# NEUROENDOCRINE ABNORMALITIES IN PARKINSON'S DISEASE

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**ABSTRACT**

Neuroendocrine abnormalities are common in Parkinson's disease ~~(PD)~~ and ~~they~~ include disruption of circadian rhythms, disturbances of glucose and bone metabolism, insulin resistance and body weight changes. They have been associated with multiple non-motor symptoms in~~of~~ PD and have important clinical implications. Some of the underlying mechanisms have been implicated in the pathogenesis of PD and ~~they~~ appear to be promising ~~research~~ targets for the development of ~~potential~~ disease biomarkers ~~of the disease~~ and neuroprotective therapies.

Here we provide a system-based review of the clinically relevant neuroendocrine abnormalities ~~clinically relevant~~observed in Parkinson's disease in order to increase ~~the~~ appreciation and awareness ~~of these disturbances~~amongst clinicians ~~by clinicians~~. We discuss the pathophysiological mechanisms, ~~associated~~ clinical implications, and pharmacological and non-pharmacological ~~therapeutic~~ interventions ~~recommended~~ based on the current evidence. We also review the recent advances ~~achieved~~ in th~~e~~is field, focusing on~~in~~ the potential targets for development of neuroprotective drugs in Parkinson's disease and suggest future areas for research.

## INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative condition characterised by both motor and non-motor symptoms (NMS). Whilst the classic motor features are attributable to nigrostriatal dopaminergic cell loss, the spectrum of NMS ~~has~~ reflect a more complex aetiology ~~with underlying~~which includes numerous neuroendocrine and metabolic abnormalities ~~implicated~~.

Neuroendocrine abnormalities in PD are important for several reasons[DB3]:

- They are ~~relatively~~ common, mainly seen in advanced stages of PD , ~~,~~ and associated with multiple NMS.
- They appear to be an integral feature of PD and not simply secondary to disruption of other physiological processes. Recent advances have shed light on their underlying pathophysiology and ~~the~~ relationship to PD, although there remain important questions regarding the effect of neurodegeneration ~~in PD~~ on the neuroendocrine axes.
- A better appreciation of the neuroendocrine abnormalities in PD and their ~~has important~~ clinical implications may allow more tailored clinical assessment and offer the opportunity for ~~and highlights potential~~ symptomatic therapeutic interventions ~~that should be part of the routine clinical assessment in PD patients.~~
- Some of the neuropeptides and hormones involved are easy to measure and quantify in various body fluids (blood/urine/saliva). Altered concentrations may correlate with disease severity and play a role in disease progression and pathogenesis. As such, they ~~could~~ represent potential peripheral biomarkers of disease state.

- Importantly, elements of the neuroendocrine system ~~they~~ could be the basis for the future development of much needed targeted therapies for NMS and neuroprotective treatments in PD.

This review does not cover all the endocrine systems or metabolic ~~abnormalities~~ systems known to be ~~altered~~ disrupted in PD, but provides a system-based overview of ~~only~~ those in which there have been recent advances ~~with~~ in terms of the clinical or therapeutic implications. We discuss the current evidence, therapeutic recommendations and future areas for research for each of these neuroendocrine and metabolic disorders ~~clinically relevant~~ in PD.

## SEARCH STRATEGY

A Pubmed/Medline search was performed for articles published in English between January 1990-December 2015. We combined searches ~~with~~ using 'Parkinson's disease' ~~using the~~and the ~~-~~keywords 'neuroendocrine', 'circadian disorder', 'suprachiasmatic nucleus', 'hypothalamus', 'melatonin', 'pineal gland', 'diabetes', 'insulin resistance', 'glucose intolerance', 'body weight', 'feeding behaviour', 'leptin', 'ghrelin', 'osteoporosis', 'bone mineral density' and 'vitamin D'. Reference lists were manually checked to ~~include~~ capture any additional articles. The final list of references was generated based on the relevance of the articles to the aim of this review.

## CIRCADIAN RHYTHM AND SLEEP DISORDERS

Circadian (daily) rhythms are present in almost all physiologic functions, of which the sleep-wake cycle is the most apparent. The system responsible for this near 24-hour rhythm is composed of central and peripheral oscillators ~~.~~ (Figure 1). The central

biological master clock is located in the suprachiasmatic nuclei ~~us~~ (SCN) of the anterior hypothalamus.[1] Melatonin is the most important endogenous entraining agent and is produced by the pineal gland during darkness. It is considered to be ~~as the~~a reliable ~~key~~ output from the endogenous clock conveying the signal from the SCN.[2]

It is well accepted that coordination of circadian rhythms is an essential element of optimal physical and mental health [3] and its disruption has been associated with metabolic disturbances,[4] disorders of the immune system,[5] increased cancer risk,[6] renal dysfunction,[7] cardiovascular disease,[8] impaired cognition, psychiatric and mood disorders.[9 10][DB4] Growing evidence suggests that alterations of the circadian system in PD patients ~~of PD~~ might contribute not only to sleep-wake cycle dysregulation but also to other NMS.

**Circadian abnormalities in PD**

Daily fluctuation~~s~~ of symptoms and loss of physiological circadian oscillations of some body functions ~~have been~~are well recognized in PD patients ~~with PD~~:~~.~~

- **Motor function**:~~.~~ Actigraphic studies have demonstrated a disruption of the physiological motor pattern, with increased activity at bedtime and reduced motor performance during the day in patients with PD which correlates with disease severity[DB5].[11 12] Moreover, PD patients ~~have shown~~display worsening of their motor symptoms with diminished motor response to levodopa therapy in the evening, unexplained by pharmacokinetic factors.[13 14]
- **Non-motor function**:~~.~~ Cardiovascular circadian rhythms are also affected in PD, with reduced heart rate variability [11 15 16] and reversal of the circadian

blood pressure profile with nocturnal hypertension.[17] [18] A lower body core temperature and reduced nocturnal fall in body temperature have also been reported, suggesting a circadian disruption of thermoregulation.[19]

- **Sleep**: Though a review of ~~the~~ sleep disorders in PD is ~~out of~~beyond the scope of this article, they are ~~very~~ common and include sleep fragmentation, insomnia, ~~sleep fragmentation,~~ REM sleep behaviour~~al~~ disorder~~s~~, restless legs syndrome~~,~~ and ~~sleep attacks and~~ excessive daytime sleepiness[DB6].[20][DB7] It is well accepted that they have a multifactorial origin including re-emergence of motor and NMS at night~~overnight~~, nocturia, side effects of ~~the~~ dopaminergic and other medication~~s~~, and degeneration of the regulatory mechanisms of the sleep-wake cycle secondary to the disease process. In addition, ~~a~~ disruption to~~of~~ the circadian sleep-wake cycle is likely to contribute to some extent to these symptoms. [DB8]Orexin neurons in the lateral hypothalamus exert a wake-promoting effect and form a mutually inhibitory circuit with the sleep-promoting neurons of the hypothalamic ventrolateral preoptic area regulating the sleep-wake cycle.[21] Some of the sleep disturbances in PD patients resemble those of narcolepsy, a sleep-wake disorder characterized by loss of orexin neurons with undetectable CSF orexin levels.[22] Studies assessing CSF orexin levels in PD have shown conflicting results, with normal levels in spinal CSF analysis [23] [24] but low intraventricular CSF levels in patients with advanced PD,[25] emphasizing the importance of CSF sampling site and stage of disease in interpreting orexin involvement in PD. In addition, two additional pathological studies have confirmed th~~at~~ damage occurs to the orexin system in PD patients, showing a severe reduction of orexin cells in the lateral hypothalamus correlating with disease severity.[26] [27] It seems plausible that altered orexin signalling contributes to excessive daytime sleepiness and other sleep disorders in PD

patients, though the clinical impact of ~~the~~ orexin system damage still needs to be determined. [28] [29]

- **PD pathophysiology**: Disrupted circadian rhythms are likely to have ~~severe~~ consequences on ~~the~~ systemic health in patients with PD. B~~and b~~ased on animal models, it has been suggested that alterations in the circadian system might accelerate the pathological processes underlying PD.[30] [DB9][DB10]

**Markers of circadian activity**

The different elements of the circadian system have not been systematically assessed in PD and the neuroanatomical site of disruption remains unknown. By contrast, several studies have assessed circadian activity in patients with PD using different peripheral markers.

- **Clock genes**: At a molecular level, circadian rhythms are regulated by several clock genes forming a set of interlocking transcription-translation feedback loops. T~~and t~~heir pattern of expression has been proposed as a peripheral marker of circadian activity.[31] A few studies have shown abnormalities in the expression of ~~various~~ clock genes in peripheral blood of~~in~~ patients with PD including a reduction in the expression [DB11]of *Bmal~~MAL~~1* ~~correlated with disease severity~~,[32] [33] *Bmal~~MAL~~2,*[34] and altered promoter methylation of *Npas~~PAS~~2* ~~*genes*~~.[35]
- **Melatonin**: As there is no pineal storage, ~~plasma~~ circulating melatonin levels faithfully reflect~~s~~ pineal activity and therefore ~~it is~~are considered a good biological marker of the circadian system.[2] Several studies have shown abnormalities in the pattern of melatonin secretion in patients with PD. A phase advance of the nocturnal plasma[DB12] melatonin and a decrease of the

night-to-daytime ratio secretion of melatonin have been shown in small studies[DB13]. [36 37] A more recent study with strict protocols on environmental conditions and behaviour to control the effects of exogenous variables showed ~~additional~~ diminished amplitude and reduced 24-hour area under the curve melatonin secretion in 20 PD patients on dopaminergic therapies with a strong correlation with excessive daytime sleepiness.[38] ~~-~~ Similar reduction in melatonin levels correlated with various alterations in sleep architecture was also reported in 30 newly diagnosed PD patients in comparison to healthy controls.[33] However, in both studies, melatonin secretion abnormalities did not show any association with disease duration, disease severity or dopaminergic therapy. Given the possible link between dopamine and the regulation of melatonin, 13 drug-naïve patients, 16 medicated PD patients and 28 age-matched controls underwent serial salivary melatonin sampling[DB14].[39] This showed an increase in melatonin in treated PD patients, though paradoxically this was associated with more circadian disruption, raising the possibility that dopaminergic replacement ~~therapy~~ and not neurodegeneration wa~~i~~s the underlying responsible mechanism[DB15].

These preliminary data suggest that impairment of the circadian system is an early feature of ~~the~~ disease, though no firm conclusions regarding the underlying mechanism can be made. T ~~and t~~hese results should be interpreted with caution due to the impact of exogenous factors such as dopaminergic therapy as a potential confounder[DB16][DB17].

**Therapeutic implications**

- **Melatonin**. Downing *et al* [40] compared the administration of melatonin 5 or 50 mg/day ~~of melatonin to~~versus placebo for a period of two~~2~~ weeks in a randomized controlled cross-over trial in 40 PD patients assessing nocturnal sleep, daytime sleepiness and daytime functioning. Actigraphy showed a minimal increment (10 minutes) in total night-time sleep in the group treated with melatonin 50 mg/day but subjective improvement ~~of the~~in sleep quality in the group ~~on lower doses~~taking 5mg/day ~~in comparison to~~compared with placebo. Another study with 18 PD patients randomized to melatonin 3 mg/day or placebo for four weeks showed ~~similar results with~~ significant improvement ~~of the~~in subjective quality of sleep but no significant differences on polysomnography between groups.[41] Based on these results, a consensus from the Movement Disorder Society concluded that there wa~~i~~s insufficient evidence on the efficacy of melatonin for the treatment of insomnia in PD.[42] Further studies with larger samples and careful protocol design are warranted[DB18].
- **Bright light therapy**:~~.~~ Though the exact mechanism remains elusive, it has been postulated that bright light therapy might restore circadian rhythmicity as it has demonstrated efficacy in the treatment of mood disorders.[43] Although ~~Though in PD i~~it has only been assessed in a few PD studies, it has shown promising results on sleep, mood and motor function.~~.~~[44] ~~though f~~Further studies with standardized protocols and rigorous designs are required to replicate these results.

## DIABETES AND GLUCOSE METABOLISM

~~Though t~~The potential association between PD and type 2 diabetes (T2DM) has long been recognised,[45] but it has only recently been the subject of more attention.[46]

**Epidemiological studies**

The prevalence of glucose intolerance has been estimated to be as high as 80% in PD patients in classical studies,[45] although more recent epidemiological data have provided ~~remain~~ conflicting data. A recent meta-analysis of case-control studies reported a negative association (OR = 0.75 [95%CI 0.58-0.98]) [47] although still observed that 2.9% of PD patients had a diagnosis of diabetes compared to only 1.6% in~~o~~n the non-PD population. Case-control studies are potentially prone to selection bias towards individuals attending specialist clinics~~,~~ and ~~also~~ cannot exclude later development of either PD or diabetes among studied patients, therefore the evidence they provide in establishing a consistent association may be less robust. Indeed these results contrast with a meta-analysis of findings from prospective studies, where pre-existing T2DM was indeed found to be a risk factor for future PD (RR = 1.26 [95%CI 1.03-1.55]; p <0.0001).~~.~~[48 49] Some of the conflicting results might ~~also~~ be explained by the heterogeneity between studies in terms of~~the~~ case ascertainment ~~of both conditions~~, and the potential for misclassification with respect to certainty of ~~both~~ diagnosis of both conditions. ~~PD and diabetes, and also~~Some studies ~~may~~ also fail to take into~~not~~ account ~~for~~ the potential role of diabet~~ic~~es ~~s~~ medications~~,~~ and ~~though~~ other environmental and ethnic factors ~~might also~~which could modulate the association in different populations.

T2DM has not only been suggested to be a risk factor for PD, but it might also exert a modifying effect on PD phenotype and disease progression. A case-control study showed that PD patients with antecedent diabetes have more severe motor symptoms and higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS), requiring treatment with higher doses of levodopa.[50] Clinical studies have shown that the presence of T2DM is associated with specific phenotypes~~,~~ including

greater postural instability, gait difficulties and cognitive impairment.[51-53] This association is clinically relevant as axial motor symptoms and cognitive impairment are generally less responsive to dopaminergic therapies and are a major cause of disability. The hypothesis that this lack of therapeutic response ~~to treatment~~ is secondary to other neurotransmitter involvement is supported by the fact that phenotypic variability was not explained by differences in nigrostriatal dopaminergic denervation on [$^{11}$C]dihydrotetrabenazine PET scans in PD patients with and without T2DM.[51]

**Pathophysiological mechanisms**

~~Though the exact mechanism whereby T2DM constitutes a risk or modifying factor for PD remains unknown, r~~Recent studies have begun to provide~~d~~ evidence in an attempt to elucidate the underlying pathways~~:~~.

- **Cerebrovascular disease**~~:~~. One might argue that the increased prevalence of vascular pathology and vascular parkinsonism in patients with T2DM might in part account for these findings. However, the association between PD and T2DM in epidemiological studies remained significant after adjustment for vascular risk factors and exclusion of participants with clinical [DB19]cerebrovascular disease.[48 49] Other MRI studies ~~using MRI[DB20] assessments~~ of the presence of cerebrovascular disease and leukoaraiosis showed no differences between groups of PD patients with or without diabetes to explain the different phenotypes.[51]
- **Dopaminergic medication**~~:~~. The effect of some ~~of the~~ anti-PD medications on glucose metabolism has been suggested as a potential confounding factor, ~~as~~ since evidence suggests a reciprocal regulation between insulin and brain dopaminergic activity. Chronic treatment with levodopa has been

shown to induce decreased glucose tolerance, hyperglycaemia and hyperinsulinaemia.[54 55] On the other hand, bromocriptine increases insulin sensitivity and improves glycaemic control, and is licensed for the treatment of diabetes.[56] However, reduced insulin-mediated glucose uptake,[54] and inhibition of early insulin secretion and long term hyperinsulinaemia and hyperglycaemia after glucose loading [57] have also been found in samples of drug-naïve patients, supporting the hypothesis that abnormal insulin signalling and glucose metabolism predate dopaminergic treatment in PD patients.

- **Cellular and molecular biology**: ~~. There is growing evidence from various areas of research suggesting a common link between diabetes and PD and i~~It has been hypothesised that aberrant insulin signalling might ultimately lead to insulin resistance and diabetes, and put ~~an~~ individuals at increased risk for PD. Mitochondrial dysfunction, neuroinflammation, increased endoplasmic reticulum stress, abnormal protein aggregation and metabolic abnormalities are common to both diabetes and PD, suggesting a pathophysiological link.[46 58]

**Therapeutic implications**

The common pathophysiological mechanisms shared by T2DM and PD are particularly relevant as they may lead to more effective treatments or disease modifying therapies ~~f~~which target both of these conditions. ~~or PD and T2DM.~~ A prospective observational study showed that treatment with metformin combined with sulfonylureas might have a protective effect on the risk of developing PD in a Taiwanese cohort of diabetic patients.[59] Special attention has focussed on the

potential neuroprotective properties of peroxisome proliferator activated receptor gamma (PPAR-γ) and its coactivator 1-α (PGC1α) due to its pivotal role in mitochondrial respiration and gluconeogenesis~~, and as potential target for neuroprotective agents in PD~~. PPAR-γ agonists thiazolidinediones, pioglitazone and rosiglitazone~~,~~ have been successfully tested[DB21] ~~for their neuroprotective potential~~ in animal models of PD though their underlying mechanisms are still unclear[DB22].[60] The potential therapeutic effect of these drugs on PD was further supported by a retrospective cohort study which showed a 28% lower rate of developing PD in those diabetic patients treated with thiazolidinediones compared to other anti-diabetic drugs.[61] These results prompted a large, multicentre, double-blind, placebo-controlled clinical trial including 210 patients randomly assigned to 45mg/day pioglitazone, 15mg/day pioglitazone or placebo to assess the potential effect on PD patients. Results failed to show any significant benefit on motor symptoms measured by the UPDRS and the authors concluded that pioglitazone is unlikely to modify clinical progression in PD at the doses studied.[62]

More promising are the preliminary clinical results shown by exenatide, a synthetic agonist for the glucagon-like peptide 1 (GLP1) receptor licensed for the treatment of diabetes, which has been evaluated as a neuroprotective agent in patients with PD (for a detailed description of potential mechanisms linking PD pathogenesis and GLP1 receptor stimulation, see review by Athauda and Foltynie).[63] An initial open label randomised controlled trial comparing 20 patients with PD treated with exenatide and 24 PD patients acting as controls showed a clinically relevant improvement in motor and cognitive domains in the treatment group after 12 months.[64] Further studies with larger samples are currently on going (ClinicalTrials.gov number NCT01971242).

## BODY WEIGHT AND ENERGY METABOLISM

Extensive research on the mechanisms ~~controlling~~ governing body weight, feeding behaviour and energy metabolism has provided insight into the complex interactions between ~~the~~ peripheral signals and the central nervous system. The classic concept of anatomically distinct ~~"~~satiety/feeding~~"~~ centres have been gradually replaced by a more complex model ~~formed by~~encompassing a network of interconnected neurons of homeostatic and hedonic systems, receiving and integrating multiple orexigenic and anorexigenic signals from peripheral tissues, nutrients and other areas of the central nervous system~~.~~ (Figure 2).~~-~~[65-67]

### Epidemiology

The mechanisms regulating food intake might be ~~involved~~ implicated in other behaviours and brain functions including learning and memory, and the~~a~~ positive association between obesity, brain atrophy and dementia is well recognized.[68] A causal relationship between being overweight and PD is more controversial and results from prospective epidemiological studies are inconclusive.[69] Some have shown a positive association of indices of obesity measured by body mass index (BMI) [70-72] and triceps skinfold thickness [73] with an increased risk of PD but these results have not been reproduced in other cohorts.[74 75]

On the other hand, the inverse association is well recognized and unintentional weight loss has been consistently reported with PD (affecting approximately 50% of patients ~~with PD~~). [71 76-78] A meta-analysis including 871 patients showed an overall reduction of 1.73kg/m$^2$ in patients with PD ~~in comparison~~compared with controls, with

a positive association with disease severity but not with disease duration.[79] This weight loss carries important clinical implications as it seems to be associated with a more severe disease progression[80] and to correlate inversely with health-related quality of life. [81]

Several mechanisms ~~-~~have been proposed to explain the weight loss in PD, although it is likely that these ~~are~~ include intrinsic disease factors, as well as both peripheral and central mechanisms ~~multiple, given the multifocal involvement of different systems in PD~~.[82]

**Parkinson's disease intrinsic factors**

- **Dopaminergic dysfunction**: ~~-~~ Due to the relevant role of dopamine in regulation of the hedonic mechanisms of feeding behaviour,[83] dopamine dysfunction producing anorexigenic signals in the hypothalamus has been proposed as one of the causes contributing to ~~the~~ weight loss in PD.
- **Levodopa**: ~~-~~ Despite the fact that ~~Though~~ weight loss has been shown to be more prominent after levodopa treatment initiation in observational studies,[84] [85] it seems that the levodopa requirement simply reflects disease severity. In addition, weight loss in PD has been well reported before treatment with dopaminergic therapies, ~~-~~[86] sometimes predating the onset of motor symptoms.[77]
- **Imbalanced energy expenditure/intake**: ~~-~~ Reduced caloric intake secondary to motor (rigidity, impaired hand coordination) and gastrointestinal (dysphagia, reduced bowel motility, upper gastrointestinal symptoms) complications have been proposed as a factor ~~of a~~driving the potential energy imbalance contributing to weight loss. However, several studies have demonstrated that weight loss occurs despite an increased energy intake in

patients with PD.[77 86] Given the correlation between weight loss and disease severity,[79 87] motor symptoms (tremor, rigidity) and motor complications (dyskinesias) could potentially increase the energy expenditure [DB23]at rest resulting in weight loss. However, other studies have demonstrated that the total daily energy expenditure is not higher in PD patients with weight loss comparing to PD patients without weight loss [88] and healthy controls,[89] arguing against the possibility that abnormally elevated energy expenditure contributes to weight loss in PD.

**Peripheral mechanisms of feeding behaviour regulation**

- **Leptin**: Measurement of leptin [87 90] and other adipokines [91] have shown no statistically significant differences in patients with PD and weight loss compared to PD without weight loss and controls. Despite results showing a trend of reduced levels in PD patients overall, ~~there is a correlation~~this is correlated with BMI and~~, therefore~~ it seems that this reduction of leptin levels ~~is more~~most likely ~~a consequence reflecting~~reflects the reduced body fat tissue content rather than being a causal factor for weight loss.
- **Ghrelin**: More interesting results come from study of ghrelin. Ghrelin levels rise with prolonged fasting and fall rapidly after food ingestion, with an overall negative correlation with body weight. In PD patients, however, there is a lower plasma ghrelin concentration in those patients with lower BMI [92] and a reduction of the rising ghrelin levels after the postprandial fall in patients with PD and idiopathic RBD,[93] suggesting dysregulation of its secretion. Since~~As~~ RBD is considered a putative pre-motor stage of PD, ghrelin has been proposed as a potential peripheral biomarker for early PD.[93] Recent studies demonstrated that ghrelin exerts a number of roles in other extra-

hypothalamic tissues ~~such as the~~(including the hippocampus and ~~the~~ mesolimbic dopaminergic system)~~,~~ and is implicated in learning and memory, reward behaviour, motivation, anxiety and depression.[94] It also activates the dopaminergic nigrostriatal system by stimulating the dopaminergic neurons of the substantia nigra, increasing the dopamine turnover in the dorsal striatum.[94] More importantly, ghrelin is reported to have neuroprotective properties in the nigrostriatal system in experimental animal models of PD.[95] Reduction of apoptosis, inflammation and enhancement of mitochondrial bioenergetics seem to mediate the neuroprotective effects of ghrelin in PD involving AMPK (5' adenosine monophosphate-activated protein kinase) and PGC1α pathways at a molecular level.[96] Interestingly, this regulatory pathway of mitochondrial function has also been suggested as a potential therapeutic target in neuroprotection for PD and T2DM [46] (~~-~~see '*Diabetes and glucose metabolism*' above). Though these findings need to be replicated in humans, ghrelin appears a promising therapeutic target for disease neuroprotection and treatment of NMS such as body weight, apathy and depression.

**Central mechanisms of feeding behaviour regulation**

- **Deep brain stimulation**: ~~.~~ ~~-~~The role of the central regulatory hypothalamic mechanisms in weight disturbances in PD has recently attracted much attention in part due to the effects of deep brain stimulation (DBS) on body weight ~~in PD~~. Rapid weight gain has been consistently reported in multiple studies of~~in~~ patients with PD after subthalamic nucleus (STN) DBS, which greatly exceeds the weight loss seen in medically treated patients.[97-100] These effects have not been seen in patients with essential tremor undergoing DBS of the motor thalamus.[101] ~~Though v~~Various mechanisms have been

postulated, buti itt seems that STN DBS may induce changes in the regulatory mechanism of the hypothalamus with normalization of energy metabolism.[102] These effects seem target dependant, being more marked when in bilateral STN stimulation (compared to unilateral STN stimulationin comparison to unilateral stimulation,[103] in the STN rather than theor globus pallidus internus (GPi) stimulation[104]) and with more medial position of the electrodes in STN DBS.[105] [DB24]A dDirect current diffusion of electrical current of the DBSfrom the site of stimulation to the hypothalamic nuclei is unlikely and a recent study assessing the global function of the hypothalamus in PD patients after DBS did not show any abnormalities of the hypothalamic-adrenal, hypothalamic-gonadal and or hypothalamic-somatotropic axes.[106] A stimulatory effect of the DBS electrode on fibre bundles projecting from or to the hypothalamic nuclei involved in the regulation of feeding behaviour and metabolism is a more plausible hypothesis, although the exact pathways remain to be elucidated. In PD patients with STN DBS, despite high leptin levels secondary to the weight gain, there is an increase of the orexigenic neuropeptide Y [107] [108] and it has been hypothesized that DBS might make the hypothalamic neurons of the infundibular nucleus resistant to the anorexigenic effect of leptin.

- **Lateral hypothalamic area**:- Only a few studies have explored the hypothalamic mechanisms of homeostatic regulation of feeding behaviour in patients with PD. Given the high prevalence of sleep abnormalities in PD patients, these studies have focused on the lateral hypothalamic area and orexin and MCH neuronal populations. These neurons play an important role in the sleep-wakefulness cycle and are also involved in energy and feeding regulation and its integration with arousal. Both neuronal populations are inhibited by leptin, activated by ghrelin and promote feeding .- (Figure 2). As described previously, pathological studies have shown a severe reduction of

both neuronal populations in PD patients which correlates with disease severity,[26 27] that could be involved in the pathogenesis of weight changes in PD patients.

- **Hedonic system**: Dysregulation of the dopaminergic mechanisms of hedonic control of feeding behaviour might also contribute to weight changes in PD. Although dopaminergic medications are generally reduced following STN DBS surgery, eating disorders secondary to behavioural changes following DBS may occur due to abnormalities on dopaminergic signalling similar to the alterations responsible for impulse control disorders, as proposed by some authors.[82] The involvement of hedonic dysregulation in weight gain in PD is supported by changes in metabolism after DBS in brain areas including the orbito-frontal and anterior cingulate cortices using PET imaging.[109]

**Therapeutic implications**

Only a few studies have assessed nutritional interventions and therefore there is not strong evidence to give general recommendations. However, it is now well accepted that nutritional assessments should be part of the routine work-up of PD patients with PD and nutritional interventions may improve the PD associated related weight abnormalities. Individualised dietetic advice can improve nutritional status and quality of life in malnourished PD patients on medical treatment [110] and nutritional interventions have also been shown to be effective in weight control in patients with PD after DBS-STN surgery.[111] Due to the interaction betweenin the small intenstine absorption in the small intestine betweenof L-dopa and amino acids[DB25], dietary interventions focusing on protein manipulation have been suggested in PD patients on treatment with L-dopa and motor fluctuations. WhilstThough there is not

~~enough~~insufficient evidence to support low-protein diets and they might induce weight loss and nutritional deficits in the long term, protein-redistribution interventions have shown an improvement in motor function with better results when carried out in early stages of the disease.[112]

## OSTEOPOROSIS AND BONE METABOLISM

Patients with PD have an increased risk of fractures, most commonly ~~involving~~ affecting the hip.~~,~~[113] ~~and their o~~Subsequent clinical outcome tends to be poorer than ~~in~~ the rest of the population.[114] A meta-analysis including nine studies showed a similar result, with a combined effect of the risk of fracture in patients with PD of 2.28 (95%CI 1.83-2.83).[113] Indeed, PD has been found to be the strongest single comorbidity contributing to fracture risk in the Global Longitudinal Study of Osteoporosis in Women cohort.[115] Several causative factors have been implicated ~~as responsible for the increased fracture risk~~ in addition to the increased rate of falls ~~intrinsic~~ inherent to the disease itself (secondary to postural instability, gait freezing, ~~cognitive impairment,~~ orthostatic hypotension~~, and~~ motor fluctuations and cognitive impairment)~~.~~ (Figure 3). Patients with PD have abnormalities of bone metabolism which also contribute~~s~~ to the increased risk of fractures. A meta-analysis ~~concluded~~ confirmed that patients ~~with PD~~ have significantly reduced bone mineral density at the femoral neck, lumbar spine, total hip and total body [113] in comparison with healthy controls. Using T-score values, the overall combined mean difference was~~is~~ significantly lower in patients with PD (-1.05; 95%CI -1.26 to -0.84).[113] Immobility and reduced body mass index, both commonly seen in PD, are risk factors for osteoporosis but ~~other~~ several other factors disrupting bone metabolism may contribute to bone loss.

**Role of vitamin D**

Vitamin D has a crucial role in bone metabolism and its deficiency results in bone loss by a compensatory hyperparathyroidism. The prevalence of vitamin D deficiency is significantly higher in PD patients ~~with PD in comparison~~compared with healthy controls (up to 55% of patients in some studies) [116] [117] and patients with other neurodegenerative conditions.~~.~~ [118] ~~which~~ This suggests that this is an intrinsic ~~factor~~ feature of the disease and not only a deficit secondary to reduced sunlight exposure. Vitamin D has ~~also~~ important effects on brain function~~ing~~ and its receptors are strongly expressed in ~~the~~ dopaminergic neurons of the substantia nigra.~~.~~ [119] It has been hypothesized that a chronic vitamin D deficiency might contribute to~~in~~ the pathogenesis of PD.[120] The potential association of these two conditions is supported by the longitudinal study by Knekt *et al* [121] which showed that pre-existing vitamin D deficiency increased the risk of developing PD in a cohort of 3173 Finnish subjects after adjustment for potential confounders (patients with highest vitamin D concentration had a RR = 0.33; 95%CI 0.14-0.80 of developing PD in comparison to the patients with the lowest concentration). A possible link at transcriptional level has also been suggested, though studies looking for an association between some vitamin D receptor polymorphisms and the risk of PD have yielded conflicting results. [122] In summary, whilst ~~Though~~ the potential pathogenic role of vitamin D deficiency in PD remains controversial, it is now generally recommended that vitamin D levels should be routinely checked and replaced if needed in all patients with PD for an adequate assessment of fracture risk.[123]

**Role of homocysteine**

Hyperhomocysteinaemia is an independent risk factor for fractures through a dual mechanism reducing bone mineral density and disrupting cross-linking of collagen.[124] Homocysteine has been shown to be elevated in L-dopa treated PD patients ~~with PD in comparison to~~compared with controls, but similar results were not found in drug naïve patients.[125] Plasma levels correlate with disease severity and high concentrations showed an increased risk of hip fractures in PD patients (RR = 2.42; 95%CI 1.21-3.63).[126] The underlying mechanism causing hyperhomocysteinaemia in PD patients is not understood, however ~~though~~ L-dopa therapy and possibly vitamin B12 and folate deficiency might be implicated.[124 125]

**Therapeutic implications**

Despite the substantial fracture risk associated with~~to~~ PD, bone health assessment and management have been largely ignored and no clinical guidelines address this issue specifically in PD patients. Taking into account these limitations, several recommendations can be made (Figure 3).

- **Fracture risk estimation**: ~~.~~ FRAX [DB26]and Qfracture are useful tools to estimate fracture risk and guide those who should undergo dual X-ray absorptiometry (DEXA) for a more accurate evaluation of bone mineral density. FRAX assessment might be slightly superior in PD patients in the neurology clinic.[127]
- **Bisphosphonates**: ~~It is unclear if patients with~~Until evidence exists to support PD patients ~~should have~~having a different DEXA threshold for anti-osteoporotic therapy, ~~so~~ it seems reasonable to apply general population recommendations regarding treatment with bisphosphonates.[123] Both risedronate and alendronate have demonstrated an improvement of bone mineral density and reduction of hip fractures in patients with PD.[128-130]

- **Vitamin D**: Levels should be routinely measured in PD patients and replaced if deficient or insufficient. Vitamin D supplementation[131] and increased sunlight exposure[132] have both demonstrated an amelioration of hypovitaminosis D, an increase in bone mineral density levels and a reduction of the fracture risk in PD patients.
- **Non-pharmacological therapies**: An integrated approach including non-pharmacological therapies such as exercise and lifestyle modifications should be included as part of a holistic care of PD.

## CONCLUSION

Metabolic and neuroendocrine abnormalities are common in PD. They have been associated with multiple NMS and several studies have demonstrated their clinical implications. Clinicians should be aware of these ~~implications~~ abnormalities and include their assessment as part of routine clinical practice. Recognition and treatment of ~~the~~ neuroendocrine and metabolic disturbances ~~in clinical practice~~ will intuitively improve PD care and patients' quality of life. The underlying pathophysiology of neuroendocrine disturbances in PD warrants further research. A better understanding of thise ~~underlying~~ pathogenesis will consequently lead to accurate peripheral biomarkers of these abnormalities ~~and disease progression~~, and will enable the development of more effective targeted therapeutic interventions and neuroprotective drugs.

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E P-F wrote the first draft, contributed to project conception and organization. PMB and TF revised and critically reviewed the manuscript for intellectual content. TTW contributed to project conception and organization, and critically reviewed the manuscript for intellectual content.

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The authors have no competing interests


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## FIGURE LEGENDS

**Figure 1. Circadian system and its dysregulation in Parkinson's disease.**

The circadian system is composed of a central pacemaker and peripheral oscillators. The SCN of the hypothalamus is the central pacemaker and its rhythmic activity is the result of the expression of ~~several~~ clock genes. It regulates the circadian rhythms of the peripheral oscillators by efferent neural and humoral signals (circulating melatonin). The SCN is entrained to the 24 hour environmental light cycle using the photic information received through the retino-hypothalamic tract and information on body functions through circulating melatonin and other time cues from peripheral oscillators. It also regulates melatonin secretion via an indirect multi-synaptic pathway reaching the pineal gland via the paraventricular nucleus of the hypothalamus and the superior cervical ganglion. Melatonin secretion during darkness is the main endogenous entraining agent of the circadian system exerting its function on peripheral oscillators and also a negative regulatory feedback on SCN activity. Main disruptions found in PD are shown in shaded boxes.

AUC, area under the curve; PVN, paraventricular nucleus; RHT, retino-hypothalamic tract; SCG, superior cervical ganglion; SCN, suprachiasmatic nucleus.

**Figure 2. Feeding behaviour regulatory mechanisms and their dysregulation in Parkinson's disease.**

Feeding behaviour is regulated by complex interactions between homeostatic and hedonic mechanisms. The hypothalamus is the central component of the homeostatic control with an interaction between both anorexigenic (CART and MSH neurons in the infundibular nucleus) and orexigenic signals (NPY and MSH synthesized by the infundibular nucleus and orexin and MCH neurons in the lateral

hypothalamic area). The activity of the hypothalamic neurons is influenced by peripheral humoral signals with opposite functions including circulating molecules, namely leptin (anorexigenic) and ghrelin (orexigenic), gut satiety peptides (CCK, OXM, PYY) and also levels of insulin, glucose or fatty acids. Leptin is an adipokine synthesized by the fat tissue reflecting the energy reserve and produces anorexigenic effects, whereas ghrelin, a peptide synthesized by the gastric mucosa during fasting, promotes feeding, weight gain and stimulates growth hormone secretion. The hedonic control (sensorial information, food reward systems) is integrated in several areas including the mesolimbic dopaminergic system, insular cortex, dorsal striatum, and anterior cingulate and orbitofrontal cortices. Main disruptions found in PD are shown in shaded boxes. Orexigenic areas are represented in diagonal line ovals and anorexigenic areas in white ovals.

AgRP, agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; DBS, deep brain stimulation; INF, infundibular nucleus; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; MSH, melanocyte-stimulating hormone; NA, nucleus accumbens; NPY, neuropeptide Y; OXM, oxyntomodulin; VTA, ventral tegmental area.

**Figure 3. Bone health assessment and management in PD patients.**