses part of the bone is almost double that of diaphysis, i.e. 50% &60% loss in the epiphysis region of femur and tibia respectively, whereas 35% and 25%, respectively in the diaphysis region of both femur and tibia[105]. This study also demonstrated that bone loss between both the compartments of trabecular and cortical bone is from different mechanisms, i.e. due to a decrease in trabecular, bone loss occurs in the epiphysis bone. Because of endocortical resorption, bone loss happens in the diaphysis. In contrast, cortical bone density is maintained in the diaphysis region of bone. One the other study using p QCT study, in complete paraplegics with a high and low neurological level of injury (thoracic D4-D7) and low (thoracic D8-D12), it

was observed a loss in the trabecular bone at the tibia was 57.5% vs 51%, in high vs low paraplegics, respectively, while the loss in cortical bone was 3.6% and 6.5%, respectively. This data indicates that the most affected bone is trabecular during the first year of paralysis than cortical bone[106].

Women are prone to osteoporosis; disabled women have a high risk of bone mass loss in comparison to men because of inevitable suppression in the estrogen hormone that occurs after menopause, So it is not surprising that women having low bone density with severe disability and are probably primarily due to lack of physical activity (reduced mobility, reduced loading on bone), and worsening of disability. Mostly initial bone loss in the lumbar spine in women with complete SCI is negligible. BMD in women with SCI is maintained or increased after post-injury over the year compared to non-injured age-matched women, in whom BMD decreases during ageing [107]. The bone loss depends on some interesting factors in SCI subjects: demineralization mainly occurs in the areas below the level of injury, which means it is area dependent[108]. Paralyzed regions are particularly affected by demineralization. It increases from proximal to distal areas; most affected areas are the distal end of the femur and proximal tibia, paraplegic weight-bearing skeleton regions rich in cancellous bones. In comparison, diaphysis of the femur and tibia regions rich in cortical bones are reserved[108,109].

As we know, a different mechanism is involved in bone loss between trabecular and cortical bone compartments; in the epiphysis region, bone loss is due to a decrease in trabecular, but in the diaphysis region, cortical bone is maintained, but through endocortical resorption and by a reduction in thickness of cortical walls, loss of bone occurs[108,109]. In tetraplegia subjects, it was demonstrated by one of the prospective studies that after 12 months of SCI, there is bone loss in trabecular and cortical regions by 19% and 3% to 4%, respectively[110]. In contrast, studies have demonstrated that lumbar spine BMD after SCI increased, decreased, or unchanged[111]. However, bone loss has occurred in individuals with SCI is confirmed by CT Scan, but bone loss is unclear in DXA scans; it may be because of astonishing factors like heterotopic ossification or neuropathic changes[112]. Despite bone losses, structural changes in bone morphology also occur after SCI. One of the MRI studies on long-standing complete SCI men and women demonstrated that they had reduced bone volume and trabecular number. In contrast, trabecular spacing has increased at the distal femur and proximal tibia compared to controls[113]. Bone area and bone geometry are also changed after SCI[114]. Another MRI study demonstrated reduced cortical thickness polar and cross-sectional moments of inertia and section modulus at mid femur because of endosteal erosion in the SCI group compared to the control[115]. One study has shown an interaction between mechanical loading and estrogen loss; postmenopausal women with SCI have 34% less trabecular spacing than pre-menopausal SCI women [116].

Factors influencing rate and magnitude of bone loss following SCI: After SCI, it has been demonstrated that inter-individual and site-specific differences in the rate of bone loss occurs. In some individuals, BMD reduction started within one-year post-injury (around 67% loss in the distal tibia trabecular BMD). Some experienced a

minor decrease within the same period in their BMD (about 1% in distal tibia trabecular BMD)[117]. Whereas some studies have shown intra-individual differences, it was found that in comparison to the distal tibia, bone loss is more significant at the proximal tibia and more marked in the epiphyses than in the diaphysis[118], with evidence that inter-site variance in bone loss may be related to bone geometry[118].

Vitamin D metabolites: Subjects with SCI have a higher prevalence of Vitamin D deficiency than the normal population. Vitamin D metabolites are changed in SCI subjects. Studies have demonstrated that due to bone resorption and hypercalciuria, suppression in the parathyroid–vitamin D axis was found during the first or second-week post-injury [Maimoun Let al 2002]. Subjects with chronic SCI are also vitamin D deficient[Vaziri ND,et al 1994]. But it seems that the value of 1,25(OH)2D was explicitly changed. But afterwards, it was seen that after traumatic spinal injury, values of plasma 25-hydroxy-vitamin D 25(OH)D tend to decrease, but in the case of chronic SCI, these values were found within their normal ranges [Roberts Det al 1998]. Whereas other studies proved that in the case of subjects with chronic SCI (32%), vitamin D defect was significantly higher 25(OH)D, in comparison to able-bodied subjects (16%), and levels of 25(OH)D were negatively correlated with PTH levels[Bauman et al. 2005]. In their study, Bauman et al. 2005 demonstrated that 100 subjects with chronic SCI have higher values of 1,25(OH)2D than controls, which might have an increased effect on 1-α-hydroxylase activity in renal tubular cells. Most probably in severe cases, like subjects with quadriplegia, due to pressure ulcers hospitalized for a longer duration [Zhou XJ,et al 1993].

OPG/RANK-L system: Osteoblast cells produce Rank-ligand that binds to its receptor, RANK, located on the surface of osteoblast and their precursors. This RANK-L system regulates the differentiation of precursors into multinucleated osteoclast, osteoclast activation and survival. By binding to RANK-L, Osteoprotegerin protects the skeleton from excessive bone resorption and helps prevent the RANK-L from interacting with RANK[Lacey DL,et al 1998]. For bone regulation OPG/RANK-L system plays an important role; these cytokines have received limited attention [Morse et al. 2008]. Studies have demonstrated that in comparison to healthy controls, SCI subjects have a lower level of serum RANK-L and higher serum OPG levels. To modulate the bone resorption process in favour of a reduction in osteoclast differentiation and activity, a higher OPG/ RANK-L ratio is essential. No significant variation was found for any cytokine with traumatic spinal injury (TSI) in early follow up of 16-71 weeks [Morse et al. 2008]. In one of the study by Morse et al. 2008in chronic subjects (TSI >2 years), according to age, an increase in OPG levels were found that is modulated by the level and severity of the injury. In contrast, in the study by Maimoun L et al. 2008, no relationship between OPG/RANK-L values and TSI was found. Whereas, at a single point in time, blood measurement of OPG/RANK-L concentrations may underestimate the changes in the local production of it within the microenvironment of bone cells[Buzi F,et al 2004].

Physical Exercise to Combat Osteoporosis: Many studies have proved that in SCI, physical activity is very beneficial [Ditor, D.Set al 2003], as physical activity helps in

increasing bone mass[Dudley-Javoroski, Set al 2012]. Bone vasculature is increased as blood flow is increased in bones by muscular activity[Heinonen, I.;et al 2013]. In response to exercise, femoral blood flows almost doubles [Heinonen, I.;et al 2013].In response to changes in metabolic activity by doing exercises, blood flow to bones is enhanced, and SCI-associated osteoporosis can be positively affected by physical activity via enhanced bone metabolism and regeneration [Tøndevold, E.et al 1983]. Wnt dysregulation through mechanical loading effects can be reversed by Weight-bearing exercises [Tan, C.Oet al 2013]. Usually, the skeleton responds to increasing mechanical strain by increasing cortical bone tissue localized to the site of the mechanical strain[Krieg, M.Aet al 2013]. For SCI subjects, weight-bearing exercise is challenging to implement, and it requires a daily time investment, so electrical stimulation (ES) and functional electrical stimulation (FES) are practical options for innervating muscles [Chandrasekaran,Set al 2020]. Studies have shown beneficial effects on bone after this treatment: reduced bone resorption, preservation of trabecular bone micro-architecture, and stimulation of new bone formation[Zerath, E et al 1995].

Other factors: Many changes are induced in body composition, such as health-related complications like diabetes mellitus [Bauman WA et al 1994] and lifestyle changes[Noreau L,et al 1995]after SCI, apart from bone demineralization[Maimoun L,et al 2004]. Thus to understand these factors which affect bone remodelling is significant. The study by Morse et al. [Morse LR et al 2008] on 82 Subjects having TSI of more than two years found no relation between osteocalcin and C-telopeptide cross-links of type 1 collagen (CTx) values and other factors like mass index, smoking history, history of heart disease, high blood pressure, and diabetes[Roberts D,et al 1999]. No effect on biochemical bone markers was found due to weight and nutrition[Roberts D,et al 1999].

Many studies have proved that in healthy subjects, age primarily affects more remodelling[Garnero P,et al 1996]. In contrast, the age factor in the case of SCI subjects is still a topic of debate as probably after injury more remarkable alteration in bone loss than age. As most studies were conducted in a subgroup of adult patients with a relatively narrow age range (20-45 years), bone turnover is almost stable at this age period. Whereas with increasing age, CTx value significantly increases[Morse LR et al 2008] whereas osteocalcin value suppressed with increasing age[Zehnder Y et al 2004], no variation in DPD or total-ALP was reported. More studies need to be conducted to learn more about the relationship between age/SCI and bone turnover, focusing on childhood and adolescence, as these two periods have not been investigated. Lower OC ($P < .05$) and significantly higher DPD ($P < .05$) concentrations were found in subjects having fracture history in comparison with the group having no fracture history[Zehnder Y et al 2004].Whereas factors like neurological lesion (complete or incomplete) and level of injury still need to be investigated to know about their impact on bone remodelling.

Closing Remarks: After SCI, Osteoporosis is a significant complication caused due to an imbalance in bone formation and resorption. In the case of SCI, bone resorption is because of the increased number of osteoclasts, whereas no such effect has been

seen in the function of osteoblast cells. Unloading is also one of the leading causes of progression of Osteoporosis after SCI. After SCI, hormonal changes occur that also contribute to the pathogenesis of osteoporosis. It is hypothesized that neural lesion itself plays a role in causing osteoporosis after SCI by taking a direct part in the denervation of bone or indirectly by disrupting vasoregulation. This review summarises all possible effects that contribute to SCI-mediated osteoporosis; understanding osteoporosis's pathogenesis after SCI helps develop new treatment strategies.

Conflict of Interest

The authors have no potential conflict of interest. All the authors have obtained the disclosure of potential conflict of interest in the prescribed format.

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