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INVITED REVIEW

Similarities, differences and overlaps between frailty and Parkinson's disease

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Parkinson's disease is a neurodegenerative disorder clinically characterized by bradykinesia, rest tremor, rigidity, and postural and gait disturbances, which are frequently observed in older people. It also shows non-motor symptoms, such as depression, anxiety, cognitive impairment and dementia. The number of patients is gradually increasing worldwide. Aging is a risk factor for the onset of Parkinson's disease, and various physiological effects of aging influence its progression. Frailty is a geriatric syndrome in which the reversible and vulnerable status between robustness and disability is affected by various physiological stressors with aging. Frailty consists of physical, psychological and social aspects. Furthermore, sarcopenia, a syndrome characterized by the loss of muscle mass, strength and function, is also significantly associated with frailty. To maintain the quality of life of older people, frailty, including sarcopenia, should be quickly and appropriately managed. Polypharmacy is an important factor causing the progression of frailty in geriatric syndrome. Although Parkinson's disease and frailty have similar symptoms, and are considered to affect each other, the clinical features and mechanisms of both largely remain unclear. Nevertheless, little literature on the relationship between frailty and Parkinson's disease is currently available. This narrative review aims to clarify the relationships between Parkinson's disease and frailty, not only on the physical, but also on the mental, cognitive, and social aspects and issues regarding polypharmacy in Parkinson's disease explored by previous studies. **Geriatr Gerontol Int 2022; 22: 259–270**.

Keywords: frailty, geriatric medicine, Parkinson's disease, polypharmacy, sarcopenia.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, in combination with rest tremor or rigidity.[1] As the disease progresses, gait disturbance, postural instability and motor fluctuations, such as the wearing-off phenomenon, shorter medication effect and dyskinesia, also occur. Since levodopa, a basic medication for PD, was first introduced,[2] the rate of mortality as a result of PD has continued to decrease significantly.[3]

The world is currently facing an aging society. According to a Japanese government report, the global population of people aged >65 years currently exceeds 60 million, as compared with 13 million in 1950.[4] Additionally, the ratio of the population of people aged >65 years in developed countries was 17.6%, as compared with 7.7% in 1950.[4] Older people usually have various comorbidities, such as hypertension, diabetes mellitus, osteoporosis and neurological disorders. Of these, PD is one of the most frequent neurodegenerative disorders among older people. Between 1990 and 2015, the prevalence of PD increased by 117.8%[5]; therefore, it is referred to as "Parkinson's disease pandemic", as the number of patients is expected to keep increasing.[6]

Aging is a risk factor for the onset of PD; therefore, patients with PD might have various physical, mental and social disabilities. Meanwhile, frailty is a current geriatric issue defined as a reversible condition between robustness and disability, focusing not only on physical status, but also on mental and social status. The relationship between PD and frailty largely remains unclear, and only a few studies on this relationship are currently available; thus, we aimed to clarify the relationships between PD and frailty in the physical, cognitive, mental, social and geriatric aspects of PD.

Concept of PD and frailty

PD was first described by a British doctor, James Parkinson, in 1817, and named by a French neurologist, Jean-Martin Charcot.[7] Over 200 years, many clinical and basic studies have been carried out. As mentioned in the previous chapter, PD presents with various clinical symptoms. Furthermore, before the onset of motor symptoms, constipation, rapid eye movement, behavioral sleep disorder, depression and anxiety are frequently observed as non-motor symptoms.[8] Furthermore, as the disease severity advances, orthostatic hypotension and cognitive impairment were observed as comorbidities. Importantly, cognitive impairment and dementia are highly prevalent in advanced PD, found in approximately 60% of patients with PD after 10 years and 80% after 20 years of disease, respectively.[9]

The Lewy body, consisting of α-synuclein, is a characteristic pathological entity of PD, and is distributed in the substantia nigra, locus coeruleus and dorsal vagal nucleus. Although the pathological progression of the Lewy body largely remains unclear, it is proposed that its deposition is initiated in the dorsal vagal nucleus, and spreads to the brainstem and cerebral cortex,[10] while it is also initiated in the olfactory bulb and spreads to the central nervous system.[11] Approximately 50–70% of dopaminergic neurons are lost at the onset of motor symptoms.[12] However, as histological changes also occur with aging, physiological and

homeostatic dysfunctions would influence the onset of PD, isolated from aging.[13] A previous epidemiological study showed that the prevalence of PD increased with age, and it was 10-fold in people their aged in their 80s compared with those aged in their 50s[14]; that is, aging is a risk factor for the onset of PD.[15]

Frailty has been introduced as a concept of geriatric syndrome regarding the preservation of the physically and mentally robust status of older generations. The term "frailty" is still not clearly defined among gerontological experts; however, the currently agreed definition is "a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors".[16] The assessment of frailty is generally expressed as two main models: the phenotype model[17] and the cumulative deficit model.[18] The phenotype model is mainly based on how many clinical features are matched on the five physical frailty criteria: (i) slow gait speed; (ii) weight loss; (iii) muscle strength; (iv) fatigue; and (v) physical activities.[16] Of these five basic evaluation domains, zero is regarded as robust, one or two as pre-frailty and three or more as frailty. The cumulative deficit model is a proportion calculated using the frailty index, which consists of various evaluation domains, including cognition, emotional status and physical functioning.

Focusing on physical frailty, the international clinical guideline was published in 2019.[19] The occurrence of comorbidities is regarded as a risk factor for frailty. Furthermore, in addition to physical frailty, cognitive and social frailty, which entirely influence each other, are also important components of gerontological medicine. Additionally, oral frailty is significant for older people, and oral hygiene is significantly associated with systemic disease and healthcare. Sarcopenia is a clinical syndrome characterized by progressive muscle weakness, decreased skeletal muscle mass and decreased physical function, causing physical disability, low quality of life and mortality, which are strictly related to frailty.[20,21]

Integrated management for frailty, including sarcopenia, is essential for older people, and geriatric aspects should always be kept in mind by medical providers. Of these, older people generally have comorbidities; thus, various medications are prescribed to manage them. However, they sometimes influence each other interdependently and are harmful to the patients. Importantly, polypharmacy is also associated with the progression of frailty in older populations.

Multidimensional effects, such as oxidative stress, mitochondrial dysfunction, homeostatic dysfunction and endocrine dysfunction, will occur during the progression of frailty, and physiological changes are thought to be shared between frailty and PD through aging.

Relationships between PD and frailty

Relationship between PD, physical frailty and sarcopenia

The relationship between PD and frailty has been gradually documented for two decades. However, few studies are, even in the present day, available about them. Furthermore, most studies are focused on the physical aspects, probably because PD has a similar syndrome to physical frailty. The previous studies on the relationship between physical frailty and PD that we know of are presented in Table 1. In summary, the prevalence of frailty in PD ranges from 3.4% to 84%,[22–37] and as high as 10%, even in prodromal PD.[35] These variable ranges of the prevalence of frailty were derived from the study setting, participants' demographics, populations and frailty assessment methods. Fried's phenotype criteria were used to assess frailty in most studies.[22-25,29,33,35,36] Several studies have used the frailty index.[29,36] Two studies used the clinical frailty scale to assess frailty.[30,32] Phenotype criteria are frequently used for the assessment of frailty due to their simplicity of use, unlike the frailty index that is thought to be a complicated technique for use in daily clinical practice.[34] The prevalence of frailty was higher in the frailty index measurement than in the phenotype model in previous studies. Furthermore, most of the studies were cross-sectional studies, and only one pathological study was carried out using the prospective cohort study design.[27] Additionally, a recent study used claim-based information to analyze the relationship between frailty and PD, as a different prospect from previous studies.[37] Frailty was generally associated with older age of patients, longer disease duration, advanced disease severity as determined by the Hoehn–Yahr stage or the Unified Parkinson's Disease Rating Scale (UPDRS) and high levodopa equivalent dose.[23,24,32,33] Furthermore, female patients with PD tended to experience frailty more frequently.

The prevalence of sarcopenia in PD ranges from 6.6 to 55.8%.[29,32,38-45] This wide range of results depends on the characteristics of the participants and the evaluation method. The relationship between sarcopenia and PD is presented in Table 2. In previous studies, sarcopenia was mostly evaluated by the European Working Group on Sarcopenia in Older People method,[20,38-40,42,44,46] and the validated version was used in an Asian study.[29] Vetrano *et al*. compared three different evaluation methods for sarcopenia in PD, resulting in the highest agreement in European Working Group on Sarcopenia in Older People and the International Working Group for Sarcopenia.[40,47] Among studies related to sarcopenia and clinical manifestations of PD, relationships between disease severity by Hoehn–Yahr stage, UPDRS, frequency of falls and sarcopenia were observed.[32,42,45] Additionally, in a report, the prevalence of sarcopenia in female PD patients was lower compared to male patients.[46] A recent meta-analysis showed that the fall incidence was higher in sarcopenic PD patients than in non-sarcopenia patients, whereas sex differences were not found in the study.[41] Considering that the relationship between sarcopenia and PD influences non-motor aspects, depression and cognitive impairment are both related to sarcopenia,[45] whereas other studies did not show the relationships between sarcopenia and non-motor aspects of PD.[32,39]

As aforementioned, Fried's phenotype criteria, an evaluation method for frailty, and symptoms of PD both share the same clinical syndrome. All Fried's phenotype criteria, weight loss, exhaustion, low gait speed and decreased physical activity, are also well-recognized symptoms of PD. Furthermore, decreased grip strength was also observed in patients with PD. Thus, it is important to consider the overlap between the over-diagnosis of frailty and PD.

All components of Fried's criteria can be found in patients with PD. First, weight loss is mainly caused by energy expenditure imbalance.[48,49] In the early stages of the disease, non-motor symptoms, such as gastrointestinal dysfunction, dysphagia and depression, are associated with food intake.[48,49] Furthermore, rigidity, rest tremor and levodopa-induced dyskinesia can consume energy.[48,49] Additionally, medication-associated weight loss might occur due to levodopa intake, resulting in increased growth hormone secretion.[50] In previous studies, weight loss in PD was physiologically found to be caused by fat loss, which is different from the weight loss found in frailty associated with sarcopenia, which is attributed to muscle mass loss.[49] However, sarcopenia is also observed in patients with PD. As it is PD-associated, frailty and sarcopenia-associated weight loss simultaneously occur in these patients. Therefore, it is difficult to distinguish sarcopenia from PD-associated weight loss. Pharmacological and non-pharmacological interventions, such as appropriate treatment for

Table 1 Previous studies associated with Parkinson's disease and physical frailty

First author	Year published	Study designs	Participants (*n*)	Frailty evaluation method	Prevalence of frailty, *n* (%)	Mean age at evaluation, years (SD)	Mean PD disease duration, years (SD)	PD evaluation method (motor)	PD evaluation method (non-motor)
Ahmed	2008	Cross-sectional	PD: 50	Phenotype model	Frailty: 16 (32.7%) Non-frail: 33 (67.3%)	70.8 ± 9.2	—	UPDRS	—
Roland *et al.* (Ref. 23)	2012	Cross-sectional	29	Phenotype model	Frailty: 1 (3.4%) Pre-frailty: 19 (65.5%) Non-frailty: 9 (31%)	66.4 ± 8.5	7.2 ± 4.6	H-Y	PDQ-39
Roland *et al.* (Ref. 25)	2012	Cross-sectional	17	Phenotype model	Frailty: 5 (29.4%) Pre-frailty: 8 (47.1%) Non-frailty: 4 (23.5%)	Frailty: 65 ± 11.2 Pre-frailty: 65 ± 9.4 Non-frailty: 68 ± 2.6	Frailty: 4.6 ± 1.8 Pre-frailty: 11.1 ± 7.9 Non-frailty: 2.8 ± 2.2	H-Y	—
Roland *et al.* (Ref. 24)	2012	Cross-sectional	PD:15 Control: 15	Phenotype model	Frailty: 4 (26.7%) Pre-frailty: 7 (46.7%) Non-frailty: 4 (26.7%)	Frailty: 63 ± 11 Pre-frailty: 65 ± 10 Non-frailty: 69 ± 1	—	—	—
Roland *et al.* (Ref. 26)	2013	Cross-sectional	13	Phenotype model	Frailty: 3 (23.1%) Pre-frailty: 6 (46.2%) Non-frailty: 4 (30.8%)	Frailty: 67 ± 9 Pre-frailty: 66 ± 9 Non-frailty: 69 ± 1	Frailty: 5.7 ± 1.2 Pre-frailty: 10.7 ± 7.9 Non-frailty: 3.3 ± 2.3	H-Y	—
Buchman	2013	Prospective	Lewy body pathology: 159 (20.1%) Nigral neuronal loss: 106 (13.4%) (All participants: 791)	Phenotype model	—	—	—	—	—
Liotta	2016	Cross-sectional	PD: 18 (All participants: 1331)	FGE	—	—	—	—	—
Torsney	2018	Cross-sectional	PD: 393	CSF	Frailty: 330 (84%)	PD: 82.8	—	CCI	Prevalence of depression, dementia or new cognitive impairment
Peball	2018	Cross-sectional	PD: 104 (Control: 434)	CSHA CSF	Frailty: 37 (35.6%)	PD: 73.8 ± 5.2	12.0 ± 7.9	H-Y MDS-UPDRS Part I–IV ADL	PDQ-39

(*Continues*)

Table 1 Continued

First author	Year published	Study designs	Participants (*n*)	Frailty evaluation method	Prevalence of frailty, *n* (%)	Mean age at evaluation, years (SD)	Mean PD disease duration, years (SD)	PD evaluation method (motor)	PD evaluation method (non-motor)
Tan	2018	Cross-sectional	PD: 93 (Control: 78)	Phenotype model Frailty index	PD Fried's criteria: (27.9%) Frailty index: (69.2)	PD: 66.0 ± 8.5	8.5 ± 5.6	H-Y MDS-UPDRS Part I–IV	—
Rennne	2018	Cross-sectional	PD: 6 (all participants: 241)	TFI	—	PD: 79.3	—	—	—
Lin	2019	Cross-sectional	76	Phenotype model	29 (38%)		PD with frailty: 2.74 (2.82) PD without frailty: 2.12 (2.70)	H-Y, UPDRS Part I–III, S&E ADL	Attention function, Executive function Memory function Visuospatial function
Ntanasi	2020	Cross-sectional	PD: 34 Prodromal PD: 49 Non-PD: 1682	Phenotype model Frailty index	Phenotype criteria PD: 5 (14.7%) Prodromal PD: 5 (10.2%) Non-PD: 65 (3.9%) Frailty index PD: 26 (76.5%) Prodromal PD: 33 (67.3%) Non-PD: 332 (19.7%)	PD: 76 (73–79) Prodromal PD: 76 (73–79) Non-PD: 73 (69–77)	—	—	—
Smith	2021	Cross-sectional	PD: 120	Phenotype model	31.2 (26%)	70.2 ± 8.0		MDS-UPDRS Part I–IV	MoCAGDS
Abraham	2021	Cross-sectional	PD: 62786	CFI	34 708 (55.3%)	—	—	—	—

Abbreviations: ADL, activities of daily living; CCI, Charlson Comorbidity Index; CFI, Claims-based Frailty Index; CFS, Clinical Frailty Scale; CSHA, Canadian Scale of Health and Aging; FGE, Functional Geriatric Evaluation; GDS, Geriatric Depression Scale; H-Y, Hoehn–Yahr stage; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire-39; SD, standard deviation; S&E, Schwab and England Activities of Daily Living Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2 Previous studies associated with Parkinson's disease and sarcopenia

Author	Year published	Study designs	Participants (*n*)	Sarcopenia evaluation method	Prevalence of sarcopenia, *n* (%)	Mean age at evaluation, years (SD)	Mean PD disease duration, years (SD)	PD evaluation method (motor)	PD evaluation method (non-motor)
Barichella	2016	Cross-sectional	PD: 235 Other Parkinsonism: 129	EWGSOP	14 (6.0%)	—	—	H-Y UPDRS Part II–III	MMSE Dysphagia SDQ score
Drey	2017	Prospective cohort	PD: 255	EWGSOP	38%	64.9 ± 5.9	—	MDS-UPDRS Part III	BDI RBDSQ Olfactory test
Vetrano	2018	Cross-sectional	210	FNIH EWGSOP IWG	FNIH sarcopenia: 40.7 (male)/27.5 (female) Severe sarcopenia: 20.0 (Male)/11.3 (female) EWGSOP Sarcopenia: 28.8 (male)/17.5 (female) Severe sarcopenia: 16.8 (male)/18.8 (female) IWG sarcopenia: 35.4 (male)/32.5 (female)	Male: 73.3 ± 7.4 Female: 74.4 ± 6.6	Male: 3.2 (1.1–7.0) Female: 4.0 (1.5–6.7)	UPDRS, ADL	MMSE
Pabell	2018	Cross-sectional	PD: 104 (Control: 434)	SARC-F	Sarcopenia: 58 (55.8)	PD: 73.8 ± 5.2 (Control: 75.3 ± 7.3)	12.0 ± 7.9	H-Y MDS-UPDRS Part I–IV ADL	PDQ-39
Yazar	2018	Cross-sectional	PD: 166 (Control: 249)	EWGSOP	—	PD: Female: 71.57 ± 5.2 Male: 72.76 ± 4.43	—	UPDRS	—
Tan	2018	Cross-sectional	PD: 93 (Control: 78)	Sarcopenia: AWGS	PD Sarcopenia: (17.2) Control (Sarcopenia: (10.3))	PD: 66.0 ± 8.5 (Control: 62.4 ± 8.4)	8.5 ± 5.6	H-Y, MDS-UPDRS Part I–IV	—
Lee	2019	Cross-sectional	PD: 52 (Control: 19)	ASMMI	21 (40.4%)	PD with sarcopenia: 63.7 ± 11.6 PD without sarcopenia: 60.3 ± 9.8 (Control: 60.3 ± 7.6)	PD with sarcopenia: 1.9 ± 2.0 PD without sarcopenia: 2.4 ± 2.4	UPDRS Part I–III, H-Y, S&E	MMSE

(*Continues*)

Table 2 Continued

Author	Year published	Study designs	Participants (*n*)	Sarcopenia evaluation method	Prevalence of sarcopenia, *n* (%)	Mean age at evaluation, years (SD)	Mean PD disease duration, years (SD)	PD evaluation method (motor)	PD evaluation method (non-motor)
Wang	2019	Cross-sectional	PD: 25 Control: 20	CHS-PCF IPAQ-SF	N/A	PD: 63.6 ± 5.5 (Control: 63.0 ± 4.1)	1.70 ± 2.15	H-Y, UPDRS Part I–III, S&E ADL	—
Ozer	2020	Cross-sectional	PD: 70 Control: 85	EWGSOP	22 (31.4%)	PD: 68.3 ± 5.9	PD: 6.0 ± 5.1	ADL, IADL	
Krenovsky	2020	Cross-sectional	PD: 53 Atypical PS: 21 Control: 30	EWGSOP	PD: 4 (7.5%) Atypical PS: 6 (28.6)	PD: 70 ± 10.1 Atypical PS: 70.3 ± 9.7 Control: 70.8 ± 2.0	PD: 61 (16.4) Atypical PS: 103 (25.8) * months	H-Y	—
Lima	2020	Cross-sectional	218	EWGSOP	PD: 103 (47.4%)	70.4 (59.9–76.8)	9.4 ± 6.9	H-Y S&E ADL	PDQ-39 GDS

Abbreviations: ADL, activities of daily living; ASMMI, Appendicular Skeletal Muscle Mass Index; AWGS, Asian Working Group for Sarcopenia; BDI, Beck Depression Inventory; Dysphagia SDQ score, Dysphagia Swallowing Disturbance Questionnaire score; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; GDS, Geriatric Depression Scale; H-Y, Hoehn–Yahr stage; IADL, instrumental activities of daily living; IWGS, International Working Group on Sarcopenia; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire-39; PS, Parkinson syndrome; RBDSQ, Rapid Eye Movement Behavioral Disorders Screening Questionnaire; S&E, Schwab and England Activities of Daily; SARC-F, Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls history questionnaire; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

PD, including dopaminergic therapy for motor symptoms and dysphagia, and nutrition support, should be correctly carried out on the patients.

Exhaustion, also known as fatigue, is a common symptom in PD, resulting in 50% of patients experiencing it in a recent meta-analysis.[51] The assessment of fatigue mainly entails the use of the Movement Disorders Society-UPDRS Part I,[52] included in the non-motor symptom chapter or questionnaire.[53] Although the pathological entity of fatigue remains unclear, it was hypothesized that Lewy bodies spread from the olfactory bulb to the limbic area, associated with anxiety and pain, independently progressed from nigrostriatal deficits.[54] In the Movement Disorders Society report on the treatment for non-motor symptoms, rasagiline is considered potentially useful; however, little literature is available on the treatment for fatigue; thus, further evidence is required to establish a management strategy.[55]

Slow gait is more frequent in patients with PD than in older people, adjusting for age as a confounder. According to previous studies, gait speed in PD is negatively correlated with age, disease severity, and Timed Up and Go test time.[56-58] Furthermore, cognitive impairment, depression and anxiety were negatively correlated with gait speed.[56] Previous experience of falls and fear of falls influences gait speed.[56] Gait speed is considered to be the effect of dopaminergic system deficits that cause bradykinesia and body imbalance. However, Bohnen *et al.* showed that cholinergic denervation, in addition to dopaminergic system failure, also contributed to slow gait speed.[59] This evidence might be consistent with the finding that cholinergic medication using rivastigmine improves gait impairment in PD patients.[60] Decreased gait speed can be treated by levodopa administration, and physiological therapy might also be useful.

During the current coronavirus disease 2019 (COVID-19) pandemic, to make matters worse, the pandemic has promoted sedentary behavior and decreased physical activities.[61-63] Thus, medical providers should pay attention to these low physical activities in patients with PD and manage them for as long as possible.

Little is known about the relationship between muscle strength and PD. Roberts *et al.* showed that grip strength was negatively correlated with motor severity in PD.[64] Furthermore, they reported that medications improved the muscle strength of PD, which hypothesized that central nervous dysfunction, including dopaminergic system failure, might contribute to muscle weakness.[64] At this point, muscle weakness derived from physical frailty and sarcopenia is different from nigrostriatal deficits in PD, possibly resulting in the combination of physical frailty and muscle weakness derived from PD.

Even in healthy older people without neurodegenerative disorders, subtle parkinsonism, which does not meet the diagnostic criteria for PD, is occasionally observed. This phenomenon is generally called the mild parkinsonian sign (MPS).[65] The MPS shows similar clinical features with PD, such as slowness, rigidity, gait and balance deficits, and tremor. Of these, tremors are relatively less frequently observed in MPS.[65] Although the method of evaluation of MPS is still to be defined, it entails at least one UPDRS item for a rating of one or higher,[66] two or more MPSs, or one sign of moderate UPDRS score.[67] The prevalence of MPS in older people varies according to the evaluation method among the 15–95% of people who expressed it.[65]

As for older people, comorbidities, such as orthopedic and other medical problems, might contribute to MPS, which is isolated from nigrostriatal neurodegeneration. However, MPS is thought to cause neuropathological alterations in Lewy body disease and vascular pathology. Furthermore, older people with MPS have a higher prevalence of hyposmia and rapid eye movement sleep disorder than normal controls.[68] Thus, MPS is a risk factor

for the development of dementia, PD and cerebral vascular disease.

Bradykinesia and slow gait speed are common symptoms in older people, and these are also found in frail people as mentioned before; thus, it is possible to misdiagnose frail people with MPS.[69] The mechanism of MPS largely remains unclear; however, the clinical syndrome of MPS should be considered when older people are examined.

PD and physical frailty share similar syndromes; therefore, medical caregivers should pay attention to the elements of frailty potentially observed in PD and, by contrast, frailty symptoms are probably derived from PD itself. Furthermore, although the mechanisms underlying the progression of PD and frailty have remained unclear for the most part, there have been several hypotheses underlying these two relationships, which are biophysiological concordance, such as inflammation, oxidative stress, and mitochondrial and endocrine dysfunctions. These are generally found during aging as homeostatic involvements.

Relationship between PD and psychological frailty

Cognitive impairment and mental illness are significant complications, as well as physical frailty, in patients with PD. Cognitive impairment and dementia have been reported to occur in 60% and 80% of patients with PD 10 and 20 years, respectively, after disease onset.[9] Furthermore, dementia is a risk factor for poor prognosis.[70]

Cognitive frailty has recently been thought to be associated with physical frailty. Ma *et al.* described the concept of these relationships, in which there were two proposed subtypes of cognitive frailty – reversible and potentially reversible cognitive frailty – causes higher mortality in older people.[71,72] Like physical frailty, it is hypothesized that cognitive frailty could occur as a result of oxidative stress, mitochondrial dysfunction and homeostatic dysfunction with aging.[73] Buchman *et al.* described the occurrence of frailty as a potential risk factor for Alzheimer's disease.[74] These relationships might be similar to the biophysiology of PD; however, at present, little literature is available on the relationship between cognitive frailty and physical frailty in PD. Lin *et al.* reported that executive dysfunction is an independent risk factor for the development of physical frailty in patients with PD.[33] In a recent neuroimaging study, lateral occipital gray matter cortex volume reduction was associated with cognitive impairment and physical frailty in PD,[75] which was distinct from the previous volumetric analysis of cognitive impairment in PD,[76,77] according to Chen *et al.* Furthermore, in previous studies that focused on physical frailty in PD, several showed the relationships between physical status and depression or cognitive impairment; however, some did not. These different results might have been caused by the number of participants and evaluation method. There is a large amount of evidence for the treatment of cognitive impairment in PD. Generally, cholinesterase inhibitors are often used to treat dementia or cognitive impairment.[55]

Depression and anxiety are common clinical manifestations of PD. These are frequently observed during the early stages of the disease.[8] Although we have reported the impact of COVID-19 on the mental status of patients with amyotrophic lateral sclerosis, it has also been impacting patients with PD during the pandemic.[78] Several reports have described the impact of COVID-19 on PD, in which mental instabilities have worsened motor symptoms.[61,79] Older people with frailty, depression and anxiety are commonly observed.[80-82] PD patients are likely to experience depression and anxiety, as well as healthy older people. Treatments for depression and anxiety are generally based on medication and psychological interventions. According to a recent Movement Disorders Society report, several medications are recommended for clinical use. Of these, pramipexole, a dopamine agonist, has antidepressant effects; in contrast, other dopaminergic and non-dopaminergic drugs for PD show little evidence of antidepressant effects at present.[55,83] Apart from basic anti-parkinsonian treatment, tricyclic antidepressants and selective serotonin/noradrenaline reuptake inhibitors are usually used for the treatment.[55] Non-pharmacological approaches, such as repetitive transcranial magnetic stimulation and cognitive-behavioral therapy, might be useful. However, few methods are available for the treatment of anxiety.[55]

Cognitive impairment, dementia and mental instability caused by depression and anxiety are common comorbidities in patients with PD. Furthermore, these cognitive and mental disorders are also found in frailty. Furthermore, they might be influenced by physical frailty and motor symptoms in PD; thus, psychological aspects should be considered to be as important as in the physical aspects of frailty and PD.

Relationship between PD and social frailty

Older people might be isolated from society and relationships with other people because of child independence, retirement from work and spousal bereavement. This social isolation might be the possible cause of the worsening physical and mental state in older people. In the literature review, older people in social isolation tend to have depression and cardiovascular disease risk factors, which reflects the social aspects of frailty; however, unified definitions and evaluation methods have not yet been established.[84,85] According to Brunt *et al.*'s conceptual model of social frailty, it consists of various social and general resources, social behaviors and activities, and self-management abilities affecting social fulfillment of basic social needs that cause subjective well-being.[86]

Meanwhile, a recent report has shown that social isolation might worsen the symptom severity of PD.[87] Furthermore, during the COVID-19 pandemic, older people and patients with PD have been forced to be isolated from society.[88,89] In addition to patients with PD, caregiver burden should be considered during this severe era. Previous studies on caregivers of patients with PD showed that they felt the burden, especially those with neuropsychiatric symptoms,[90] and just like those of patients with Alzheimer's disease.[91] Considering this difficult pandemic era, Subramanian recommended virtual video conference support with various experts for PD patients to maintain their quality of life.[92] Hence, patients must be treated using a multidisciplinary approach.

Relationship between PD and oral frailty

Oral frailty has recently been recognized. In Japan, the promotion of 80–20 by the Japanese Ministry of Health, Labor and Welfare and the Japan Dental Association – preserving 20 teeth by the age of 80 years – has for decades been a nationwide healthcare achievement. The proportion of older people between the ages of 75 and 84 was 51.2% in 2016, and the number of achievers has been increasing gradually (Ministry of Health Labor and Welfare: Survey of Dental Diseases. 2016. https://www.mhlw.go.jp/toukei/list/dl/62-28-02.pdf). Tooth loss is significantly associated with physical health and cognitive decline in older people, as well as with frailty, which is not the case for PD.[93] According to Hanaoka and Kashihara, there was no significant difference in the incidence of dental caries between patients with PD and controls.[94] Additionally, the frequency of dental caries has an association with cognitive decline and disease severity.[94] A recent nationwide

cohort study in Taiwan and South Korea showed that oral hygiene was associated with the onset of PD.[95,96] Although the mechanism remains unclear, one hypothesis is the association of systemic inflammation, which is consistent with an increased prevalence myocardial infarction and ischemic stroke in patients with periodontal disease.[97,98] Although few studies on the relationship between oral healthcare and patients with PD are available, oral hygiene must be considered important from the point of view of oral frailty.

Tooth loss is also associated with difficulties in swallowing,[99,100] and both were associated with mortality in a previous study.[101] Swallowing disturbance is common in PD, and this causes patients with PD to develop aspiration pneumonia, even ending in mortality.[102,103] Dysphasia is likely to be observed in the advanced stage of PD; however, it could be objectively found even in the early stages of the disease.[104] In a previous meta-analysis, 35–82% of patients with PD experienced dysphagia.[105] Aspiration pneumonia is a relevant comorbidity in PD, and a previous study showed that 70% of the associated mortality was due to aspiration pneumonia,[103] and the incidence has increased, although the mortality tended to decrease for decades.[106] The prevalence of aspiration pneumonia in PD differed from the study demographics: 2.4% in-hospital patients,[107] 3.8–4.9% on the nationwide survey[106] and the mortality of PD was higher than that of controls.[108] According to a previous study, patients with dementia having Lewy bodies tended to have a higher prevalence of aspiration pneumonia than those with PD, and older and demented patients with PD frequently had aspiration pneumonia.[109] It still remained to be elucidated that levodopa has an impact on dysphagia, as Sutto *et al.* described.[110]

Furthermore, patients with PD frequently experienced xerostomia in a previous study.[111] As mentioned before, patients with PD have a potential risk of oral frailty because of oral hygiene-related comorbidities. Additionally, patients with PD tend to be less conscious of oral health care because of various entities, such as motor disability, cognitive impairment or dementia and socioeconomic situations.[112,113]

Oral frailty is associated with sarcopenia; thus, preserving oral hygiene is essential, although the management of oral healthcare in patients with PD is still challenging, and few studies are currently available. Oral rehabilitation is a crucial factor in oral frailty. It improves the quality of life and oral function of older people.[114,115] To prevent oral frailty, medical and dental care providers should collaborate with each other.[116] This applies to patients with PD, and it should be kept in mind that oral hygiene is significantly associated with sarcopenia and frailty.

Polypharmacy in patients with PD

Polypharmacy is an issue usually encountered in older people; however, there is an obvious definition for it.[117] According to the World Health Organization's statement in 2019, it is generally recognized as the use of five or more ordinal drugs. Importantly, the appropriate management of multiple drugs is required.[118] According to an epidemiological study in Japan, older people who took six or more medications had a higher risk for adverse drug reactions at admission.[119] Furthermore, patients with more than five medications had a high risk of falls.[120]

As many medications for PD have been developed over decades, various pharmacotherapeutics, such as levodopa, dopamine agonists, monoamine oxidase-B inhibitors, adjunctive drugs to levodopa-like catechol-O-methyltransferase inhibitors, zonisamide and istradefylline, are usually used as tailor-made therapies for each PD patient.[121] Furthermore, device-aided therapy, such as deep brain stimulation and levodopa-carbidopa continuous infusion gel (LCIG), are considered when oral medications are not sufficient to manage PD symptoms. Recently, transdermal medication has been introduced to achieve continuous dopaminergic stimulation. Although it was recently hypothesized that intermittent dopaminergic stimulation can cause the onset of motor complications, transdermal medication is thought to be consistent with continuous dopaminergic stimulation. Additionally, as the disease progresses, various comorbidities, such as cognitive impairment, depression and orthostatic hypotension, are frequently found in patients with PD. These comorbidities are different from dopaminergic neuron failure; thus, acetylcholinesterase inhibitors, antidepressants and other noradrenergic drugs are required in addition to anti-parkinsonian drugs.[55]

A recent prescription data-based analysis in Japan showed that daily dose frequencies and the number of tablets of anti-parkinsonian drugs both increased with disease duration.[122] These results might be attributed to the lower medication adherence among patients with PD. However, increasing the number of anti-parkinsonian drugs, including adjunctive medications, is generally inevitable for advanced stage PD patients to maintain their quality of life. Due to the pathophysiological complexity of PD and comorbidities, polypharmacy is common among PD patients.[123] These results were consistent with those of community-dwelling older adults.[124] In a cross-sectional study, patients in the PD with polypharmacy group tended to have lower cognitive impairment than those in the PD with non-polypharmacy group.[125] It is still unclear whether medication reduction contributes to the improvement of cognitive impairment among PD patients; however, a previous study showed that cognitive improvement was observed in patients receiving LCIG therapy.[126] Additionally, LCIG therapy contributes to the reduction of medication efficiently among patients with advanced PD in a large-scale cross-sectional study.[127] Nevertheless, polypharmacy has a possible influence on physical aspects, such as falls and

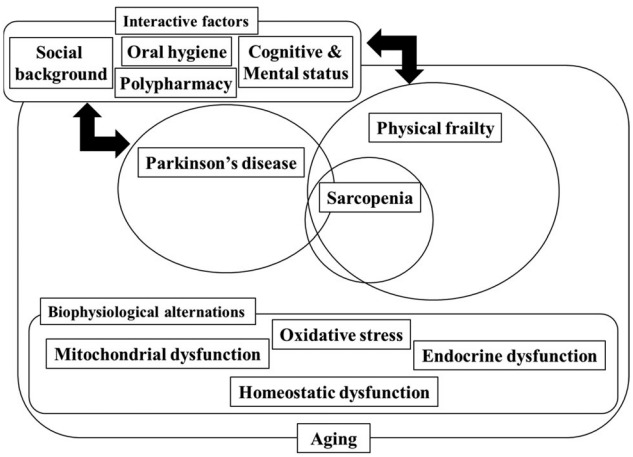

Figure 1 Conceptual diagram. With aging, various physiological alternations occur in individuals. Aging is a risk factor of the onset of Parkinson's disease (PD) and frailty. Sarcopenia is a component of frailty. Biophysiological alternations with increasing age exert an influence on both PD and physical frailty. Furthermore, various interactive factors, such as cognitive and mental status, social background, oral hygiene, and polypharmacy, might also influence both PD and frailty. PD and physical frailty have similar symptoms.

frailty, among older people.[128] However, just like with cognitive effects, little evidence is available on the relationship between physical conditions and polypharmacy among people with PD. In older people, polypharmacy is significantly associated with falls; however, it is unclear whether this applies to patients with PD. Generally, as PD advances, the daily dose and frequency of anti-parkinsonian medications gradually increase, as mentioned earlier. Furthermore, in addition to anti-parkinsonian medications, pharmacotherapy for various comorbidities is usually required. Thus, medical care providers should devise a treatment approach for patients with PD. For instance, a once-daily transdermal patch is a resolution, as well as the implementation of continuous dopaminergic stimulation . At a more advanced stage of PD, device-aided therapy, such as LCIG, will probably have a positive impact in terms of polypharmacy and medication adherence. Furthermore, multidisciplinary interventions are required to improve polypharmacy and drug adherence in patients with PD.[123] The concept of relationships between frailty and PD is shown in Figure 1.

How to manage frailty in patients with PD

How we manage frailty remains to be elucidated. To our knowledge, although scarce literature is available for the interventional study between frailty and PD, a Japanese study using a robotic neurorehabilitation method on frail PD and non-PD patients showed significant improvement in motor abilities.[129] Rehabilitation and exercise, therefore, could be beneficial for the prevention of frail progression in PD patients at present; however, further studies are required to establish the evidence. Nutritional support, and mental and social interventions, are simultaneously required.[130,131] Furthermore, medical providers should pay attention to the oral hygiene of patients with PD. In summary, multidisciplinary care is required to prevent the progression of frailty in patients with PD.

Conclusions

We mentioned various relationships and aspects between frailty and PD through geriatrics prospects in the literature. To our knowledge, this is the first review article that focuses on the relationship between frailty and PD and related geriatric issues beyond the physical aspects.

What is more important for neurologists, gerontologists and general practitioners, and all people who take care of patients with PD in daily clinical practice, is to find the vulnerability quickly and prevent frailty. Furthermore, although management strategies for PD with frailty or sarcopenia have still not been established, the prevalence of these geriatric syndromes should be quickly recognized by medical care providers, and managed appropriately in terms of nutrition, rehabilitation, social support and typical medications for PD.

In conclusion, all those who take care of the patients with PD have to keep in mind that there are potentially more cases of frailty hidden among patients with PD than expected, and care for patients with PD should focus not only on the physical aspects, but also on the mental, social and pharmacotherapeutic aspects.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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