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BALANCE, MOBILITY AND FALLS IN PARKINSON’S DISEASE
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Abstract

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disease which is characterized by resting tremor, rigidity, bradykinesia and postural instability. Advanced PD is often complicated by falls, immobilisation and progressive deterioration of overall physical capability that may jointly contribute to a reduced quality of life and even to increased mortality.

The purpose of this study was to identify risk factors for falls and mortality in PD, to assess the clinical correlates of balance and mobility, and to evaluate the association between orthostatic hypotension (OH), balance and mobility. From a total population of approximately 205,000 inhabitants, 125 patients with idiopathic PD were included in the study. Baseline medical data including occurrence of recent falls were collected, and patients were clinically tested for balance, mobility and orthostatic blood pressure reactions. Falls were thereafter prospectively recorded for two years using fall diaries and follow-up calls. Mortality was documented by reviewing the hospital charts four years after the baseline examination.

In the cross-sectional part of the study, one-third of the patients reported recent falling. Disease duration and severity, recent falling and use of a walking aid were predictors of increased postural sway in PD. Advanced age and severity of the disease were related to impaired balance and mobility in PD patients. Severity of the disease and increased postural sway were independent risk factors for recent falling in PD, whereas measures of mobility were less important in this manner.

Fifty-three percent of the patients had OH in the orthostatic test. Patients with OH had significantly increased postural sway in standing compared to patients without OH. On the contrary, OH was not associated with mobility and walking speed. In the present data, OH was not associated with the risk of falling in PD.

Sixty-three percent of the study patients experienced falls and almost half of the subjects fell recurrently during the two-year follow-up. History of falling and disease severity indicated increased risk of recurrent falls in PD, while patients with slow walking speed had an increased risk of mortality. The results show that balance impairment and falls are common features in PD. Slow walking speed may be associated with increased mortality in PD.

Keywords: accidental falls, mobility, mortality, orthostatic hypotension, Parkinson disease, postural balance
To my family, especially Vesku
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Abbreviations

Δ x  maximum lateral deflection
Δ y  maximum anterior–posterior deflection
ACE  angiotensin converting enzyme
ADL  activities of daily living
ATII  angiotensin II
β-CIT  2β-carboxymethoxy-3β-(4-iodophenyl)tropane
BDI  Beck Depression Inventory
BP  blood pressure
bpm  beats per minute
CI  confidence interval
CM/Pf  centromedian and parafascicular thalamic nuclei
CNS  central nervous system
COMT  catechol-O-methyltransferase
CT  computed tomography
DA  dopamine receptor agonist
DBS  deep brain stimulation
EMG  electromyography
FOG  freezing of gait
GPe  external globus pallidus
GPi  internal globus pallidus
HR  heart rate
H&Y  Hoehn & Yahr
ICD  impulse control disorder
LB  Lewy body
Length x  path length in lateral direction
Length y  path length in anterior-posterior direction
LN  Lewy neuritis
MAO-B  monoamine oxidase-B
MMSE  Mini-Mental State Examination
MPTP  1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine
MRI  magnetic resonance imaging
NMDA  N-methyl-D-aspartate
OH  orthostatic hypotension
OR  odds ratio
PD  Parkinson’s disease
PET  positron emission tomography
PIGD  postural instability and gait difficulty
PPN  pedunculopontine nucleus
PSP  progressive supranuclear palsy
RBD  REM sleep behavior disorder
REM  rapid eye movement
SD  standard deviation
SNC  substantia nigra, pars compacta
SNR  substantia nigra, pars reticularis
SPECT  single photon emission computed tomography
STN  subthalamic nucleus
TD  tremor dominant
TUG  Timed Up & Go
UPDRS  Unified Parkinson’s Disease Rating Scale
VA/VL  ventral anterior and ventrolateral thalamic nuclei
Vim  thalamic ventral intermediate nucleus
List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:


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1 Introduction

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disease with a multifactorial etiology. The major motor symptoms of PD result from the degeneration of dopaminergic cells within the substantia nigra and the subsequent dopamine depletion in the striatum. PD is characterized by resting tremor, rigidity, bradykinesia (slowness of movement) and postural instability. In the industrialised countries, Parkinson’s disease affects about 0.3% of the entire population, more than 1% of those older than 60 years and up to 4% of those older than 80 years (de Lau & Breteler 2006). Therefore, together with Alzheimer’s disease, PD is one of the most commonly encountered neurodegenerative disorders in clinical practice.

Postural instability is usually the last motor symptom of PD to appear and it reflects progression to advanced stages of the illness. There is evidence suggesting that non-dopaminergic deficits emerging in later stages of the disease are related to the presence of postural instability in PD as these symptoms often respond poorly to dopaminergic therapy (Bonnet et al. 1987). However, even though the pathophysiological background of the balance impairment in PD still remains poorly understood, several components, including abnormal postural reflexes, gait abnormalities and detection and integration of sensory information are thought to contribute to the postural instability in PD.

Advanced PD may be associated with recurrent falls, immobilisation and progressive deterioration of overall physical fitness that may jointly contribute to a reduced quality of life and even to increased mortality (Coughlin & Templeton 1980, Grisso et al. 1991, Bennett et al. 1996, Hely et al. 1999, Bloem et al. 2001a, Wood et al. 2002). Up to 70% of PD patients experience falls (Wood et al. 2002). Previous prospective studies have identified independent risk factors for falling in PD, including history of falls, fear of falling, dementia, disease duration, and loss of arm swing (Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002), but the exact pathophysiology of falls remains unsolved. Trauma mostly due to falls is responsible for more than 30% of the acute events bringing patients with PD to emergency clinics (Martignoni et al. 2004, Temlett & Thompson 2006).

The purpose of the present study was threefold: to identify risk factors for falls and mortality in PD, to assess the clinical correlates of balance and mobility in PD, and to evaluate the association between orthostatic hypotension, balance and mobility in PD.
2 Review of the literature

2.1 Parkinson’s disease

2.1.1 General aspects

Parkinson’s disease was first described in 1817 by James Parkinson in his monograph “An Essay on the Shaking Palsy” (Parkinson 1817). Currently the disease is characterized by resting tremor, rigidity, bradykinesia/hypokinesia (slowness of the initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and postural instability.

The diagnosis of PD is mainly clinical. The current diagnostic criteria for parkinsonism require the presence of at least two of the following symptoms: resting tremor, bradykinesia, rigidity, and postural instability. Several sets of diagnostic clinical criteria for PD have been proposed (Gibb & Lees 1988, Hughes et al. 1992, Gelb et al. 1999), the most commonly used being the United Kingdom Parkinson’s Disease Society Brain Bank criteria (Table 1) (Gibb & Lees 1988). The final diagnostic confirmation depends on neuropathology. The accuracy of the clinical diagnosis of idiopathic PD in clinical and clinico-pathological studies has been approximately 70% or higher (Hughes et al. 1992, Litvan et al. 1998, Hughes et al. 2001, Schrag et al. 2002), and diagnostic accuracy as high as 98% has been reported in specialist clinics (Hughes et al. 2002).

Computed tomography (CT) scans and magnetic resonance imaging (MRI) of the brain do not usually show any specific changes in PD, but they can be used to exclude other causes of parkinsonism. Dopamine transporter imaging using $[^{123}\text{I}]\beta$-CIT SPECT or $[^{18}\text{F}]$ fluorodopa PET can be used to estimate nigrostriatal neuronal loss in PD (Brooks 1997).
Table 1. The United Kingdom Parkinson’s Disease Society brain bank diagnostic criteria for Parkinson’s disease (Gibb & Lees 1988).

<table>
<thead>
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<th>Step</th>
<th>Criteria</th>
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| 1    | Diagnosis of parkinsonism  
Bradykinesia and at least one of the following: muscular rigidity, 4–6 Hz resting tremor, postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction |
| 2    | Features tending to exclude Parkinson’s disease as the cause of parkinsonism  
History of repeated strokes with stepwise progression of parkinsonian features  
History of repeated head injury  
History of definite encephalitis  
Oculogyric crisis  
Neuroleptic treatment at the onset of symptoms  
More than one affected relative  
Sustained remission  
Strictly unilateral features after three years  
Supranuclear gaze palsy  
Cerebellar signs  
Early severe autonomic involvement  
Early severe dementia with disturbances of memory, language and praxis  
Babinski’s sign  
Presence of a cerebral tumour or communicating hydrocephalus on computed tomography (CT) scan  
Negative response to large doses of levodopa (if malabsorption is excluded)  
1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) exposure |
| 3    | Supporting features for the diagnosis of Parkinson’s disease (three or more required for diagnosis of definite Parkinson’s disease)  
Unilateral onset  
Rest tremor present  
Progressive disorder  
Persistent asymmetry affecting the side of onset most  
Excellent response (70–100%) to levodopa  
Severe levodopa-induced chorea  
Levodopa response for five years or more  
Clinical course of ten years or more |

PD symptoms progress gradually with time and several rating scales are available for clinical assessment. The most commonly used scales include the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al. 1987) and the Hoehn &
Yahr (H&Y) staging (Hoehn & Yahr 1967). The motor symptoms are usually unilateral at onset, but gradually spread to the contralateral side. The side of initial involvement tends to remain the most severely affected throughout the course of the disease. The progression of motor impairment in PD is usually not linear, and faster progression rates in early PD as well as slowing down of the disease process in more advanced stages of the disease have been suggested (Bonnet et al. 1987, Lee et al. 1994).

Prior to the availability of effective symptomatic treatment, the progression of motor symptoms led to severe disability in less than ten years (Hoehn & Yahr 1967). In the post-levodopa era latencies of up to 40 years to reach H&Y stage 4 or 5 have been reported (Lucking et al. 2000). Tremor as the initial symptom in contrast to other presenting symptoms seems to predict a slower progression of disease (Marttila & Rinne 1977). However, an older age of disease onset, a poorer response to levodopa therapy, gait disturbance and non-motor symptoms such as dementia and cognitive impairment are risk factors for a more rapid progression of symptoms (Marttila & Rinne 1977, Goetz et al. 1988, Marder et al. 1991).

Postural instability is generally the last motor symptoms to manifest itself and it reflects progression to advanced stages of the illness. It predisposes patients to falls and injuries and often responds poorly to dopaminergic therapy. Early onset of prominent postural instability is atypical of idiopathic PD and rather suggests some other cause of parkinsonism, especially that of progressive supranuclear palsy (PSP) (Wenning et al. 1999).

As the disease progresses, patients start to experience non-motor features, including autonomic dysfunction, neuropsychiatric symptoms, and sleep disorders. These are thought to result from the degeneration of cholinergic, serotonergic and catecholaminergic neurotransmitter systems (Schapira 2008). Non-motor symptoms contribute significantly to disability and decreased quality of life in advanced PD (Hely et al. 2005, Chaudhuri et al. 2006). It has been suggested that close to 90% of PD patients have at least one non-motor symptom, and that about 10% exhibit five non-motor symptoms (Shulman et al. 2001). Autonomic symptoms like orthostatic hypotension (OH), bladder disturbance, constipation or erectile dysfunction are usually associated with more advanced stages of PD, even though they may be present even in the early phases of the disease (Haapaniemi 2001, Pursiainen 2007). More than 50% of patients have been reported to have disabling symptoms of autonomic dysfunction in everyday life (Magerkurth et al. 2005).
OH in PD is related to impaired baroreflex-cardiovagal functions and sympathetic cardiac and also partially extracardiac denervation (Goldstein et al. 2005). Furthermore, medications used to treat PD, including levodopa, selegiline and dopamine receptor agonists (DAs), may result in or contribute to OH (Calne et al. 1960, Schoenberger 1991, Lyttinen et al. 1997, Dooley & Markham 1998, Haapaniemi et al. 2000, Montastruc et al. 2000). A community-based study reported a 47% prevalence of OH in PD (Allcock et al. 2004), whereas up to two-thirds of PD patients recruited from hospital clinics may feature with OH (Senard et al. 1997, Wood et al. 2002). The prevalence of symptomatic OH may be as high as 20% (Senard et al. 1997). In general elderly populations, OH has been associated with frequent falls and even increased mortality (Rutan et al. 1992, Räihä et al. 1995, Masaki et al. 1998).

A substantial proportion of PD patients will eventually develop dementia as a prevalence of 78% has been reported in a long-term prospective study (Aarsland et al. 2003). A systematic review has indeed concluded that 24% to 31% of patients with PD have dementia, and that up to 4% of the people with dementia in the general population could be due to dementia associated with PD (Aarsland et al. 2005). Depression and anxiety are common comorbidities affecting up to 50% of PD patients (Burn 2002, Schrag 2004). Other psychiatric symptoms such as hallucinations and psychosis may be both PD- and treatment-related and are thought to occur in up to 40% of patients (Schrag 2004, Williams & Lees 2005, Chaudhuri et al. 2006). Impulse control disorders (ICD), such as gambling or sexual behavior, associated with the use of DAs occurs in up to 10% of patients (Weintraub et al. 2008a). Sleep disturbances, especially rapid eye movement (REM) sleep behavior disorder (RBD) and excessive daytime sleepiness, are seen in many PD patients (Chaudhuri et al. 2006). Anosmia and hyposmia are so common in PD that smell-testing has been suggested as an early marker to identify patients at risk of developing PD (Chaudhuri et al. 2006). Basal ganglia dysfunction has also been associated with impairments in preattentive cortical auditory processing (Pekkonen et al. 1998). Other complaints of PD patients include abnormal sensory symptoms (pain, paresthesias), fatigue, diplopia or blurred vision, and dry mouth (Weintraub et al. 2008a).
2.1.2 Epidemiology and etiology

Epidemiology

Both the incidence and prevalence rates of PD vary greatly between different studies and study populations. In the industrialised countries, PD affects about 0.3% of the entire population, more than 1% of those older than 60 years and up to 4% of those older than 80 years (de Lau & Breteler 2006). Therefore, together with Alzheimer’s disease, PD is one of the most commonly encountered neurodegenerative disorders in clinical practice.

The reported standardized incidence rates of PD are 5–26 per 100 000 person-years (Twelves et al. 2003, von Campenhausen et al. 2005, de Lau & Breteler 2006). The incidence of PD increases with age both in men and women. Onset of PD is rare before the age of 50 years, and a sharp increase of the incidence is seen after the age of 60. The overall incidence rate in men has been reported to be as high as two times that of women (de Lau & Breteler 2006). The incidence rates for parkinsonism are slightly higher than that of PD and also increase with age (Bower et al. 1999). In Finland, during the pre-levodopa era an annual incidence of 16.6 per 100 000 was reported (Marttila & Rinne 1976), whereas during the post-levodopa period, a total age-adjusted annual incidence rate of 14.9 per 100 000 individuals for PD has been reported (Kuopio et al. 1999).

Underdiagnosis of PD is common as in door-to-door prevalence studies up to 42% of cases were first diagnosed at the time of the survey (Tison et al. 1994). A systematic review estimated that the prevalence of PD in Europe is approximately 108 to 257 per 100 000 (von Campenhausen et al. 2005). Among persons over the age 65, the prevalence of PD has been estimated at 1800 per 100 000 individuals (1.8%). The prevalence increases from 600 per 100 000 (0.6%) for persons from 65 to 69 years of age to 2600 per 100 000 (2.6%) for those from 85 to 89 years of age (de Rijk et al. 2000). The prevalence of parkinsonian signs is higher than that of idiopathic PD with the overall prevalence estimates of 14.9% for 65–74 years of age, 29.5% for 75–84 years of age and 52.4% for those 85 and older (Bennett et al. 1996). During the pre-levodopa period the prevalence of PD in Finland was estimated at 120 per 100 000 (Marttila & Rinne 1976). More recently the age-adjusted prevalence of PD in Finland was 166 per 100 000 (Kuopio et al. 1999).
**Etiology**

PD is considered to be a multifactorial disorder. Although the specific etiology of the disease is still not completely understood, both environmental and genetic factors are thought to contribute. It has been estimated that about 90% of PD cases are sporadic, and monogenetic forms are estimated to cause about 10% of PD cases (de Lau & Breteler 2006).

Epidemiological studies have revealed a number of factors that may increase the risk of developing PD (Olanow & Tatton 1999). These include exposure to well water, pesticides, herbicides, industrial chemicals, wood pulp mills, farming, and living in a rural environment. Exogenous toxins, including trace metals, cyanide, lacquer thinner, organic solvents, carbon monoxide and carbon disulfide, as well as endogenous toxins such as tetrahydroisoquinolines and beta-carbolines, are thought to result in parkinsonism. However, cigarette smoking, coffee or caffeine intake and the use of non-steroidal anti-inflammatory drugs seem to lower the risk of developing PD (Ross et al. 2000, Chen et al. 2003, Allam et al. 2004). Iron intake and the consumption of dairy products and milk are considered to increase the risk of PD (Chen et al. 2002, Powers et al. 2003). Other nutritional aspects, on the other hand, such as reduced caloric intake, polyunsaturated fatty acids and dietary consumption of vitamin E are thought to have protective effects against PD (Hellenbrand et al. 1996, de Rijk et al. 1997, de Lau et al. 2005a). The higher incidence and prevalence rates of PD in men has led to the hypothesis that the female sex hormones might have neuroprotective effects (Benedetti et al. 2001, Currie et al. 2004), but the role of oestrogens in PD is still disputed.

Supporting evidence for a possible environmental cause of PD relates to the toxin 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which is a by-product of the illicit manufacture of a synthetic heroin analogue. Drug addicts who have taken MPTP have developed a syndrome that resembled PD both clinically and pathologically (Langston et al. 1983). Although the search for MPTP-like environmental risk factors has been extensive, no such agent has been identified in PD patients to date.

Although PD has conventionally been considered to have an environmental background, the genetic predisposition of the disease has long been suspected: clinical observations reveal that patients often have an affected relative. In Finland the relative risk of PD among the first degree relatives of patients has been shown to be 2.9, and the cumulative incidence of PD by the age of 90 years is 3.3 times higher among the first degree relatives of patients than in the controls.
(Autere et al. 2000). Nowadays, there are over ten distinct genetic loci associated with familial forms of PD. At least two genes, α-synuclein and leucine-rich repeat kinase 2 (LRRK2), are known to cause autosomal-dominant PD, whereas genes like parkin, PINK1 and DJ-1 can cause autosomal recessive forms of parkinsonism (Gasser 2007). Genetic polymorphism may predispose to idiopathic PD (Eerola-Rautio 2008).

2.1.3 Pathogenesis and pathophysiology

Pathogenesis

The major motor symptoms of PD result from the degeneration of dopaminergic cells within the substantia nigra and the subsequent dopamine depletion in the striatum, first described in 1960 (Ehringer & Hornykiewicz 1960). The degeneration of dopaminergic substantia nigra pars compacta (SNc) neurons is a slowly evolving process and, therefore, PD may take decades to develop. Humans are estimated to have 120,000 to 220,000 dopaminergic neurons in the substantia nigra of each hemisphere, and when more than 50% of these cells are lost, patients start to develop signs and symptoms typical of PD (Hamani & Lozano 2003). The pathological hallmarks of PD are eosinophilic, intrasytoplasmic inclusions called Lewy bodies (LBs) and dystrophic Lewy neuritis (LNs) seen in the surviving neurons (Lang & Lozano 1998b). The LBs are mainly composed of fibrillar forms of the α-synuclein protein.

PD is a disorder that not only affects the dopaminergic nerve cells of the substantia nigra, but also other regions and neurotransmitter systems. The pathological process associated with sporadic PD increases in extent and severity with disease duration. In the brain, the first signs of α-synuclein aggregation are seen in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and in anterior olfactory structures. In the next stage inclusion bodies appear in the great raphe nucleus, the reticular formation and the locus coeruleus. Next, the pathological process extends to the basal portions of the midbrain and forebrain, including the pedunculopontine nucleus (PPN). At this stage, the deficits also appear in the SNc, and the presymptomatic phase gives way to the clinically recognizable PD. Cortical involvement gradually follows (Braak et al. 2006, Braak & Del Tredici 2008). Deficits in the sympathetic, parasympathetic and enteric nervous systems are also seen (Braak & Del Tredici 2008).
The cell death in PD occurs by way of apoptosis rather than necrosis (Tatton & Olanow 1999). Oxidative stress together with mitochondrial and proteosomal dysfunction seem to be central factors interacting in the pathogenesis of PD. The source of increased oxidative stress is unclear, but may include, besides increased metabolism of dopamine, mitochondrial dysfunction, increased levels of reactive iron and impaired antioxidant defence pathways (Jenner 2003). Mitochondrial dysfunction, especially defects in the mitochondrial complex-I of the respiratory chain seem to play a major role in the pathogenesis of PD as decreases in complex-I activity has been found in the SNc of PD patients (Schapira et al. 1990). This could lead not only to a bioenergetic defect and to cell damage through free oxygen radicals, but also to the development of apoptosis. Glutamate-induced excitotoxicity, reduced capability to up-regulate neurotrophic factors in response to cell injury and inflammatory responses may also contribute to the pathogenesis of PD (Olanow & Tatton 1999).

The fact that α-synuclein is the principal component of LBs in sporadic PD in conjunction with the finding that mutations in the gene encoding α-synuclein can lead to familiar PD suggests that accumulation of α-synuclein may be central to the development of PD (Olanow & Tatton 1999, Moore et al. 2005). The precise physiological function of α-synuclein is unclear, but it has been suggested that is plays an important role in regulating synaptic vesicle size and recycling with particular relevance to dopamine storage (Moore et al. 2005). The protein is naturally thought to be an unfolded molecule that can self-aggregate (Weinreb et al. 1996). The mechanism by which the aggregations of α-synuclein exert their neurotoxic effect is unclear, but numerous cellular pathways are thought to be involved (Moore et al. 2005). Excessive production of misfolded proteins may exceed the capacity of the ubiquitin-proteosome system to degrade them, leading to cellular dysfunction and apoptosis (Olanow 2007). Gene mutations may also alter the structure of α-synuclein, making it more prone to self-aggregation and perhaps more resistant to proteosomal degradation (Polymeropoulos 1998). Proteosomal inhibition has been associated with increases in α-synuclein fibrillization (McNaught et al. 2004). Mitochondrial complex-I inhibitors can lead to aggregation and accumulation of α-synuclein, and other forms of oxidative and nitrosative stress also promote α-synuclein aggregation (Sherer et al. 2002, Sherer et al. 2003). Additionally, mutations in parkin gene are thought to be of importance in the pathogenesis of PD as the encoded parkin protein functions mainly to target misfolded proteins for degradation (Moore et al. 2005). Some
evidence suggests that LBs do not appear deleterious to cells, and may even be cytoprotective (McNaught & Olanow 2006).

Pathophysiology

The term basal ganglia refers to a group of subcortical nuclei that include the striatum, the globus pallidus, the subthalamic nucleus (STN) and the substantia nigra. The striatum consists of two macroscopic nuclei, the caudate nucleus and the putamen. The globus pallidus is subdivided into an external segment (GPe) and an internal segment (GPi). Furthermore, the substantia nigra comprises two main subdivisions, the pars compacta (SNc) and the pars reticulata (SNr). Other nuclei, including the thalamus and the PPN, also play a major role in basal ganglia functioning (Yelnik 2002, Visser & Bloem 2005).

The main information flowing to the basal ganglia arises from the cerebral cortex. Striatal information is transferred through the direct pathway to the GPi and SNr, then to the thalamus, and from there to the frontal cortex, the supplementary motor area and the prefrontal cortex. Another pathway, the indirect pathway, involves the GPe, then the STN, the GPi and the SNr. Output from the GPi and SNr goes largely to the ventral anterior and ventrolateral nuclei of the thalamus (VA/VL), which project back to the cerebral cortex. Lesser basal ganglia projections reach the intralaminar centromedian and parafascicular thalamic nuclei (CM/Pf) and brainstem structures such as the superior colliculus, the PPN, and the reticular formation (Yelnik 2002, Visser & Bloem 2005, Galvan & Wichmann 2008). The PPN has prominent projections to the basal ganglia, mainly the SNc and the STN (Pahapill & Lozano 2000).

The striatum, and to a lesser degree the globus pallidus and STN, also receive prominent dopaminergic input from the SNc. The direct pathway carries dopamine D1 receptors, while the nigrostriatal projections in the indirect pathway carry D2 receptors. Dopamine has an excitatory effect on D1 receptors and an inhibitory effect on D2 receptors. The direct and indirect pathways are thought to have opposing actions: direct pathway activation inhibits GPi/SNr activity, thereby disinhibiting thalamocortical interactions, while the indirect pathway does the opposite. Therefore, the nigrostriatal dopaminergic projections are essential in balancing the activity of the direct and indirect pathways (Yelnik 2002, Visser & Bloem 2005, Galvan & Wichmann 2008).

A model for basal ganglia function in normal and in dopamine deficiency states, such as PD, has been proposed (Albin et al. 1989) (Figure 1). In PD, the
balance between the excitatory discharge of cholinergic interneurons and the dopaminergic input in the striatum is disturbed (Ganong 2005). The dopamine deficiency produces dysfunction in the striatum, leading both to decreased activity flowing from the GABAergic striatal neurons to the GPi and SNr and to increased activity flowing from the GABAergic projections to the GPe and further to STN. Synergistically these changes lead to an increase in GPi and SNr activity, followed by increased inhibitory discharges to thalamocortical and brainstem neurons (Bergman & Deuschl 2002, Yelnik 2002, Hamani & Lozano 2003, Galvan & Wichmann 2008). The resulting cortical suppression leads to bradykinesia, rigidity and tremor. The descending projections from the basal ganglia to the brain stem, and especially to the PPN, are thought to play a role in the pathophysiology of gait and postural disturbances seen in PD (Pahapill & Lozano 2000, Bergman & Deuschl 2002).
Fig. 1. Simplified functional model of the basal ganglia in persons with normal motor control and with Parkinson's disease. Continuous lines indicate excitatory connections and dotted lines indicate inhibitory connections. Line thickness represents strength of stimulation/inhibition. CM, centromedian thalamic nucleus; VA/VL, ventral anterior and ventrolateral thalamic nuclei (Lang & Lozano 1998a and Jellinger 2001, modified by author).

2.1.4 Medical treatment

To date PD remains an incurable disease. Current available treatment of PD has not been shown to significantly alter the progression of the underlying neuronal
degeneration, and until now no clinical trial has provided definitive evidence for pharmacological neuroprotection. The drugs used to treat PD either boost the levels of dopamine in the brain or mimic the effect of dopamine.

Before the introduction of levodopa in the 1960’s, symptomatic therapy for PD consisted mainly of anticholinergic agents. Anticholinergics are believed to correct the disequilibrium between striatal dopamine and acetylcholine activity and are specifically effective against tremor. The anticholinergics used to treat PD specifically block muscarinic receptors. Their symptomatic effect, however, is limited and side-effects such as blurred vision, urinary retention, constipation and impaired cognitive function limit their utility (Horstink et al. 2006b, Singh et al. 2007).

Levodopa, introduced in the 1960s, revolutionized the treatment of PD as it provided symptomatic benefits to virtually all PD patients (Birkmayer & Hornykiewicz 1961, Cotzias 1968). It acts as a precursor of dopamine, and is usually administered together with peripheral dopadecarboxylase inhibitors (carbidopa or benserazide) to prevent its peripheral conversion to dopamine and the resultant nausea and vomiting (Horstink et al. 2006b, Singh et al. 2007). Although levodopa is effective in treating motor symptoms in PD, it does not affect the non-motor symptoms sufficiently (Horstink et al. 2006a). Long-term levodopa treatment is associated with numerous adverse motor effects that limit its use (Olanow et al. 2004). It seems that these motor complications are at least partly caused by the short half-life of levodopa, leading to pulsatile rather than constant stimulation of dopamine receptors (Olanow et al. 2004). Another concern of levodopa therapy is the question whether levodopa is neurotoxic or not. The metabolism of levodopa can indeed produce reactive oxygen radicals, but to date, based on laboratory and in vivo studies, the neurotoxicity of levodopa has not been reliably confirmed (Olanow et al. 2004).

Dopamine receptor agonists (DAs) can be divided into two main classes: the ergot derivates (bromocriptine, cabergoline, dihydroergocryptine, lisuride and pergolide) and the non-ergot derivates (apomorphine, piribedil, pramipexole and ropinirole). The main symptomatic antiparkinsonian effect is thought to be mediated through D2-receptor agonist activity and it would also explain the most common side effects (nausea and vomiting, orthostatic hypotension, psychosis, hallucinations and somnolence) (Horstink et al. 2006b, Singh et al. 2007). DAs seem to be effective as monotherapy in PD and may be used to delay the need for levodopa. However, after a few years of DA monotherapy most patients need levodopa as a replacement or adjunct treatment to control their PD symptoms.
The use of ergot derivates has been limited because of the possible risk of pleuropulmonary/retroperitoneal fibrosis and of fibrotic heart-valve reactions (Van Camp et al. 2004, Dhawan et al. 2005, Antonini & Poewe 2007).

Selegiline and rasagiline inhibit the action on monoamine oxidase-B (MAO-B) and prevent the breakdown of dopamine, leading to greater dopamine bioavailability (Horstink et al. 2006b). A small symptomatic effect of selegiline monotherapy has been shown in a meta-analysis, but the main use of MAO-B inhibitors is as adjunctive therapy to levodopa (Ives et al. 2004). However, concurrent use with levodopa may lead to potentiated side-effects and thus the levodopa dose can in many cases be decreased by adding a MAO-B inhibitor to treatment. Concerns that selegiline used in combination with levodopa increases mortality rates (Ben-Shlomo et al. 1998) have been allayed (Olanow et al. 1998).

Therapeutic doses of catechol-O-methyltransferase (COMT) inhibitors entacapone and tolcapone reduce the peripheral metabolism of levodopa, extend its plasma half-time and prolong the action of each levodopa dose (Horstink et al. 2006b). They are used mainly in combination with levodopa and seem to reduce levodopa requirements in PD patients (Brooks et al. 2008). Reports of severe hepatotoxicity have limited the use of tolcapone (Leegwater-Kim & Waters 2006).

Amantadine, an antiviral agent, was found by chance to be effective in PD. It is thought to block N-methyl-D-aspartate (NMDA) glutamate receptors, to have an anticholinergic effect and also to release presynaptic dopamine stores by an amphetamine-like action. Amantadine is effective in reducing levodopa-induced dyskinesias, but no long-term duration of effect has been shown (Horstink et al. 2006b). Its central nervous system (CNS) effects include restlessness, confusion, depression and hallucination, and amantadine is therefore poorly tolerated by elderly PD patients (Singh et al. 2007).

The greater understanding of the pathophysiological changes seen in PD has led to the introduction of neurosurgical procedures in the treatment of this disease. The target of such procedures is the disrupted activities of the thalamic nuclei, the GPi or the STN. As ablative procedures (pallidotomy, thalamotomy) are still associated with a risk of permanent complications, especially when bilateral lesions are created, long-term electrical stimulation through implanted electrodes is more commonly used as a potentially reversible and adjustable treatment method. Thalamic ventral intermediate nucleus (Vim) deep brain stimulation (DBS) has been used in the treatment of severe parkinsonian tremor (Benabid et al. 1991). At present, DBS is most commonly targeted at the GPi and especially at
the STN, because STN-DBS improves all cardinal symptoms in PD, including motor fluctuations (Lang & Lozano 1998a, Piper et al. 2005, Erola 2006). A new area of interest is the possibility of using the PPN as a target in treating parkinsonian symptoms (Lozano & Snyder 2008). However, the number of patients treated with PPN-stimulation is very limited, and therefore, PPN-DBS is not in routine use. Furthermore, continuous duodenal infusion of levodopa and apomorphine infusion can also be used in patients with advanced PD, when oral therapy is not effective (Wolters 2007).

Treatment-related complications

The major limitation of levodopa long-term use is the development of treatment-related complications such as motor fluctuations and dyskinesia (involuntary movement). With advancing PD, the motor improvement after a levodopa dose becomes reduced in duration and PD symptoms reappear causing wearing-off (end-of-dose) fluctuations. In the beginning, wearing-off may be subtle and take the form of mild sensory symptoms in a limb, or a vague feeling of malaise or depressed mood (Bhidayasiri & Truong 2008). The fluctuations become increasingly unpredictable with disease progression and levodopa therapy duration, and can lead to disabling fluctuations with rapid on-off phenomenon. Additionally, dyskinesias related to peak-dose levels of levodopa and/or DAs may occur. They are typically choreiform but may involve dystonia or myoclonus as well. Patients may also experience a loss of benefit from a usually effective dose (dose failure) (Olanow et al. 2004, Horstink et al. 2006a, Weintraub et al. 2008b). Treatment-related motor complications occur in up to over 70% of patients using levodopa for less than 10 years (Rajput et al. 2002). One meta-analysis has found up to a 40% likelihood of motor fluctuations and dyskinesias after just 4–6 years of levodopa therapy (Ahlskog & Muerter 2001). Patients with young-onset PD seem to be more prone to developing motor complications than old-onset patients (Schrag et al. 1998).

2.2 Postural control in humans

Postural control relies on sensory information from the vestibular, proprioceptive and visual systems. Effective integration of sensory information about the environment and body and limb position is essential for control of balance. Normal postural control and locomotor functions necessitate complex
neurobiomechanical processes involved in maintaining upright posture, initiating and terminating gait, and moving the body toward the desired location. When faced with balance perturbations, fast and appropriate corrective responses are required to prevent a fall (Bohnen & Cham 2006).

Control of balance involves several different areas of the human central nervous system (CNS). Commands for voluntary movement originate in cortical association areas. Posture is continually adjusted not only before but also during movement. Movement is smoothed and coordinated by the medial and intermediate portions of the cerebellum and its connections. The basal ganglia and the lateral portions of the cerebellum are part of a feedback circuit to the premotor and motor cortex that is concerned with planning and organizing voluntary movement. Although the spinal pattern generators can produce basic locomotor rhythm in humans, brainstem structures are necessary to activate and regulate the rhythm (Ganong 2005). The PPN is a brainstem nucleus with connections to the limbic system, the basal ganglia, the thalamus and the reticular formation, and is thought to play a central role in generating movement (Pahapill & Lozano 2000).

During small perturbations of postural stability, young healthy subjects seem to use an ankle strategy (with a distal-to-proximal activation of postural reactions) to control body sway. With larger perturbations, the postural correction pattern changes to the use of a hip strategy, and outside the limits of the hip strategy, a stepping and stumbling corrective strategy is used to prevent a fall (Horak et al. 1992). Moreover, normal postural responses can be subdivided into passive and active stabilizing factors. Normally small postural disturbances are countered by passive stretching of muscles and ligaments, and larger perturbations activate both automatic and voluntary muscular responses (Bloem 1992).

2.2.1 The basal ganglia and control of balance

The basal ganglia’s specific role in postural control is complex and still poorly understood. The basal ganglia have long been regarded as being predominantly involved in motor control. However, they are now increasingly recognized as playing an additional role in sensory processing, cognition and behavior. Functions of the basal ganglia that might be relevant for postural control include: storing and automatic execution of motor plans, motor flexibility (adaptive behavior to environmental changes), somatosensory integration, muscle tone regulation, gain control of automatic postural responses, and cognition, motivation and emotional aspects of behavior (Visser & Bloem 2005).
Additionally, several information-processing tasks of the basal ganglia have been proposed. According to one theory, the function of the basal ganglia is to filter cortical input and feed relevant output back to the frontal cortex (Bar-Gad et al. 2000). Another theory is that the basal ganglia act as a controller involving a desired model output and an error distribution system (Baev et al. 2002).

2.3 Postural instability and falls in Parkinson’s disease

Postural instability and gait disturbance are common features in PD, often leading to an increased risk of falling, injuries, and the need for medical care (Coughlin & Templeton 1980, Grisso et al. 1991, Bloem et al. 2001a, Wood et al. 2002). Postural instability reflects progression to more advanced stages of PD and is often associated with severe disability. Advanced PD is associated with recurrent falls, immobilization and progressive deterioration of overall physical fitness that jointly contribute to a reduced quality of life and even to increased mortality (Bloem et al. 2004) (Figure 2).

Gait disturbances are closely related to postural instability in PD. The typical parkinsonian gait is characterized by stooped posture, short steps, reduced arm swing and slow turns. Freezing of gait (FOG) can occur on turning, in narrow spaces, upon reaching a destination and in stressful situations, and it is strongly associated with motor fluctuations (Okuma & Yanagisawa 2008). The patient may suddenly either become unable to start walking (start hesitation), fails to continue to move forward (akinesia) or may show suffling forward with small steps. Similar to postural instability and falls, FOG is also regarded as a rather late feature of PD, even though it may also occur in very early stages of idiopathic PD (Bloem et al. 2001d, Bloem et al. 2004). Sudden FOG may disturb balance and thereby represent one cause of falls in PD, and similarly to falls, FOG often responds poorly and sometimes paradoxically to treatment with dopaminergic medication (Bloem et al. 2004).
2.3.1 Clinical assessment of postural instability

Due to the multicomponent and integrated nature of the control of postural stability, a single, all-encompassing measure of balance does not exist, and therefore the accurate evaluation of postural instability in PD requires the use of multiple tests of balance. Whenever possible, patients should be examined both during optimal response to antiparkinsonian treatment (on phase) and in a practically defined off phase.

During a clinical examination, postural stability is commonly assessed by interviewing and observing the patient, and by rating balance performance during stance and gait tasks. Questions regarding falling frequency, fear of falling and the need for walking aids can be asked. Interviewing the spouse or care giver may provide valuable additional information.
Steady standing can be tested feet together or apart, with stride, tandem or single-limb stance, or by the Romberg test. The functional reach test (Duncan et al. 1992) can be used to assess perturbations of standing balance by self-initiated movements. Walking, step height, and trunk stability while turning can be observed. The UPDRS, including the retropulsion test (sternal push or shoulder pull, with or without prior warning), can be employed. However, the qualitative assessment of these clinical tests do not necessarily provide accurate estimates of balance in PD as the results neither correlate well with more objective measures of postural stability such as dynamic posturography (Bloem et al. 1998) nor predict future falls (Bloem et al. 2001a).

More complex, functional tasks can also be used to evaluate a patient’s ability to maintain balance. Patient’s ability to climb stairs or lift objects can be tested. The Timed Up & Go (TUG) test (Podsiadlo & Richardson 1991), the “stops walking when talking” test (Lundin-Olsson et al. 1997), and the “multiple tasks” test (Bloem et al. 2001c) can also be used. Additionally several scales such as the Webster scale (Webster 1968), the Tinetti mobility index (Tinetti 1986), the Berg balance scale (Berg et al. 1992), the dynamic gait index (Whitney et al. 2000), and the clinical gait and balance scale (Thomas et al. 2004) have been used for the objective evaluation of gait and dynamic balance in PD. A patient’s ability to integrate sensory information to maintain stability can be measured with the Sensory organization test (Cohen et al. 1993). Fear of falling can be measured, for example, by using the Activities-specific confidence scale (Adkin et al. 2003).

In the laboratory, static balance can be assessed by measuring direct postural sway during quiet stance (Viitasalo et al. 2002, Adkin et al. 2005). Indirect recording of ground reaction forces as the patient stands on a platform equipped with force transducers can also be used (Beckley et al. 1991, Schieppati & Nardone 1991, Bloem et al. 1995, Bloem et al. 1996), this method even allowing assessment of balance and postural reflexes (Beckley et al. 1991, Schieppati & Nardone 1991, Bloem et al. 1995, Bloem et al. 1996, Toole et al. 1996) under different sensory conditions (Trenkwalder et al. 1995, Toole et al. 1996). A potentiometer attached to the body and mounted to a platform can be used to assess the movements of the patient’s the center of gravity (Horak et al. 1992, Bloem et al. 1995, Bloem et al. 1996). Infrared emitting diodes have also been used to evaluate body motion and balance in PD (Pastor et al. 1993, Jobbagy et al. 1998).
2.3.2 Postural instability

Even though balance impairment is universally recognized as a major feature of PD occurring typically in more advanced stages of the disease (Bonnet et al. 1987), the fundamental pathology and pathophysiology of postural instability is not yet fully understood. However, there is evidence suggesting that non-dopaminergic deficits emerging in later stages of the disease are related to the presence of postural instability in PD (Bonnet et al. 1987). Several components of balance control, including abnormal postural reflexes, gait abnormalities and detection and integration of sensory information, are thought to contribute to the postural instability in PD.

Balance during static standing

The average position of the center of pressure during quiet standing in parkinsonian subjects is shifted to a more posterior one compared to normal controls (Schieppati & Nardone 1991), possibly representing an adaptive mechanism to compensate for the stooped posture associated with the tendency to lean forward.

Body sway seems to be reduced early in the course of the disease, possibly because patients actively co-contract their muscles and stiffen their body owing to a fear of falling (Horak et al. 1992, Schieppati et al. 1994). It has been proposed that this small amount of postural sway is related to high intrinsic musculoskeletal stiffness in PD (Dietz et al. 1988). This stiffening strategy reduces the viscoelastic properties of the body, which normally form the first line of defence against postural perturbations (Bloem et al. 2001d). Other studies concerning postural sway during quiet standing have shown increased (Rocchi et al. 2002, Viitasalo et al. 2002, Maurer et al. 2003, Adkin et al. 2005) or within normal range (Bronte-Stewart et al. 2002) postural sway in PD compared to controls. Significant left/right asymmetries (Rocchi et al. 2002) and increased medio-lateral postural sway have also been reported (Mitchell et al. 1995, Viitasalo et al. 2002). The amount of postural sway has been shown to be most marked in patients with severe or long-duration PD (Viitasalo et al. 2002).

Horak et al. (Horak et al. 1992) reported reduced postural sway in the absence of vision, whereas other authors have reported normal sway in this condition (Bronstein et al. 1990, Bronte-Stewart et al. 2002, Smiley-Oyen et al. 2002, Maurer et al. 2003).
Dynamic balance, gait and mobility

Postural reactions generated in response to external sensory and motor perturbations during standing are also impaired in PD. Dynamic posturography studies applying motor perturbations have shown greater destabilizing body displacements, increased destabilizing motor responses, and delayed and reduced corrective responses (Beckley et al. 1991, Bloem et al. 1995, Bloem et al. 1996, Frank et al. 2000). Moreover, increased destabilizing responses to “toes up” rotations are present in PD patients with severe postural instability, but not in patients with mild to moderate instability (Beckley et al. 1991). In contrast, it seems that PD patients have normal electromyography (EMG) latencies with floor translations (Horak et al. 1992). Decreased protective arm responses to unexpected postural perturbations have been reported (Morris et al. 2001). It has also been shown that the limits of stability in PD are narrow (Horak et al. 1992, Schieppati et al. 1994) and that PD patients tend to overestimate their limits of stability (Kamata et al. 2007). It should be noted that abnormal postural reflexes may be the consequence, rather than a cause, of the postural instability in PD (Bloem et al. 1992).

The clinical characteristics of PD, especially in more advanced stages of the disease, include stooped posture, slow gait, and short steps. Complex motor tasks, such as gait initiation and turning are impaired in PD (Morris et al. 2001). Additionally, PD patients show changes in spatiotemporal and kinematic characteristics of gait, including gait asymmetry, abnormal stride variability, increased double support time and reduced angular excursions of lower limbs. On the other hand, the ability to modulate cadence seems to remain unaffected (Morris et al. 1999, Baltadjieva et al. 2006).

The TUG test, in which the patient is timed while he rises from a chair, walks 3 meters, turns, walks back and sits down again, has been shown to be a reliable and valid test for quantifying mobility in PD patients (Morris et al. 2001). The test has revealed differences in performance between PD patients and healthy elderly subjects, and between PD patients in different phases of clinical fluctuation (Morris et al. 2001). PD patients require more time to complete gait tasks than control subjects (Adkin et al. 2005). Dual-tasking such as the “stops walking when talking” test has been shown to cause no problems for most PD patients (Bloem et al. 2000), but in the “multiple tasks” test PD patients performed significantly worse than controls (Bloem et al. 2001b). Interestingly, in the “multiple tasks” test PD patients seem to prioritize cognitive tasks over motor
tasks (Bloem et al. 2001b), possibly because they cannot process simultaneous or sequential tasks adequately.

**Postural strategies**

PD patients seem unable to adjust their postural reflexes (referred to as postural inflexibility) during changes in support conditions and it seems that they have difficulty in selecting and sequencing motor programs, which themselves may be intact (Schieppati & Nardone 1991, Horak et al. 1992, Bloem et al. 1995). However, PD patients do seem to detect and respond to postural perturbations, though they tend to select inappropriate responses: e.g. they employ both ankle and hip strategies simultaneously rather than sequentially in response to postural perturbations, and moreover, a reversed proximal-to-distal activation sequence of stabilizing responses, even in response to small perturbations, has been reported (Bloem 1992, Horak et al. 1992). These abnormalities together with enhanced destabilizing responses have been shown to correlate with disease severity (Beckley et al. 1991). Patients with PD have difficulties in initiating a compensatory step in response to perturbation of balance (King & Horak 2008), and anticipatory postural adjustments prior to self-initiated movements may be impaired as well (Traub et al. 1980).

**Proprioception, vision and vestibular function**

Different modes of afferent sensory information must be centrally integrated to produce appropriate postural responses. It has been suggested that PD patients lack the ability of normal subjects to use sensory or cognitive information for their postural responses or to use appropriate somatosensory information (Bloem et al. 2001d, Maurer et al. 2003, Boonstra et al. 2008). However, other investigators have suggested that PD patients have no difficulty in using sensory information to control balance, but instead they use abnormally coordinated inflexible postural responses (Horak et al. 1992). PD patients seem to have difficulty in changing between different sensory modalities (De Nunzio et al. 2007) and a generalized impairment of the scaling and habituation of the postural responses evoked whenever there is a sudden change of sensory conditions (Valkovic et al. 2006a, Valkovic et al. 2006b).

The processing of proprioceptive signals may be disturbed in PD, leading to hypometric postural responses (Jacobs & Horak 2006). The afferent
proprioceptive information to the basal ganglia is thought to be normal in PD, but these signals are perhaps abnormally processed within the basal ganglia due to defective higher level integration (Visser & Bloem 2005). Visual control of posture in PD may be impaired because of oculomotor disturbances, an inability to suppress inappropriate visual information, or incorrect central processing of visual information (Bronstein et al. 1990, Bronstein et al. 1996). Studies with sensory perturbations, such as repeated exposures to moving visual environments, show increased postural sway in PD (Bronstein et al. 1990, Bronte-Stewart et al. 2002, Maurer et al. 2003). Moreover, there are results showing that PD patients are more dependent on visual information for maintaining balance than controls (Bronstein et al. 1990). It appears that patients’ responses to synergistic vestibular and visual inputs are essentially normal (Maurer et al. 2003), and that mildly or moderately affected PD patients show essentially normal responses to galvanic vestibular stimulation, suggesting that vestibular dysfunction is not responsible for the balance impairment in PD (Pastor et al. 1993).

### 2.3.3 Falling

Many studies focusing on the issue of Parkinson’s disease and falling have used selected samples such as outpatients from specialist clinics or known fallers and non-fallers. It is only recently that a few reports on prospective evaluation of falls in PD have been published.

Compared with the general population, the risk of falls and near-falls in PD has been shown to be two- and threefold, respectively (Teno et al. 1990), and the relative risk of sustaining recurrent falls during a 6-month period has been found to be as much as 9-times higher for PD patients (Bloem et al. 2001a). In retrospective studies investigating the past three to twelve months, 38–64% of PD patients have reported falls (Paulson et al. 1986, Koller et al. 1989, Ashburn et al. 2001a, Balash et al. 2005, Rudzinska et al. 2008). However, recent prospective studies with follow-up periods covering up to twelve months suggest that even a higher proportion (up to 70%) of PD patients experience falls (Gray & Hildebrand 2000, Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002). The number of patients with recurrent falls has ranged from 25% to 51% (Gray & Hildebrand 2000, Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002, Balash et al. 2005).

Balance impairment in PD is thought to be progressive (Bonnet et al. 1987). Falls are rare during the first years of idiopathic PD (Wenning et al. 1999). The
risk of falls in PD is a bell-shaped function of disease severity (Pickering et al. 2007), and is thought to reach a maximum near the H&Y stage 3 and to decrease in later stages because of decreased mobility (Wood et al. 2002). Unlike in the general population, most falls in PD seem to occur during walking, stopping, turning, standing up and bending down maneuvers (Bloem et al. 2004). Most falls in PD are thought to occur indoors during the on phase when the patient’s PD symptoms are well controlled, with or without dyskinesias (Bloem et al. 2001a).

**Risk factors for falling**

Previous retrospective and prospective studies using univariate analysis have associated several variables, some of them PD-related, with falling in PD (Table 2).

In a recent meta-analysis of available prospective studies of falling in PD, prior falls during the preceding year was the strongest predictor of falling in PD, but even subjects with no prior falls had a considerable risk of sustaining future falls (Pickering et al. 2007). A prospective study by Ashburn et al. (Ashburn et al. 2001b) showed that none of the disease-specific variables were independently predictive of falling in PD. Other prospective studies have identified several independent risk factors for falling in PD. Wood et al. (Wood et al. 2002) described previous falls, loss of arm swing, duration of PD and dementia as independent predictors of falling in PD in their prospective study with a follow-up period of one year. Bloem et al. (Bloem et al. 2001a) concluded that prior falls, disease severity and the Romberg test were the best diagnostic predictors of falling, whereas recurrent falls were best predicted by disease severity and prior falls.

Neither static nor dynamic posturography has been shown to discriminate between PD patients with and without falls adequately (Nardone & Schieppati 2006). The Tinetti mobility index, the Berg balance scale as well as other measures of mobility and dynamic balance are able to discriminate between PD patients with and without falls (Smithson et al. 1998, Bloem et al. 2001a, Landers et al. 2008), but postural sway, dynamic balance and gait variables fail to predict future falls in PD (Ashburn et al. 2001b). PD patients with falls have been shown to perform worse in the TUG test and in the functional reach test than non-fallers, and they have had greater postural sway whilst performing a dual task, but not in quiet standing (Ashburn et al. 2001a). Impaired mobility and dynamic balance have been associated with recurrent falling in PD (Dennison et al. 2007). Patients
with falls have been shown to perform significantly worse in tests measuring balance and gait (TUG, ability to tandem stance and duration of tandem stance) than non-fallers, and slow performance in the TUG test is among the independent risk factors for previous falls (Balash et al. 2005). The “stops walking when talking” test does not predict falling in PD (Bloem et al. 2000), whereas the use of multiple balance tests has been shown to help to discriminate between patients with and without falls (Jacobs et al. 2006). Patients with the postural instability and gait difficulty (PIGD) type of PD have been shown to have a higher risk of falling compared to the tremor dominant (TD) phenotype (Rudzinska et al. 2007).

Autonomic dysfunction seen in PD may lead to OH and thus contribute to postural instability and falls in PD. Previous studies have shown conflicting results on the role of OH as a risk factor for falls in PD. OH in PD has been associated with falls in some studies (Gray & Hildebrand 2000, Dennison et al. 2007), while other studies have found no such association (Koller et al. 1989, Bloem et al. 2001a, Wood et al. 2002). One retrospective study has concluded that approximately 3% of falls in PD are caused by symptomatic OH (Michalowska et al. 2005), and another study has prioritized orthostasis as one of the risk factors for recurrent falls in PD (Dennison et al. 2007).

Patients with PD seem to have reduced muscular strength and trunk mobility (Bridgewater & Sharpe 1998) and these deficits might result in improper balance corrections in PD. There is also evidence that PD patients have reduced bone mineral density, resulting in an increased risk of fractures (Vaserman 2005). Finally, it should be noted that in addition to the disease-related factors, PD patients also share the same risk factors for balance impairment and falls as elderly subjects in general. Therefore, factors such as dementia, depression, sensory changes in the legs, age-related changes in vision, heart disease or environmental factors may contribute to balance impairment in PD.
Table 2. Factors associated with falling in PD in univariate analysis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous falls</td>
<td>Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002</td>
</tr>
<tr>
<td>Higher level of disability</td>
<td>Koller et al. 1989, Robinson et al. 2005, Dennison et al. 2007</td>
</tr>
<tr>
<td>Decreased arm swing during gait</td>
<td>Wood et al. 2002</td>
</tr>
<tr>
<td>Impaired hand and foot agility or coordination</td>
<td>Koller et al. 1989, Robinson et al. 2005, Dennison et al. 2007</td>
</tr>
<tr>
<td>Inability to arise from a chair (proximal leg and trunk muscular weakness)</td>
<td>Koller et al. 1989, Robinson et al. 2005, Dennison et al. 2007</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Gray &amp; Hildebrand 2000, Martignoni et al. 2006, Dennison et al. 2007</td>
</tr>
<tr>
<td>Factor</td>
<td>Studies</td>
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<tr>
<td>-----------------------------------------------------------------------</td>
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<tr>
<td>Daily use of alcohol</td>
<td>Gray &amp; Hildebrand 2000</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Balash et al. 2005</td>
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<tr>
<td>Polypharmacy (use of more than 3 medications, especially use of</td>
<td>Ashburn et al. 2001a</td>
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<tr>
<td>cardiovascular medications)</td>
<td></td>
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<tr>
<td>Use of benzodiazepines</td>
<td>Bloem et al. 2001a</td>
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</table>

**Injuries associated with falls**

Trauma mostly due to falls is responsible for more than 30% of the acute events bringing patients with PD to emergency clinics (Martignoni et al. 2004, Temlett & Thompson 2006). In a questionnaire study of 100 PD patients, bone fractures were reported by 13% of patients (Koller et al. 1989). Another questionnaire-based study reported that 65% of falls in PD resulted in injury and over 75% of these injuries required health care services. Over 30% of falls resulted in a fracture and 40% of fractures required surgery (Wielinski et al. 2005). In a three-month prospective study (Gray & Hildebrand 2000), 40% of falls in PD resulted in injury. Propulsion, freezing, lightheadedness, dyskinesia and turning were associated with injurious falls. The most common injuries were bruises and scrapes, and the most common locations of injuries were the lower and upper extremities. One third of the falls resulted in a need for assistance, but the need for medical care was rare. Balash et al. (Balash et al. 2005) showed in their retrospective study that 11% of PD patients reported medically intervened falls, including injurious falls leading to skin lacerations, bone fractures and subdural hematoma.
Patients with parkinsonism (not just PD), especially those using neuroleptics, have a more than two-fold increased risk of sustaining a fall-related fracture (Vestergaard et al. 2007). Some 25% of all patients have suffered a hip fracture within 10 years after diagnosis of PD (Johnell et al. 1992), and the rehabilitation process after a hip fracture is slower and less successful among PD patients than among the controls (Jonsson et al. 1995). Hip fractures in PD are associated with a higher than normal morbidity and mortality (Coughlin & Templeton 1980). Female sex, older age, low bone-mass index, and low bone-mineral density have been shown to be risk factors for hip fractures in PD (Sato et al. 1999). Concomitant dementia in PD is also associated with an increased risk of hip fractures in PD (Melton et al. 2006). The incidence of wrist fractures appears to be considerably lower than in the controls, perhaps because of the absence or slow activation of protective arm movements (Genever et al. 2005). Postural instability and hip fractures are important risk factors for nursing home admission in PD (Hely et al. 1999).

### 2.3.4 Interventions to improve postural control and prevent falling

**Antiparkinsonian treatment**

Most investigators agree on the fact that antiparkinsonian treatment does not adequately improve balance and prevent falls in PD. Several authors have shown that although levodopa improves UPDRS scores, it worsens or does not affect postural instability in PD (Bloem et al. 1996, Frank et al. 2000, Adkin et al. 2005, Nardone & Schieppati 2006). Balance impairment may even be worsened by the adverse effects of dopaminergic medication, such as OH, dyskinesias, and confusion (Bloem 1992, Robinson et al. 2005). On the contrary, it has been suggested that postural stability may be improved by using dopaminergic agents to decrease rigidity (Bartolic et al. 2005).

Even though some abnormalities in sway velocity and frequency seem to be reduced by levodopa therapy (Rocchi et al. 2002, Maurer et al. 2003), falls and balance impairment in PD are largely unresponsive to levodopa (Koller et al. 1989, Bloem et al. 1996). Dopaminergic treatment seems to worsen left/right asymmetry (Rocchi et al. 2002) and to increase sway magnitude, especially in the medio-lateral direction (Bronte-Stewart et al. 2002, Rocchi et al. 2002, Maurer et al. 2003). Levodopa worsens or does not affect impairments during floor rotations.
and/or translations (Bloem et al. 1996, Maurer et al. 2003). Postural inflexibility is also thought to be refractory to levodopa therapy (Horak et al. 1992).

Some gait abnormalities (stride length, gait velocity, joint angular amplitudes) can be improved to close to normal with dopaminergic treatment (Blin et al. 1991, O’Sullivan et al. 1998, Shan et al. 2001). However, temporal gait parameters such as stride and swing duration and stride time variability — those gait impairments associated with falls in PD (Schaafsma et al. 2003) — seem to be resistant to treatment (Blin et al. 1991, O’Sullivan et al. 1998).

It has been suggested that stereotactic surgery might improve balance impairment in PD. However, even though unilateral pallidotomy does improve postural stability in PD, it seems that long-term benefits of pallidotomy on postural stability are rare (Bronte-Stewart et al. 2002). In the study of Rocchi et al. (Rocchi et al. 2002), treatment with levodopa increased postural sway, whereas treatment with deep brain stimulation of either the STN or the GPi decreased it. In other studies, the effects of STN stimulation on postural instability and gait were reported to equal those of levodopa during both unperturbed and externally perturbed stance, and overall, STN stimulation showed inconsistent responses in postural sway and gait variables (Maurer et al. 2003, Kelly et al. 2006, Visser et al. 2008). One meta-analysis on the effects of stereotactic neurosurgery on postural instability and gait in PD concluded that bilateral GPi stimulation, bilateral STN stimulation, and to a lesser extent, unilateral pallidotomy significantly improve postural control in PD (Bakker et al. 2004). The effects of these treatments were more pronounced during the off phase than during the on phase. However, if axial symptoms, like falling and gait hesitation, are present during the on phase and have no response to levodopa, they generally do not respond significantly to DBS (Krack et al. 2003). The role of electrical stimulation of the PPN on major motor features of PD (including postural instability and gait abnormalities) has also been a subject of interest (Pahapill & Lozano 2000). Preliminary results with quite a small number of patients suggest that PPN DBS may improve some aspects of postural instability and gait in PD (Stefani et al. 2007, Weinberger et al. 2008).

Physical therapy

Due to the defective basal ganglia function, PD patients appear to be more reliant on cortical control, especially frontal-cortical mechanisms, to initiate and execute complex movements. The current basis of physical therapy in PD is to teach
patients to bypass the basal ganglia pathology and to cope with impairments and disabilities (Morris 2000).

Maintaining general fitness, muscle force and upright posture are usually the initial goals of physical therapy in PD (Morris 2000) and repetitive exercises to improve these qualities have been shown to be effective in PD (Comella et al. 1994, Schenkmam et al. 1998, Ellis et al. 2005). Home-based physical therapy has also been shown to improve functional activity in PD (Nieuwboer et al. 2001). However, the evidence supporting conventional physical therapy for treatment of gait difficulties in PD is not strong (Rubinstein et al. 2002). On the other hand, the use of visual, auditory or proprioceptive cues and cognitive strategies can help parkinsonian patients to move more easily (de Goede et al. 2001). For example, avoiding a dual task performance while walking seems to help PD patients to maintain longer stride length, and auditory cues can help to avoid periods of freezing (Morris et al. 1996, Burleigh-Jacobs et al. 1997).

Home-based exercise program has shown a trend towards a reduction in fall events and injurious falls in PD (Ashburn et al. 2007), whereas gait and step training have resulted in a reduction in falls and improvements in gait and dynamic balance (Protas et al. 2005). Specific exercise programs using treadmill training may improve mobility, reduce postural instability and fear of falling in PD patients (Cakit et al. 2007). According to a recent meta-analysis, exercise interventions in PD are beneficial to physical functioning, health-related quality of life, strength, balance and walking speed. However, the role of physical therapy in reducing falls in PD needs further research (Goodwin et al. 2008).

### 2.4 Mortality in Parkinson's disease

The main mortality study before the introduction of levodopa is that of Hoehn and Yahr in 1967 (Hoehn & Yahr 1967). They reported that, among patients evaluated at a specialist clinic between 1949 and 1964, the risk of death associated with parkinsonism was approximately three times that reported for the general population of the same age, race, and sex. The first reports after the introduction of levodopa were promising as they suggested that mortality was reduced compared with that of the general population (Zumstein & Siegfried 1976, Joseph et al. 1978, Diamond et al. 1987). However, later studies have reported an increase in mortality in PD despite the widespread use of levodopa and other antiparkinsonian medications: dopaminergic substitution seems to result in a reduction of the mortality ratio from about 3.0 to 1.5 (Curtis et al. 1984, Rajput et
The initial improvement of mortality figures in the first few years of the levodopa era suggests that the benefit of a good early response is lost in the long term as the disease progresses (Clarke 1995). Therefore, it has been suggested that PD progresses at the same rate now as it did in the pre-levodopa era, and that treatment is likely to have its greatest impact on mortality early in the disease when most features are responsive to levodopa (Hely et al. 2005). However, once the relatively levodopa nonresponsive features such as postural instability and gait disturbance appear, the mortality rate rises (Hely et al. 1999).

Recent prospective studies have reported mortality rates from 1.5 to 4.1 in PD patients compared to the controls (Ebmeier et al. 1990, Ben-Shlomo & Marmot 1995, Louis et al. 1997, Morgante et al. 2000, Herlofson et al. 2004, de Lau et al. 2005b, Hely et al. 2005) with the lowest mortality rates (1.5–1.8) in population-based studies (Herlofson et al. 2004, de Lau et al. 2005b). The mortality rate in parkinsonism may be greater than that in idiopathic PD (Uitti et al. 1996, Herlofson et al. 2004).

The early mortality studies already recognized that the risk of death was greater among the patients with parkinsonian signs other than tremor (Hoehn & Yahr 1967). A more recent study has confirmed that patients with both rest tremor and pronounced asymmetry of symptoms have a better prognosis than patients with neither of these clinical characteristics (Elbaz et al. 2003). An increased risk of death has been associated especially with the presence of gait disturbance or with impaired mobility among people with parkinsonism or Parkinson’s disease (Ebmeier et al. 1990, Bennett et al. 1996). The severity of the disease, the rate of worsening, as well as a poor response to levodopa have also been associated with mortality in PD (Hely et al. 1999, Marras et al. 2005). Dementia (Hughes et al. 2004, de Lau et al. 2005b) and depression (Hughes et al. 2004) have also been shown to be independent risk factors for mortality in PD. At least a part of the reduced life expectancy in PD patients can be ascribed to their increased risk of becoming demented (de Lau et al. 2005b).

Patients with young-onset PD may have a worse prognosis than those with later disease onset (Elbaz et al. 2003, Herlofson et al. 2004), but the opposite has also been suggested (Hely et al. 1999, Kempster et al. 2007). There is also some debate about whether women have higher relative mortality rate compared to men, as originally suggested by Hoehn and Yahr (Hoehn & Yahr 1967). However, more recent population-based studies have found no sex difference in mortality rates in PD (Ebmeier et al. 1990, Ben-Shlomo & Marmot 1995, Herlofson et al. 2004).
suggesting that the worse survival rate of women seen in some studies (Curtis et al. 1984, Diamond et al. 1990) may be due to the recruitment of more severely disabled women.

In previous studies pneumonia has been the most often known cause of death in patients with PD (Hoehn & Yahr 1967, Parkinson Study Group 1998, Hely et al. 1999), probably due to immobility and the increased risk of aspiration due to dysphagia. However, ischaemic heart disease and malignant neoplasms seem to be more common in controls than in PD patients (Hoehn & Yahr 1967, Beyer et al. 2001). Hip fractures resulting from falls have been associated with a mortality-rate of almost 50% within the next six months (Coughlin & Templeton 1980).
3 Purpose of the study

The purpose of the present study was to identify risk factors for falls and mortality in PD, to assess the clinical correlates of balance and mobility in PD, and to evaluate the association between orthostatic hypotension, balance and mobility in PD. The more specific aims of the individual studies were:

1. To identify the clinical determinants of postural sway and to identify risk factors for falling in PD.
2. To evaluate the clinical correlates of balance and mobility, and to identify risk factors for falling in PD.
3. To assess the clinical correlates of orthostatic hypotension and its association with balance and mobility in PD.
4. To assess the prevalence of falling in PD, and, using a prospective study design, to evaluate the clinical correlates and risk factors for falling and mortality in PD.
4 Subjects and methods

The study was carried out during the years 2002–2008 in the Department of Neurology, Oulu University Hospital, and was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. The principles of the Declaration of Helsinki were followed. Informed consent was obtained from all the study patients before their inclusion in the study.

4.1 Subjects

All patients with idiopathic PD from the Oulu region (the city of Oulu and the municipalities of Hailuoto, Haukipudas, Ii, Kempele, Kiiminki, Muhos, Oulunsalo, Tymävä, Yli-Ii and Ylikiiminki), diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank criteria (Gibb & Lees 1988) by experienced neurologists in Oulu University Hospital and having follow-up contacts with the Department of Neurology, were invited to participate in this study. Patients in institutional care were excluded. From a total population of approximately 205,000 inhabitants, 217 potential cases were identified and 164 agreed to participate in the study. During the two-year follow-up two subjects were found to have been misdiagnosed and not have idiopathic PD, and they were therefore excluded from the study. Of the remaining 162 patients, thirty-six were excluded as they were not able to stand unsupported, and one patient was excluded because of a concurrent severe infectious disease. The remaining 125 patients participated in the study.

Postural sway was measured in 120 patients (I, II, III and IV) with five patients excluded because of severe dyskinesia or other severe motor complications related to PD. The TUG test (II, III and IV) was completed by 122 patients (one patient was excluded because of severe dyskinesia and further two because they were unable to walk the required distance), and the timed 30-meter walking test (Frändin & Grimby 1994) to assess walking speed (II, III and IV) by 119 patients (three further patients were unable to walk the longer distance). Orthostatic testing (III and IV) could be performed in 120 patients (five patients were excluded because of severe dyskinesia or other motor complications related to PD).

Falls were prospectively recorded in all the 125 study patients for two years (IV). During this follow-up period five patients withdrew their consent, and eight patients were lost to the follow-up. The mean duration of the follow-up with the
lost patients was 14.5 months (range from 1 to 21 months). Eighteen patients had died by the time the mortality records were reviewed four years after the baseline clinical examination (IV). Figure 3 shows the selection procedure for the patients and the study protocol.

The baseline clinical characteristics of the study patients are presented in Table 3. The antiparkinsonian treatment of the patients, the concomitant medical conditions and medications are presented in Table 4. Seven patients had either undergone thalamotomy or had a deep brain stimulator.

The patients excluded from the study were significantly older and had a longer duration of PD compared to the patients included in the study (mean (SD) age 76.3 (8.0) vs. 67.9 (10.2) years, mean (SD) duration of disease 10.6 (8.7) vs. 6.1 (4.9) years, respectively), whereas the patients not consenting (mean (SD) age 71.2 (10.9) years, mean (SD) duration of disease 6.5 (4.7) years) did not differ significantly from the patients included in the study.

---

**Fig. 3.** Selection procedure for the patients, and the study protocol.
Table 3. Baseline clinical characteristics of the study patients (n = 125).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>83/42</td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>67.9 (10.2)</td>
</tr>
<tr>
<td>Mean duration of PD, yrs (SD)</td>
<td>6.1 (4.9)</td>
</tr>
<tr>
<td>Mean UPDRS total score (SD)</td>
<td>45.2 (18.9)</td>
</tr>
<tr>
<td>Mean UPDRS ADL score (SD)</td>
<td>13.8 (6.2)</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>25.0 (11.2)</td>
</tr>
<tr>
<td>Mean Hoehn &amp; Yahr stage (SD)</td>
<td>2.3 (0.7)</td>
</tr>
<tr>
<td>Motor fluctuations present, n (%)</td>
<td>62 (49.6)</td>
</tr>
<tr>
<td>Dyskinesia present, n (%)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Freezing of gait present, n (%)</td>
<td>21 (16.8)</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>26.5 (2.8)</td>
</tr>
<tr>
<td>Levodopa, n (%)</td>
<td>102 (81.6)</td>
</tr>
<tr>
<td>Mean levodopa dose, mg/day (SD)</td>
<td>412.0 (343.8)</td>
</tr>
<tr>
<td>High current physical activity, n (%)</td>
<td>27 (21.6)</td>
</tr>
<tr>
<td>Use of walking aid, n (%)</td>
<td>45 (36.0)</td>
</tr>
<tr>
<td>Fear of falling, n (%)</td>
<td>75 (60.0)</td>
</tr>
<tr>
<td>Recent falling, n (%)</td>
<td>45 (36.0)</td>
</tr>
<tr>
<td>OH present, n (%)</td>
<td>63 (52.5)</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of daily living; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension.
Table 4. Antiparkinsonian treatment, concomitant medical conditions and medications of the study patients (n = 125).

<table>
<thead>
<tr>
<th>Antiparkinsonian treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Levodopa</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Selegiline</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>87 (70)</td>
</tr>
<tr>
<td>Levodopa + selegiline/entacapone</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Levodopa + dopamine agonist + selegiline/entacapone</td>
<td>41 (33)</td>
</tr>
<tr>
<td>Dopamine agonist + selegiline</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Thalamotomy or deep brain stimulator</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant medical conditions</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>63 (50)</td>
</tr>
<tr>
<td>Obstructive pulmonary disease</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>29 (23)</td>
</tr>
<tr>
<td>Hypothyreosis</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Adult-onset diabetes mellitus</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>40 (32)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>11 (9)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>18 (14)</td>
</tr>
<tr>
<td>ATII receptor blockers</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>32 (26)</td>
</tr>
<tr>
<td>Opioid derivatives</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>15 (12)</td>
</tr>
</tbody>
</table>

ACE, Angiotensin converting enzyme; ATII, Angiotensin II.

4.2 Methods

4.2.1 Baseline clinical examination

All the patients were clinically examined and tested during the on phase by the same investigator in the neurological outpatient clinic of Oulu University Hospital.
The medical data were collected by reviewing the hospital charts and were verified by interviewing the patients. The severity of the PD symptoms and signs was assessed using the UPDRS and the H&Y staging. Visual acuity was measured using the Snellen chart.

**Questionnaires**

The patients filled in a questionnaire on their daily living conditions, possible fear of falling, use of any walking aids, and measures taken to prevent falling. Cognitive functioning was evaluated using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) and the presence of depression with the Beck Depression Inventory (BDI) questionnaire (Beck et al. 1961). Leisure time physical activity was assessed using the modified Paffenbarger questionnaire (Greendale et al. 1995, Korpelainen et al. 2003) in which the patients were asked to recall their participation in physical activities during their lifespan, corresponding to the ages of 15, 30 and 50 years old and their current age.

**Postural sway**

Static balance was measured using an inclinometric device (Figure 4) (Vitasalo et al. 2002). The measuring rod, the height of which could be adjusted for the various heights of the subjects, transmits sway movements of the body to the detecting inclinometric sensor module that is located on the lower end of the rod. The bottom end of the rod is attached to a special joint structure that was designed to prevent rotation of the rod, as opposed to sideways movement in any direction, during the measurement.

The movement of the measuring rod was calculated separately for the lateral (x) and the anterior–posterior (y) directions. The measured sway parameters were the maximum deflections for the lateral (Δx) and anterior–posterior (Δy) directions, the total path length of the postural sway, and the path length in both the lateral and anterior–posterior directions, the average sway velocity, and the total sway area. The path length was obtained by calculating the distance between the sequential location points of each sample, and after that, summing the values. After that, the algorithm of the software approximated the outlines of the measured x/y sway and calculated the assessed area.
Fig. 4. The inclinometric single-link pendulum device for assessing postural sway consists of a belt fastened firmly to a subject at the level of the sacrum, an inflexible measuring rod, an inclinometric module and a joint structure lying on the ground connected with a power unit and a computer. The movement of the measuring rod (Dx,y) is calculated separately in lateral (x) and antero–posterior (y) directions at the level of the estimated height (h) of the center of gravity, α being the measured inclination.

The postural sway measurements were performed after device calibration without any prior practice sessions under standardized conditions and were recorded twice during normal standing, each time with eyes open and with eyes closed. The duration of each recording was 60 seconds. The mean values of two successive recordings were used in the analyses. During the measurements the patients stood with no shoes on, with their feet together and their arms by their sides. During the recordings in the eyes-open test the patients were asked to look straight ahead at a mark on the wall facing them.

Mobility

Dynamic balance and mobility was assessed using the TUG test and the timed 30-meter walking test. In the TUG test, the patient is timed while he rises from a
chair, walks 3 meters, turns, walks back and sits down again. The TUG test was performed two times consecutively, and the mean score was used in further analyses. The timed 30-meter walking test was used to calculate the walking speed. In all the tests the patients were asked to walk at a brisk but comfortable and safe speed with the help of their standard (if any) walking aid.

**Blood pressure measurements**

Blood pressure (BP) and heart rate (HR) were measured with an automated sphygmomanometer (Omron M4, Omron Healthcare Co. Ltd., Kyoto, Japan) at rest, after standing up, and after 1, 2 and 3 minutes of standing. OH was defined as at least a 20 mmHg reduction in systolic BP or at least a 10 mmHg reduction in diastolic BP within three minutes of standing, with or without symptoms (Kaufmann 1996).

**4.2.2 Recording of falls**

At baseline, the history of falling was ascertained by asking the patients for the number of falls they had had indoors and outdoors during the preceding three months, a fall defined as an unexpected event when the person came to rest unintentionally on the ground or on some other lower level. When retrospective falls were concerned, a faller was defined as someone having had at least one fall either indoors or outdoors during the preceding three months, whereas a non-faller was defined as a person who reported having no falls at all.

After the baseline examination the patients were prospectively followed for possible falls for two years, the follow-up time of two years being considered long enough to categorize the patient as a recurrent faller or non-recurrent faller. Patients were asked to keep fall diaries at home (Luukinen et al. 1994), and the information on falls was gathered using telephone interviews with the patients (and if necessary with their spouses or other care givers) every third month. A fall was again defined as an unexpected event when a person came to rest unintentionally on the ground or on some other lower level. For prospective analysis, a recurrent faller was defined as someone who had had at least two falls during the two-year follow-up period, whereas a non-recurrent faller was defined as a person who reported no falls or only one fall during the period. Patients with recurrent falls were analysed because they would better reflect balance impairment than patients with a single random fall (Melzer et al. 2004).
4.2.3 Recording of mortality

Data on all-cause mortality of the study patients were collected by reviewing the hospital charts four years after the baseline examination. Information on the date of death and on the underlying and immediate causes of death was taken from the Cause of Death Register maintained by Statistics Finland.

4.2.4 Statistical methods

The data were analyzed using the SPSS for Windows software, version 12.0 (I, II and III) and version 16.0 (IV).

The baseline variables were compared between the fallers and non-fallers (I and II), patients with and without OH (III), recurrent and non-recurrent fallers and between the patients who had died during the study and those still alive (IV), using the unpaired \( t \) test for the continuous data and the Chi-square test or Fisher’s exact test for the categorical data. A non-parametric approach with the Mann-Whitney \( U \) test was used when a possible problem with the assumption of Gaussian distribution was found. For the statistical analyses, UPDRS total score was defined as a sum of UPDRS parts I, II, III and IV. UPDRS “bradykinesia” was defined as UPDRS item 31, and UPDRS “postural stability” as UPDRS item 30. UPDRS “tremor” was defined as a sum of UPDRS items 20 (a–e), and UPDRS “rigidity” as a sum of UPDRS items 22 (a–e) (I and II). Furthermore, for the analysis related to the leisure time exercise level, physical activity indices at different ages and a lifetime activity index were calculated (III and IV). The exercise level indices were divided into tertiles, and for the final analysis the variables were dichotomized: the combined low- and moderate-activity category was compared with the high-activity category.

In Study I patients were categorized into different motor subtypes according to the method proposed by Jankovic and colleagues (Jankovic et al. 1990, Burn et al. 2006). The subtypes are referred to as tremor dominant (TD), postural instability and gait difficulty (PIGD), or indeterminate. An average global tremor score was calculated as the mean of the following items: right and left arm tremor (as determined by history), tremor at rest of either face, lips, or chin, tremor in all four limbs, and action or postural tremor in both arms (as determined by examination). A mean score for the PIGD phenotype was calculated as the mean of the following five items: falling, freezing of gait, walking difficulty (as determined by history), and gait and postural stability (as determined by
examination). The TD group was defined as patients with a ratio of mean tremor/mean PIGD score greater than or equal to 1.5, whereas the PIGD group included all patients with a ratio less than or equal to 1.0 (Jankovic et al. 1990, Burn et al. 2006).

To assess how well the various measured risk factors could predict different sway parameters (I) and dynamic balance and mobility impairment (II), multiple linear regression analysis was performed using all the variables associated with the sway measures, the TUG-test score and the walking speed in the univariate analyses. In the exploratory analyses, Pearson correlation coefficients were used for normally distributed continuous variables, and Spearman correlation coefficients were used to assess the data that either had ordered categories or were not normally distributed.

A multiple logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for recent falling (I and II), recurrent falling and mortality in PD (IV). Variables were grouped into categories (patient characteristics, disease severity, concomitant medical conditions, antiparkinsonian and other medication, and fear of falling, use of a walking aid, and measures taken to prevent falling), and forward stepwise regression procedures were used to select the most predictive variables within each category. A similar stepwise analysis was then performed to select the statistically significant predictive variables from all the categories of predictors. The significant risk factors in the final multivariate model are reported using ORs and their 95% CIs. The level of significance for all the tests was set at $p < 0.05$. The Benjamini and Hochberg False Discovery Rate method was used to adjust for multiple comparisons (II, III and IV) (Benjamini & Hochberg 1995).
5 Results

5.1 Falling in PD (I)

From the whole study population, 45 patients (36.0%) reported a history of falling during the preceding three months. Among the 120 patients with postural sway measurements, 40 patients (33.3%) reported at least one fall during the preceding three months, and 27 patients (22.5%) reported two or more falls. The mean number of falls indoors was 1.9 (range 0 to 70) and outdoors 0.8 (range 0 to 20). For the fallers the median number of falls both indoors and outdoors was 1. Three subjects reported over 50 falls. Eighty-eight patients were classified as having a PIGD-type PD, 17 were TD, and 15 patients were indeterminate.

The recent fallers had significantly longer disease duration than the non-fallers \( (p = 0.010) \), and they tended to be older (Table 5). The fallers also had significantly higher UPDRS total scores \( (p < 0.001) \), motor subscores \( (p = 0.015) \), activities of daily living (ADL) subscores \( (p < 0.001) \), and H&Y stages \( (p = 0.018) \) than the non-fallers. Dyskinesia and freezing were present more often among the fallers \( (p = 0.011 \text{ and } p = 0.030 \text{ respectively}) \), but there was no difference in the prevalence of motor fluctuations between the fallers and the non-fallers. Most recent fallers had a PIGD subtype of PD. The daily levodopa dose was significantly higher \( (p = 0.007) \) among the fallers. Fear of falling was more common among the fallers than non-fallers, and the fallers used walking aids more frequently.

5.2 Postural sway and recent falling in PD (I)

The mean values of the sway parameters measured with eyes open and eyes closed are summarized in Table 6. With eyes open the patients with recent falls had a significantly larger sway area than the non-fallers \( (p = 0.021) \), and a larger maximum deflection both in the anterior–posterior directions \( (\Delta y) \) \( (p = 0.016) \) and in the lateral directions \( (\Delta x) \) \( (p = 0.006) \). The sway measures also differed significantly between the patients with and without recent falls in the eyes closed condition \( (p = 0.042, \ p = 0.008 \text{ and } p = 0.025, \text{ respectively}) \). No statistically significant difference in postural sway was found between the TD and PIGD types of PD.
Table 5. Characteristics of the patients with and without recent falling (n = 120).

<table>
<thead>
<tr>
<th></th>
<th>Recent falling (n = 40)</th>
<th>No recent falling (n = 80)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>24/16</td>
<td>55/25</td>
<td>0.3411</td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>70.5 (8.3)</td>
<td>67.1 (10.8)</td>
<td>0.055</td>
</tr>
<tr>
<td>Mean duration of PD, yrs (SD)</td>
<td>7.6 (6.2)</td>
<td>4.8 (3.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>Mean UPDRS total score (SD)</td>
<td>53.7 (20.1)</td>
<td>39.9 (15.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean UPDRS ADL score (SD)</td>
<td>17.0 (6.1)</td>
<td>11.8 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>28.5 (12.8)</td>
<td>22.9 (9.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mean Hoehn &amp; Yahr stage (SD)</td>
<td>2.4 (0.7)</td>
<td>2.1 (0.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>Motor fluctuations present, n (%)</td>
<td>24 (60.0)</td>
<td>33 (41.3)</td>
<td>0.0531</td>
</tr>
<tr>
<td>Dyskinesia present, n (%)</td>
<td>12 (30.0)</td>
<td>9 (11.3)</td>
<td>0.0111</td>
</tr>
<tr>
<td>Freezing of gait present, n (%)</td>
<td>10 (25.0)</td>
<td>8 (10.0)</td>
<td>0.0301</td>
</tr>
<tr>
<td>PIGD-type PD</td>
<td>37 (92.5)</td>
<td>51 (42.5)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>26.1 (2.8)</td>
<td>26.7 (2.9)</td>
<td>0.323</td>
</tr>
<tr>
<td>Mean BDI (SD)</td>
<td>6.5 (5.4)</td>
<td>4.5 (3.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>Levodopa, n (%)</td>
<td>35 (87.5)</td>
<td>62 (77.5)</td>
<td>0.1901</td>
</tr>
<tr>
<td>Mean levodopa dose, mg/day (SD)</td>
<td>543.8 (436.7)</td>
<td>333.8 (264.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dopamine agonist, n (%)</td>
<td>18 (45.0)</td>
<td>37 (46.3)</td>
<td>0.8971</td>
</tr>
<tr>
<td>Selegiline, n (%)</td>
<td>20 (50.0)</td>
<td>43 (53.8)</td>
<td>0.6981</td>
</tr>
<tr>
<td>Entacapone, n (%)</td>
<td>11 (27.5)</td>
<td>14 (17.5)</td>
<td>0.2041</td>
</tr>
<tr>
<td>Fear of falling, n (%)</td>
<td>32 (80.0)</td>
<td>41 (51.3)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Use of a walking aid, n (%)</td>
<td>24 (60.0)</td>
<td>18 (22.5)</td>
<td>&lt;0.0011</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of daily living; PIGD, postural instability and gait difficulty; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory. p between patients with and without recent falling; 1 Chi Square test, all other: unpaired t test.
Table 6. Mean (SD) postural sway in patients with and without recent falling and according to PD type (n = 120).

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 120)</th>
<th>Recent falling (n = 40)</th>
<th>No recent falling (n = 80)</th>
<th>p</th>
<th>TD-type PD (n = 17)</th>
<th>PIGD-type PD (n = 88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes open</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>2.7 (3.0)</td>
<td>3.8 (4.0)</td>
<td>2.2 (2.2)</td>
<td>0.021</td>
<td>1.8 (1.9)</td>
<td>3.0 (3.3)</td>
<td>0.161</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>0.56 (0.35)</td>
<td>0.64 (0.32)</td>
<td>0.52 (0.36)</td>
<td>0.081</td>
<td>0.55 (0.31)</td>
<td>0.56 (0.37)</td>
<td>0.876</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>33.4 (20.7)</td>
<td>38.1 (18.8)</td>
<td>31.0 (21.2)</td>
<td>0.078</td>
<td>32.8 (18.4)</td>
<td>33.7 (21.8)</td>
<td>0.864</td>
</tr>
<tr>
<td>Length y (cm)</td>
<td>18.2 (11.9)</td>
<td>20.8 (10.4)</td>
<td>17.0 (12.4)</td>
<td>0.096</td>
<td>19.3 (13.7)</td>
<td>18.2 (12.1)</td>
<td>0.733</td>
</tr>
<tr>
<td>Length x (cm)</td>
<td>23.2 (15.8)</td>
<td>26.1 (13.6)</td>
<td>21.7 (16.8)</td>
<td>0.153</td>
<td>23.5 (16.1)</td>
<td>23.4 (16.4)</td>
<td>0.978</td>
</tr>
<tr>
<td>∆ y (cm)</td>
<td>2.3 (1.0)</td>
<td>2.7 (1.3)</td>
<td>2.1 (0.8)</td>
<td>0.016</td>
<td>2.0 (0.7)</td>
<td>2.4 (1.1)</td>
<td>0.145</td>
</tr>
<tr>
<td>∆ x (cm)</td>
<td>2.4 (1.2)</td>
<td>2.8 (1.3)</td>
<td>2.2 (1.1)</td>
<td>0.006</td>
<td>2.0 (1.1)</td>
<td>2.5 (1.3)</td>
<td>0.140</td>
</tr>
<tr>
<td>Eyes closed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>4.2 (4.9)</td>
<td>5.5 (5.7)</td>
<td>3.6 (4.3)</td>
<td>0.042</td>
<td>2.4 (1.7)</td>
<td>4.7 (5.4)</td>
<td>0.084</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>0.72 (0.41)</td>
<td>0.82 (0.43)</td>
<td>0.68 (0.40)</td>
<td>0.077</td>
<td>0.67 (0.42)</td>
<td>0.74 (0.43)</td>
<td>0.535</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>43.9 (24.8)</td>
<td>49.1 (25.9)</td>
<td>41.5 (24.0)</td>
<td>0.117</td>
<td>40.9 (25.2)</td>
<td>45.3 (26.1)</td>
<td>0.525</td>
</tr>
<tr>
<td>Length y (cm)</td>
<td>25.1 (13.7)</td>
<td>28.6 (15.9)</td>
<td>23.4 (12.2)</td>
<td>0.076</td>
<td>22.4 (11.8)</td>
<td>25.6 (14.7)</td>
<td>0.379</td>
</tr>
<tr>
<td>Length x (cm)</td>
<td>28.3 (18.3)</td>
<td>31.7 (17.6)</td>
<td>26.5 (18.4)</td>
<td>0.143</td>
<td>27.4 (20.4)</td>
<td>29.1 (18.9)</td>
<td>0.739</td>
</tr>
<tr>
<td>∆ y (cm)</td>
<td>2.9 (1.4)</td>
<td>3.3 (1.6)</td>
<td>2.6 (1.2)</td>
<td>0.008</td>
<td>2.3 (0.8)</td>
<td>3.0 (1.5)</td>
<td>0.062</td>
</tr>
<tr>
<td>∆ x (cm)</td>
<td>2.8 (1.5)</td>
<td>3.2 (1.6)</td>
<td>2.6 (1.4)</td>
<td>0.025</td>
<td>2.2 (0.9)</td>
<td>3.0 (1.6)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Length y, path length in anterior–posterior direction; Length x, path length in lateral direction; ∆ y, maximum anterior–posterior deflection; ∆ x, maximum lateral deflection; TD, tremor dominant; PIGD, postural instability and gait difficulty. Significance for postural sway parameters between the patients with and without recent falling and between the TD and PIGD types of PD using the unpaired t test.
The total UPDRS scores and UPDRS motor subscores correlated significantly with almost all the sway measures. The UPDRS ADL subscores, tremor and rigidity scores were significantly associated with several sway measures, but overall the correlation coefficients were low. The UPDRS “bradykinesia” score also correlated significantly with all the sway measures, but none of the sway measures correlated significantly with the UPDRS “postural stability” score.

Using multiple linear regression analysis, the final models explained 13.7% of the eyes-open sway area variance, 13.1% of the maximum deflection in the anterior–posterior direction (Δy) variance, and 20.5% of the maximum deflection in the lateral direction (Δx) variance. In the eyes-closed condition the final models explained 17.0% of the sway area variance, 15.4% of the maximum deflection in the anterior–posterior direction (Δy) variance and 28.5% of the maximum deflection in the lateral direction (Δx) variance. From the exploratory analyses six variables (UPDRS total score, history of falls during the past three months, number of falls indoors during the past three months, duration of PD, use of dopamine agonists and use of a walking aid) emerged which in different combinations significantly predicted the postural sway (Table 7).

5.3 Mobility and recent falling in PD (II)

For all study patients, the mean (SD) time spent on the TUG test was 13.0 (7.3) s and the mean (SD) walking speed was 1.2 (0.4) m/s. Patients with recent falling had a significantly slower walking speed than those with no recent falling (1.1 (0.4) m/s vs. 1.2 (0.3) m/s, \( p = 0.027 \)), and showed a trend towards a longer time spent on the TUG test (15.1 (9.0) s vs. 11.9 (5.8) s, \( p = 0.067 \)).

Moderate correlations were found between the measures of the walking tests and the UPDRS scores and the H&Y stages. The UPDRS “rigidity” scores correlated with both the TUG-test score and walking speed, whereas the UPDRS “tremor” and UPDRS “postural stability” scores only correlated with the TUG-test score. Significant correlation was found between most of the sway measures and the TUG-test scores and the walking speed.
Table 7. Significant predictors of different sway measures in stepwise multiple linear regression analysis in PD patients (n = 120).

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient (95% CI)</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eyes open</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sway area:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model R² = 0.137,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 2.653, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS total score (per one point increment)</td>
<td>0.040 (0.011 to 0.068)</td>
<td>0.014</td>
<td>0.006</td>
</tr>
<tr>
<td>Falls during the past 3 months vs. none (referent)</td>
<td>1.299 (0.203 to 2.395)</td>
<td>0.553</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Δ y:</strong> Model R² = 0.131,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 0.931, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS total score (per one point increment)</td>
<td>0.015 (0.005 to 0.025)</td>
<td>0.005</td>
<td>0.004</td>
</tr>
<tr>
<td>Falls during the past 3 months vs. none (referent)</td>
<td>0.404 (0.020 to 0.787)</td>
<td>0.194</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Δ x:</strong> Model R² = 0.205,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 1.056, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease (per one year increment)</td>
<td>0.069 (0.025 to 0.113)</td>
<td>0.022</td>
<td>0.002</td>
</tr>
<tr>
<td>Use of dopamine agonist vs. none (referent)</td>
<td>−0.697 (−1.088 to −0.306)</td>
<td>0.197</td>
<td>0.001</td>
</tr>
<tr>
<td>Falls during the past 3 months vs. none (referent)</td>
<td>0.524 (0.094 to 0.954)</td>
<td>0.217</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Eyes closed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sway area:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model R² = 0.170,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 4.253, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of a walking aid vs. none (referent)</td>
<td>2.050 (0.359 to 3.742)</td>
<td>0.854</td>
<td>0.018</td>
</tr>
<tr>
<td>Number of falls indoors during the past 3 months (per one fall increment)</td>
<td>0.124 (0.033 to 0.215)</td>
<td>0.046</td>
<td>0.008</td>
</tr>
<tr>
<td>Use of dopamine agonist vs. none (referent)</td>
<td>−1.867 (−3.463 to −0.272)</td>
<td>0.805</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Δ y:</strong> Model R² = 0.154,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 1.150, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of a walking aid vs. none (referent)</td>
<td>0.785 (0.337 to 1.234)</td>
<td>0.227</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of falls indoors during the past 3 months (per one fall increment)</td>
<td>0.033 (0.008 to 0.057)</td>
<td>0.012</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Δ x:</strong> Model R² = 0.285,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 1.221, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease (per one year increment)</td>
<td>0.106 (0.056 to 0.157)</td>
<td>0.025</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of dopamine agonist vs. none (referent)</td>
<td>−0.869 (−1.325 to −0.412)</td>
<td>0.231</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of a walking aid vs. none (referent)</td>
<td>0.674 (0.183 to 1.165)</td>
<td>0.248</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Δ y, maximum anterior–posterior deflection; Δ x, maximum lateral deflection.

Table 8 shows the statistically significant predictors of mobility in PD. Using multiple linear regression analysis the final models explained 42.4% of the TUG-test score variance and 44.9% of the walking speed variance. Severity of the
disease as measured by the UPDRS total score and age significantly predicted the values of the TUG-test score, whereas the UPDRS motor subscore, the use of DAs and the use of a walking aid were significantly associated with walking speed. The regression analysis for walking speed was adjusted for age because the patients on DA medication were younger than patients not receiving DAs.

Table 8. Significant predictors of the TUG-test score (n = 122) and walking speed (n = 119) in the stepwise multiple linear regression analysis in PD patients.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression coefficient (95% CI)</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timed Up &amp; Go test: Model R² = 0.424</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 5.523, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS total score (per one point increment)</td>
<td>0.200 (0.143 to 0.256)</td>
<td>0.028</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (per one year increment)</td>
<td>0.225 (0.123 to 0.327)</td>
<td>0.052</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>−11.257 (−18.082 to −4.431)</td>
<td>3.446</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Walking speed: Model R² = 0.449</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of the Estimate = 0.276, p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of a walking aid vs. none (referent)</td>
<td>−0.226 (−0.353 to −0.100)</td>
<td>0.064</td>
<td>0.001</td>
</tr>
<tr>
<td>UPDRS motor score (per one point increment)</td>
<td>−0.012 (−0.017 to −0.007)</td>
<td>0.003</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dopamine agonist vs. none (referent)</td>
<td>0.187 (0.072 to 0.302)</td>
<td>0.052</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (per one year increment) *</td>
<td>−0.004 (−0.011 to 0.002)</td>
<td>0.003</td>
<td>0.174</td>
</tr>
<tr>
<td>Constant</td>
<td>2.023 (1.605 to 2.440)</td>
<td>0.094</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* The model has been adjusted for age. TUG, Timed Up & Go; UPDRS, Unified Parkinson’s disease rating scale.

5.4 Risk factors for recent falling in PD (I and II)

A multivariate model of risk factors for recent falling in PD was created. The UPDRS total score (OR 1.04, 95% CI 1.01–1.07) and the sway area in the eyes-open test (OR 1.25, 95% CI 1.02–1.54) were found to be independent risk factors for recent falling in the final logistic regression analysis. In Study II the TUG test and walking speed were included in the logistic multivariate regression analysis, but were not found to be independent risk factors for recent falling in PD (TUG test OR 0.99, 95% CI 0.82–1.04, walking speed OR 0.63, 95% CI 0.13–3.17).

5.5 Orthostatic hypotension, balance and recent falls in PD (III)

The mean (SD) systolic and diastolic BP and HR at rest and during the orthostatic test are presented in Table 9. Sixty-three (52.5%) patients had OH in the
orthostatic test, there being no significant difference in the gender, age, duration of PD, UPDRS scores or H&Y stages between patients with and without OH. Furthermore, there was no difference in the presence of motor fluctuations, dyskinesia or freezing between the groups. As for any contrast between patients with and without OH, there was no difference in the proportion of patients with high current physical activity, with fear of falling or who used walking aids. Falling during the past three months had occurred in 25 (39.5%) patients with OH and in 16 (28.1%) patients without OH ($p = 0.614$). There was no difference in the mean number of falls during the past three months in patients with or without OH.

The patients with OH were significantly more often on levodopa or levodopa + entacapone medication than patients without OH (58 vs. 39 patients, $p = 0.001$ and 18 vs. 7 patients, $p = 0.028$, respectively), but there was no difference in the mean (SD) daily levodopa or entacapone dose [445.2 (318.7) mg vs. 334.7 (348.9) mg, $p = 0.102$ and 246.0 (425.0) mg vs. 115.8 (327.2) mg, $p = 0.061$, respectively], or in the proportion of patients using dopamine agonists or selegiline. No statistically significant difference was observed in concomitant medical conditions and medications between the patients with and without OH.

Table 10 shows the results of the TUG test, walking speed, and the postural sway measures in patients with and without OH. There was no difference in the TUG test and walking speed between patients with or without OH. The patients with OH had significantly increased postural sway when compared to the patients without OH. Postural sway area, velocity, and path length in the patients with OH were 1.5 to 2 times that of patients without OH, and in the patients with OH postural sway was more markedly increased in the lateral direction than in the anterior–posterior direction.
Table 9. The mean (SD) systolic and diastolic BP and HR at rest and in the orthostatic test, and the clinical correlates of orthostatic hypotension in the study patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 120)</th>
<th>Orthostatic hypotension (n = 63)</th>
<th>No orthostatic hypotension (n = 57)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP at rest, mmHg</td>
<td>141.6 (20.3)</td>
<td>144.4 (20.8)</td>
<td>138.5 (19.4)</td>
<td>0.116</td>
</tr>
<tr>
<td>Diastolic BP at rest, mmHg</td>
<td>79.4 (10.1)</td>
<td>80.1 (10.8)</td>
<td>78.7 (9.2)</td>
<td>0.460</td>
</tr>
<tr>
<td>HR at rest, bpm</td>
<td>66.5 (12.1)</td>
<td>67.3 (12.3)</td>
<td>65.6 (11.9)</td>
<td>0.433</td>
</tr>
<tr>
<td>Orthostatic test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆ Systolic BP, mmHg</td>
<td>−15.2 (22.4)</td>
<td>−28.6 (18.7)</td>
<td>−0.3 (15.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>∆ Diastolic BP, mmHg</td>
<td>−4.8 (12.5)</td>
<td>−11.2 (12.1)</td>
<td>2.3 (8.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>∆ HR, bpm</td>
<td>8.1 (12.4)</td>
<td>8.1 (15.1)</td>
<td>8.2 (8.8)</td>
<td>0.937</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>41/22</td>
<td>39/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>69.7 (8.6)</td>
<td>66.6 (11.4)</td>
<td></td>
<td>0.488</td>
</tr>
<tr>
<td>Mean duration of PD, yrs (SD)</td>
<td>5.9 (4.3)</td>
<td>5.6 (5.1)</td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>Mean UPDRS total score (SD)</td>
<td>45.3 (17.5)</td>
<td>43.6 (19.3)</td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>Mean UPDRS ADL score (SD)</td>
<td>14.1 (6.3)</td>
<td>12.9 (5.9)</td>
<td></td>
<td>0.734</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>24.4 (10.0)</td>
<td>25.2 (11.9)</td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>Mean Hoehn &amp; Yahr stage (SD)</td>
<td>2.2 (0.6)</td>
<td>2.2 (0.6)</td>
<td></td>
<td>0.993</td>
</tr>
<tr>
<td>Motor fluctuations present, n (%)</td>
<td>36 (57.1)</td>
<td>21 (36.8)</td>
<td></td>
<td>0.419¹</td>
</tr>
<tr>
<td>Dyskinesia present, n (%)</td>
<td>15 (23.8)</td>
<td>6 (10.5)</td>
<td></td>
<td>0.447¹</td>
</tr>
<tr>
<td>Freezing of gait present, n (%)</td>
<td>12 (19.0)</td>
<td>6 (10.5)</td>
<td></td>
<td>0.614¹</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>26.7 (2.8)</td>
<td>26.4 (2.9)</td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>High current physical activity, n (%)</td>
<td>31 (49.2)</td>
<td>33 (57.9)</td>
<td></td>
<td>0.734¹</td>
</tr>
<tr>
<td>Fear of falling, n (%)</td>
<td>37 (58.7)</td>
<td>37 (64.9)</td>
<td></td>
<td>0.804¹</td>
</tr>
<tr>
<td>Walking aids, n (%)</td>
<td>25 (39.7)</td>
<td>18 (31.8)</td>
<td></td>
<td>0.734¹</td>
</tr>
<tr>
<td>Recent falling, n (%)</td>
<td>25 (39.7)</td>
<td>16 (28.1)</td>
<td></td>
<td>0.614¹</td>
</tr>
<tr>
<td>Mean number of recent falls (SD)</td>
<td>2.0 (8.8)</td>
<td>2.5 (10.3)</td>
<td></td>
<td>0.830</td>
</tr>
</tbody>
</table>

BP, Blood pressure; HR, heart rate; bpm, beats per minute; ∆ Systolic BP, Mean maximal fall in systolic blood pressure after standing up in the orthostatic test; ∆ Diastolic BP, Mean maximal fall in diastolic blood pressure after standing up in the orthostatic test; ∆ HR, Mean maximal change in heart rate after standing up in the orthostatic test; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of daily living; MMSE, Mini-Mental State Examination.

Statistical significance between patients with and without orthostatic hypotension: ¹ Chi Square test, all others unpaired t test. The Benjamini and Hochberg False Discovery Rate method was used to adjust for multiple comparisons.
Table 10. Mobility and balance in the PD patients with and without OH.

<table>
<thead>
<tr>
<th></th>
<th>Orthostatic hypotension (n = 63)</th>
<th>No orthostatic hypotension (n = 57)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mobility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG test (s)</td>
<td>13.0 (7.0)</td>
<td>13.2 (7.8)</td>
<td>0.865</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.3)</td>
<td>0.806</td>
</tr>
<tr>
<td><strong>Postural sway</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>3.7 (3.7)</td>
<td>1.7 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>0.65 (0.39)</td>
<td>0.43 (0.21)</td>
<td>0.001</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>38.8 (23.2)</td>
<td>25.9 (12.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Length y (cm)</td>
<td>20.4 (13.1)</td>
<td>15.1 (8.9)</td>
<td>0.015</td>
</tr>
<tr>
<td>Length x (cm)</td>
<td>27.4 (17.7)</td>
<td>17.3 (9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ y (cm)</td>
<td>2.6 (1.2)</td>
<td>2.1 (0.6)</td>
<td>0.012</td>
</tr>
<tr>
<td>Δ x (cm)</td>
<td>2.8 (1.3)</td>
<td>2.1 (1.0)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). TUG, Timed Up & Go; Length y, path length in anterior–posterior direction; Length x, path length in lateral direction; Δ y, maximum anterior–posterior deflection; Δ x, maximum lateral deflection. Significance for measures of mobility and balance between patients with and without orthostatic hypotension using the unpaired t test. The Benjamini and Hochberg False Discovery Rate method was used to adjust for multiple comparisons.

5.6 Falling during the two-year follow up (IV)

During the two-year follow-up of falls altogether 3125 incidents were reported by 79 (63.2%) patients. Forty-six patients (36.8%) did not fall during the follow-up. Twenty patients reported one fall only and were therefore classified as non-recurrent fallers together with the patients not reporting any falls at all, while 59 (47.2%) patients were classified as recurrent fallers. Twenty-two patients reported two to five falls, 16 patients six to ten falls, and 15 patients experienced 11 to 100 falls. Six patients reported falling at least two times a week, some of them even several times a day. Detailed information on fall circumstances and consequences was obtained for 370 falls. Patients experiencing falls on a weekly or daily basis were generally not able to report detailed information on their fall circumstances.

Altogether 126 fall injuries were reported. Forty-five falls caused pain without visible injury, 65 falls caused bruises or other soft tissue injuries not requiring specific medical care, and 10 falls caused lacerations or other soft tissue injuries requiring medical attention. Six fractures were reported (1 hip fracture, 2 wrist fractures, 2 rib fractures and 1 finger fracture). Fifteen falls led to an emergency department visit, and a further nine falls caused admission to a hospital ward.
The recurrent fallers had significantly longer PD duration and more severe disease than the non-recurrent fallers (Table 11). FOG ($p = 0.027$) was present more often among the recurrent fallers than the non-recurrent fallers. The non-recurrent fallers were currently physically more active ($p = 0.027$), whereas the recurrent fallers reported past falls ($p < 0.001$) and used walking aids more frequently ($p = 0.011$). The daily levodopa dose was significantly higher ($p = 0.002$) among the recurrent fallers, but there was no difference in the proportion of patients using levodopa, DAs, selegiline or entacapone. In addition, there was no difference in concomitant medical conditions and medications between the recurrent fallers and the non-recurrent fallers. The recurrent fallers took more time to complete the TUG test ($p = 0.020$), and showed a trend towards a slower walking speed than the non-recurrent fallers ($p = 0.091$) (Table 11). At baseline, the recurrent fallers had significantly increased postural sway compared with the non-recurrent fallers. In the multivariate logistic regression analysis, a history of falling (OR 3.02, 95% CI 1.23–7.44) and the UPDRS activities of daily living (ADL) score (OR 1.13, 95% CI 1.04–1.22) were found to be independent risk factors for recurrent falling in PD.
Table 11. Baseline characteristics and mobility and postural sway of the recurrent and non-recurrent fallers.

<table>
<thead>
<tr>
<th></th>
<th>Recurrent fallers</th>
<th>Non-recurrent fallers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 59)</td>
<td>(n = 66)</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>38/21</td>
<td>45/21</td>
<td>0.656</td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>68.9 (10.4)</td>
<td>67.1 (10.1)</td>
<td>0.373</td>
</tr>
<tr>
<td>Mean duration of PD, yrs (SD)</td>
<td>7.5 (5.7)</td>
<td>4.8 (3.6)</td>
<td>0.010</td>
</tr>
<tr>
<td>Mean UPDRS total score (SD)</td>
<td>51.6 (21.0)</td>
<td>39.4 (14.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean UPDRS ADL score (SD)</td>
<td>16.2 (6.8)</td>
<td>11.6 (4.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>28.1 (12.6)</td>
<td>22.3 (9.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Mean Hoehn &amp; Yahr stage (SD)</td>
<td>2.4 (0.7)</td>
<td>2.1 (0.6)</td>
<td>0.012</td>
</tr>
<tr>
<td>Motor fluctuations present, n (%)</td>
<td>34 (57.6)</td>
<td>28 (42.4)</td>
<td>0.139</td>
</tr>
<tr>
<td>Dyskinesia present, n (%)</td>
<td>15 (25.4)</td>
<td>10 (15.2)</td>
<td>0.210</td>
</tr>
<tr>
<td>Freezing of gait present, n (%)</td>
<td>15 (25.4)</td>
<td>6 (9.1)</td>
<td>0.027</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>26.3 (3.0)</td>
<td>26.7 (2.7)</td>
<td>0.458</td>
</tr>
<tr>
<td>Levodopa, n (%)</td>
<td>51 (86.4)</td>
<td>51 (77.3)</td>
<td>0.225</td>
</tr>
<tr>
<td>Mean levodopa dose, mg/day (SD)</td>
<td>526.3 (406.5)</td>
<td>309.9 (235.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>High current physical activity, n (%)</td>
<td>7 (11.9)</td>
<td>20 (30.3)</td>
<td>0.027</td>
</tr>
<tr>
<td>Use of a walking aid, n (%)</td>
<td>29 (49.2)</td>
<td>16 (24.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>Fear of falling, n (%)</td>
<td>40 (67.8)</td>
<td>35 (53.0)</td>
<td>0.139</td>
</tr>
<tr>
<td>Recent falling, n (%)</td>
<td>32 (54.2)</td>
<td>13 (19.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>OH present, n (%)</td>
<td>33 (58.9)</td>
<td>30 (46.9)</td>
<td>0.225</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG test (s)</td>
<td>14.8 (9.3)</td>
<td>11.5 (4.5)</td>
<td>0.020</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>1.16 (0.42)</td>
<td>1.28 (0.32)</td>
<td>0.091</td>
</tr>
<tr>
<td><strong>Postural sway</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm$^2$)</td>
<td>3.5 (3.9)</td>
<td>2.1 (1.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>0.64 (0.42)</td>
<td>0.49 (0.25)</td>
<td>0.016</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>38.6 (25.1)</td>
<td>29.0 (14.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>Length y (cm)</td>
<td>20.8 (13.7)</td>
<td>16.1 (9.7)</td>
<td>0.029</td>
</tr>
<tr>
<td>Length x (cm)</td>
<td>26.9 (19.3)</td>
<td>20.0 (11.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>$\Delta$ y (cm)</td>
<td>2.6 (1.2)</td>
<td>2.1 (0.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>$\Delta$ x (cm)</td>
<td>2.7 (1.3)</td>
<td>2.2 (1.0)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of daily living; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; TUG, Timed Up & Go; Length y, path length in anterior–posterior direction; Length x, path length in lateral direction; $\Delta$ y, maximum anterior–posterior deflection; $\Delta$ x, maximum lateral deflection. Significance between recurrent fallers and non-recurrent fallers: 1 Chi Square test, all others unpaired t test.
5.7 Mortality at hospital chart review (four years after baseline) (IV)

Eighteen patients had died by the time of the hospital chart review four years post baseline (Table 12). One of them was hospitalized and underwent surgery because of a fall-related patellar fracture and died postoperatively because of acute myocardial infarction. One patient died because of hip fracture-related pneumonia, and a further four patients died because of PD-related pneumonia. Two patients died of cancer. Eight patients died because of complications resulting from coronary heart disease, and two further patients died of intracerebral haemorrhage.

Table 12. Characteristics of the patients who had died before the hospital chart review four years after baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dead (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>16/2</td>
</tr>
<tr>
<td>Mean age at baseline, yrs (SD)</td>
<td>75.0 (6.4)</td>
</tr>
<tr>
<td>Mean age at death, yrs (SD)</td>
<td>77.1 (6.4)</td>
</tr>
<tr>
<td>Mean time to death since diagnosis, yrs (SD)</td>
<td>9.6 (8.0)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
</tr>
<tr>
<td>Fall-related deaths, n</td>
<td>2</td>
</tr>
<tr>
<td>PD-related pneumonia, n</td>
<td>4</td>
</tr>
<tr>
<td>Complications of coronary heart disease, n</td>
<td>8</td>
</tr>
<tr>
<td>Cancer, n</td>
<td>2</td>
</tr>
<tr>
<td>Intracerebral haemorrhage, n</td>
<td>2</td>
</tr>
</tbody>
</table>

Mortality was associated with higher age, more severe disease, and cognitive decline (Table 13). Patients who died had also used walking aids more often. There was no significant difference in antiparkinsonian medications or in concomitant medications between the patients who died and those still alive. Cardiovascular disease and type 2 diabetes mellitus were present more often among the patients who died than among those still alive. Patients who died also showed significantly impaired baseline mobility in the TUG test ($p = 0.005$) and a slower walking speed ($p < 0.001$) compared to the patients still alive (Table 14). There was no difference in the baseline postural sway measures. There was no difference in the proportion of recurrent fallers between the patients who died and those still alive (61.1% vs. 44.9%, $p = 0.302$). In the multivariate logistic regression analysis, after adjusting for age, the slow walking speed (OR 16.28, 95% CI 1.85–142.97) was the only independent risk factor for mortality in PD.
Table 13. Baseline characteristics of the patients who had died before the hospital chart review four years after baseline and of those still alive.

<table>
<thead>
<tr>
<th></th>
<th>Dead (n = 18)</th>
<th>Alive (n = 107)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>16/2</td>
<td>67/40</td>
<td>0.064&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean age, yrs (SD)</td>
<td>75.0 (6.4)</td>
<td>66.8 (10.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean duration of PD, yrs (SD)</td>
<td>7.6 (7.8)</td>
<td>5.8 (4.2)</td>
<td>0.473</td>
</tr>
<tr>
<td>Mean UPDRS total score (SD)</td>
<td>60.8 (22.3)</td>
<td>42.6 (17.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean UPDRS ADL score (SD)</td>
<td>19.2 (6.7)</td>
<td>12.8 (5.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean UPDRS motor score (SD)</td>
<td>33.3 (14.2)</td>
<td>23.6 (10.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean Hoehn &amp; Yahr stage (SD)</td>
<td>2.7 (0.9)</td>
<td>2.2 (0.6)</td>
<td>0.042</td>
</tr>
<tr>
<td>Motor fluctuations present, n (%)</td>
<td>9 (50.0)</td>
<td>53 (49.5)</td>
<td>0.971&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyskinesia present, n (%)</td>
<td>6 (33.3)</td>
<td>19 (17.8)</td>
<td>0.274&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Freezing of gait present, n (%)</td>
<td>2 (11.1)</td>
<td>19 (17.8)</td>
<td>0.779&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>24.8 (2.5)</td>
<td>26.8 (2.8)</td>
<td>0.034</td>
</tr>
<tr>
<td>Levodopa, n (%)</td>
<td>16 (88.9)</td>
<td>86 (80.4)</td>
<td>0.627&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean levodopa dose, mg/day (SD)</td>
<td>669.4 (509.1)</td>
<td>368.7 (289.1)</td>
<td>0.056</td>
</tr>
<tr>
<td>High current physical activity, n (%)</td>
<td>1 (5.6)</td>
<td>26 (24.3)</td>
<td>0.194&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Use of a walking aid, n (%)</td>
<td>14 (77.8)</td>
<td>31 (29.0)</td>
<td>&lt; 0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fear of falling, n (%)</td>
<td>14 (77.8)</td>
<td>61 (57.0)</td>
<td>0.173&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recent falling, n (%)</td>
<td>9 (50.0)</td>
<td>36 (33.6)</td>
<td>0.272&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>OH present, n (%)</td>
<td>10 (55.6)</td>
<td>53 (49.5)</td>
<td>0.645&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of daily living; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension. Significance between the patients who died and those still alive: <sup>1</sup> Chi Square test, <sup>2</sup> Fisher’s Exact test, all others unpaired t test. The Benjamini and Hochberg False Discovery Rate method was used to adjust for multiple comparisons.
Table 14. Mobility and postural sway in patients who died and those still alive.

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 107)</td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG test (s)</td>
<td>21.5 (12.6)</td>
<td>11.6 (4.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>0.88 (0.33)</td>
<td>1.28 (0.35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postural sway</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm(^2))</td>
<td>3.3 (1.7)</td>
<td>2.6 (3.2)</td>
<td>0.393</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>0.67 (0.27)</td>
<td>0.54 (0.36)</td>
<td>0.166</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>40.2 (15.7)</td>
<td>32.3 (21.2)</td>
<td>0.143</td>
</tr>
<tr>
<td>Length y (cm)</td>
<td>22.0 (7.7)</td>
<td>17.6 (12.4)</td>
<td>0.163</td>
</tr>
<tr>
<td>Length x (cm)</td>
<td>27.4 (12.0)</td>
<td>22.5 (16.2)</td>
<td>0.234</td>
</tr>
<tr>
<td>( \Delta ) y (cm)</td>
<td>2.5 (0.6)</td>
<td>2.3 (1.1)</td>
<td>0.410</td>
</tr>
<tr>
<td>( \Delta ) x (cm)</td>
<td>2.8 (1.0)</td>
<td>2.4 (1.2)</td>
<td>0.209</td>
</tr>
</tbody>
</table>

TUG, Timed Up & Go; Length y, path length in anterior–posterior direction; Length x, path length in lateral direction; \( \Delta \) y, maximum anterior–posterior deflection; \( \Delta \) x, maximum lateral deflection. Significance for mobility and postural sway parameters between the patients who died and those still alive used the unpaired \( t \) test.
6 Discussion

6.1 General aspects

Postural instability is one of the cardinal features of PD. Advanced PD is associated with recurrent falls, immobilisation and progressive deterioration of overall physical fitness that jointly contribute to a reduced quality of life and, eventually, to an increased mortality (Coughlin & Templeton 1980, Grisso et al. 1991, Bennett et al. 1996, Hely et al. 1999, Bloem et al. 2001a, Wood et al. 2002). Up to 70% of PD patients experience falls (Wood et al. 2002). Previous prospective studies have identified independent risk factors for falling in PD, including history of falls, fear of falling, dementia, disease duration, and loss of arm swing (Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002), but the exact pathophysiology causing falls remains unsolved. Trauma mostly due to falls is responsible for more than 30% of the acute events bringing patients with PD to emergency clinics (Martignoni et al. 2004, Temlett & Thompson 2006).

Many studies focusing on the issue of PD and falling have used selected samples such as outpatients from specialist clinics or known fallers and non-fallers. It is only recently that a few reports on prospective evaluation of falls in PD have been published. The present study is one of the largest population-based report so far to identify the clinical correlates of balance and mobility in patients with PD, and to identify the risk factors for falls and mortality in PD. The study patients are representative of typical home-dwelling persons with PD from a population of 205 000 inhabitants. The two-year follow-up period of the present study enhances the importance and value of the results. Additionally, we tested the patients for cognitive function, and were able to study the effects of concomitant medical conditions and medications on mortality and falling in PD. Unlike some other papers investigating fall rates and risk factors for falling in PD (Ashburn et al. 2001b, Wood et al. 2002), we decided to study recurrent falls because two or more falls would better reflect balance impairment than a single random fall (Melzer et al. 2004).

We acknowledge some limitations to the present study. Several consecutive unpaired \( t \) tests or Chi Square tests were performed between the fallers and non-fallers in Study I. The level of statistical significance was set at \( p < 0.05 \). However, the use of a more conservative Bonferroni adjustment would have
altered the criteria for statistical significance, thus reducing the chance of a Type I error.

A self report was used to assess the frequency of falls during the previous three months. The recall-based study method may underestimate the true incidence of falls and this should be taken into account when reviewing the results (Cummings et al. 1988). However, the registration of falls occurring over the previous three months has been shown to be reliable (Luukinen et al. 1994). Although the highest numbers of reported falls may be rough estimates rather than true incidences of falls, the results were not biased due to misclassification since the patients were classified into fallers and non-fallers.

Thirteen patients with adult-onset diabetes participated in the study, but no neurophysiological testing was performed to assess peripheral neuropathy. Patients in institutional care and those unable to complete the measurements of balance and mobility were excluded from the study, which needs to be taken into consideration when interpreting the results. However, patients who had either undergone thalamotomy or had a deep brain stimulator were included in the study. Overall, the number of deaths was small, resulting in rather broad confidence intervals for the slow walking speed. Moreover, the MMSE is a very crude measure of cognitive function in PD, and other factors such as executive dysfunction may better predict falling (Allcock et al. 2009) or mortality in PD.

6.2 Postural sway and falling in PD (I)

According to the present data, high UPDRS total scores and increased postural sway are independent risk factors for recent falling in PD. Disease duration and severity, recent falling, use of dopamine agonists and use of a walking aid are significant predictors of static balance in standing as measured with posturography. The observed inverse association between the use of dopamine agonists and sway is probably due to the treatment guidelines where dopamine agonists are recommended as the first-line antiparkinsonian treatment for relatively young PD patients. However, in the present study age itself was not significant enough to be included in the final models.

In the cross-sectional part of the present study 33.3% of patients had fallen during the past three months. The number of patients with recurrent falling (two or more falls) was 23% in this study and has ranged from 25% to 51% in previous studies (Bloem et al. 2001a, Wood et al. 2002). Concerning the motor complications of PD, we identified dyskinesia as being associated with falls, as
has also been reported earlier (Gray & Hildebrand 2000, Robinson et al. 2005), but contrasting with others (Wood et al. 2002) motor fluctuations were not significant in this regard. Fear of falling was more common among the fallers than the non-fallers, a fact that has also been identified earlier (Bloem et al. 2001a, Wood et al. 2002, Robinson et al. 2005). Our study also suggests that fallers suffer more often from depression than non-fallers, a result consistent with previous reports with smaller study populations (Ashburn et al. 2001a, Wood et al. 2002).

The current regression models predicted between 13.1% and 28.5% of the postural sway variance. Toole et al. (Toole et al. 1996) were able to explain a larger amount of variability. The difference between these studies may be due to different devices being used to assess postural sway. The variables used in the regression models by Toole et al. also differed from those used in the present study. Although the majority of the variability in sway remained unexplained in the present study, the models predicted almost one third of the variability. In our data, a large sway area was a significant risk factor for falling. Simple and practical tools for predicting increased sway and postural impairment might help to identify patients at risk of future falling. Information on walking aids, recent falling, antiparkinsonian medication and duration and severity of PD are easy to achieve, and no complex measuring equipment are required.

Balance disturbances in PD patients have previously been assessed by recording ground reaction forces while the subject stands on a platform equipped with force transducers (Beckley et al. 1991, Schieppati & Nardone 1991). These studies have revealed an association between balance impairment and abnormal postural reflexes in the lower extremities of PD patients. By tracking the movements of the center of gravity, several studies have confirmed the abnormality of postural reflexes in PD and have also shown that postural sway is increased in PD (Bloem et al. 1995, Bloem et al. 1996). Postural sway, especially in lateral directions, is markedly increased in PD patients compared to healthy controls (Viitasalo et al. 2002). It has also been shown earlier that body sway is a significant risk factor for falling in the general population (Nevitt et al. 1989, Lord et al. 1994, Maki et al. 1994, Stalenhoef et al. 2002, Lajoie & Gallagher 2004). Until now, however, there have been no studies focusing on the role of body sway regulation as a risk factor of falls in PD. The present study shows that the sway area and maximum deflection in the anterior–posterior and lateral directions are significantly greater in PD patients with a history of recent falling than in those without.
Only a few studies have quantified postural sway and examined its clinical associates in PD. Toole et al. (Toole et al. 1996) have introduced a regression approach to examine the multicomponent nature of balance in persons with parkinsonism. The effect of levodopa on postural sway in PD has also been studied (Rocchi et al. 2002). One previous study conducted by our research group (Viitasalo et al. 2002) has shown that the amount of postural sway is significantly greater in severely affected PD patients than in healthy controls, and that the amount of postural sway correlates with the severity of the disease and some UPDRS items. However, the present results show that most postural sway measures correlate with the UPDRS total and motor scores, and with the UPDRS bradykinesia score, and, interestingly, that the UPDRS tremor and rigidity scores correlate with different sway measures: tremor correlates with sway velocity, total path length and the path length in lateral and anterior–posterior directions, whereas rigidity correlates with the sway area and maximum deflection in the lateral and anterior–posterior directions, the same variables that distinguish patients with and without recent falling from each other. In the present study the postural sway parameters did not correlate with the UPDRS “postural stability” scores, the present results thus supporting the concept that the assessment of balance requires more accurate tests than the traditionally used retropulsion test (Bloem et al. 2001a, Wood et al. 2002).

6.3 Mobility and balance in PD (II)

In our data, advanced age and severity of the disease were found to be related to impaired mobility and balance in PD patients. Furthermore, our results suggest that the measures of postural sway may better predict recent falling in PD than measures of mobility or walking speed.

It has been suggested that different types of postural control are regulated by separate neural circuits in the basal ganglia (Burleigh et al. 1995, Horak et al. 1996). Thus the tests used to measure dynamic balance and postural sway in the present study could be measuring different aspects of balance regulation as the correlations between the measures of mobility, walking speed and postural sway, although statistically significant, were quite low. Consequently, it appears that both the dynamic balance and postural sway should be assessed separately when evaluating balance impairment in PD.

The UPDRS motor subscore, the use of a walking aid and the use of DA significantly predicted walking speed, whereas the UPDRS total score and
patient’s age significantly predicted the time spent on the TUG test. The present results suggest that age plays a significant role in the TUG test, which is a more complex task than the walking task undertaken in the timed 30-meter walking test. The use of DAs had a positive predictive effect on the walking speed variance even after adjusting for patient age in the analysis. There was no difference in the duration of disease, in the UPDRS total score or the UPDRS motor subscore when the patients on DA medication were compared to patients not on DA medication.

The TUG test has been shown to be a reliable and valid test for quantifying mobility both in elderly people and in PD subjects (Podsiadlo & Richardson 1991, Morris et al. 2001). The test has also revealed differences in performance between PD patients and healthy elderly subjects, and between PD patients in different phases of clinical fluctuation (Morris et al. 2001). Supporting the results of Brusse et al. (Brusse et al. 2005), we also found a high correlation between the TUG-test score and the UPDRS total score, the motor and ADL subscores and the “bradykinesia” score. Furthermore, our results show a trend towards a worse performance in the TUG test and an even more apparent slowness in the walking speed of the patients with recent falling than in those without it. However, previous results concerning the association between the TUG test and falls in PD are conflicting (Ashburn et al. 2001a, Balash et al. 2005, Robinson et al. 2005), possibly due to the differing age structure of the study populations. Nevertheless, age seems to be a significant predictor of the impairment of mobility and dynamic balance in PD, and lower or higher age may be a serious factor associated with absence of falling and repeated or habitual falling.

6.4 Orthostatic hypotension, balance and falls in PD (III)

Over 50% of the study patients had OH in the orthostatic test. The patients with OH had significantly increased postural sway in standing compared to patients without OH, but no differences were found in mobility and walking speed. It appears that the tests for mobility and postural sway could measure different aspects of balance regulation, and that OH is apparently more associated with static than dynamic balance.

Neuropathological changes in PD are found in the brain, along the spinal cord, the paravertebral and prevertebral autonomic ganglia and in the gastrointestinal tract neurons (Olanow & Tatton 1999). Some previous studies have suggested the existence of neural circuits that integrate vestibular and autonomic information.
(Balaban & Beryozkin 1994, Ruggiero et al. 1996, Kerman & Yates 1998, Kerman et al. 2000), and that an association between cardiovascular dysautonomia and falls in PD (Martignoni et al. 2006). However, the exact underlying association between balance and OH still remains obscure. It is possible that the presence of OH directly causes dizziness and thereby increases postural sway, though none of the postural sway measurements in the present study had to be aborted because of symptomatic OH. Additionally, it has been suggested that the vestibular system directly affects vascular tone in order to offset OH during changes in posture (Kerman & Yates 1998). However, whether these vestibulo-sympathetic reflexes are intact or not in PD has, to our knowledge, not been studied. Nonetheless, the current results further support the concept that the control of body balance and OH are closely linked.

The reported prevalence of OH in PD has varied due to differences in the definition of OH, the methods used to measure postural BP reactions, and the patient selection. A recent community-based study reported a 47% prevalence of OH in PD (Allcock et al. 2004), whereas PD patients recruited from hospital clinics may reveal a prevalence of OH of up to two-thirds (Senard et al. 1997, Wood et al. 2002). The prevalence of symptomatic OH may be as high as 20% (Senard et al. 1997). In our cohort, over 50% of the patients had OH in the orthostatic test.

Several disease-related and patient-related variables have been associated with OH in PD (Orskov et al. 1987, van Dijk et al. 1993, Senard et al. 1997, Allcock et al. 2004, Allcock et al. 2006, Oka et al. 2007). These include the more advanced stages of the disease, old age, male sex, the PIGD phenotype of PD, low MMSE scores and visual hallucinations. However, we found no association between OH and gender, age, the MMSE score, or the duration and severity of the disease. The logical explanation for this important discrepancy between the studies is that inconsistency probably arises from differences in patient selection and patient characteristics.

OH has also been related to antiparkinsonian medication including levodopa, selegline and dopamine agonists (Calne et al. 1960, Schoenberger 1991, Lytinen et al. 1997, Dooley & Markham 1998, Haapaniemi et al. 2000, Montastruc et al. 2000), and accordingly, our patients with OH also used levodopa more often compared to patients without OH. In the present study, although the total levodopa dose was the same between the patients with and without OH, patients with OH were more often on levodopa therapy. Therefore, it is possible that the patients with OH had more severe PD, but that their degree of
motor impairment was underestimated due to the therapeutic effect of levodopa during the on phase. Accordingly, one might conclude that increased postural sway and frequent OH could simply be residual deficits resulting from the levodopa treatment of more advanced PD patients. Moreover, in some patients, OH might occur in association with antiparkinsonian medication.

It has been also claimed that falling in PD is associated with OH (Gray & Hildebrand 2000, Martignoni et al. 2006), though some studies, including ours, have failed to confirm such an association (Koller et al. 1989, Bloem et al. 2001a, Wood et al. 2002). Even though many falls in PD result from sudden changes in posture, or from attempts to perform more than one activity simultaneously with walking or balancing (Bloem et al. 2004), it seems that the cause of these falls is primarily the underlying balance disorder and not OH associated with a sudden loss of consciousness (Bloem et al. 2001a).

6.5 Falls and mortality in PD (IV)

The present two-year prospective study design showed that slow walking speed is an independent risk factor for mortality in PD, whereas a history of falling and high UPDRS activities of daily living scores are risk factors for recurrent falling. Over 60% of our PD patients experienced falls and almost 50% of the patients fell recurrently.

The presence of levodopa-nonresponsive features of postural instability and gait disturbance have been associated with an increased risk of death in PD (Bennett et al. 1996, Hely et al. 1999). It has also been suggested that among patients with gait or balance disorders, such as corticobasal degeneration, the average survival is reduced to 7 years once recurrent falls are present (Wenning et al. 1998), and that the onset of falls in PD indicates an advanced stage of the disease with poor prognosis (Wenning et al. 1999). Moreover, it seems that fractures resulting from falls further worsen the prognosis and increase mortality in PD (Coughlin & Templeton 1980). Our results support these previous findings and further highlight the importance of gait disturbance as a significant risk factor for mortality in PD.

Few studies have investigated the rate of injuries from falls in PD. One meta-analysis of six prospective studies of falling in PD reported the proportion of injurious falls to be approximately 25% (Pickering et al. 2007). A 6-month prospective study of moderately affected PD patients (Bloem et al. 2001a) reported a 62% rate of soft tissue injuries but no fractures. Other studies also
support the concept that soft tissue injuries from falls in PD are common, but serious injuries rare (Paulson et al. 1986, Koller et al. 1989, Gray & Hildebrand 2000), even though a fracture rate as high as 33% has been reported (Wielinski et al. 2005). Falls have been claimed to be responsible for more than 30% of the acute events that bring patients with PD to emergency clinics (Martignoni et al. 2004). Our results in the present study broadly confirm these previous findings: 126 of the 370 falls resulted in injury, giving a 34% rate of injurious falls and six fractures were reported during the two-year follow-up period.

In retrospective studies 38% to 64% of PD patients have reported falling (Paulson et al. 1986, Koller et al. 1989, Ashburn et al. 2001a), whereas in prospective studies (Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002) up to 70% of patients have reported falling. A recent meta-analysis concluded that 46% of PD patients had fallen during a 3-month follow-up period (Pickering et al. 2007). Our results are again in broad agreement with the previous studies. In the cross-sectional part of our study over 30% of the patients reported at least one fall during the prior three months, and during the two-year follow-up period falling was reported by 63% of the patients. Forty-seven percent of the patients were classified as recurrent fallers.

Several risk factors for falling in PD have been identified, and when considered together, they seem to define a consensus on the falling risk factors in PD. Several studies indicate that the severity and duration of the disease (Koller et al. 1989, Gray & Hildebrand 2000, Bloem et al. 2001a, Wood et al. 2002, Schaafsma et al. 2003, Balash et al. 2005, Wielinski et al. 2005), gait and balance disturbances (Gray & Hildebrand 2000, Wood et al. 2002, Schaafsma et al. 2003, Balash et al. 2005, Dennison et al. 2007), previous falls (Ashburn et al. 2001b, Bloem et al. 2001a, Wood et al. 2002), fear of falling (Ashburn et al. 2001b), and dementia (Wood et al. 2002, Wielinski et al. 2005) are all risk factors for falling in PD. Furthermore, previous studies have shown that urinary incontinence (Balash et al. 2005), daily intake of alcohol (Gray & Hildebrand 2000), and OH (Gray & Hildebrand 2000, Dennison et al. 2007) are also associated with falling in PD. A recent meta-analysis concluded that the best predictor of falling is the occurrence of two or more falls in the previous year (Pickering et al. 2007). However, the present study showed that high UPDRS scores and increased postural sway are also independent predictors of recent falling in PD. Nevertheless, in line with previous studies, we also found that a history of falling and high UPDRS ADL scores are independent risk factors for recurrent falling in PD.
In the present study, the tests for dynamic balance and mobility seemed to discriminate well between the recurrent fallers and the non-recurrent fallers, and perhaps even better between the patients who died during the study and those who did not. Moreover, the recurrent fallers showed increased postural sway when compared to the non-recurrent fallers. It would seem, therefore, that in order to identify PD patients who are at risk of falling, both postural sway and mobility are worth assessing. However, a simple assessment of walking speed seems to be sufficient for giving a rough estimate of a patient’s risk of mortality.

The purpose of the present study was to assess the clinical correlates of balance and mobility, and to identify risk factors for falls and mortality in PD. Even though more research is needed on interventions aimed at fall prevention in PD, the present results suggest that some aspects need to be considered when working with PD patients. Asking about falls or near-falls as a part of history taking is essential, and patient education on the increased risk of falling in PD is needed. Patients considered at high risk of future falls because of their illness history or clinical examinations require careful assessment of possible ways to prevent falling and fall-related injuries. PD patients may also benefit from treatment aimed at maintaining general fitness or focusing on physical therapy. Furthermore, antiparkinsonian and concomitant medications should be critically evaluated, and some patients could benefit from orthostatic testing. The use of walking aids and possible protective equipment should be considered or recommended. Last but not least, changes in the domestic environment could reduce falls. These could include simple things such as furniture distribution in the kitchen or bedroom, hand rails in the bathroom or toilet or getting rid of loose carpets in the apartment.
7 Conclusions

The results of the present study allow one to draw certain conclusions concerning balance, mobility and falls in PD: Balance impairment and falls are common features in PD, and a slow walking speed may be associated with increased mortality in PD.

1. Disease duration and severity, recent falling and use of a walking aid are predictors of increased postural sway in PD. One-third of the patients in the present study reported recent falling. High UPDRS total scores and increased postural sway are risk factors for falling in PD.

2. Advanced age and severity of the disease are related to impaired balance and mobility in PD patients. The severity of the disease and increased postural sway seem to be the most important independent risk factors for falling in PD, whereas measures of mobility seem to be less important in this manner.

3. Patients with OH seem to have significantly increased postural sway in standing compared to patients without OH. However, OH was not associated with mobility and walking speed. In the present data, OH was not associated with the risk of falling in PD.

4. Sixty-three percent of the study patients experienced falls and almost half of the subjects fell recurrently during the two-year follow-up. Both a history of falling and disease severity indicate increased risk of recurrent falls in PD, while patients with slow walking speed may have an increased risk of mortality.
References


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Original publications


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1013. Törni, Sami (2009) Factors affecting outcome after primary intracerebral hemorrhage


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Maarit Matinolli

BALANCE, MOBILITY AND FALLS IN PARKINSON’S DISEASE

Maarit Matinolli