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RESEARCH ARTICLE

THE CLINICAL RELEVANCE OF OSTEOPOROSIS WITH SPINAL CORD INJURY: A COMPREHENSIVE ASSESSMENT OF THE LITERATURE

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Abstract

Spinal cord injury is the most disabling condition that affects one's life. 12,500 new cases of SCI are recorded each year in North America, according to the National Spinal Cord Injury Statistical Centre. Depending upon the level of injury, quadriplegia or paraplegia is caused by SCI. Due to a lesion in the dorsal spine, Paraplegia is caused, while a lesion at the cervical level results in quadriplegia. Osteoporosis can develop in severe spinal cord injury. Due to immobilization, SCI patients develop long bone loading. Bone loss in SCI Subjects begins shortly after injury, as proved by some of the studies, whereas bone resorption was at its peak approximately three months after injury. Other factors that may involve bone loss are hormones like parathyroid,vitamin D3, sex steroids, thyroid hormone, and leptin. Receptor activator of nuclear factor-κB ligand may be upregulated in SCI people as a result of serious bone resorption caused by neurological impairment and disability, according to studies, Molecular mechanisms, such as RANKL dysregulation and Wntsignaling disruption may also influence the pathophysiology of osteoporosis associated with SCI. Our study endeavors to address every facet of the contemporary cellular and physiological processes that lead to osteoporosis associated with SCI.

Introduction:-

A devastating and incapacitating disorder, spinal cord injury causes abrupt loss of motor, sensory and autonomic function that is independent of the degree of damage experienced [1–2]. SCI has a very tremendous impact on the affected patients and their caretakers. Annual cases of SCI are 11.5–53.4 cases per million. In a developed nation, over 1 million people are affected alone in North America with direct lifetime costs of around $1.1-4.6 million USD each [3]. Due to a lesion in the dorsal spine, paraplegia is caused, while a lesion at the cervical level results in quadriplegia [2]. Osteoporosis can occur in individuals with severe spinal cord damage (SCI). Because SCI patients are mostly immobilised, they experience prolonged bone loading. In clinical terms, disuse is the main cause of

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osteoporosis, which is typified by a variety of conditions such as low bone density, poor bone quality, and an elevated risk of fragility fractures [2, 4]. Bone loss in SCI subjects begins shortly after injury, as proved by some of the studies, whereas bone resorption was at its peak approximately three months after injury. Other factors that may involve bone loss are hormones like parathyroid (PTH), vitamin D3, sex steroids, thyroid hormone, and leptin [2]. According to research, the main reasons for bone resorption in SCI patients, such as neuronal damage and disability, may be linked to an overexpression of the receptor activator of nuclear factor-κB ligand (RANKL) [2]. RANKL dysregulation and Wntsignaling disruption are two molecular mechanisms that may also play a role in the pathophysiology of osteoporosis associated with SCI [2]. Conversely, by reducing the overexpression of RANKL, the estrogenic action may prevent bone resorption [2]. Due to their frequent rapid and severe loss of bone density, SCI participants are at a significant risk of developing issues connected to paralysis-induced inactivity [2]. Bone loss mostly happens in two stages. Within 18 to 24 months after the injury, there is a fast resorption of bone in the first phase, whereas in the second phase, bone loss occurs gradually and is followed by inhibited bone production [2]. Because of this, around 40% of participants with chronic SCI develop fractures, which are twice as likely to occur as in those without SCI [2].

Bone Homeostasis &Wnt Pathway

Wnt pathways play a significant part in bone homeostasis to mechanical loads. Research has demonstrated that the coreceptor complex (Frizzled receptor, LRP-5, and LRP-6) is present in osteoblast cells. Wnt Protein attaches itself to these receptors in osteoblast cells, facilitating the translocation of cytoplasmic-catenin into the osteoblast's nucleus.Thus, there is activation of transcription of genes due to translocation that promotes differentiation and activity of osteoblast cells and results in bone formation [5].

Wnt Ligands also play a vital role in bone homeostasis. Ligand Wnt3a may play a role in stimulating osteogenic differentiation by activating TAZ by PP1A-mediated dephosphorylation. While trabecular bone density may increase if there is overexpression of Wnt10b Ligand by enhancing osteoblastogenesis, deficiency of Wnt10b may decrease bone density and will promote adipogenic differentiation of MSCs. Furthermore, Wnt6, Wnt10a, and Wnt10b stimulate MSC differentiation to osteoblasts while inhibiting MSC adipogenic differentiation via the canonical Wnt pathway [5].

Studies have proved that if there are heterozygous WNT1 mutations then it leads to early-onset forms of osteoporosis, as these mutations disturb bone remodeling and subsequent imbalance in bone homeostasis [5].In individuals with spinal cord injuries (SCI), there is a significant increase in bone loss in the epiphysis region, compared to the diaphysis region, with a 50% reduction in the epiphysis area of the femur and a 60% reduction in the epiphysis area of the tibia. In contrast, bone loss in the diaphysis area of both the femur and tibia stands at 35% and 25%, respectively. This difference is noted in two types of bone tissue: trabecular and cortical. Specifically, the loss of bone in the epiphysis area is attributed to a decrease in trabeculae and endocortical resorption is the reason behind bone loss in the diaphysis area [2].In comparison to man, women are more prone to osteoporosis,in comparison to disabled man, disabled women are at a high risk of bone loss because of inevitable suppression in the estrogen hormone that occurs after menopause so this is the major reason that having low bone density with a severe disability is common in diabled women in addition to primary cause ie physical activity /reduced mobility [2].The extent of bone loss in individuals with spinal cord injuries (SCI) is influenced by several intriguing factors. Primarily, it occurs in the regions below the point of injury, indicating that the severity of bone loss varies across different areas. The areasmost commonly affected are those that bear weight, such as the distal end of the femur and the proximal tibia, which are part of the weight-bearing skeleton and contain a high concentration of cancellous bone. This is particularly true for individuals with paraplegia. In women with complete SCI, the loss of bone density in the lower back is minimal. Furthermore, women with SCI tend to either maintain or even increase their bone density over a year following the injury, compared to women of the same age who have not sustained an SCI. In contrast, women without SCI experience a decline in bone density with age[7].

RANK and RANKL

A 28-amino acid signaling peptide and 616 amino acids make up the human RANK receptor. Additionally, it has a RANK domain that has a 21-amino acid transmembrane domain, a 383-amino acid C-terminal cytoplasmic region, and an N-terminal extracellular domain of 184 amino acids. The surface of osteoclasts and their progenitors has this receptor, which is present in a variety of cell types, including fibroblast cells, T cells, B cells, dendritic cells, and preosteoblastic cells[9].One of the studies on RANK knockdown mice by Jiang, Y, and Perlot, T demonstrated that in these mice there isinhibited osteoclast expression along with osteopetrosis development [9].The TNF superfamily

includes RANKL, which has great species conservation. Human chromosome 13q14 contains the RANKL gene, which is around 36 kb in size. Additionally, a variety of tissues, including bone, mammary glands, and lymphoid tissue, express it. In bones, osteoblasts, osteoblast precursors, and stromal cells all express RANKL. Perlot, T et al. demonstrated in their study that osteoblast cells express high levels of RANKL to activate osteoclastogenesis[9].

Bone Remodelling is very essential for maintaining bone homeostasis, it is a natural process of continuously replacing damaged and old bones with new bones to maintain bone strength, and elasticity [2], For bone remodeling, Osteoclast and osteoblast cells are responsible. Osteoclast cells originate from hematopoietic cells responsible for bone resorption whereas osteoblast cells originate from mesenchymal cells, responsible for bone formation [2], Primary cause of SCI-induced bone loss is Unbalanced bone remodeling, thus the excess supply of Osteoclast results in bone resorption whereas undersupply of osteoblast is needed for cavity repair, these may be the crucial factor for SCI induced osteoporosis, It is proved clinically that Bone Resorption increases in SCI Subjects thus there is an increased level of hydroxyproline, pyridoxine, deoxypyridinoline, and type I collagen C-telopeptide in Urine sample of SCI Subjects [10]. Marked reduction in whole body Glucose has been found in SCI Subjects, this could be due to a proportional reduction in muscle mass, and denervation of skeletal muscle that causes insulin resistance, insulin resistance is another major cause that leads to osteoporosis following SCI, In cases of Chronic SCI Subjects it has been reported that growth factors and their second messengers, such as IGF-1, was found to be suppressed [11], average plasma IGF-1 level, was found to be significantly lower in SCI Patients in comparison to control [12], Similarly in another study by Shetty et al showed that in comparison to ambulatory controls, tetraplegia Patients had suppressed average plasma IGF-1 level. Suppressed levels of GH and IGF-I may also lead to Insulin resistance, different studies have suggested that due to suppressed levels of IGFs, bone loss after SCI may be caused at least in part,However,a Study by Maimoun et al [10], did not demonstrate any correlation of growth factors in accelerated bone resorption following SCI.

According to Bucay, N.et al [13], Osteoprotegerinis one of the members of the tumor necrosis factor (TNF) superfamily, which consists of 401 amino acids, after its cleavage it is only composed of a mature form of 380 amino acids. The structure of OPG lacks cytoplasmic and transmembrane domains.OPG is mainly expressed in lung, muscle, and bone tissues. In its soluble form OPG Is mainly known to act as a competitor for RANKL, manystudies demonstrated its osteoprotective role, whereas its overexpression demonstrates an osteopetrosis phenotype while its deficiency or underexpression leads to osteoporosis development.

Review

Estrogen is a potentially useful substance that reduces pro-inflammatory responses and speeds up healing in both males and females with SCI. Some cytokines, including interleukin 2 (IL-2), interleukin 3 (IL-3), and tumor necrosis factor (TNF)-alpha, are increased while tumor necrosis factor beta is downregulated when the body's estrogen levels are suppressed. The elevated levels of these cytokines induce thedownregulation of OPG and upregulate the receptors that activate the nuclear factor-B ligand (RANKL), elevated levels of RANKL contribute to osteoclast differentiation and thus contribute to increasing bone resorption [14].

On the other hand, when the body has more estrogen, certain cytokines, such as IL-2/IL-3/TNF alpha, are downregulated, while TNF beta is upregulated. This leads to a cascade of increased OPG and decreased RANKL production. Particularly in diseases like SCI that are more likely to cause osteoporosis, osteoblast differentiation happens more quickly, maintaining bone integrity [14].

In SCI Patients, aging is another factor that contributes to bone Loss [15], In one of the cross Sectional studies by Garland et al [7], 31 complete SCI women Aged 2 to 44 years post-injury, divided the patients into three groups according to their age, as the youngest, middle, and oldest. The BMD reduction in their Knee between the groups was 38, 41, and 47% respectively in comparison to control age groups, following the mean Reduction of BMD in the hips was 18, 25, and 25% in comparison to BMD of Control Subjects of respective age group. Furthermore, the mean reduction of knee BMD in the oldest injured group was 54% in comparison to the youngest control group. One of the Prospective 6 months' follow-up studies on 30 acute SCI patients has demonstrated a dramatic elevation of bone resorption markers like urinary deoxypyridinoline and urinary N-telopeptide of type I collagen within the first week of the injury and peaking around 10 to 16 weeks. The peak value of the bone resorption marker was ten times higher than the upper limit, and upto 6 months of follow up this resorption marker did not return to normal values [15].

One of the cross-sectional studies by Pietschmann et al [16], reported that at one-month follow-up of SCI patients after injury, urinary hydroxyproline/creatinine ratios were significantly higher in comparison to controls.Similarly, another cross-sectional study by Maimoun, L [10], reported that levels of urinary and serum bone resorption markers such as type I collagen C-telopeptide (CTXu and CTXs) were substantially increased by a factor of 5 and 2.5, in SCI Patients approximately 3 months after injury.

A very different variation rate is shown by bone formation marker in comparison to bone resorptionmarker, as one of the Prospective Follow up Study by Roberts D, et al [17], demonstrated that in Acute SCI Subjects there is a minor rise in serum osteocalcin Levels after an injury during 6 months follow up. In Osteoblast cells, 1,25(OH)2 vitamin D directly stimulates secretion of Osteocalcin so Elevation in Serum Osteocalcin can be directly explained by the low level of 25(OH)2 vitamin D concentration, As studies have demonstrated that osteocalcin protein is directly stimulated by 1,25(OH)2 vitamin D in osteoblasts and osteosarcoma cells [18], Whereas Maimoun et al [10] in his cross Sectional study demonstrated that in SCI Subjects, serum osteocalcin levels were significantly higher 3 months after injury in comparison to control, Similar findings were observed by Zehnder Y [19] in his longitudinal study that in 6 Acute SCI Subjects, serum osteocalcin levels were normal and then Serum Osteocalcin levels were continuously increased until the end of the study 6 months later.

Similarly,Maimoun et al [10], in their cross-sectional study, demonstrated that in SCI Subjects approximately Three months after injury levels of serum bone alkaline phosphatase (B-ALP), remained unaltered, thus from the above-discussed studies we can conclude that Osteocalcin and B-ALP could reflect different aspects of bone formation. Similarly, Zehnder Y [19], in his cross-sectional Study reported normal bone formation markers in chronic SCI patients. Thus we can also conclude that by reporting the levels of bone turnover markers an imbalance between elevated levels of bone resorption and normal or minor elevated bone formation markers after SCI also plays a major role in the pathogenesis of bone loss and fracture in SCI patients.

In Post Menopausal women having osteoporosis,Fractures frequently occur at the wrist, femoral neck, hip, and lumbar spine, whereas person having chronic Spinal cord Injury, the most vulnerable anatomic regions to fracture are the epiphyses of the Distal femur and Proximal Tibia.

Histomorphometric investigations of bone samples taken right after SCI have shown that osteoblast and osteoclast activity are up, followed by an increase in osteoclastic activity and a decrease in osteoblastic activity. The first few months following SCI are characterized by a suppression of osteoblastic activity, which eventually recovers to pre-injury levels. The chronic phase of SCI is characterized by ongoing osteoclastic activity and bone resorption. Hence, the clinical observations of hypercalcemia and hypercalciuria as well as markedly increased indicators of bone resorption confirm this uncoupling link between osteoblast and osteoclast.

Vitamin D deficiency is quite widespread among SCI subjects; according to some research, up to 93% of them suffer from it. When the blood level is 50 nmol/L, vitamin D deficiency is defined, but when it is 75 nmol/L, vitamin D insufficiency is defined. Studies have demonstrated that lower level of testosterone level, Poor Immunity, and Poor respiratory system function the indications of lower serum vitamin D (25-(OH)D), Regarding the optimal amount of Vitamin D that is needed for bone and muscle health in case of chronic SCI, only small amount of data is available, more research is needed to be done to assess the vitamin D serum levels of adults with chronic SCI, It is advised to consume 1000–2000 IU or 25–50 mcg of vitamin D3 (cholecalciferol) daily to keep the body's vitamin D levels stable [20].

Mechanick JL, et al [21], in their retrospective analysis of 88 Subjects,demonstrated that Significant Suppression in PTH ($p < .000009$) and 1,25-D ($p < .02$) levels along with the elevated level of Phosphorus ($p < 0.03$) and prolactin ($p < .03$) were observed in SCI Subjects in comparison to Subjects with traumatic brain injury, SCI Subjects were mostly hypoalbuminemia ($p < .003$) in comparison to TBI Subjects.SCI subjects with complete paraplegia(ASIA A) have more suppressed PTH ($p < .03$) and higher urinary urea nitrogen ($p < .05$) levels in comparison to subjects with Incomplete injuries (ASIA B-D). Similarly,albumin levels were also lower in Complete SCI SCI Subjects but not incomplete, SCI in comparison to TBI Subjects($p < .05$). These differences were not found between patients with tetraplegic and paraplegic SCI. ASIA motor scores did not correlate with any of the measured parameters but when used as a covariate did abolish differences in PTH and 1,25-D among the study groups by ANOVA.

The FDA-approved medication Abaloparatide, a modified parathyroid hormone-related peptide, is used to treat severe osteoporosis and may have anabolic effects; however, it is unclear how it may affect bone loss brought on by SCI. Micro-computed tomography (micro-CT) analysis showed that abaloparatide did not stop SCI-induced changes in trabecular or cortical bone, but mice administered a subcutaneous injection of either vehicle or 20 μg/kg/day abaloparatide for 35 days showed higher osteoblast (241%) and osteoclast (247%) numbers as well as a mineral apposition rate (131%) than mice given the vehicle. Another study found that 80 μg/kg/day abaloparatide therapy reduced the loss of cortical bone thickness caused by SCI (93%) compared to SCI-vehicle mice (79%) but did not stop the loss of trabecular bone or the increase in cortical porosity. The aforementioned data implies that abaloparatide protects cortical bone from the harmful effects of SCI by boosting bone formation. It also aids in the increase of procollagen type I N-terminal propeptide, a marker of bone formation [22].

As a result of the abnormally high ionized calcium Levels in the acute phase of SCI, Hypercalciuria is mostly prevalent in them but during the chronic phase of SCI, they get back to normal levels. These changes in calcium levels in the acute phase are followed by changes in calcium regulatory hormone levels. As anticipated for this negative feedback loop, the serum intact parathyroid hormone (iPTH) level was observed to be lowered during the acute and subacute phases of SCI (1-4 months). Only one research has documented a reduced level of PTH in the chronic phase of SCI, which was linked to normal ionized calcium levels. It rises in the chronic phase as opposed to the acute phase, but it remains within or below the lower reference limits. The study suggests that "low-grade increased calcium release," which in turn shows chronically heightened bone resorption even after years of damage, is the cause of this reduction in PTH Level. Bone Metabolism is also maintained by Sex hormones,estrogen hormone plays a major role in preventing osteocyte apoptosis, and both sex hormones i.eestrogen and androgen inhibit bone resorption and promote bone formation via many mechanisms, during SCI, sex hormone production, and secretion also inhibited, Studies have shown that during the acute phase of injury, levels of testosterone hormone declines significantly in acute SCI Patients in comparison to healthy controls with no further change after week 16 post-injury [23].

The main characteristics of osteoporosis that result in decreased bone strength and an increased risk of fracture are decreased bone mineral density and degeneration in bone microstructure. Bone geometry factors have been proven to be linked to fracture risk. Research has indicated that individuals with SCI who have experienced lower limb fractures have decreased bone mineral density (BMD) compared to those who have never experienced a fracture. brittleness A very prevalent and unresolved result of SCI is fractures, which are induced by slight trauma in SCI subjects during transfers between surfaces, turning in bed, or even during rehabilitation training sessions.Fragility fracture is very common among SCI Subjects in comparison to the general population and occurs mostly in the lower extremity, very few or even no fractures were reported in the upper extremities, The Majority of fractures occur in the tibia and femur especially at epiphyseal sites in the ankle and knee joints [23].The degree of spinal cord injury, the etiology of SCI, and white race are the main factors linked to an increased risk of fracture. Compared to incomplete SCI, complete extension of SCI, longer duration of SCI, usage of opiates and anticonvulsants, higher Charlson Comorbidity Indices, and heavy alcohol intake, incomplete SCI is more likely to result in fractures [24].

Vitamin D deficiency is the most common cause of osteoporosis in SCI, according to laboratory screening for the disease. This is because vitamin D is essential for calcium absorption, and a lack of it causes secondary hyperparathyroidism, which increases osteoclastic bone resorption to release calcium from the skeleton and maintain appropriate serum calcium levels. Additional variables that are linked to bone loss or an elevated risk of fracture following SCI include diabetes mellitus, hyperthyroidism, anemia, liver illness, and renal disease.The following laboratory tests are therefore performed on all adult SCI subjects: serum 25-hydroxyvitamin D (25-(OH)D), complete blood cell count, ionized calcium or albumin-corrected serum calcium, phosphate, intact parathyroid hormone, creatinine (and estimated glomerular filtration rate), bone-specific alkaline phosphatase and transaminases, hemoglobin A1C, thyroid-stimulating hormone, and 24-hour urine collection for calcium and creatinine excretion testing. Prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol levels, and morning fasting bioavailable testosterone for men are among the tests used to evaluate the hormonal state of all premenopausal women and men [25]. Serum protein electrophoresis is used to evaluate multiple myeloma or monoclonal gammopathy in patients with vertebral compression fractures of unknown etiology. If Cushing's disease is suspected, a 24-hour urine cortisol/overnight dexamethasone suppression test may be considered, and if coeliac disease is suspected, anti-tissue transglutaminase immunoglobulin A antibody levels may be measured. Following SCI-specific diagnostic methods, a bone mineral density test is performed for sublesional osteoporosis.

In both acute and chronic SCI, suppressed Levels of Vitamin D and abnormal Parathyroid hormone (PTH) are very common, Suppress PTH levels in acute SCI Subjects are observed due to hypercalcemia that accompanies increased bone resorption,Low PTH levels may contribute to SCI-induced bone loss. Through suppressing the expression of sclerostin, PTH may mediate its Anabolic effect on bones, Some animal studies have demonstrated that the Production of sclerostin is suppressed by PTH and thus It has been clinically demonstrated that Intermittent PTH treatment in humans stimulates bone Formation, Whereas Different Intervention such as functional electrical stimulation and stationary biking, also have potential to increase bone density by increasing PTH levels [26]. For SCI-induced bone loss, sclerostin plays a major role. Sclerostin is mainly produced by osteocyte cells and is a potent inhibitor of bone formation and growth Sclerostin is encoded by the sost gene. Due to Mechanical unloading,Sclerostin is upregulated thus due to its upregulation Wnt/β-catenin signaling in osteoblasts is reduced,Recent pieces of evidence also demonstrated the catabolic role of sclerostin,As sclerostin also plays a role in up-regulation of RANKL and down-regulation of OPG expression by osteocytes thus contributes in osteoclast differentiation and activity leading to bone resorption [27]. The study by LiX et al [28], investigated that Sclerostin receptor, SOST knockout mice have high bone mass bone volume, bone formation, and bone strength. Thus he concluded that sclerostin is a negative regulator of a powerful, evolutionarily conserved bone formation pathway that acts on both trabecular and cortical bone.In Human beings, in diseases mechanical unloading occurs that leads to paralysis, or inability to walk.Therefore, there may be a substantial correlation between sclerostin and bone loss in conditions like spinal cord injury. Strokes can also induce paralysis, and sclerostin levels are quite high in those with mobility difficulties [26]. Sclerostin Antibody treatment helps in bone formation and suppresses bone resorption on both trabecular and endocortical bone surfaces and accelerates bone formation on periosteal surfaces [29].

Sclerostin Antibody treatment helps in bone formation suppresses bone resorption on both trabecular and endocortical bone surfaces and accelerates bone formation on periosteal surfaces.In the first human investigation, postmenopausal women and healthy males were given a sclerostin monoclonal antibody (AMG 785). AMG 785 or placebo (3:1) was administered subcutaneously (0.1, 0.3, 1, 3, 5, or 10 mg/kg) or intravenously (1 or 5 mg/kg) to 72 healthy participants in the Phase 1 RCT, double-blind, placebo-controlled, ascending, single-dose trial in which all individuals were monitored for eighty-five days. Serum C-telopeptide (sCTx), a bone resorptive marker, decreased in response to dosage, but procollagen type 1 N-propeptide (P1NP), bone-specific alkaline phosphatase (BAP), and osteocalcin increased. An increase in BMD was observed in the AMG 85 treated group in comparison with placebo on day 85 [30]. Training regimens that include electrical stimulation and functional electrical stimulation (FES) are appealing exercise models for SCI that promote the growth of new bone. According to a pilot study on eight men with acute thoracic motor complete SCI, a single electrical stimulation session reduces the bone resorptive marker, c-telopeptide, within 48 hours of treatment. ES of the quadriceps muscle in an upright stance also reduces bone loss and preserves the trabecular bone micro-architecture at the distal femur in seven SCI subjects as opposed to five SCI subjects who stood without stimulation and fifteen SCI subjects who did not stand or receive any stimulation. A large volume of FES cycling may lower the risk of fracture in the fracture-prone location by partially reversing bone loss [26].

Pharmacological interventions (Bisphosphonates)

Nowadays many Pharmacological treatments are available for osteoporosis treatments like Denosumab, strontium ranelate, selective estrogen receptor modulator drugs, and bisphosphonates. Risedronate (Actonel, Procter & Gamble, Cincinnati) is a pyridinyl bisphosphonate, that is very effective in Postmenopausal women with osteoporosis as it decreases the risk of vertebral and non-vertebral Fractures.This drug is also effective in increasing bone Mineral Density. Studies have demonstrated that Post Menopausal Osteoporotic Women who were daily receiving oral alendronate, an aminobisphosphonate, have progressive bone mass in the Hip, Spine, and total body, and these women have reduced risk of vertebral fractures, Progression of Vertebral deformities, and height loss [23,31].

In one of the non-randomized control clinical trials in which 24 spinal cord injury patients within 6 weeks of injury were enrolled in the study, in this study 14 subjects were on pamidronate drug and 10 did not, they investigated that Patients who were receiving intravenous pamidronate had improved BMD in comparison to controls, and Ambulatory Patients had also significantly Higher BMD in comparison to non-ambulatory less N-telopeptide Patients. Patients who were on Intravenous pamidronate treatment had reduced excretion levels of the urinary bone-breakdown product N-telopeptide [32].

Summary of Study that Uses Pharmacological treatment to change the loss of BMD Following SCI:

Study	Treatment	Injury/Duration and Level	Dose, Duration & Frequency	Imaging Device	Change In BMD	Supplement	Level of Evidence
Minaire et al., 1981[33]	disodium dichloroethylene diphosphonate	Acute SCI, T1-T12, complete paraplegia)	400 or 1600 mg/day for 3.5 months	Photon absorptiometry	Little effect in BMC at distal tibia (for 400 mg)	-	Fair
Pearson et al., 1997[34]	Cyclical Etidronate	Within 6 weeks, C5-T12	Orally 800mg/day for 2 weeks, this was repeated after 13 weeks	DXA	in ambulatory-treated patients, only BMD was maintained	-	Poor
Nance et al., 1999[32]	Intravenous Pamidronate	6weeks, C4-T12	30-mg infusion/month for 6 months	DXA	Greater BMD improvementat hip, femoral, and tibial diaphyses, In ambulatory Patients less bone loss at femoral and tibial epiphyses	Calcium: 1000 mg daily	Poor
Sniger and Garshick, 2002[35]	Alendronate	27 years, C4 (incomplete), (single case)	Daily: 1. Alendronate: 10mg, 2. Vitamin D: 400mg, 3. Calcium carbonate 500mg, daily for 2 years	DXA	At spine and lower legsIncreased BMD was seen	Vitamin D: 400 mg/d Calcium carbonate: 500 mg/d	Single case study
Zehnder et al., 2004 [36]	Alendronate	0.1-29.5 years, T1-L3, (all with complete SCI)	10mg + 500 mg calcium daily for 24 months	DXA	In comparison to Control group, BMD remained stable at distal tibia, tibial diaphysis and total hip .	Elemental calcium: 500g/d	Fair
Bauman et al., 2005 [37]	Intravenous Pamidronate	22 to 65 days, ASIA A, Acute SCI	60 mg given at 1, 2, 3, 6, 9, 12 months	DXA	No changes in long term (12, 18,24 months) although reported early (1,3,6 months) reduction in bone loss in total leg BMD	Calcium: at least 700 mg/d in diet	Fair
de Brito et al., 2005 [38]	Alendronate	13.1-255.7 months, ASIA A, B, C	10 mg (+1000 mg Calcium), daily for 6 months	DXA	Incresed BMD Generally	Calcium: 1000 mg/d	Fair
Mechanick et	Intravenous Pamidronate	Acute SCI, AIS A, B,	90 mg over 4 hours	-	Suppressed level of bone resorption	-Calcium: 1,000 mg	-

al., 2006[39]		C	(single dose)		biomarkers, BMD not tested	daily, - Calcitriol: 0.25 µg daily	
Gilchrist et al., 2007 [40]	Alendronate	Within 10 days, C4-L2	70 mg once weekly, for 12 months	DXA	Total and hip BMD was 5.3% and 17% greater in intervention group respectively. Effects sustained for more 6 months after treatment discontinued	-	Fair
Shapiro et al., 2007[41]	Intravenous Zoledronate	10-12 weeks, C2 to T12	4 or 5 mg (administered once)	DXA	BMD and CSA increased at proximal femur only at 6 months, and for 12 months at the femoral shaft	Calcium: 800 mg, Vitamin D: 800 IU (both from diet)	Fair
Bubbear et al., 2011[42]	Intravenous Zoledronate	Within 3 months, C4-L3	4 mg (administered once)	DXA	Higher BMD at total hip (12.4%) trochanter (13.4%), and lumbar spine (2.7%) up to 12 months	-	Fair
Bauman et al., 2015 [43]	Intravenous Zoledronate	Within 3 months ASI A, B (all with compete SCI)	5 mg (administered once)	DXA	Reduction of BMD loss at the hip but not at the knee	Calcium carbonate: 1250 mg/d Vitamin D: only for participants with levels <20 ng/ml	Poor
Haider et al., 2019 [44]	Teriparatide (in previous study) followed by oral alendronate	15±9 years, ASI A, B, C (C1-L5)	Teriparatide: 12-24 months Alendronate: 70 mg once weekly for 12 months	DXA	Significant increase in aBMD at the spine 2.5% and in BMC at femoral epiphysis, metaphysis, and diaphysis, 15%, 7.7%, and 3.0%, respectively. - no clear results at the tibia	Vitamin D (cholecalciferol 1000 IU) daily - calcium carbonate: 1000 mg daily	Fair
Gifre et al., 2016 [45]	Denosumab	15±4 months, C4-T8 (ASIA 12A, 1B, 1C)	60 mg every 6 months for up to 12 months	DXA	Lumbar and femoral BMD wereincreased by 8 %&3% respectively.	Calcium and Vitamin D	Fair

Conclusions:-

Osteoporosis is a serious consequence of spinal cord injury because of an imbalance between bone growth and resorption. After SCI, bone resorption increases because of the increased number of osteoclast cells, whereas osteoblast cells have not shown this impact. Additional aspects that contribute to the pathophysiology of osteoporosis following SCI include hormone imbalance and unloading. The Wnt Pathway is important for bone

health, and disruption in the Wntsignaling pathway following SCI may be a contributing factor to the pathophysiology of SCI.

References:-

1. Ara Z, Walliullah S, Al-Otaibi ML, Srivastava RN: Perspective Chapter: Pathophysiology of Spinal Cord Injury and Effect of Neutraceuticals in Providing Potential Health Benefits. InSpinal Cord Injury-Current Trends in Acute Management, Function Preservation and Rehabilitation Protocols. 2023, 8:10.5772/intechopen.106275
2. Ara Z, Rastogi D, Al-Otaibi ML, Waliullah S: Impact on Musculoskeletal after Spinal Cord Injury. Int J Mol Biol Biochem. 2022, 1:1-22.http://www.irphouse.com/ijmbb22/ijmbbv10n1_01.pdf.
3. Ara Z, Singh A, Raj S, Walliullah S, Srivastava RN: Spinal Cord Injury Prevalence and Treatment Modalities. InSpinal Cord Injury-Current Trends in Acute Management, Function Preservation and Rehabilitation Protocols. 2023, 8:10.5772/intechopen.105214
4. Ara Z, Pandey S, Pant S, Tripathi RM, Rastogi D, Waliullah S: Osteoporosis, Its Pathophysiology and Effect of Nutraceuticals. www. ijphrd. com. 2023, 14:385. 10.37506/ijphrd.v14i3.19435
5. Huybrechts Y, Mortier G, Boudin E, Van Hul W: WNT signaling and bone: lessons from skeletal dysplasias and disorders. Frontiers in Endocrinology. 2020, 9:165. 10.3389/fendo.2020.00165
6. Dionyssiotis, Y, Trovas, G., Galanos, A: Bone loss and mechanical properties of tibia in spinal cord injured men. J Musculoskelet Neuronal Interact. 7, 1:62-68.
7. Garland DE, Adkins RH, Stewart CA,: Regional osteoporosis in women who have a complete spinal cord injury. J Bone Joint Surg [Am. 83:1195-1200.
8. Anderson, D.M.; Maraskovsky, E.; Billingsley, W.L: A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature. 1997, 390:175-179.
9. Hsu,H.;Lacey,D.L.; Dunstan, C.R.; Solovyev, : Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc. Natl. Acad. Sci. USA. 1999, 96:3540-3545. 10.1073/pnas.96.7.3540
10. Maimoun, L., Couret, I., Micallef, J.P., : Use of bone biochemical markers with dual-energy x-ray absorptiometry for early determination of bone loss in persons with spinal cord injury. Metabolism. 51:958-963. 10.1053/meta.2002.34013
11. Aksnes, A.K., Hjeltnes, N., Wahlstrom, : Intact glucose transport in morphologically altered denervated skeletal muscle from quadriplegic patients. 271:593-600. 10.1152/ajpendo.1996.271.3.E593
12. Bauman, W.A., Spungen, A.M., : Blunted growth hormone response to intravenous arginine in subjects with a spinal cord injury. Hormone and Metabolic Research. 26:152-156. 10.1055/s-2007-1000798
13. Bucay, N.; Sarosi, I.; Dunstan,: osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev. 1998, 12:1260-1268.
14. Shams, R.; Drasites, K.P.; Zaman, V.; Matzelle, D.; Shields, D.C.; Garner, D.P.; Sole: C.J.; Haque, A.; Banik, N.L. The Pathophysiology of Osteoporosis after Spinal Cord Injury. Int. J. Mol. Sci. 2021, 22:3057-10. 10.3390/ijms22063057
15. Jiang SD, Dai LY, Jiang LS: Osteoporosis after spinal cord injury. Osteoporosis International. 2006, 17:180-92.
16. Pietschmann P, Pils P, Woloszczuk W, Maerk R, Lessan D, Stipicic J (1992: Increased serum osteocalcin levels in patients with paraplegia. 30:204-209.
17. Roberts D, Lee W, Cuneo RC, : Longitudinal study of bone turnover after acute spinal cord injury. J Clin Endocrinol Metab. 83:415-422. 10.1210/jcem.83.2.4581
18. Price PA, Baukol SA (1980: 1,25-dihydroxyvitamin D3 in creases synthesis of the vitamin K-dependent bone protein by osteosarcoma cells. J Biol Chem. 255:11660-11663. 10.1016/S0021-9258(19)70182-3
19. Zehnder Y, Luthi M, Michel D, Knecht H, : Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: a cross-sectional observational study in 100 paraplegic men. Osteoporos Int. 15:180-189.
20. Mahitthiharn K, Kovindha A, : Prevalence and influencing factors of spinal cord injury-related osteoporosis and fragility fractures in Thai people with chronic spinal cord injury: A cross-sectional, observational study. The. Journal of Spinal Cord Medicine. 2023, 4:458-65. 1080/10790268.2022.2054763
21. Mechanick JL, Pomerantz F, Flanagan S, Stein A, Gordon WA, Ragnarsson KT: Parathyroid hormone suppression in spinal cord injury patients is associated with the degree of neurologic impairment and not the level of injury. Archives of physical medicine and rehabilitation. 1997, 1:692-6. 10.1080/10790268.2022.2054763

22. Sahbani K, Pan J, Zaidi M, Cardozo CP, Bauman WA, Tawfeek HA: Abaloparatide prevents immobilization-induced cortical but not trabecular bone loss after spinal cord injury. The. FASEB Journal. 2023, 37:22984. 10.1096/fj.202300109RR
23. Abdelrahman S, Ireland A, Winter EM, Purcell M, Couplaud S: Osteoporosis after spinal cord injury: Aetiology, effects and therapeutic approaches. Journal of Musculoskeletal & Neuronal Interactions. 2021, 21:26.
24. Bethel M, Weaver FM, Bailey L,: Risk factors for osteoporotic fractures in persons with spinal cord injuries and disorders. Osteoporosis International. 2016, 27:3011-21.
25. Craven BC, Cirnigliaro CM, Carbone LD, Tsang P, Morse LR: The pathophysiology, identification and management of fracture risk, sublesional osteoporosis and fracture among adults with spinal cord injury. Journal of Personalized Medicine. 2023, 8:966. 10.3390/jpm13060966
26. Battaglino RA, Lazzari AA, Garshick E, Morse LR: Spinal cord injury-induced osteoporosis: pathogenesis and emerging therapies. Current osteoporosis reports. 2012, 10:278-85. 10.1007/s11914-012-0117-0
27. Balemans W, Ebeling M, Patel N,: Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Human molecular genetics. 20011, 10:537-44. 10.1093/hmg/10.5.537
28. Li X, Ominsky MS, Niu QT,: Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. Journal of Bone and Mineral Research. 2008, 1:860-9. 10.1359/jbmr.080216
29. Tian X, Jee WS, Li X, Paszty C, Ke HZ: Sclerostin antibody increases bone mass by stimulating bone formation and inhibiting bone resorption in a hindlimb-immobilization rat model. Bone. 20111, 48:197-201. 10.1016/j.bone.2010.09.009
30. Padhi D, Jang G, Stouch B, Fang L, Posvar E: Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. Journal of bone and mineral research. 20111, 26:19-26. 1002/jbmr.173
31. Liberman UA, Weiss SR, Bröll J, : Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. New England Journal of Medicine. 1995, 30:1437-44. 10.1056/NEJM199511303332201
32. Nance PW, Schryvers O, Leslie W, Ludwig S, Krahn J, Uebelhart D: Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. Archives of physical medicine and rehabilitation. 1999, 3:243-51. 10.1016/S0003-9993(99)90133-8
33. Minaire P, Berard E, Meunier PJ, Edouard C, Goedert G, Pilonchery G: Effects of disodium dichloromethylene diphosphonate on bone loss in paraplegic patients. The. Journal of Clinical Investigation. 19811, 68:1086-92.
34. Pearson EG, Nance PW, Leslie WD, Ludwig S: Cyclical etidronate: its effect on bone density in patients with acute spinal cord injury. Archives of physical medicine and rehabilitation. 1997, 1:269-72. 10.1016/S0003-9993(97)90032-0
35. Sniger W, Garshick E: Alendronate increases bone density in chronic spinal cord injury: a case report. Archives of physical medicine and rehabilitation. 20021, 83:139-40. 10.1053/apmr.2002.26828
36. Zehnder Y, Risi S, Michel D: Prevention of bone loss in paraplegics over 2 years with alendronate. Journal of bone and mineral research. 2004, 19:1067-74. 10.1359/JBMR.040313
37. Bauman WA, Wecht JM, Kirshblum S, Spungen AM, Morrison N. Cirnigliaro C, Schwartz E. Effect of pamidronate administration on bone in patients with acute spinal cord injury. Journal of Rehabilitation Research & Development. 2005, 1:42.
38. Moran de Brito CM, Battistella LR, Saito ET, Sakamoto H: Effect of alendronate on bone mineral density in spinal cord injury patients: a pilot study. Spinal cord. 2005, 43:341-8.
39. Mechanick JI, Liu K, Nierman DM, Stein A: Effect of a convenient single 90-mg pamidronate dose on biochemical markers of bone metabolism in patients with acute spinal cord injury. The. journal of spinal cord medicine. 2006, 1:406-12. 10.1080/10790268.2006.11753890
40. Gilchrist NL, Frampton CM, Acland RH: Alendronate prevents bone loss in patients with acute spinal cord injury: a randomized, double-blind, placebo-controlled study. The. Journal of Clinical Endocrinology & Metabolism. 20071, 92:1385-90. 10.1210/jc.2006-2013
41. Shapiro J, Smith B, Beck T, Ballard P, Dapthary M, BrintzenhofeSzoc K, Caminis J: Treatment with zoledronic acid ameliorates negative geometric changes in the proximal femur following acute spinal cord injury. Calcified tissue international. 2007, 80:316-22.
42. Bubbear JS, Gall A, Middleton FR, Ferguson-Pell M, Swaminathan R, Keen RW: Early treatment with zoledronic acid prevents bone loss at the hip following acute spinal cord injury. Osteoporosis international. 2011, 22:271-9.

43. Bauman WA, Cirnigliaro CM, La Fountaine MF, Martinez L, Kirshblum SC, Spungen AM: Zoledronic acid administration failed to prevent bone loss at the knee in persons with acute spinal cord injury: an observational cohort study. Journal of bone and mineral metabolism. 2015, 33:410-21.
44. Haider IT, Simonian N, Saini AS, Leung FM, Edwards WB, Schnitzer TJ: Open-label clinical trial of alendronate after teriparatide therapy in people with spinal cord injury and low bone mineral density. Spinal Cord. 2019, 57:832-42.
45. Gifre L, Vidal J, Carrasco JL: Denosumab increases sublesional bone mass in osteoporotic individuals with recent spinal cord injury. Osteoporosis International. 2016, 27:405-10.