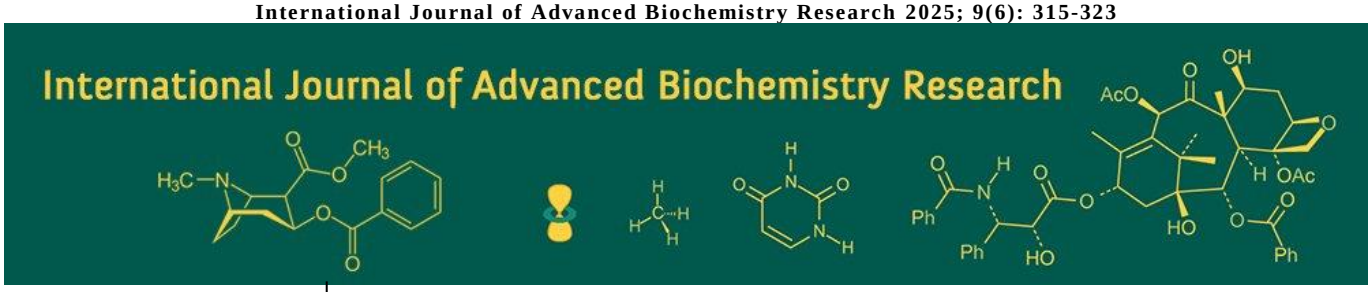

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Insights into the mechanism of neuro-osseus overlap in Parkinson's disease

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Abstract
Parkinson's disease (PD) is a motor dysfunction disorder in which many patients also report of non-motor manifestations such as osteoporosis. Disease cure is challenging due to unavailability of prescribed treatment formats. Discovery of pathways of central modulation of bone mass and the stimulation of brain functions hints towards a loop with which the brain and bone interact. The current review critically analyses the basic and clinical literature pertaining to PD induced osteoporosis and reexamines the functional loop of bone in regard to maintaining metabolic dyshomeostasis in neurodegenerative conditions. It also explores newer overlaps for brain and bone axis in regards to finding common denominations and common mechanisms contributing to the pathogenesis of the two and questions whether early markers of autonomic nervous system (ANS) dysfunctions, could be recognized as important cues for late onset osteoporosis in PD. The contribution of DA in cases of parkinsonism is already established. PD induced bone loss is also reported. However there remains a conundrum for the participation of centrally regulated DA stimulating PD induced bone loss which needs further investigation.

Keywords: Parkinson's disease, osteoporosis, fracture, dopamine, acetylcholine

Introduction
Parkinson's disease (PD) is basically a motor disorder affecting the dopaminergic neurons in the basal ganglion. As the disease progresses, these neurons get depleted from the pars compacta region of substantia nigra (SNpc) and cause a severe decline in the levels of striatal dopamine (DA). Although PD is primarily a motor disease, patients also suffer non-motor manifestations such as psychiatric, sleep disorders and disturbances of autonomic nervous and sensory system. Non-motor symptoms are reported to precede the motor feature (Behl *et al*., 2022) [9]. It is reported that 91% women and 61% men suffering from PD also report osteopenia and osteoporosis that culminated into fractures (Kim *et al*., 2022) [30]. Osteoporosis is a non-motor manifestation in PD where physical changes as weak gait, posture and impairment bone mineral density (BMD) act as determinants of fall associated fractures (Koo *et al*., 2023) [31].
Similar to PD, osteoporosis is a gradual epidemic, which occurs typically in the later quadrants of life (Cooper *et al*., 1992) [15]. Its pathophysiology involves musculoskeletal, micro architectural loss of bone that later culminates into a fracture. A Global Longitudinal Study of Osteoporosis in Women (GLOW) identifies PD as the strongest determinant for fractures. PD induced bone loss is poorly understood making it difficult for medical practitioners to treat patients since it lacks a formal treatment regimen. Discovery of pathways of central modulation of bone mass and the stimulation of brain functions through bone derived osteocalcin has indicated towards a loop with which the bone and brain interact. (L. Liu *et al*., 2023 [37]; Xiong *et al*., 2021) [70].
Here in this study, we critically review the basic and clinical studies pertaining to PD induced osteoporosis and their molecular and cellular junctions. We question whether PD starts outside the CNS and could the dysfunctional ANS be recognized as an important check points for basal ganglia disease. We need to reexamine the functional loop of bone in reference to maintaining metabolic homeo and dyshomeostasis in neurodegenerative conditions such as PD (T.-Z. Liang *et al*., 2025 [35]; Lin *et al*., 2021) [36].

Bone remodeling and osteoporosis

Bone remodeling is a regulated process where bone resorption happens almost at the same rate as a fresh bone is formed. Basic multicellular units (BMUs) that comprise the remodeling unit of bone include osteoclasts, osteocytes, osteoblasts, and the lining cells (Parfitt, 2000) [48]. The bone marrow niche contains these cells along with hematopoietic elements, adipocytes, reticulo-endothelial cells lining the sinusoids and mesenchymal stromal cells (Chi *et al*., 2023) [14]. During bone remodeling, osteoclasts resorb old bone which is then replaced by fresh mineralized matrix by osteoblast cells. This process promotes the supply of calcium in the extracellular space and provides strength and elasticity to the skeleton. However when this process of resorption is greater to that of formation, bone loss begins. Besides, systemic and local alterations lead to deleterious alterations in bone mass. Likewise, at peak bone acquisition processes, formation rate is more than resorption, thus culminating into net gain of bone mass (Akhiiarova *et al*., 2023) [3].

The initiating sources and signals (auto-, para- or endocrine in manner) for bone remodeling originate not only from activated osteoblasts but also from other organs and tissues (Karsenty & Khosla, 2022) [29]. A critical interaction in the osteoblast-osteoclast communication scheme is the RANK-RANKL-OPG interaction. Osteoblast secret RANKL and OPG that promotes or inhibits osteoclastogenesis by binding to RANK (Fu *et al*., 2023) [22]. While RANKL promotes preosteoclast fusion to differentiate them into mature osteoclast, OPG inhibits it. Matrix components such as TGF-β, insulin-like growth factor 1 (IGF-1), collagen, osteocalcin, calcium, and mineral and protein are released once osteoclast induce bone resorption. Growth factors released assist in the recruitment of new osteoblasts on the bone and begin the process of collagen synthesis and bio mineralization (Xiao *et al*., 2023) [69]. Other than local cues, external signals (such as PTH, growth hormone, IL-1, estrogen deprivation) enhance the recruitment and differentiation of multinucleated giant bone-resorbing osteoclast and/or bone forming osteoclast cells (B. Liang *et al*., 2022) [34].

Central control of bone metabolism: an overview

Recent evidences suggest that the brain neurons can regulate the bone metabolism. Much studied molecule in this regard is leptin. This is an adipocyte-derived hormone which acts via its receptor ObRb from the hypothalamus to regulate physiological functions like energy metabolism, glucose homeostasis, and bone remodeling. It is also reported that *ob/ob* mice-leptin deficit reported increased bone mass despite having hypogonadism and hypercorticosteronemia (T. Liu *et al*., 2024) [38]. Multiple types of nerves are present within the bone microenvironment and periosteum that indicate that additional neuropeptides and receptors are involved in the remodeling process of bone. Besides the osteoblast, the microenvironment of the bone has many neuropeptide receptors on various other cell types as immune cells, osteoclasts and adipocytes thus suggesting an indirect neuronal signaling pathway. Osteoblasts that express a functional beta2-adrenergic receptor (β2AR) receive a sympathetic tone *in vivo* (W. Sun *et al*., 2023) [62].

Various stages of PD and its pathophysiology: The Unified Parkinson's Disease Rating Scale (UPDRS) is an immensely applied rating instrument for PD (Ebersbach *et al*., 2006 [18]; Sheng *et al*., 2021) [58] and incorporates 31 items in three subcategories: 1. Mentation, Mood and Behavior, 2. Daily Activities Index 3. Motor Examination (Poewe & Mahlknecht, 2009) [52]. The UPDRS umbrellas extrapyramidal motor examination that is reflective of the physical performance measurements (Pahwa *et al*., 2006) [47]. Quality of life of patients is severely affected by both motor effects (eg, disabling tremor, falls) and non-motor symptoms (eg, anxiety, depression) (Sanchez-Luengos *et al*., 2022) [54]. PD is categorized into five levels in which the first stage shows mild symptoms of tremor or shaking in the limb. This symptom is enhanced during second stage as a bilateral propagation to both limbs and sections of the body (Behl *et al*., 2022) [9]. Stage three is more severe and includes the inability in standing and walking. Physical movements become noticeably slow with most patients unable to perform their daily tasks. *In vivo* evidences from these patients hinted that DA receptors were involved in their arthritic type manifestations. In RA patients the DA receptors are upregulated at bone remodeling interfaces and their activation seemed to have proinflammatory effects and inhibited osteoblast activation. Thus, suggesting, that DA pathway in bone remodeling and joint erosion in RA could open future perspectives to target the susceptibility of bone losses in PD patients (Schwendich *et al*., 2022) [57]. The vagal dorsal motor nucleus is the area that is affected earliest by the expression of Lewy body and *a*-synuclein pathology in PD. Researchers also questioned whether vagotomy could decreased PD occurrences and concluded that although overall vagotomy did not influence the incidence PD, truncal vagotomy was better against development of PD (X. Sun *et al*., 2022 [63]; Tysnes *et al*., 2015) [65]

The Dopaminergic-Cholinergic Overlap

Action of DA

PD leads to marked reduction in the number of DA neurons and its levels in the striatum (Zhou *et al*., 2023) [75]. DA signals are propagated in many cells through its receptors. There are five classes of DA receptors: D1 to D5 that have a composition of seven transmembrane G- protein coupling. Signals coming from D1- receptors transduce from G proteins to adenylyl cyclase, leading to cyclic adenosine monophosphate (Cooper *et al*., 1992) [15] and activating protein kinase A (PKA) (Zhang *et al*., 2022). D2-type receptors inhibit the actions of the D1 type receptor (Isaacson *et al*., 2023) [28]. In CNS, DA functions as monoaminergic neurotransmitter where it helps in regulation of neuro-endocrine functioning and movement. Outside the CNS, DA is a local chemical messenger providing a base for noradrenaline and adrenaline, the major neurotransmitter of the sympathetic nerve system (SNS), and also as a adreno-medullary hormone. DA affects insulin production in the pancreas and also regulates the digestive system. Reduced DA-D2-like receptor signaling is implicated in PD (Sonne *et al*., 2025) [60]. There is ambiguity for the role that DAergic signaling plays in PD induced bone loss (Figueroa & Rosen, 2020) [20]. Tomita *et al* used methamphetamine in studying the correlation between CNS activity and bone metabolisms and found it to affect bone turnover negatively leading to osteoporosis (Márquez-Grant *et al*., 2022 [39]; Tomita *et al*., 2014) [64]. Deletion of DA transporter (DAT) in mice

(Hanami *et al*., 2013) [26] effected calcium and phosphorus metabolism. Histological and biomechanical results of the skeleton of such mice showed reduced bone mass and shorter femur length. Li *et al*, found functional DA receptors on pre-osteoblast MC3T3-E1 cell lines that induced mineralization (Lee *et al*., 2015) [33]. Li *et al*'s findings are interesting but incomplete as they failed to show the presence of tyrosine hydroxylase activity. Besides DA effecting the osteoblasts, their receptors and active transporters (DAT) could influence osteogenesis. Thus it could be speculated that DAergic signaling affects bone homeostasis through a direct effect on the osteoclast to differentiate and the results from the deletion of DAT gene show weakening of skeletal structure and integrity. An incidence of polymorphism (SNP) in the DA receptor D4 and a concomitant decrease of BMD of Japanese men also resurfaced (Yamada *et al*., 2003) [71]. DA receptor D3 and D4 which come under the umbrella of D2-type receptors also have been linked to decreased osteoclastogenesis. Leucine-rich repeat kinase 2 (*Lrrk2*) gene mutation are also implicated in both inherited and idiopathic PD. Lrrk2 is essential for midbrain DA neurons survival and development and also is implicated in the canonical Wnt pathway. Knocking down the Lrrk2 gene in both mice and fibroblastic cells shows increase levels of brain β-catenin and altered tibial bone architecture (Simpson *et al*., 2022) [60]. Hanami *et al*. showed that signaling through D2 channel suppresses human osteoclastogenesis (Hanami *et al*., 2013) [26]. Such intriguing results hint towards a molecular and cellular overlap, that could decode the association of bone loss in PD. Vagus nerve dysfunctions are reported to affect the brain DA and (Ziomber *et al*., 2012) [76] have suggested a close knit between the impairment of the peripheral vagus nerve causing an inhibition of brain DA. The contribution of DA in cases of parkinsonism is already established (Ali, 2020) [4]. PD induced bone loss is also reported (Ali, 2020) [4]. However there remains a conundrum for the participation of centrally regulated DA stimulating PD induced bone loss which needs further investigation.

Action of Acetylcholine (ACh)

Acetylcholine (ACh) mediates both the brain and the periphery (Ali & Rajini, 2016) [6]. It acts via its two main types of receptors: nicotinic acetylcholine (nAChRs) and muscarinic acetylcholine (mAChRs). There are convergent evidences which show that early changes in cholinergic transmission could lead to incidence of PD. It is seen that within the basal forebrain cholinergic neurons of PD patients, there is accumulation of a-synuclein which coincides apparently with the presence of Lewy bodies and neuronal loss in the SNpc (Sam & Bordoni, 2025) [53]. Also the cholinergic interneurons of striatum (1%-2%) have larger perikarya as compared to other striatal neurons. They are reported to exude spontaneous tonic activity which results in abundant widely branched axons (Nosaka & Wickens, 2022) [43]. These cholinergic interneurons from striatum are devoid of typical synaptic contacts on other neurons giving them predominant "volume" neurotransmission or paracrine feature. It is plausible that the cholinergic interneurons could influence the remaining populations of striatal neurons behaviorally? (Pisani *et al*., 2007) [51]. In bone, ACh stimulates the differentiation and proliferation in osteoblasts and its inhibition causes decreased mineral content and fracture healing (V. Ozturk & Baris, 2025) [46]. By binding the acetylcholine receptor (nAChR) ACh up-regulates osteoclasts apoptosis thus decreasing bone resorption (Eimar *et al*., 2013) [19]. Current research in ACh induced bone modulation reports the involvement of vagal nerve in maintaining bone homeostasis by controlled stimulation of OPG and RANKL through macrophage TNFα expression (Wu *et al*., 2024). Cholinergic activity in bone favors bone mass accrual. This has been substantiated with *in vitro* data that cholinergic activity induces proliferation of bone cells. The i*n vivo* data also showed that the inhibited cholinergic activity causes bone loss, whereas its stimulation favored accrual of bone mass (Gadomski *et al*., 2022) [23].

Mechanism of bone loss in PD

DA signaling

Principally DAergic neurons are involved in three main systems in the brain: nigrostriatal system (NS)**,** mesolimbic system**,** and mesocortical system. NS neurons play an important role in the control of movement and start in the region of substantia nigra and terminate at caudate nucleus and putamen. Mesolimbic neurons originate in the ventral tegmental area (VTA) and extend to other parts like amygdale, hippocampus and nucleus accumbens. The mesolimbic system helps in reinforcing the effect (rewarding) of drugs. The mesocortical system affects functions such as planning and problem solving through DAergic axons projections to the prefrontal cortex (Missale *et al*., 1998 [40]; Sonne *et al*., 2025) [60] AMPK deficiency has been linked to PD induced osteoporosis (Figueroa & Rosen, 2020) [20]. *In vitro* studies with adenosine 5-monophosphate activated protein kinase (AMPK) modulators revealed that they regulate bone cell function (Molinuevo *et al*., 2010) [41]. Some *in vivo* studies in mice showed that AMPK deficiency (both α and β) subunits caused bone loss. Could it be that the imbalances of the mitochondrial bioenergetics trigger a paracrine translation in PD induced bone loss (Valenti & Atlante, 2025) [66]?

ACh signaling

While PD induced cholinergic deficits in the mid brain can cause memory loss and cognitive dysfunction (Pasquini *et al*., 2021) [50], cholinergic activity is reported to enhance bone mass by increasing osteoblast proliferation (Shi & Chen, 2024) [59]. Nicotinic and muscarinic cholinergic receptors affect bone turnover with nicotinic stimulation causing increase in osteoclasts apoptosis (Zhen *et al*., 2022) [74]. Muscarinic stimulation *in vitro* increases osteoblasts proliferation (Gerosa & Lombardi, 2021) [25]. Acetylcholinesterase is reported to stimulate bone cell proliferations, differentiations, cell to cell contact and mesenchymal stem cells (MSC) migration in bone physiology (Zhai *et al*., 2020) [72].

Brain-gut axis signaling

Hu *et al* reported functional DA receptors on pre-osteoblast MC3T3-E1 cell lines that induced mineralization (Hu *et al*., 2015). His studies however were inconclusive as there was no tyrosine hydroxylase (TH) expression on pre-osteoblast

MC3T3-E1 cell lines. Could the source of DA here be of paracrine regulations as it was not from osteoblasts themselves? Of late autopsy studies on PD patients also recognize vagal dorsal motor nucleus regions of the brain, to be early affected in PD. The brain- gastrointestinal system connects via brain dorsal motor nucleus of the vagus innervations (Braak *et al*., 2003) [12]. Recent clinical trials (Vargas-Caballero *et al*., 2022) [67] have also indicated pathologically alteration of vagal nerve in PD patients. Postmortem immunohistochemical studies have found that dorsal motor nucleus is one of the brain areas that is affected earliest by *a*-synuclein and Lewy body pathology in PD. It is also important to mention that vagus nerve stimulation (VNS) is a novel therapy for the control of epilepsy. Also two large double-blind randomized clinical trials with several studies, have confirmed the potential involvement of VNS in different types of epilepsy (Ben-Menachem, 2002) [10]. However, how the VNS is impacting cases of epilepsy, depression or for that matter early stages of PD is nebulous. However many questions regarding the efficacy of vagus nerve modulating the function of central monoaminergic systems have been raised. Onset of PD may be linked with neurodegeneration and functional impairment of the vagus nerve, leading to inhibition of mesolimbic and mesocortical DA system in the brain. Also mental disorders could follow after inhibition of the limbic DA system. The bone homeostasis through α7nAchR is also reported to be regulated by VNA and that VNA regulates bone homeostasis by controlling Mac1-positive cell expressing TNFα -mediated RANKL and OPG expression in physiological conditions. Partially raised serum OPG levels were also observed in α 7nAchR-deficient mice that were significantly restored by deletion the gene encoding for TNFα. This suggested that α7nAchR regulated OPG levels through factors other than TNFα and IL-1β. Macrophages via α7nAchR cause VNS that regulates bone mass by modulating osteoclast formation by inhibiting intracellular cAMP and subsequent transcription of c-Fos and NFATc1. At this junction it could be hypothesized that a vagal neural activity has some role to play in looping the bone and brain interaction either at the cholinergic, dopaminergic or both interfaces

Others: The DAergic activity within the SNpc is also modulated by glutamatergic and GABAergic innervations. Serotonergic neurons can also impair release of striatal DA in PD (Buck *et al*., 2022) [13]. Loss of DA neurons from basal ganglia causes disease with characteristic motor symptoms (Obeso *et al*., 2008) [44]. Changes in DA interactions both within and outside the basal ganglia region need to be considered when looking at the wider symptoms reported in PD patients. Some researchers have also emphasized that glutamatergic system is also important in modulating PD symptoms with cognitive and motor impairment. At the bone interface glutamate plays a significant role in nerve-bone and bone-bone paracrine signaling which controls metabolic activities, especially in relation to remodeling after mechanical loading (Deng *et al*., 2024) [17]. PD is a proteinopathy (Braak *et al*., 2003) [12] that causes many neuropathological alteration along with loss of DAergic neurons. There is also marked increase in astroglia, microglial and lymphocyte infiltration. Damier *et al* also report increased astroglial population in the postmortem brain tissue of PD patients (Damier *et al*., 1993). Of late, the brain-derived neurotrophic factors (BDNF) have also caught much attention for their proposed involvement in PD induced osteoporosis. BDNF are required for neuronal plasticity, survival and differentiation, regulating functions as food metabolism. They are present abundantly in osteoblasts hinting towards their role in bone remodeling (Park *et al*., 2024). Likewise, the orphan nuclear receptor Nurr1 expressed in the CNS is imperative for terminal differentiation of dopaminergic (DA) neurons from the ventral midbrain region. This receptor, however, also finds expression in other organs as bone. Lee *et al* studied Nurr1 during osteoblast differentiation in MC3T3-E1 cells and calvarial osteoblasts that were taken from Nurr1 null newborn pups. They showed that reducing Nurr1 expression, stimulated the expression of osteoblast marker genes as collagen type I alpha 1 (COL1A1), osteocalcin (OCN) and the activity of alkaline phosphatase (ALP) negatively. Many studies have also addressed PD induced osteoporosis by looking into blood-based biomarker of PD, even though a direct correlation between the two is absent (considering an intact blood-brain barrier).To date, identification of three blood-based biomarkers are reported that have been implemented in independent cohorts of patients. Lower uric acid count is indicative of increased risk for PD (Al-Nusaif *et al*., 2022) [7]. Likewise Ahn *et al* report that serum uric acid could benefit bone metabolism as an antioxidant in postmenopausal women (Ahn *et al*., 2013) [2].

Future directions: Current research should aim at understanding the bone losses incurred in neurodegenerative diseases as PD. It should address if there is any common denomination and any common mechanism contributing to the pathogenesis which affects the world population. Does the springing of PD- like features / parkinsonian features trigger early onset markers of bone loss? Recently we reported that the MPTP and CPF animal model of PD displayed bone deterioration along with behavioral symptoms of PD. We attributed this alteration of bone to endocrine alterations in the serum of the animals (Ali *et al*., 2019). Examining this association at still deeper levels is imperative for devising interventions to slower subsequent disability. Increase in disability and mortality linked with fractures in the older population, warrant new determinants of PD associated osteoporosis. Further studies in the area are required to bridge the gap of occurrence of osteoporosis in neurodegeneration conditions, where bone biopsies and serum/ cerebrospinal fluid could be simultaneously be screened for content of downstream biomarkers. Unfortunately, at present research for bone health in PD situations is lacking because treatments for patients was formulated by neurologists and not general physicians. Trials focused more on neurological alterations and not on bone quality. Dopamine deficiency in the basal ganglia is known to trigger a milieu of oxidative stress, mitochondrial dysfunction and neurotoxicity leading to Parkinson's disease. Current research should address if this dopamine deficiency can trigger osteotoxicity, eventually leading to osteoporosis. Evidences also suggest that there is a neurally modulated control in fracture healing, bone development, bone mass control, and osteoporosis. Conclusively, taken together new insight of an overlap of the brain and bone axis need to be considered in neurodegenerative conditions as Parkinson's disease where osteoporosis manifests as a non-motor offshoot as seen in Tab.1 and Fig. 1

Table 1: Cohort/Clinical studies addressing bone health with Parkinson's disease (PD)

S. No	Study Design	Parameters studied	Outcome	References
1.	Randomized controlled trail on bone health in PD (Proactive and Integrated Management and Empowerment in Parkinson's Disease randomized controlled trial (PRIME-UK RCT)) PD (n=182)	Bone health metric studied: dual X- ray, absorptiometry (DXA), fracture risk assessment (FRAX) tool, National Osteoporosis Guideline Group UK (NOGG) risk category	28% -fragility fractures; 40.7% - recurrent episodes of fall; 28.6%-MOF intervention threshold; 12.1%-FN-BMD ≤ -2.5	(Naylor *et al*., 2025) [42]
2.	Prospective Cohort study within a randomized, placebo-controlled trial PD (n=47)	Elderly women (≥ 75% years) from UK; Assessed for fracture risk from using FRAX tool, PD status; BM; Fall; muscle strength; medication use	PD patient (N= 47; 0.9%) had ~2x higher risk of osteoporotic fractures. Reduce BMD explained only part of the risk. Lower muscle strength and increase fall risk were significant contributors. Implications noted for improving FRAX by including PD and muscle strength measures	(Schini *et al*., 2023) [55]
3.	Case- Control Study evaluating BMD and vitamin D in PD PD (n=124) C (n=116)	BMD (Lumbar and femoral), serum and vitamin D levels,Hoehn and Yahr staging, UPDRS scores, clinical features of PD	PD patient had significantly lower BMD and vitamin D levels vs control; deficits appeared in early stage and worsened with disease progression	(E. Ozturk *et al*., 2020) [45]
4.	Cross section study from Chinese midlands ↓ BMD in PD PD (n=54) C (59)	BMD- lumbar spine femoral neck and hip - (DXA). Serum level-calcium & phosphorus, and homocysteine were measured to determine BMD's association with PD severity.	The BMD of FN and hip ↓females than in males in the healthy group. In the PD group, BMD in the hip was significantly ↓ in females compared to males	(Gao *et al*., 2015) [24]
5.	Prospective observational study	402 hip fracture patient aged ≥ 60 years; ASA score MMSE, Barthel index (BI), hoehn & yahr scale; functional outcome assessedvia BI, Tinetti Test (TT), Timed Up and go test (TUG); length of stay, complications; Discharge management	19 (4.7%) had PD. Function outcomes at discharge were similar (BI, TT, TUG, *P*>0.05). PD patient had more grade ‖ (52.6% v/s 26.1% OR = 4.304, P = 0.008) and grade V complications (15.8% v/s 4.4%; OR= 7.785, P= 0.012), longer hospital stay (β = 0.119, p = 0.024), and worse BI at 6 months (p = 0.038)	(Bliemel *et al*., 2015) [11]
6.	Case control: Dopaminergic drug and the risk of fracture PD(n=23) C (n=41)	6 month drug monitoring (antidepressant, antipsychotic, benzodiazepine)	Hip and femur fracture	(Arbouw *et al*., 2011) [8]
7.	BMD in PD cases: Male vs Female PD(n=108) C (n=216)	Hip, lumbar, spine and total body BMD - DEXA	Female PD patients have ↓ hip BMD	(Lam *et al*., 2010) [32]
8.	Correlation b/w PD and low BMD PD(n=82) C (n=68)	Lumbar and spine DEXA	PD patients ↓ BMD at lumbar, spine and femoral neck	(Abou-Raya *et al*., 2009) [1]
9.	Bone changes in PD.	BMD by DEXA Sera analysed (calcium, vitamin D, bone alkaline phosphatase (BALP) and urinary N-terminal telopeptide of type I collagen (NTx).	BMD of PD patients' ↓. PD patients ↓ vitamin D ↑ BALP and NTx levels.	(Abou-Raya *et al*., 2009)
10.	Prospective cohort study (women) PD(n=73) C (n=7760)	Hip fracture using DXA	Hip fracture PD (n=11) C (n=839)	(Schneider *et al*., 2008) [56]

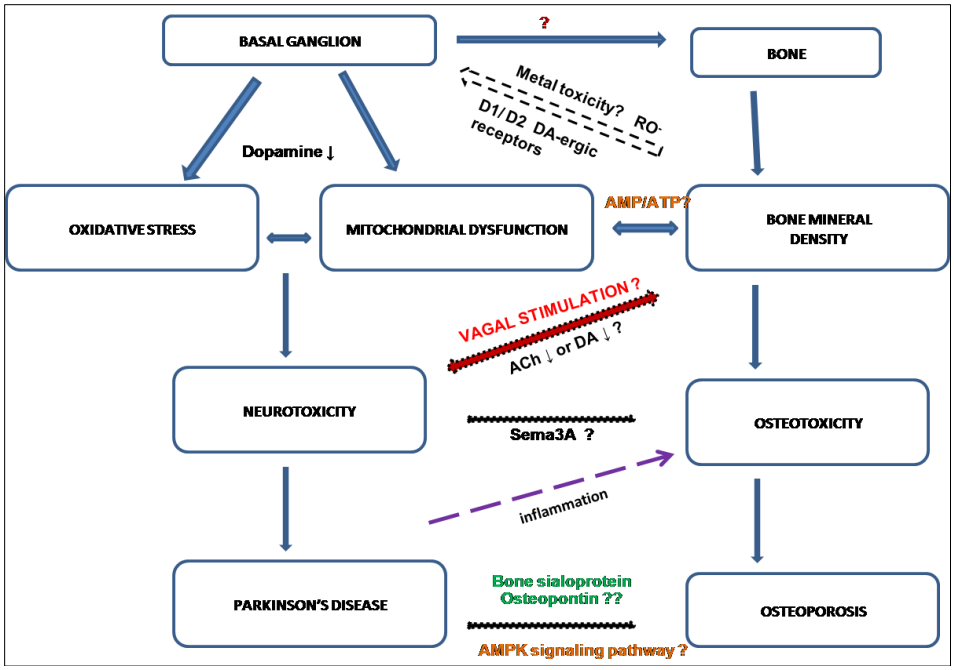

Fig 1: Proposed hypothesis for the neuro-osseus overlap in Parkinson's disease induced osteoporosis CRediT authorship contribution statement

SJA conceptualized, acquired funding and writing (original /reviewed and editing), KB formal analysis, resources, visualization, SP investigation and methodology.
No part of the manuscript has been compiled using AI tool
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