Falls in Older People with Type 2 Diabetes Mellitus

Implications for specific and generic risk detection

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Implications for specific and generic risk detection

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Contents

The leaves fall, the wind blows, and the farm country slowly changes from the summer cottons into its winter wools.
Henry Beston, Northern Farm

Preface

For the first time in human history, the population of older adults (60+) is about to outnumber all other (younger) age categories. This enormous boom of the ageing population poses some major challenges to the older individual, his/her surroundings, health care services and society. In any age category but especially in older adults, a satisfying quality of life starts with a good physical health. Initiatives to ensure or optimize the quality of life of the aged are therefore required.

This doctoral thesis takes a closer look at fall risk factors among older adults with Type 2 Diabetes Mellitus (T2DM). As falls and T2DM are both very common in the older population and form major threats to one's quality of life, prevention strategies for falls, T2DM and especially the detrimental association seem mandatory. Before appropriate and specific prevention programs can be developed, a proper understanding and identification of population specific risk factors should however be obtained. In the initial *Chapter 1* the background on falls and diabetes and its inter-relationships will be outlined based on the extensive existing scientific literature. Part One and Part Two contain our own studies. Part One presents our main paper in which risk factors for falls are identified among a mixed cohort of older adults with and without T2DM by means of an extensive baseline assessment in combination with a one-year follow-up for falls *(Chapter 2)*. In Part Two some potentially crucial and intriguing but often less focused interfering fall risk factors are scrutinized. The influence of peripheral nerve function and cognition on gait and postural control were assessed in older adults with and without T2DM *(Chapter 3 and 4)* whereas the impact of different types of footwear on gait was assessed in healthy older women *(Chapter 5)*. The final chapter *(Chapter 6)* provides a critical reflection of the findings of this doctoral thesis in relation to the existing literature. Important points of interest for health care workers (physiotherapists in particular) are highlighted and concepts for future research are suggested.

I sincerely hope that this doctoral thesis may capture the reader's attention, contribute to the existing domain-specific scientific insights and knowledge, and may improve the geriatric clinical practice.

Tine Roman de Mettelinge,
Ghent, 2013

Chapter 1

General introduction

1

BACKGROUND

During the past decades, getting older became the academic scope of many researchers in a wide field of sciences. Today, people reach higher ages than ever before. Although increased human longevity can be seen as a triumph for research and development, it is a double-edged sword as it poses major unique challenges to the society. Pension schemes, health care costs and senior accommodations are only a few aspects which need to be reconsidered. The main purpose of each involved party lies in the ambition to ensure optimal quality of life for the older adult. For most older adults, being independent is crucial in terms of quality of life and this often assumes the preserved ability to ambulate. These walking abilities can however easily be complicated by a very common event in the aged, namely falling. Falls may cause a tremendous amount of morbidity, mortality, activity restriction and premature nursing home admissions. Different medical health care services, but physiotherapy in particular, play a vital role in rehabilitating older adults after a fall and even more in preventing (new) falls. Accurate risk detection is always the first step in developing and implying successful prevention strategies. This doctoral thesis will therefore focus on fall risk detection in older people and more specifically in older people suffering from Type 2 Diabetes Mellitus (T2DM), a disease that threatens a constantly growing subpopulation of the aged.

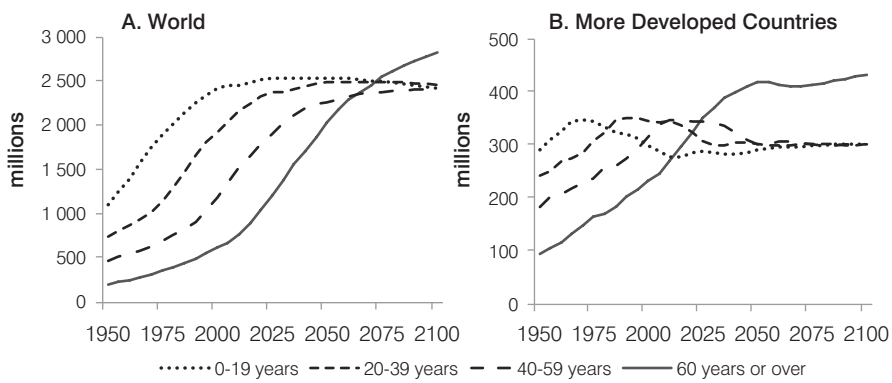

Figure 1.1 Older (60+) people will outnumber children (0-19) in 2050 across the world (A) and before 2025 across the more developed countries (B), adapted with permission of the United Nations [1]

The world is ageing fast and older adults are the fastest growing segment of the increasing global population. According to the United Nations approximately 810 million (11%) persons in the world were aged 60 years or older in 2012 [1]. This number is estimated to increase up to more than 2 billion (22%) in 2050, thereby outnumbering the proportion of children and youngsters (0-19 years) for the first time in human history (Figure 1.1) [1]. A historical take-over is actually already occurring in the more developed regions (Figure 1.1) [1]. This global trend can also be observed in Belgium in an even superlative gradation: currently 1 out of 4 (24%) people living in Belgium are aged 60 years or older and this will grow to 1 out of 3 in 2050 (31%) [1].

Due to advanced medical care and improved facilities, many ageing adults currently experience good health and enjoy a nice quality of life. Ageing should therefore not be considered as a disease in itself. Nevertheless, a substantial proportion of older people are confronted with predominating impairments that actually influence and even undermine their daily activities and quality of life. These impairments are often denominated as "geriatric giants" and generally include urinary incontinence, depression, memory loss and falls or immobility. It is noteworthy that falls may as well exacerbate the other geriatric giants as the others may deteriorate the fall status (Figure 1.2).

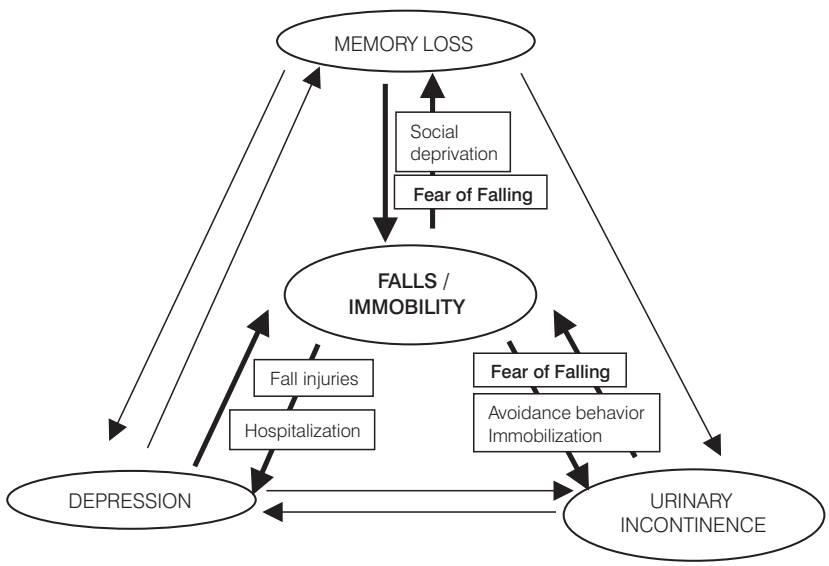

Figure 1.2 The interplay of the "geriatric giants"

Falling is considered a geriatric giant for good reasons. About 35% of the community-dwelling older adults (65+) fall at least once a year [2-7]. In residential settings incidence may even increase up to 50% [8]. Approximately 30% to a half of the falls pass without physical implications. The direct physical consequences of the other half to 70% of the falls are divers and range from minor injuries such as superficial abrasions, bruises, lacerations, strains and sprains to major injuries such as fractures, head injuries and even fatalities [9,10]. Tinetti *et al.* showed in a large prospective study that 23% of the fallers experienced *serious* fall injury events [11]. Of these fall-related injuries, the one with the worst outcome is a hip fracture. By 1 year after a hip fracture only 35 to 38% of the patients is able to restore independent walking [12,13] and 20 to 50% dies [12,14]. Prevalence rates of falls [5,10,15,16] and injurious falls [17] increase with age, with an annual incidence increasing up to 50% in older adults aged 80 or more [18]. Figure 1.3 shows the proportion of people aged 65 or older who participated in our prospective fall study who reported at least one injurious or non-injurious fall during a 12-month follow-up period.

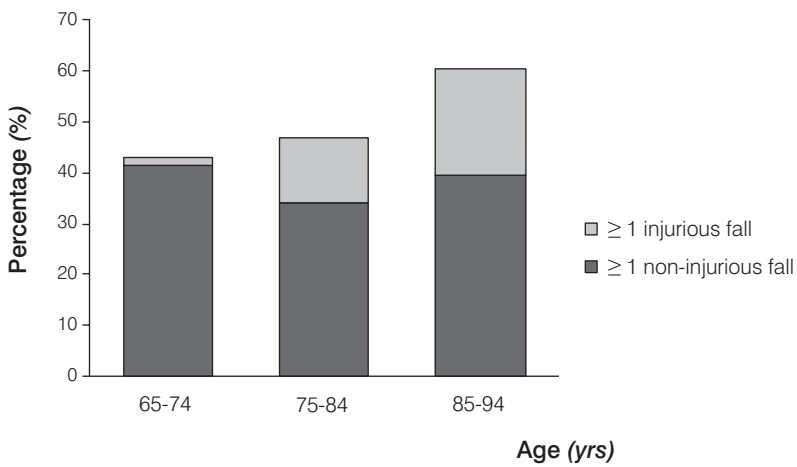

Figure 1.3 Proportion of non-injurious and injurious fall events for different age categories during a one-year follow-up period (N=173) (Unpublished)

Although the abovementioned numbers are staggering ('giant'), they are mostly based on self-reported data and may therefore even underestimate true fall-related rates.

Besides physical discomfort, fall incidents may also provoke psychological complaints such as depression and fear of falling. The psychological consequences of a fall, which are often more subtle than the physical consequences, may however seriously affect quality of life and may therefore not be ignored. Fear of falling for example may dramatically hamper one's confidence leading to self-restriction or avoidance of activities and has clearly proven to be an independent risk factor for falling itself [19].

In an attempt to prevent falls and its many consequences, a number of initiatives and intervention strategies have been suggested, varying from environmental modification and education to medicinal optimization and exercise programmes. The largest body of evidence exists for exercise. From her systematic review including 44 randomized controlled trials about exercise and fall prevention, Sherrington *et al.* concluded that exercise can prevent falls in older people [20]. Both group and home-based exercise programs, usually containing balance and strength training, have clearly proven to reduce the rate of falls and the risk of falling in older adults [6,20,21].

The actual existing framework of the Belgian nomenclature for physiotherapists encompasses the opportunity to offer these successful exercise interventions. The Belgian Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV)-nomenclature [22] provides since 2002 a conditional indication for 60 therapeutic sessions per year with maximal refund by medical insurance (Fb-nomenclature). To meet this part of the nomenclature with the given financial contribution, older (65+) adults with a positive fall history additionally need to fulfill a given set of future fall prone motor criteria with prescribed cut-off scores [22] (Table 1.1).

Table 1.1 Criteria for meeting Fb-pathology

Age	The patient is 65 years or older
Fall history	The patient fell at least once and is prone to fall again based on the scores of some clinical cut-off scores on some common motor assessment tests*
Motor*	Timed Up & Go (TUG) Test score > 20" **AND** Tinetti Test score < 20/28 **OR** Timed Chair Stands (TCS) Test score > 14" *(#)*

(#) Both tests should be administered

Although the criteria of the Belgian nomenclature for physiotherapists are based on very useful and reliable tools and as such are appropriate for "generic" older adults, one could and should ask whether they are adjusted to specific though potentially crucial pathology-related aspects that increase the risk of falling. A number of age-related diseases such as hypertension, cardiovascular impairments, cognitive decline, cataracts, osteoporosis, osteoarthritis, stroke, Parkinson's Disease and Type II Diabetes Mellitus (T2DM) imply a supplementary risk for falling and fall-related injuries. Some of these diseases (such as Parkinson's Disease, Rheumatoid Arthritis and stroke) fit in other sections of the nomenclature (E-pathologies) but others, such as diabetes, do not. As T2DM is becoming a major concern in the ageing population, one could wonder whether it should not be legitimate to think about integrating this disease in any way in the nomenclature. This was one of the incentives to establish profound research in this area.

Diabetes is one of the most common age-related diseases, reaching epidemic proportions worldwide. According to the World Health Organization (WHO), the disease globally affects approximately 347 million people and the diabetes deaths will double between 2005 and 2030 [23]. The current prevalence of T2DM in Belgium is estimated at 800 000 people [24]. Older individuals with diabetes are at increased risk for falls [25-29], injurious falls [26] and hip and other fractures [30]. Maurer *et al.* found that the fall incidence rate for adults aged 70 years or older with and without diabetes mellitus was 78% and 30% respectively [31]. Diabetes is a complex disease involving many organs and systems of the inner body. A lot of diabetes-related complications such as peripheral nerve dysfunction, foot ulcers, visual deterioration, urinary incontinence, renal disorders, cognitive decline, … are known as potential mechanisms for falls and may therefore also contribute to the increased fall incidence rates in this given population. To appropriately treat and manage these complications, older adults with diabetes also often take a lot of medications, thereby again increasing their fall risk. Given the numerous disease-related complications which may contribute to a remarkably increased fall risk, a revision of the existing nomenclature for physiotherapy within the scope of T2DM might be justified.

The following three chapters of this General Introduction will outline the existing scientific evidence concerning fall risk factors in general, T2DM as morbidity and the (potential) interrelationships between them, i.e. T2DM as a potential risk factor for falls.

Key points

- The number of age-related diseases such as T2DM increases with the ever-growing proportion of older people.
- Approximately one third of community-dwelling older adults fall at least once a year.
- Fall incidence and fall-related injuries increase with age and ageing.
- Falls may lead to dramatic physical and psychological complaints.
- Older adults with T2DM are at increased risk for falls and injurious falls.
- Current nomenclature for physiotherapeutic interventions in Belgium might need some extensions for specific older subgroups with chronic pathologies such as T2DM.

FALL RISK FACTORS

One of the cardinal rules in scientific research lies in clearly describing terms with well-founded definitions outlined in the existing literature. Although most researchers in this area refer to the same underlying meaning of the word "fall", lots of definitions and descriptions have been suggested to describe the event as such. Currently, the most accepted and most frequently used definition of a fall is the one that Tinetti *et al.* proposed in 1988 as "an event, which results in a person coming to rest unintentionally on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard" [2]. More than fifteen years later this definition was confirmed and recommended by Lamb *et al.* on behalf of the Prevention of Falls Network Europe (ProFaNE) Consensus [32]. Therefore this definition was also used in this research project. Classifications into "fallers" or "non-fallers" are more ambiguous. Per definition a "nonfaller" is a person who did not fall and a "faller" is someone who fell at least once over a defined time period, mostly covering 6 or 12 months. Some researchers prefer to classify individuals who fell twice or more into "recurrent" or "multiple fallers". This approach is based on the fact that single falls are more likely assumed to be occasional, meaning that they might be the result of an accident (e.g. environmental hazard) whereas multiple falls may be more indicative for subversive intrinsic fall risk factors (e.g. physiological predisposition to falling, chronic disease) [33]. Recurrent or multiple fallers would therefore benefit most from fall prevention efforts [34], which emphasizes the clinical importance of a carefully considered classification of fallers. Single fallers have been proven to be more similar to nonfallers than to recurrent fallers on a range of medical, physical and psychological risk factors [33,35,36]. According to Delbaere *et al.* single fallers should however not be categorized as nonfallers when an injury occurred [37]. Taking into account these considerations, we defined a "faller" as an older individual who experienced multiple falls (≥ 2) or a single injurious fall during the next 12 months and a "non-faller" as an older individual who did not fall or suffered a single non-injurious fall.

Falls in older people are rarely caused by a single risk factor but mostly occur as a result of the interplay between intrinsic, extrinsic and situational factors. Intrinsic risk factors are characteristics or conditions that are inherent to the individual and not seldom may affect postural control (= "subject- or patient-related"). It generally concerns age- or disease-related decrements (poor vision, joint stiffness, sarcopenia, Parkinson's disease, …) which complicate the maintenance of balance, thereby increasing fall risk. Extrinsic risk factors are the environmental hazards that provoke (rather than cause) fall incidents such as a wet floor, darkness, wearing high-heeled shoes, ... (= "environment-related"). If no major intrinsic risk factors are present, a healthy older adult is generally capable to compensate for the environmental hazards

in time and prevent a fall. Situational risk factors are related to activities of daily living, e.g. rushing to the bathroom or rushing to answer the telephone (= "activity-related"). Table 1.2 summarizes several commonly accepted intrinsic, extrinsic and situational fall risk factors. Extrinsic and situational risk factors can for the greater part be managed by sensitization, recommendations, advices and warnings. On the contrary, to deal with (modifiable) intrinsic risk factors more intensive (physio)therapeutic interventions are needed. Therefore, this doctoral thesis will mainly focus on intrinsic risk factors.

The following paragraphs provide an outline of the most important intrinsic, extrinsic and situational fall risk factors and their mechanisms, based on existing evidence.

Intrinsic fall risk factors

In general, the intrinsic risk factors can be divided into functions ("*(F)*" in Table 1.2) needed to maintain postural control and prevent falling, and intrinsic characteristics ("*(C)*" in Table 1.2) that may interfere with the preventive performance of these functions. Balance and gait impairments are considered the most important intrinsic fall risk factors [38]. Other strong risk factors are fear of falling, previous falls and muscle weakness. Therefore, factors as postural control, gait and muscle weakness and characteristics as age, gender, previous falls, fear of falling, medications and pathological conditions will be shortly discussed.

Postural control

Postural control is defined as the act of maintaining, achieving or restoring a state of balance during any posture or activity [39]. Individuals with a hampered postural control are unable to perform the needed action as defined and will as such be at increased risk for falling. Since postural control is no "one-system-one-function" human attribute but the result of a complex interaction of input, cognitive analysis and interpretation and eventual appropriate output (Figure 1.4.), this human radar might easily be violated.

With regard to the input level, accurate postural control involves a coordinated set of sensorimotor processes that continually encode and compare information from somatosensory (mainly proprioceptive) (70%), vestibular (20%) and visual (10%) feedback [40-42]. If one of these three systems is complicated due to situational (e.g. unstable surface) or pathological conditions (e.g. peripheral neuropathy or visual deficits) the contribution of the other systems will become more important in the maintenance of postural control. The somatosensory system encompasses

Table 1.2 Examples of intrinsic, extrinsic and situational fall risk factors.

Intrinsic Risk Factors	Extrinsic Risk Factors	Situational Risk Factors
Postural Control *(F)*	Environmental Hazards	Risky Behaviour
Gait *(F)*	Poor footwear	Dual Tasking
Muscle Weakness *(F)*	Type of Dwelling	…
Flexibility *(F)*	Lighting	
Performance *(F)*	Walking Surface	
↑	Loose Carpets	
	Marital Status	
Age *(C)*	Education years	
Gender *(C)*	…	
Previous Falls *(C)*		
Fear of Falling *(C)*		
Medications *(C)*		
Pathological Conditions *(C):* - Visual deficit - Parkinson's Disease, stroke, … - Cognitive disorder, depression - Urinary incontinence - …		

sensations of pain, temperature, tactile sensations (i.e. touch, tickle, pressure, vibration) and proprioceptive sensations. Proprioceptive input provides information concerning the position and movement of the body segments in relation to each other and to the surrounding. The vestibular system is in charge of informing about the head position and movements in relation to gravity whereas the visual system determines the orientation of the eyes and head in relation to objects in the environment [43]. Deficiencies in the somatosensory, vestibular and visual systems occur with ageing [44,45]. Also, age-related deteriorations of muscle structures and functions have been shown. The resulting loss of postural control has repeatedly been associated with an increased fall risk [2,6,8,41,46-51].

Appropriate muscle responses and functions are required to implement the response on integrated and analyzed afferent information. Adequate motor abilities are not only essential for the maintenance of static postures and the performance of dynamic

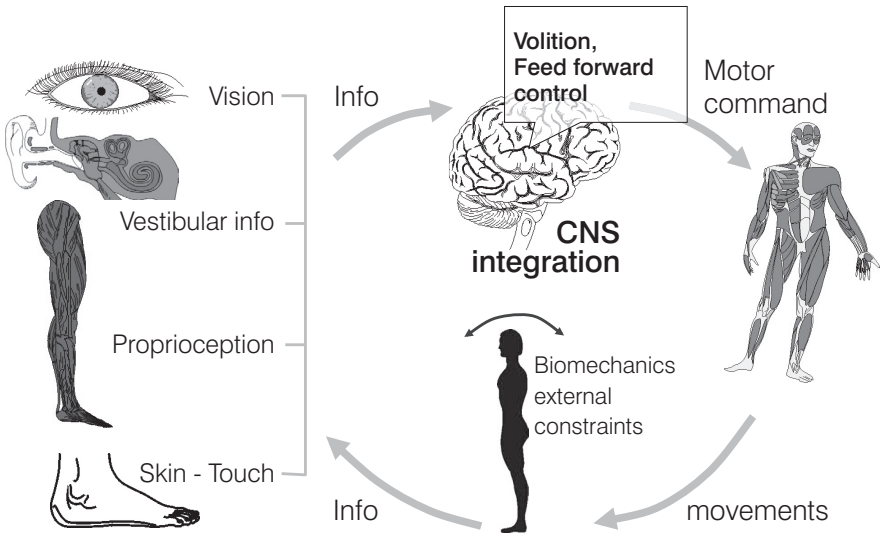

Figure 1.4 Postural control (Adapted with permission from Prof. Dr. Måns Magnusson)

activities, they also play an important anticipatory role by initiating voluntary movements or increasing muscle activity in anticipation of a predicted disturbance.

As postural control is a detrimental factor for falls, appropriate assessment in view of profiling the risk for this matter is highly mandatory. A number of clinic balance tests such as the Tinetti Test, Berg Balance Scale, Functional Reach, Timed Up & Go (TUG), Romberg, tandem stance and one-leg stance can be used to assess postural control. These tests are easy to administer and give the practitioner a general idea of one's postural abilities. However, the majority of these tests have only one outcome measure or score that not always encompasses the quality of execution. Predictive values of clinical measures towards falls are thereby limited to an arbitrary categorization of postural control [52-54]. Postural control can also be assessed by means of devices such as force platforms or accelerometers. Static or dynamic sway analyses by use of force platforms provide valid information of postural control that can be used to predict fall risk [55]. Force platforms register location and displacements of the Center of Pressure and might yield precise insights in balance disturbances due to deliberately varying input (changes in visual, somatosensory or vestibular information) and/or conditions (changes in surface or dual tasking). Quantitative sway measurements have proven to have high sensitivity in predicting

future falls [55-57]. During quiet upright stance conditions, fallers show larger sway amplitudes, especially in medio-lateral direction and during standing with the eyes closed [50,58-60].

Disturbed posturographic or clinical postural outcomes render an objective appraisal of one's postural abilities. With respect to the interpretation of hampered postural control, however, less effort is put in detecting the underlying mechanisms during a general fall risk assessment. Aside of eventual testing of output functions such as muscle strength or flexibility, the input and central integration is often less integrated in any evaluation. Nevertheless, decrements in aspects such as somatosensation or cognitive performance may be of great importance for ineffective postural performance. They even may substantially interfere in preventive measures aimed to improve postural control and should therefore be taken into account during profiling the fall risk of older persons with impaired postural abilities.

When postural control is disturbed, crucial questions arise with respect to eventual treatment. For this matter it can be mentioned that based on an impressive Cochrane Review, Gillespie *et al.* concluded that multifaceted intervention programs including balance exercises have shown to improve postural control and reduce fall incidence [6]. As such, pinpointing decrements in postural control abilities is an important asset for remediation and prevention of falls.

Gait

Postural control plays a key role in dynamic mobility-related activities such as walking. Although walking was previously assumed to be an automated motor task, requiring minimal higher-level cognitive input, recent research has provided conclusive evidence to the contrary [61-63]. Dual task paradigms (which will be discussed further on page 21) and gait analyses in older adults with cognitive impairments have proven that gait performance also relies on cognitive functions, especially attention and executive functioning.

Despite their multifactorial etiology, falls have one common feature: the majority occur during upright transfers and therefore walking [10,64,65]. Similarly to postural control, assessment of gait is necessary. Gait can easily be measured using various clinical tools such as 10-meter walking test, Tinetti test, … Although indicative and feasible in cases of obvious deterioration, more subtle gait changes which are more subtly associated with an increased fall incidence cannot be detected by clinical observation alone [64]. Technical gait analysis using the GAITRite® electronic walkway has proven to be valid and reliable for measuring spatiotemporal gait parameters [66-70] and as such was used for gait analyses in our own experiments.

The GAITRite® System consists of a portable walkway embedded with pressure-activated sensors. When a subject walks across the walkway, these sensors capture footfalls by detecting the timing of sensor activation and the distances between the activated sensors. The application software then calculates a wide range of spatial and temporal gait parameters. Figure 1.5 gives an overview of several common spatial (a) and temporal (b) gait parameters. Spatial (distance) and temporal (timing) parameters are expressed or at least calculated as a function of steps or strides. As such the step length represents the distance from the heel point of the current footfall to the heel point of the previous footfall (left to right or right to left foot) whereas the stride length represents the distance between the heel points of two consecutive footfalls of the same foot (left to left or right to right) (Figure 1.5 a).

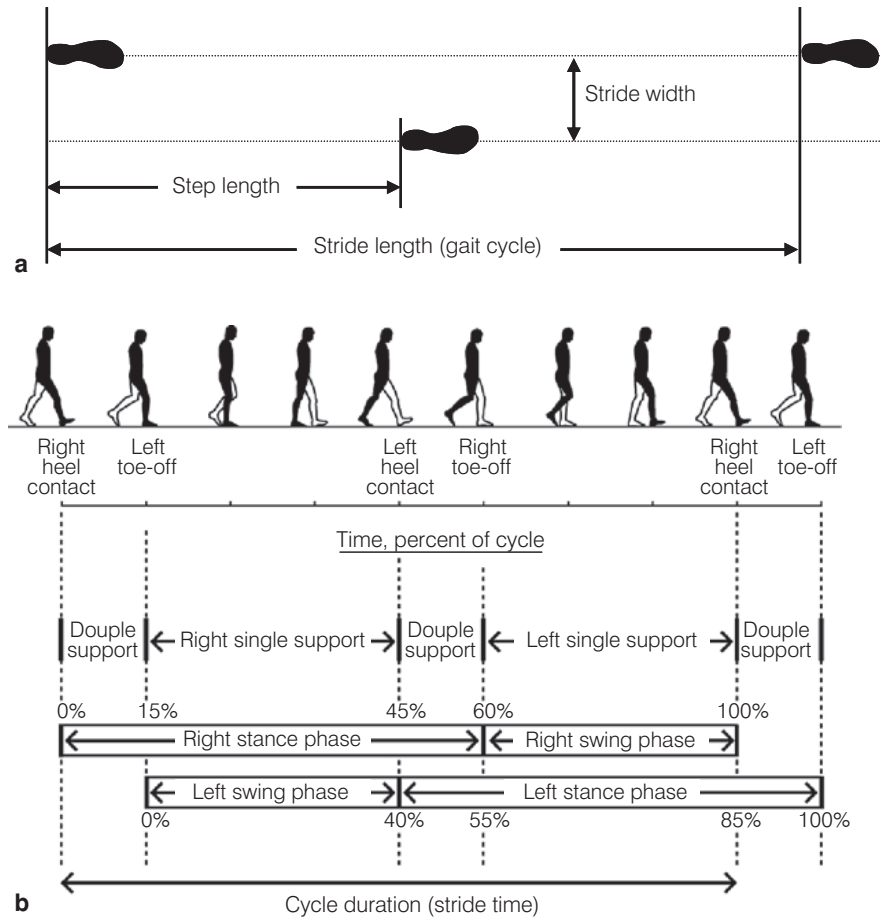

Figure 1.5 Spatial (a) and temporal (b) gait parameters [64]

The altered gait pattern of healthy older adults is generally characterized by reduced gait speed [71-73], shorter step and/or stride lengths [71,72] and increased gait variability [74]. Increased step time, stance time and single or double support time have also been reported. An increased gait variability, expressed as increased coefficient of variation [(standard deviation/mean) × 100], indicates an unstable gait pattern. Gait speed [75,76] and stride-to-stride variability (in both stride length and stride time) have repeatedly been identified as independent predictors of falling [75,77-79]. Some authors, however, suggested that decreased stride length and gait speed and prolonged double support time might be stabilizing compensatory adaptations related to the anticipation of fear of falling [77,80].

Muscle weakness

As a result of the ageing process, a number of changes in the human muscles can be noticed. The degenerative loss of skeletal muscle mass, quality and strength is denominated as "sarcopenia", derived from the Greek words *sarx* = 'flesh' and *penia* = 'a lack of' or 'loss'. The loss of the number of muscle fibers is the principal cause of sarcopenia, although fiber atrophy (the loss of muscle mass) of the remaining fibers, particularly among fast-twitch type II fibers, is also involved [81]. A lot of other age-related morphologic, physiologic and biochemical changes have been identified [82]. Furthermore, a recent review demonstrated that not only the muscle itself but also the communicating neural pathways to skeletal muscles are impaired with advancing age [83]. All these age-related changes result in a progressive loss of all muscle functions, i.e. power (explosive strength), strength (maximal amount of force exerted in a single attempt) and endurance (capacity to resist muscular fatigue, particularly when the resistance is submaximal) [81]. Moreover, muscle strength declines 2-5 times faster than muscle mass [84,85] and low muscle strength, but not low muscle mass, has been associated with poor physical function in older adults [86]. As a result of the decreased muscle power [87], strength [88] and endurance [89] older adults are suggested to be more susceptible to accidental falls and resultant injuries. Decreased (lower extremity) muscle strength [47,90] has been identified as an independent fall risk factor.

Again evaluation of this potential detrimental factor is highly legitimate. Muscle function can be measured by clinical tests such as 5-repetition sit-to-stand, by manual muscle testing, the use of more objective devices such as dynamometers, or by electromyography (EMG). Hand grip strength measured with a hand-held dynamometer is very useful in the identification of sarcopenia [91], is a good marker of physical performance in older people [92] and can predict falling [16,93,94] and recurrent falling [16,95,96]. Therefore, this tool was used in our prospective study.

Age

Fall rates increase with age [5,15-17] and old age has clearly been identified as an important risk factor for falls [16,97,98]. In a way, advanced age can even be considered as a main primary intrinsic risk factor since ageing inevitably involves a lot of progressing fall-inducing physiological alterations. The substantial age-related changes in postural control [44], gait [71-74] and skeletal muscle function [81-85,99] and their associations with increased fall risk are described above.

Gender

Women have higher fall rates than age-matched men [10,16,65,100]. Despite contradictory findings in his systematic review, Gama *et al.* concluded that being a woman at an advanced age may actually be a predictor of falls [101]. It might be that the substantially smaller lean body mass and concomitant decreased muscle mass/strength and functional outcome of older women compared to older men [102] contributes to this finding. In addition, woman appear to suffer worse fall consequences. The increased fracture rate in older females [10] might be attributed to the increased prevalence of osteoporosis in this group. Women are also at increased risk of developing fear of falling [103]. Finally, female gender has independently been associated with functional decline after falling [9].

Previous falls

Older individuals who experienced a fall in the past, are highly susceptible to fall again in the future. One or more previous falls may lead to the development of fear of falling [103] and is a strong predictor for falls [5,8,16,34,37,95,96,101,104,105].

Fear of falling (FoF)

Besides the fall related physical burdens, falls may trouble the mind of an older individual, resulting in psychological and emotional complications such as depression, being afraid of possible institutionalization and FoF, which in turn may lead to substantial activity restriction as a kind of safety coping strategy. Scheffer *et al.* identified at least one previous fall, being female and being older as main risk factors for developing FoF [103]. On the other hand, FoF also paradoxically increases falling [19,93,95,106]. This might be partly explained by the fact that people with FoF show an adopted cautious gait characterized by alterations in spatiotemporal gait parameters [77,80]. FoF can thus be considered a major fall consequence as well as a major fall risk factor.

Prevalence of FoF generally varies between 20.8 and 85% [103]. Even though previous falls are found to be the main risk factor for developing FoF, FoF is not per definition the result of a fall. Over 50% of persons with FoF did not experience a fall

before [103]. Legters concluded that FoF is claimed to have an average prevalence of 30% or more in older adults who do not have a history of falling and that this rate doubles in older adults who have fallen before [107].

Medications

Older adults use more medications because of the co-existence of multiple diseases. Both the number and the type of medications may be of importance in relation to falls. Groups of medications that have been associated with an increased fall risk are those working upon the central nervous system namely anti-epileptics [108-110] and psychotropic medications such as benzodiazepines, antidepressants and antipsychotics [8,101,105,108-113]. The association of analgesics or cardiovascular medications with falls is controversial [109].

Besides dosage and duration of these medication intakes, the number of medications –regardless of medication class– has also been shown to increase fall risk [34,114-116]. An excessive medication intake is called "polypharmacy" and is usually considered if ≥ 4 medications are taken. However, recent findings suggest a cut-off of 5 medications or more in the context of fall risk among older adults [116,117].

Pathological conditions

Visual deficits

Although the contribution of the visual system to accurate postural control is considered to be relatively low compared to that of the somatosensory (proprioceptive) and vestibular system [40-42], impaired vision has been shown to be a risk factor for falls [118,119]. Poor visual acuity [120,121], decreased depth perception [47,118,122] and lessened contrast sensitivity [118,122] are the visual deficits that have been related to falls the most. If a deterioration in one of the postural control systems (Figure 1.4) occurs or one system is challenged, the other systems will try to compensate for these difficulties in order to maintain stability. As such, visual input becomes even more important when a firm and stable surface is replaced by a soft and more unstable surface because proprioceptive input from feet and ankles is then reduced [122]. Impairments in more than one postural control system e.g. visual and sensorimotor system, superimposes fall risk [123]. The contribution of vision in postural control is best demonstrated by increased sways when standing with the eyes closed.

Neurological impairments

It might not be surprising that older adults who suffer neuromuscular disorders affecting gait and balance, such as Parkinson's Disease [16,104] and stroke [124], are at increased risk for falling.

Less obvious but epidemiologically very relevant are the associations between falls and neuropsychological diseases such as depressions and cognitive deterioration.

As one of the geriatric giants, depression can be considered a common problem in the older population. Approximately 15% of older community-dwelling people and 32% of residential care-dwelling people report significant depressive symptomatology [125]. Depression and depressive symptoms have repeatedly been identified as increased fall risk factors [37,47,94,96]. The underlying mechanisms of this relationship are not fully understood so far. Maybe a co-existing general physical disability, poor sleep and/or psychotropic drug utilization may contribute to the increased fall risk.

About 36.5 million people were estimated to live with dementia in 2010 with a new case of dementia every 4 seconds [126]. Older persons with dementia are 2 to 3 times more likely to fall compared to older persons without dementia [101,127,128]. The increased fall risk is also true for older adults suffering from mild cognitive impairment (MCI) [129], which can be described as an intermediate state between normal age-related cognitive changes and dementia. Poor executive functioning has clearly been associated with gait alterations [61,130,131]. Executive functions include goal-directed behavior, problem solving, planning, organization, the ability to initiate and stop actions, anticipate and adapt to changing situations, direct attention and working memory. Executive functioning is generally associated with the frontal cortex, including the dorsolateral prefrontal cortex, which in turn has been related to dual tasking and to gait variability [62], supporting the idea that fall risk partially depends on executive functioning [132]. Herman *et al.* and Mirelman *et al.* predicted the risk of future falls by performance on executive functioning and attention tests conducted 2 and 5 years earlier respectively [132,133].

Musculoskeletal disorders

Musculoskeletal disorders encompass a large group of conditions in which one or more parts of the musculoskeletal system is injured. The muscles, joints, bones and/or surrounding structures might be affected in a chronic way or due to an acute trauma. Musculoskeletal disorders such as lower limb tendinitis or osteoarthritis may directly increase fall risk by pain-induced alteration of gait performance. Scoliosis, foot or other structural lower limb deformations may displace the body center of gravity, thereby altering postural control. Musculoskeletal disorders affecting gait and posture are quite common and therefore become a potential aggravating fall risk factor.

Internal disorders

With an estimated prevalence of 30 to 50% in community-dwelling women aged 65 or older [134], urinary incontinence can be considered a geriatric giant for good reasons. In contrast to stress incontinence, urge incontinence is significantly increases the risk for falling by 26% [135,136] and fractures by 34% [136].

Chronic kidney disease is also an important risk factor for falls, and the risk correlates negatively with creatinine clearance [137-139]. A low creatinine clearance (of <65ml/min) is associated with a 3.7-fold increased fall risk [139]. The creatinine clearance is important for the conversion of calcidiol to the metabolically most active form of vitamin D [139]. Since a vitamin D deficiency is associated with decreased muscle strength, balance and functional mobility [139], this might explain the findings of an impaired renal function as fall risk factor.

Some cardiovascular disorders such as drop attacks, syncope and orthostatic hypotension may be responsible for "unexplained falls". Notwithstanding the fact that syncope may lead to a fall, "syncope" and "fall" are generally considered two different entities as definitions of falls mostly exclude falls due to loss of consciousness [140]. However, extension of current fall definitions is sometimes suggested in order to reduce falls without attributable diagnosis and to acknowledge the existing overlap between syncope and falls [140]. With respect to cardiovascular disorders orthostatic hypotension is often thought to be a strong risk factor for falls. Orthostatic hypotension is however found to be a relatively unimportant or rare cause of falls [141]. Furthermore, since orthostatic hypotension can be of an intermittent nature, older adults may test negatively during fall risk assessment but may nevertheless suffer from postural blood pressure drops and falls during a follow-up period [141]. If orthostatic hypotension was positively tested, measures may however be taken to prevent falls induced by orthostatic hypotension.

Another predominating internal geriatric disease with staggering fall incidence rates [31], is T2DM. Since older adults with diabetes are the main target population of this doctoral thesis, a comprehensive overview of the disease and its main chronic complications will be provided in the next chapter of this General Introduction (page 23 and further). The increased fall rates in T2DM are commonly accepted, but therefore not that well understood. Nevertheless, T2DM is a morbidity in which remarkably all above mentioned pathological fall risk factors (visual, neurological, …) quite often occur as chronic complications. The potential interrelationships between T2DM and falls will therefore be summarized in the final chapter of this General Introduction (page 33 and further).

Extrinsic fall risk factors

Among the extrinsic risk factors for falling objects lying around on the floor such as loose carpets, toys of grandchildren and electric cords, are the most self-explanatory causes provoking a fall. Other environmental hazards that have been associated with

falls are poor lighting, wet (slippery) or uneven surfaces [18], lower monthly incomes [97], living in a house rather than an apartment [97] and widowhood [142]. Type of footwear is also mentioned as an important extrinsic fall risk factor that can easily be examined and remedied.

Type of footwear

Gait and balance alterations might occur due to wearing suboptimal shoes, consequently increasing fall risk. Altered proprioceptive input and somatosensory feedback is suggested to be the underlying mechanism. Walking barefoot [143], in socks [143] or with high-heeled shoes [144] has been shown to increase indoor fall risk. Nevertheless, the majority of community-dwelling older adults wears slippers within their homes and one out of three walks barefoot or with socks [145]. A heel height of 2.5 cm or greater nearly doubled fall risk in a prospective study among older community-dwelling adults [146]. Menant *et al.* has shown that high heels or shoes with soft soles should be discouraged in older people [147] and that a standard laced shoe with a low collar and a slip-resistant sole of standard hardness with or without tread grooves should be recommended since this type of shoe has proven to provide optimal dynamic stability when walking on even and uneven surfaces [147-149].

From our own assessments we noticed that a lot of preferences and questions concerning shoe types exist among the participants. In several cases also apologies or explanations were made that their performance would probably be better or at least deviant if they should have used other shoes. This rendered us to look for comparable experiences or specific advice in literature. The personal experience together with the remarkable fact that in published fundamental and clinical evaluation of gait appropriate description of footwear was seldom given, inspired us to conduct a study regarding the effect of different types of footwear on gait performance.

Situational fall risk factors

Risky behavior such as climbing a ladder to replace a lamp, consuming too much alcoholic beverages or inattentive behavior might provoke fall events. Among older adults in general, however, dual tasking is the most common situational factor leading to falls. Many activities of daily living are performed simultaneously (e.g. ironing while watching a movie, cooking while listening the weather forecast on the radio, having a conversation while hanging the wash, moving in busy traffic situations, …), thereby requiring divided attention.

Dual tasking

The clinical experience of Lundin-Olsson *et al.* that some frail older patients stopped the walking when starting a conversation while walking [150], is probably the birth of dual task paradigms in scientific research. They supposed that this gait freeze occurred because walking demands attention, just like holding a conversation. Instead of doing two things at the same time, the frail older patients only fulfilled one task (holding a conversation) at the expense of the other task (walking). This is the main principle of dual tasking.

The phenomenon of "stops walking when talking" inspired researchers to reconsider the automaticity of walking. If walking would be an automated activity, there would be no need to stop walking when talking. Later on, walking has indeed been proven to require minimal higher-level cognitive input [61-63]. Because central resources decline in older individuals, dual task ability also deteriorates [151]. The introduction of dual tasks in gait analyses showed that gait patterns were indeed altered when compared to single task conditions (i.e. walking alone). During dual task conditions decreases in gait speed and swing time and increases in stride time and swing time variability have been observed among older adults [152-154]. These effects have been associated with poor executive functioning [152,155], which is a strong fall risk factor itself (see above). Dual tasking induced gait changes are significantly associated with an increased risk for falling amongst older adults [156].

Dual task walking might be viewed as a functional measure of executive functioning [132] as both functions rely on the dorsolateral prefrontal cortex [62]. Both dual task walking ability and executive functioning have been related to future falls [132]. When two tasks are expected to be performed simultaneously, difficulties can arise if at least one task is too demanding or if cognitive reserves and attentional capacities are low. Beauchet *et al.* found that the effects of dual tasks on gait performance depend on the type of the given cognitive dual task concordant with the attentional load [153]. Generally, arithmetic dual tasks (e.g. counting backwards) cause significantly greater gait alterations than verbal fluency dual tasks (e.g. animal naming) [153,157]. As both ambulation and the arithmetic dual task rely on the working memory, the increased competitive interaction with executive functions might explain this finding. Verbal fluency mainly depends on semantic memory. Woollacott *et al.* concluded that not only the type but also the complexity of the second task contributes to an increased attentional demand [158]. Alternatively, effects of dual tasks might also be more pronounced in older individuals with limited cognitive capacities. Dual task related gait decrements are significantly larger in aged groups suffering from MCI [159,160] or dementia [160] compared to older adults with intact cognitive abilities.

Multifactorial etiology

Mostly, a fall (considering the definition we use) in an older individual is the result of a complex interaction of intrinsic, extrinsic and situational factors. As more than 400 potential risk factors for falling have been identified in previous research [161], one must realize that it is utopic and not realistic to administer each fall risk factor and predict fall incidence with a 100% sensitivity. However, the risk of falling [2] and recurrent falling [162] increases with the number of risk factors. We therefore tried to pay attention to the most important intrinsic (gait, balance, previous falls, fear of falling, medication intake, …) and extrinsic (shoes, type of dwelling) risk factors in the experiments of this doctoral thesis. Furthermore, we simulated situational conditions by introducing dual task paradigms in gait analyses. Since the role for physiotherapists in preventing falls and rehabilitation after a fall particularly concerns intrinsic fall risk factors, these will however receive our main attention.

Key points

- A fall is defined as "an event, which results in a person coming to rest unintentionally on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard"
- Falls have a multifactorial etiology.
- Poor gait and postural control are main risk factors for falling.
- These intrinsic risk factors are aggravated by age, type and number of medications and pathological conditions (other intrinsic risk factors) and/or by type of footwear (extrinsic risk factors).
- Previous falls and fear of falling are strong predictors for future falls.

TYPE 2 DIABETES MELLITUS

Background

With about 90% of the people with diabetes having T2DM, this is the most common form of diabetes. Worldwide, up to 1 out of 6 adults aged 65 years or over suffers from T2DM [163]. In the United States this number increases to as much as 26.9% [164]. Furthermore, prevalence rates are likely to be even higher than current estimates because a substantial proportion of T2DM patients does not (yet) realize that they suffer from T2DM as the onset may occur up to seven years before clinical diagnosis [165]. The emerging pandemic can be attributed to the outline of several global trends: ageing population, rising levels of obesity and inactivity, and greater longevity among T2DM patients due to improved management [166]. T2DM usually develops slowly and is associated with overweight and genetic predisposition. It is mostly diagnosed in older people which explains the previous name "maturity-onset diabetes". However, since more and more children are diagnosed with T2DM, this term is no longer preferred. As persons with T2DM can control their condition by other methods than insulin, T2DM is also called "non-insulin-dependent diabetes".

Before elucidating the pathogenesis of T2DM it might be useful to bear in mind that the maintenance of normal sugar level in the blood is achieved by three ways: (i) derived from carbohydrates in the food (largest part), (ii) derived from glycogen if blood sugar level falls to much, and (iii) derived from fat- and protein reserves if supply of carbohydrates stopped and glycogen stock is exhausted. With the help of insulin, a hormone secreted by the β-cells of the pancreas (islets of Langerhans), cells throughout the body absorb glucose and use it for energy. Insulin is needed to transport glucose from the bloodstream to the cells and to allow glucose to enter body cells. If blood glucose levels increase after a meal, the pancreatic islets will react by stimulating insulin secretion into the blood to transport glucose to the cells. Like other hormones, insulin also acts as a key opening the gate of functions or cells of the human body (activation of insulin-receptors). In the case of insulin it concerns the doors of body cells in order to stimulate the cellular uptake of glucose from the blood. However, in T2DM the body cells of the tissues are less sensitive for insulin due to excess weight in which muscle, liver and fat cells do not use insulin properly. Insulin resistance usually precedes the development of T2DM by many years and is a consequence of chronic systemic inflammatory responses. Obesity, overnutrition and/or inactivity lead to the accumulation of lipids and excess storage of lipids in liver and muscles (triglycerides), resulting in incomplete oxidation and oxidative stress [167,168]. This lipid accumulation is directly associated with insulin resistance. However, recent research hypothesizes that the

excess lipid accumulation and concordant oxidative stress can also damage mitochondrial function, which is crucial in the pathogenesis of T2DM. Mitochondria are located in nearly every body cell and are responsible for producing energy. In T2DM mitochondria are smaller and have a decreased function [169]. Failure of complete oxidation (mitochondrial dysfunction) can again lead to accumulation of lipid intermediates, incomplete fatty acid oxidation products, and reactive oxygen species (ROS), inducing both insulin resistance (muscle, liver, adipose) and altered secretion (β-cells) [167]. In response to the decreased insulin sensitivity, the pancreatic β-cells produce more insulin. However, after a while they are exhausted and further damaged by oxidative stress. Besides the already existing insulin resistance, a deficient secretion of insulin is then a fact. It is therefore suggested that oxidative stress acts as the main pathogenic mechanism of both insulin resistance and β-cells dysfunction [168].

An insufficient insulin secretion or the presence of insulin resistance leads to an accumulation of sugar in the blood instead of being absorbed by body cells. Consequently, body cells are starved of energy for optimal functioning despite high blood glucose levels. The body will try to remove the elevated sugar in the blood by the urine ("glycosuria"), which may lead to frequent urination ("polyuria"), thirst and frequent drinking ("polydipsia"). If not treated timely, a long-lasting or excessive hyperglycemia may result in a diabetic coma. In the early stages of diabetes there might however be no symptoms. Lab analyses of blood are thus required to diagnose prediabetes or diabetes. The following tests can be used for diagnosis of T2DM: Oral Glucose Tolerance Test (OGTT), Fasting Plasma Glucose (FPG) test, HbA1c test. Table 1.3 gives an overview of the criteria for the diagnosis of T2DM.

Table 1.3 Criteria for the diagnosis of diabetes

		Normal	Prediabetes	Diabetes
OGTT	*(mg/dL)*	< 140	140-199	≥ 200
FPG	*(mg/dL)*	< 100	100-125	≥ 126
HbA1c	*(%)*	< 5.7	5.7-6.4	≥ 6.5
	(mmol/mol)	< 39	39-46	≥ 48

Chronic complications

T2DM is a chronic disease with particularly chronic complications. However, some acute complications might occur, especially in cases of poor adherence to medical care and treatment. Hypoglycemia or low blood glucose level (FPG < 70 mg/dL) and hyperglycemia or a high blood glucose level (FPG > 126 mg/dL) are the most common acute complications. Since some chronic complications have shown to be risk factors for falling as single entities (in older adults *without* T2DM) and can therefore be hypothesized to substantially increase fall risk, the chronic complications of T2DM will be discussed more elaborately. Chronic complications of diabetes are very common in T2DM and present very divers. They are mostly the result of vascular damage. A conscientious management of diabetes including strict diet, exercise and medical measures (optimizing glycemic and blood pressure control) is fundamental to minimize chronic complications.

Neuropathy

About 50% of all people with diabetes have some form of nerve damage. Prevalence increases with age, duration of diabetes and worsening of glucose tolerance. Nerve damage generally develops due to long-lasting excessive blood glucose injuring the walls of tiny blood vessels that nourish nerves, especially in the legs.

Figure 1.6 illustrates the different types of nerve fibers (motor, sensory and autonomic; myelinated or not; large or small) and their respective functions. Sensory nerves send messages to the brain about pain, temperature and touch. Motor nerves tell muscles when and how to move and autonomic nerves control body systems that digest food, pass urine and regulate blood pressure.

Diabetic neuropathies are a heterogeneous group of nervous disorders that may cause a substantial loss of quality of life. The explanation of all types of diabetic neuropathies lies beyond the scope of this thesis. Therefore, only the most common form will be elaborated, distal symmetric polyneuropathy, accounting for 75% of all diabetic neuropathies [171].

Diabetic distal symmetric polyneuropathy mainly affects feet, legs and hands (*"stocking-glove distribution"*) and may involve small fibers, large fibers, or both. Although both motor and sensory nerve conduction is affected, sensory symptoms are usually most prominent [172]: burning or electric-like pain, disturbed perception of vibration and temperature, increased sensitivity to touch and numbness of the feet. People with distal symmetric polyneuropathy sometimes have the apparent paradox of numbness and exquisite sensitivity at the same time [172] and often describe

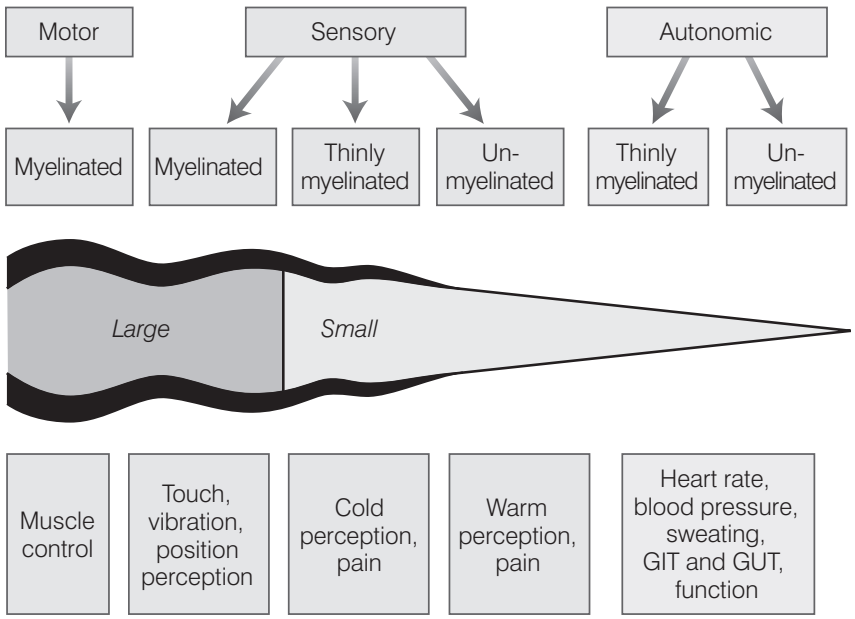

Figure 1.6 Simplified view of the peripheral nervous system [174]
GIT, gastrointestinal tract; GUT, genitourinary tract

feelings of tingling feet (pins and needles), ants running over their feet, stockings while barefoot, dead feet, … Which symptom predominates varies substantially from patient to patient [172]. In advanced stages, neuropathy can be so predominant that patients do not feel pain anymore, rendering a situation in which small injuries may remain unnoticed and the "diabetic foot syndrome" (see page 28) is entering the clinical picture of T2DM.

Nerve conduction studies are preferably used to detect diabetic neuropathies. However, they are (too) expensive to use in routine clinical practice. Therefore, a number of simple and rapid clinical screening instruments have been proposed: 10 g Semmes-Weinstein monofilaments, 128 Hz tuning fork, biothesiometry, ankle reflex, Diabetic Neuropathy Symptom (DNS) score, Diabetic Neuropathy Examination (DNE) score. In this doctoral thesis information concerning peripheral nerves was obtained by participants' general practitioner, DNS and vibration perception threshold (VPT) using the Bio-Thesiometer® (Bio Medical Instrument co, Ohio, USA).

Nephropathy

High blood glucose levels resulting from the diabetes disease may destroy the associated tiny blood vessels (capillaries) of the nephrons in the kidneys. The glomeruli thicken and leak more albumin than normal in the urine ("micro-albuminuria"). Usually, this early stage has no symptoms. As diabetic nephropathy progresses, increasing numbers of glomeruli are destroyed and urine albumin increases to the point that it may be detected by ordinary urinary analyses. These later stages may lead to swollen feet and legs and rises in blood pressure, cholesterol and triglyceride levels. In advanced stages the kidney may even stop working completely ("end-stage renal disease" or "kidney failure") and the diabetic person needs replacement therapy via dialysis or kidney transplant.

Diabetic nephropathy occurs in 20-40% of patients with diabetes [173].

Retinopathy

Approximately one third of people with diabetes is affected by retinopathy [174,175]. It involves damage to the microvasculature of the retina as a result of the prolonged exposure to diabetes-induced metabolic changes.

There are two major types of diabetic retinopathy: nonproliferative and proliferative. The less severe nonproliferative form develops first and is the most common form. In an advanced stage new blood vessels are created by growth factors in an attempt to compensate for the damaged vessels (proliferative stage). Symptoms include blurred vision (loss of sharpness and inability to see fine details), slow vision loss over time, trouble seeing at night, floaters (tiny particles drifting inside the eye) and shadows or missing areas of vision. These visual deficits may hamper postural control with potential detrimental effects. Regular eye exams are thus very important.

Again, individuals with diabetes who have poor glycemic control, genetic factors, high blood pressure and a longer duration of diabetes are more likely to develop retinopathy. Individuals suffering from diabetes are also at increased risk for other eye diseases such as glaucoma (increased pressure in the eye) and cataracts (cloudiness of the eye lens).

Cardiovascular and atherosclerotic complications

Besides damage to smaller blood vessels or capillaries called "microvascular complications" (such as the above-mentioned neuropathy, nephropathy and retinopathy), excessive blood glucose levels in T2DM may also affect larger blood vessels: macrovascular complications. It is hypothesized that these cardiovascular complications are mainly caused by endothelial dysfunction due to oxidative stress [168], which in

turn results from excess lipid accumulation in cases of overnutrition (obesity) and decreased physical activity, as explained earlier.

Approximately one out of every three people with diabetes aged 50 or more have peripheral arterial disease [164]. This condition is characterized by atherosclerotic occlusive disease of the lower extremities. The most common symptom of peripheral arterial disease is intermittent claudication, defined as pain, cramping, or aching in the calves, thighs, or buttocks that appears reproducibly with walking exercise and is relieved by rest [176]. Individuals with peripheral arterial disease are at increased risk for lower-extremity amputation and cardiovascular or cerebrovascular disease such as heart attack and stroke.

Heart attacks and strokes (cardiovascular diseases) strike people with diabetes more than twice as often as people without diabetes [164]. As much as two out of three people with diabetes die from heart disease or stroke [164]. Coronary heart disease and cardiomyopathy are other common cardiovascular complications of diabetes.

Diabetic foot syndrome

The diabetic foot syndrome is an umbrella term covering several foot problems that may occur as a consequence of diabetes. It generally concerns diabetic foot ulcerations, diabetic foot infections and/or neuropathic osteoarthropathies of the heel bone and joint. Foot ulcers occur in approximately 15% of patients with diabetes [177] and precede about 85% of diabetic foot and lower extremity amputations [178]. They are considered to be one of the most expensive diabetes-related complications to treat [179].

The main intrinsic causes of the diabetic foot lie in two other chronic diabetes complications: neuropathy and peripheral arterial disease. As explained earlier, peripheral nerve damage may result in a disturbed or significantly attenuated somatosensation. As such, rubbing shoes, pebbles or other small objects in the shoes leading to blisters or small injuries may remain unnoticed. Furthermore, the skin of the feet is more vulnerable to increased mechanical stress since autonomic neuropathy may reduce hydration resulting in less elastic skin properties. On top of that, poor blood supply complicates proper healing of open wounds which may easily infect. Foot problems may substantially debilitate one's walking abilities and quality of life.

Apart from good diabetes control, regular (daily) podiatric inspection and care are thus essential in order to timely notice and nurse wounds and prevent foot ulcers, gangrene and amputations.

Limited joint mobility (LJM)

LJM is a common complication of T2DM. LJM is often characterized by hand and finger stiffness but other (large) joints may also be involved. Glycosylation of collagen is believed to be the major underlying mechanism. Although LJM is a painless complication, the stiffness and contractures may lead to a substantial mobility reduction (decreased range of motion).

Cognitive deterioration and depression

A less self-evident chronic complication of T2DM is cognitive decline. In recent years, cognitive deficits have been identified in patients with diabetes [180-182], even at early stages of the disease [183]. Several prospective studies have positively associated diabetes with cognitive decline [184-186]. Strong associations were found between dementia and diabetes, particularly if treated with insulin [187]. Positive relationships were found with vascular dementia [187,188] but also with Alzheimer's disease [187-189] and MCI [188], with relative risk ratios of 2.5 (95% CI: 2.1-3.0), 1.5 (95% CI: 1.2-1.8) and 1.2 (95% CI: 1.0-1.5) respectively [188]. The metabolic syndrome and cardiovascular burden caused by diabetes have been associated with reduced cognitive function and structural brain abnormalities [190]. However, the underlying mechanisms are still disputable and it is suggested that the etiology of cognitive impairment in diabetes may not be restricted to vascular pathology [191]. Among others executive functioning [192-195] and attention [193,196], which are crucial for adequate gait performance and dual tasking as explained earlier, belong to the affected cognitive domains. So far, however, detailed cognitive assessments are not routinely carried out among diabetic patients.

Besides cognitive impairments and dementia, patients with diabetes are more likely to suffer another mental disorder: depression. Depression [197,198] and depressive symptoms [199] are significantly more prevalent in older adults with T2DM compared to older adults without T2DM. Individuals with diabetes are twice as likely to have diagnosed depression [200,201]. The prevalence of depression in diabetes is estimated at 30% [199,201] and the presence of depressive symptoms has been associated with a significant worsening of glycemic control [199], an increased risk for diabetic complications and hyperglycemia [202]. Furthermore, depressive symptoms are associated with volume reductions in frontal and temporal brain regions [203] and with poor cognitive functioning and cognitive decline, particularly with advancing age [204,205]. It is recommended to evaluate both depressive symptoms and cognitive functions because they might influence each other in the given test results.

Falls

Given the markedly increased incidence and prevalence rates of falls in older adults with T2DM, falls could be considered a (functional) complication of T2DM. The existing and lacking evidence concerning this item will be discussed later (page 33).

Management

The pathophysiology of diabetes and any of its complications starts with increased blood glucose levels. Diabetes management will therefore focus on lowering blood glucose levels. The California Healthcare Foundation/American Geriatric Society Panel on Improving Care for Elders with Diabetes suggested that a reasonable goal for HbA1c in relatively healthy elderly with good functional status should be 7% (53 mmol/mol) or lower [206]. For older adults who are frail, have life expectancy <5 years and in whom the risk of intensive glycemic control may outweigh its benefit, a less stringent target of 8% is recommended [206]. Glucose levels should ideally range between 70 and 130 mg/dL before meals and be less than 180 mg/dL two hours after starting a meal [164]. In the very early stages of the disease, changes in lifestyle (diet and exercise) may be sufficient to control blood glucose levels but over time, oral agents and even insulin injections are needed to manage T2DM. Vijan suggested that if changes in lifestyle in those with mild diabetes has not resulted in improved blood sugars within six weeks, pharmacological therapy should be initiated [207]. Management of T2DM in the aged should be specifically targeted towards the needs of the older adults [202,208].

Glucose-lowering agents

The standard approach for pharmacological T2DM treatment is focused on improving glycemic control, as reflected by serum levels of HbA1c. The recommended first-line pharmacological treatment of diabetes is metformin because of its effectiveness in lowering blood glucose (by sensitizing the liver to insulin), the low risk of hypoglycemia and relatively low adverse effect profile [208]. Most patients with diabetes have worsening glycemic control over time and will require increased doses or an additional agent to maintain adequate glycemic control. There are a lot of anti-diabetic agents available but some may cause mild to severe side effects such as hypoglycemia or weight gain [202,207]. This is also the case for insulin [209]. Replacing or additional insulin injections might be needed if oral agents are no longer sufficient to achieve adequate glycemic control.

Diet

A diabetic diet that promotes weight loss is important. In their review, Davis *et al.* concluded that the best diet type to obtain weight loss in T2DM is controversial [210]. Nevertheless, most researchers agree on the beneficial effect of low glycemic index (GI) diets to improve glycemic control with significant decreases in HbA1c up to 0.5% [211-213]. The GI provides a measure of how quickly blood glucose levels rise after eating a particular type of food, relative to consumption of pure glucose (glucose has a glycemic index of 100). Examples of food with a low GI (≤ 55) are beans, seeds, grains and most vegetables and sweet fruits.

Exercise

Besides the direct effects of weight loss on glucose levels, a Cochrane meta-analysis comparing exercise with no exercise in T2DM showed that exercise significantly improved glycemic control, reduced visceral adipose tissue and reduced plasma triglyceride levels even without weight loss [214]. Exercise among adults with T2DM improves (i) physical fitness, (ii) antropometric measures (improved body composition by decreasing fat mass and/or increasing lean mass), and (iii) metabolic fitness (improved insulin sensitivity and cardiovascular risk profile). *Aerobic* exercise results in a decrease in HbA1c and improved insulin sensitivity with better outcomes for more vigorous exercise programs [215]. *Resistance* training is also useful and the combination of both types of exercise may be most effective [215,216]. Umpierre *et al.* concluded from his meta-analysis that aerobic and/or resistance exercise can lower HbA1c by 0.6-0.8% [217]. There is some evidence that *interval* training in T2DM improves glucose control and increases mitochondrial capacity [218]. According to the American Diabetes Association guidelines, people with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic exercise and at least twice per week resistance training [173].

Self-management

Patients are generally advised to monitor fasting and premeal glucose levels at home. Education should inform the patient about possible side effects of anti-diabetic agents, learn the patient to recognize and treat hypoglycemia and stimulate practicing regular self-testing to monitor blood glucose levels at home. People with diabetes should learn how diet, exercise and anti-diabetes agents are working. Figure 1.7 illustrates the importance of a well-balanced diabetes management.

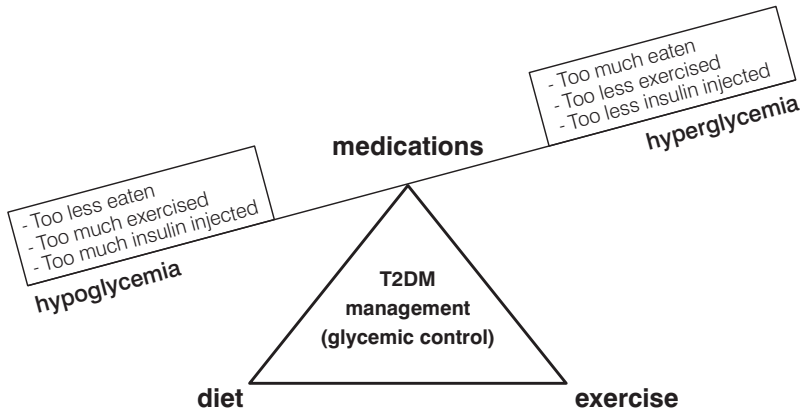

Figure 1.7 T2DM management: monitoring glycemic control

Although monitoring blood glucose levels is important in older adults with T2DM, evidence suggests that greater reductions in morbidity and mortality may result from control of other cardiovascular risk factors (such as dyslipidemia, hypercholesterolemia, hypertension and smoking) than from tight glycemic control alone [173].

Key points

- Diabetes occurs due to (i) the inability of the pancreas to secrete (enough) insulin, and/or (ii) resistance of the body to insulin, resulting in an accumulated blood glucose level and energy deficiency in the cells and organs.
- Besides microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (peripheral artery disease, heart attack, stroke, …) pathologies, a third category of underappreciated chronic complications in T2DM including cognitive decline, depression and falls, should be considered.
- Diabetes management aims to achieve and maintain glycemic control through a combination of lifestyle (diet and exercise) and medical measures.

TYPE 2 DIABETES MELLITUS AND FALLS

Diabetes has repeatedly been identified as risk factor for falls [25-29,31,219-222], injurious falls [26], hip and other fractures [30,223]. Prevalence rates of falls in older adults with T2DM are however scarce. Fall incidence in older adults with diabetes was found to be more than twice the fall incidence rate in older adults without diabetes [31]. Despite these staggering numbers, little is known about the underlying mechanisms leading to the increased fall rates among older adults with T2DM.

The most common and well-known diabetic complication, i.e. peripheral neuropathy and/or its related symptoms, has been associated with an increased fall incidence [29,224,225], seemingly based on its interference on the observed disturbances in gait and balance in T2DM.

Spatiotemporal *gait* parameters are worse in older adults with diabetes compared to older adults without diabetes. Diabetic gait patterns have been characterized by decreased gait velocity, step and/or length and cadence and increased stride time, stance width, double support time and gait variability [221,226,227]. Based on a systematic review, Allet *et al.* concluded that velocity in patients with diabetes (mean age 47.6 to 73.5 years) ranges from 0.7 to 1.24 m/s which is significantly lower than that of controls (mean age 43.2 to 73.9 years) where velocity generally ranges from 0.9 to 1.47 m/s [226]. The presence of diabetic peripheral neuropathy has been associated with aggravated alterations in gait (variables) [228,229]. However, other authors found no differences in gait performance between diabetic adults with and without neuropathy [221,230,231].

As explained earlier in this doctoral thesis, *postural control* relies on adequate somatosensory, vestibular and visual input. Under normal conditions the somatosensory system, in particular the proprioceptive input provided by large (myelinated) sensory nerves, is the most important afferent contributor for postural control. Impaired postural control when standing or walking in T2DM can therefore be considered as a functional consequence of peripheral neuropathy, potentially resulting in instability and finally in fall events. Similarly to gait performance, postural stability is impaired (greater sways) in people with diabetes, especially if their condition includes neuropathy [232,233]. Lord *et al.* found vibration sense to be significantly correlated with sway [233]. However, there is still a lack of consensus concerning the actual cause (diabetes itself or diabetes-related neuropathy) for balance disturbances in T2DM [232]. Bonnet and Ray suggested that perturbations in visual or vestibular systems might affect quiet stance even more than diabetic neuropathy [234].

Finally, neuropathic processes are suggested to affect (lower limb) *muscular function* in older adults with T2DM [235].

Besides neuropathy, other mediators of peripheral muscle and cardiac muscle dysfunction in diabetes hampering exercise capacity, have been suggested: inflammatory cytokines [235] and endothelial dysfunction [236]. Furthermore, lower VO_{2peak} values have been found to directly correlate with decreased insulin sensitivity [236].

Apart from the controversial role of peripheral neuropathy, a lot of other diabetes-related complications such as foot ulcers, limited joint mobility (musculoskeletal disorders), nephropathy (chronic kidney disease), retinopathy (visual deficits), urinary incontinence, depression and cognitive decline (neurological impairments) might increase fall risk since they are proven risk factors for falls in older adults without diabetes (see Intrinsic Fall Risk Factors, Pathological Conditions on page 17-19). Therefore, the finding of Schwartz *et al.* that reducing diabetes-related complications may prevent falls [237] is plausible.

As explained earlier, the increased fall risk among older adults with T2DM can be seen as an (underappreciated) chronic diabetes-related complication. The primary strategy to reduce fall risk among older adults with T2DM is therefore probably similar as the strategy to minimize other chronic complications and lies in an adequate *disease management or glucose control*. As explained earlier in this doctoral thesis, exercise training interventions lower HbA1c. Additionally, exercise programs have also been shown to improve exercise performance capacity (VO_{2peak}) [238,239], decrease adipose tissue mass [238], reduce arterial blood pressure [240], and even enhance pancreatic βcell function [241]. Exercise can thus improve glucose control as well as cardiorespiratory measures, consequently reducing diabetes-related complications. Besides lifestyle management, blood glucose can be controlled by pharmacological agents such as oral anti-diabetics and insulin injections. However, self-management of T2DM in older adults can be complicated by some age-related factors such as cognitive dysfunction [242]. Furthermore, hypoglycemia has been shown to be more common in older adults because of impaired renal and hepatic metabolism, polypharmacy or non-adherence to medications and erratic or poor food intake [243]. Also, hypoglycemia may be masked by comorbidities such as dementia, depression or stroke [208]. In conclusion, management of T2DM in the aged should be set individually and special attention is needed for conditions that may complicate self-care and hypoglycemia awareness.

The existing literature concerning *specific fall preventive exercise programs* among older adults with T2DM is scarce. Allet *et al.* found that specific training can improve gait speed, balance, muscle strength and joint mobility in diabetic patients but correctly argued that the influence of these improvements on falls needs to be explored in future research [244]. Multifactorial exercise programs, usually containing

balance and strength training exercise have been proven to effectively reduce falls in older adults [6,20,21]. These findings should however be confirmed for older adults with T2DM.

Although diabetes has repeatedly been associated with an increased fall risk, studies investigating the underlying mechanisms and potential effects of complications on falls in older adults with diabetes are lacking. Therefore, it can be stated that based on the available evidence nor diabetes per se, neither the existence of one or more diabetes-related complications can be ruled out as causal factor for gait and balance disturbances, and thereby falls. Nevertheless, one can hypothesize that the same fall-related functions ("*F*" in Table 1.2) are affected in older adults with T2DM, albeit to a greater extent since the intrinsic characteristics ("*C*" in Table 1.2) might be aggravated by diabetes-related complications. This doctoral thesis primarily aims to assess this hypothesis by investigating a set of established fall risk factors among older adults with and without T2DM.

Key points

- Diabetes is a risk factor for falls but the underlying reasons are still unclear.
- Peripheral neuropathy has been associated with alterations in gait, postural control and muscular function but its actual contribution to these hampered functional outcomes is controversial.
- A lot of diabetes-related complications might increase fall risk since they are proven risk factors for falls in older adults without diabetes.
- Fall prevention in older adults with T2DM starts with an adequate disease management. Specific fall preventive exercise programs are likely to be beneficial but should be confirmed in future research.

AIMS AND OUTLINE

This doctoral thesis aims to identify and understand risk factors for falling among the ever-growing population of older adults with T2DM (Part One). Although fall prevention has been an area of active research over the past 15 years and multiple useful risk strategies have been suggested, some interfering factors are still not incorporated into standard fall risk assessments. Therefore, the importance of several often proposed but less focused aspects in gait, balance and fall prevention screenings will be assessed (Part Two).

Part One: Fall risk factors

For the first time in history, the issue of ageing globally claims attention in different domains of the society with inevitable shifts in socioeconomic characteristics and changes in health services. Scientific researchers face a huge challenge in investigating, understanding and treating age-related normal and pathological conditions.

During the last decades, one has realized that falling is a major problem in the aged population with a number of potentially drastic consequences for the individual and health care facilities. Consequently, fall-related research (epidemiology, risk factors, consequences, screening, prevention, …) has boomed in the older population and a lot of risk factors for falling have been established. However, these studies are mostly limited to the general (relatively healthy) older population whereas the sharp rise in the ageing population implies a corresponding rise in age-related diseases. Extrapolation of data from the given (healthy) general older population to the diseased older adults may be inadequate as fall risk profiles may be quite different or contain factors that are not as prominent in the average older person. A lot of fall risk factors are also chronic complications of T2DM, which raises the hypothesis that older adults suffering this age-related disease might be at increased risk for falling. However, there is currently too little evidence to confirm this hypothesis. Therefore, the primary aim of this doctoral thesis was to administer fall incidence and investigate fall risk factors among a mixed cohort of older adults with and without T2DM *(Chapter 2)*.

Part Two: Additional screening as part of fall prevention strategies

Currently, a lot of conflicting results exist concerning the impact of peripheral neuropathy on gait, balance and falls. A correct diagnosis of (a type of) peripheral neuropathy requires extensive and invasive investigations using nerve conduction studies or electromyography. These methods are, however, very expensive and unfeasible for everyday clinical practice. We therefore aimed to assess vibration sense, recorded by an inexpensive, portable and easy to use tool, in relation to postural control and falls in older people with and without T2DM *(Chapter 3)*.

Cognition has unanimously been proven to play a crucial role in gait performance and fall risk. Nevertheless, cognitive assessments are still not implemented in routine fall risk screenings. Furthermore, cognitive impairment is suggested to be another chronic complication of T2DM. So far, however, studies that investigate the potential interference of cognitive decrements on physical parameters in this specific older subpopulation (T2DM) are lacking. The impact of decrements in the peripheral (peripheral neuropathy) and central (cognition) nervous system on gait in older adults with T2DM was therefore investigated *(Chapter 4)*.

As explained previously in the general introduction, fall risk might also be enhanced or even induced by extrinsic factors like environmental characteristics at home or an ever present issue such as the footwear a person is wearing. With respect to this latter issue a quite interesting ascertainment was made rendering immediate food for thought. During our measurements we established that a lot of participants expressed their own ideas and preferences concerning footwear with respect to their gait performance in the test and in daily life. We therefore hypothesized that different types of footwear could indeed result in different functional outcome measures in gait analyses. Although in clinical measurements the influence would probably be relatively low, it might be more relevant when technical support is used due to finer analysis potential. Since a lot of decisions and predictions are made based on marginal differences on cut-off scores of these finer analyzed parameters, footwear used during testing could become of greater importance. Cut-off values for gait velocity have been determined in relation to falls [76,245], physical performance [245-247], sarcopenia [248], frailty [249], risk for hospitalization [250] and even life expectancy [251]. Small differences in gait velocity due to inappropriate or 'confounding' footwear might thus imply misinterpretations of one's walking abilities with eventual crucial misclassifications. Still, descriptions of types of footwear often seem to be lacking in mobility-related research among older adults. Our last aim was therefore to investigate the potential effects of different types of footwear on gait in healthy older women and provide recommendations concerning footwear to the older individual and researchers *(Chapter 5)*.

The experiments discussed in *Chapter 2*, *3* and *4* are performed among a mixed cohort of older adults with and without T2DM whereas the study of *Chapter 5* considered a different sample, i.e. healthy older women.

Aims	Research Questions
1. To administer fall incidences and investigate fall risk factors among a mixed cohort of older adults with and without T2DM *(Chapter 2)*.	a) What is the fall incidence and fall risk of older adults with T2DM compared to older adults without T2DM? b) Which fall risk factors could be identified among a matched cohort of older adults with and without T2DM? c) Which fall risk factors are significantly different between older adults with and without T2DM? d) Which factors mediate the diabetes/falls relationship?
2. To investigate vibration perception, recorded by a simple tool, in relation to postural control and falls in older people with and without T2DM *(Chapter 3)*.	a) Does the indication of peripheral neuropathy interferes with quiet standing performance and with fall incidence? b) Should the integration of a simple screening (VPT) for peripheral neuropathy in any physical (fall risk) assessment among older adults be recommended?
3. To investigate the impact of diabetes and peripheral neuropathy on gait among a mixed cohort of older adults with and without T2DM *(Chapter 4)*.	a) Does T2DM affect gait? b) Does diabetic peripheral neuropathy affect gait?
4. To investigate the impact of cognitive decrements on gait in older adults with T2DM *(Chapter 4)*.	a) Does reduced cognitive function affect gait in older adults with T2DM? b) Does cognitive dual task walking affect gait? c) Do the effects of T2DM on gait depend on the task condition?
5. To investigate the potential effects of different types of footwear on gait in healthy older women *(Chapter 5)*.	a) Does the type of footwear affect gait among healthy older women and how? b) Does the addition of a motor or cognitive task affect gait patterns and how? c) Do the effects of different types of footwear on gait depend on the task condition?

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PART ONE

Fall risk factors

one

Chapter 2

Understanding the Relationship between Type 2 Diabetes Mellitus and Falls in Older Adults: a Prospective Cohort Study

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Abstract

Background Older adults with type 2 Diabetes Mellitus are at increased risk of falling. The current study aims to identify risk factors that mediate the relationship between diabetes and falls.

Methods 199 older adults (104 with diabetes and 95 healthy controls) underwent a medical screening. Gait (GAITRite®), balance (AccuGait® force plate), grip strength (Jamar®), and cognitive status (Mini-Mental State Examination and Clock Drawing Test) were assessed. Falls were prospectively recorded during a 12-month follow-up period using monthly calendars.

Results Compared to controls, diabetes participants scored worse on all physical and cognitive measures. Sixty-four participants (42 diabetes vs. 22 controls) reported at least one injurious fall or two non-injurious falls ("fallers"). Univariate logistic regression identified diabetes as a risk factor for future falls (Odds Ratio 2.25, 95%CI 1.21-4.15, $p=0.010$). Stepwise multiple regressions defined diabetes and poor balance as independent risk factors for falling. Taking more medications, slower walking speed, shorter stride length and poor cognitive performance were mediators that reduced the Odds Ratio of the relationship between diabetes and faller status relationship the most followed by reduced grip strength and increased stride length variability.

Conclusions Diabetes is a major risk factor for falling, even after controlling for poor balance. Taking more medications, poorer walking performance and reduced cognitive functioning were mediators of the relationship between diabetes and falls. Tailored preventive programs including systematic medication reviews, specific balance exercises and cognitive training might be beneficial in reducing fall risk in older adults suffering from diabetes.

Key words Geriatrics; Falls; Type II Diabetes Mellitus

Introduction

Diabetes Mellitus and falls are common in the older population and can therefore be considered 'geriatric giants'. They both pose major threats to an older person's quality of life. According to the World Health Organization, diabetes globally affects approximately 347 million people and diabetes deaths will double between 2005 and 2030 [1]. Each year, approximately one in three community-dwelling older adults aged 65 or over suffers one or more falls [2]. Older women with diabetes are 1.6 times more likely to have fallen in the previous year and twice as likely to have had injurious falls [3]. Diabetes Mellitus has been identified as a risk factor for falls [4,5] and fall-related injuries and fractures [6] in a number of prospective studies.

Poor balance has been determined as a major risk factor for falls in older adults [7]. Many diabetes-related complications, such as peripheral neuropathies [8], cerebro-vascular accidents [9], sarcopenia [10], poor low-contrast visual acuity and poor depth perception [11] have also been associated with reduced balance performance [7]. Other complications from diabetes, such as urinary incontinence [12], dementia [13], mild cognitive impairment [14] and depressive symptoms [15], have been identified as risk factors for falls in older adults without diabetes. However, due to a lack of comprehensive prospective studies focusing on fall risk detection in older adults with diabetes, it is unclear whether these factors mediate the relationship between falls and diabetes. The aims of this study are therefore (i) to establish distinguishing factors between older adults with and without diabetes on a range of established fall risk factors, (ii) to document fall rates and determine fall risk factors in a matched cohort of older adults with and without diabetes, and (iii) to identify mediating risk factors of falling that explain the relationship between diabetes and falls in older adults. This will assist in designing tailored fall prevention programs in this population.

Materials and Methods

Ethics Statement

The Ethical Committee of the Ghent University Hospital gave approval to this study and all participants signed an informed consent.

Participants

199 older adults were enrolled in this study. The general practitioner or medical specialist of each participant confirmed the presence or absence of type 2 Diabetes Mellitus. Inclusion criteria were: (i) aged 60 years and above, (ii) living in the community

or residential aged care setting, (iii) able to understand instructions, (iv) able to walk independently with or without walking aids, (v) absence of stroke, Parkinson's disease or other major neurological conditions, and (vi) absence of musculoskeletal disorders impeding them to walk unaided for 10m (e.g. amputations, major rheumatic conditions in the lower extremity). Seventy-two (69.2%) older adults with diabetes and 43 (45.3%) healthy controls were recruited from residential aged care settings. Eleven (10.6%) community-dwelling older adults with diabetes and 52 (54.7%) community-dwelling healthy controls were recruited through online advertising, flyer distribution and by word of mouth. Another 21 (20.2%) older adults with diabetes were recruited from the Endocrinology Clinic at the Ghent University Hospital, Belgium.

Personal and Medical History

Socio-demographic data and medical history were recorded by means of a self-report questionnaire. Participants were asked about previous falls, fear of falling (yes/no), number of medications and pathological conditions potentially interfering with fall risk such as depression or urinary incontinence. Peripheral nerve function was assessed by determination of the Vibration Perception Threshold, which has proven reliability and validity towards assessment of neural dysfunction in people with diabetes [16]. It was determined using a Bio-Thesiometer® (Bio Medical Instrument co, Ohio, USA) by three measurements on four distinct points (medial malleolus and big toe on both feet). For each location the mean of three values was calculated.

Physical Measurements

Muscle Strength

Grip strength (kg) of the dominant hand was recorded using the Jamar® dynamometer (Sammons Preston Rolyan Inc., Bolingbrook, IL) while seated in an armless chair with shoulders adducted and neutrally rotated and elbow flexed at 90°, forearms in neutral position and wrist between 0 and 30° of dorsiflexion [17]. Participants were instructed to squeeze the handle as hard as possible [18]. The maximal grip score of three trials was retained.

Gait

Gait velocity (cm/s), stride length (cm) and stride length variability (%) were captured by the portable electronic GAITRite® walkway system (8.3m x 0.89m; CIR Systems Inc., Havertown, PA, USA) with proven validity [19]. Stride length variability was calculated as the ratio of the standard deviation to the mean. Participants were asked to walk at a self-selected normal walking speed wearing comfortable footwear with a low and wide heel and a thin, grooved and moderately hard sole. Thirty-four percent (n=68) used their usual walking aid such as crutches, walkers or canes. Participants were instructed to start walking two meters before the GAITRite® mat and keep

walking for two meters beyond the mat to minimize acceleration and deceleration effects.

Balance

Limits of stability (LOS) were determined by use of a force plate (AMTI® AccuGait, Advanced Mechanical Technology Inc., Watertown, MA, USA). Sampling rate was set at 50Hz and data were filtered with a cut-off frequency of 5Hz by a 4-th order low-pass Butterworth filter. Participants were instructed to position their feet shoulder-with apart and lean forward, backward, to the left and to the right as far as possible without moving their feet. LOS were expressed as maximal medio-lateral and antero-posterior displacement (cm) of the Center of Pressure (COP) and sway area (cm^2). The sway area is the surface of an ellipse wherein 95% of the COP samples are predicted to be enclosed (95% confidence ellipse).

Cognitive Measurements

The Mini-Mental State Examination (MMSE) was used as a general cognitive screening instrument [20]. The Clock Drawing Test (CDT) was done to estimate executive functioning. Four items as proposed by Thalmann *et al.* were selected: item 2 (12 numbers are present), item 5 (number '12' correctly placed), item 25 (hands have correct proportions) and item 34 (participant reads time correctly) [21]. A validated algorithm to combine results from the MMSE and the CDT was used to estimate executive functioning [21]. MMSE score of 27 or more was coded as 3, and MMSE score of 26 or less was coded zero. The four CDT items were coded as 0 or 1 for items 2, 25 and 34; and as 0 or 3 for item 5. These recoded scores of the MMSE and the CDT were then combined to a single score (MMSE-CDT) with a maximum of 9, representing a good cognitive function. A cut-off score of less than 7 on the MMSE-CDT was used to classify participants as having reduced cognitive functioning.

Falls Follow-Up

After baseline measurements falls were monitored during 12 months using monthly fall calendars. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [22]. If a fall occurred, participants were telephoned and asked about the circumstances and fall injuries such as bruises, lacerations or fractures. Participants who reported multiple (>1) falls or at least one fall with injury were categorized as "fallers" whereas participants who experienced no fall or one non-injurious fall were considered "nonfallers" [23]. Two participants were lost to follow-up (1 control withdrew, 1 diabetes died) and were not included in statistical analyses.

Statistical analyses

Univariate and multivariate logistic regression models were applied to investigate the association between diabetes and falls, and between covariates (demographic, medical, physical, cognitive) and falls. Covariates with a univariate statistical significance of $p \leq .1$ were first entered in separate logistic regression models to determine how much they reduced the diabetes-falls Odds Ratio (OR). Covariates that mediated this relationship were then combined in a final logistic regression model. Marker variables such as "previous falls" were not selected as possible predictors in multivariate models as such marker variables often cancel out the impact of other risk factors and are therefore not helpful in assisting our understanding of why falls occur [24]. Independent Samples t tests (continuous variables) and Chi Square tests (categorical variables) were performed to compare healthy controls and older adults with diabetes. Data were analyzed using SPSS.20 for Windows (SPSS, Inc., Chicago, IL). For reasons of voluntary withdrawal, illness and absence at the time of the test procedure eight participants (2 controls and 6 with diabetes) did not complete gait analysis, fifteen (2 controls and 13 with diabetes) had no LOS data and four (4 with diabetes) performed no grip strength measurement.

Results

Mean age of the 199 participants was 76.9 ± 9.4 (range 60-94) and 126 (63.3%) were female. Participants with diabetes (n=104) were older than controls (n=95), with a mean age of 78.4 (SD 8.7) and 75.1 (SD 9.9) respectively (Table 2.1). They took 2.1 (SD 0.7) anti-diabetic agents on average and 44.1% were insulin-dependent. Fifty-six (28.4%) participants reported multiple falls during the 12 months follow up, eight (4.1%) reported one injurious fall, thirty-two (16.2%) reported 1 non-injurious fall and 101 (51.3%) reported no falls. Forty-two (40.8%) older adults with diabetes reported one single injurious fall or multiple falls compared to 22 (23.4%) healthy controls.

Univariate analyses showed that those who suffered multiple non-injurious falls or at least one injurious fall were more likely to have diabetes mellitus, have urinary incontinence, walk with mobility aids, report falls in the previous year and report fear of falling compared to nonfallers. Fallers were also older, took significantly more medications, performed worse on hand grip strength, walked slower with smaller strides and greater variability, had smaller medio-lateral limits of stability and performed worse on the MMSE. Participants with Diabetes Mellitus performed significantly worse on all physical and cognitive measures when compared to healthy controls (Table 2.1).

Table 2.1 Comparison of the Univariate Risk Factors between Healthy Controls and Diabetes Patients (N=199). Univariate Risk Factors of Experiencing at Least One Injurious Fall or Multiple (Noninjurious) Falls during 12 Months of Follow-Up (N=197)

Risk Factor	Controls (n = 95)	Diabetes (n = 104)	*p* Value	Nonfallers (n = 133)	Fallers (n = 64)	Odds Ratio (95% CI)
Demographic/Medical						
Age *(years)*	75.14 ± 9.86	78.41 ± 8.73	.014	75.8 ± 9.4	78.8 ± 9.3	1.38 (1.01-1.87)*
Female	62 (65.3)	64 (61.5)	.659	80 (60.2)	44 (68.8)	1.46 (0.77-2.74)
Body Mass Index *(kg/m²)*	27.46 ± 4.19	29.39 ± 5.73	.007	28.2 ± 4.9	29.1 ± 5.5	1.20 (0.89-1.60)
Community-dwelling	52 (54.7)	32 (30.8)	.001	62 (46.6)	22 (34.4)	1.67 (0.90-3.09)
Walking Aids	22 (23.2)	46 (44.2)	.003	39 (29.3)	29 (45.3)	2.00 (1.08-3.70)*
Number of medications	3.9 ± 3.1	9.0 ± 2.9	<.001	6.1 ± 3.9	7.6 ± 3.8	1.46 (1.07-2.00)
Diabetes Mellitus	0 (0.0)	100 (100)	-	61 (45.9)	42 (65.6)	2.25 (1.21-4.18)**
Depression	12 (12.6)	22 (21.2)	.133	20 (15.0)	14 (21.9)	1.58 (0.74-3.38)
Urinary Incontinence	18 (18.9)	22 (21.2)	.726	18 (13.5)	21 (32.8)	3.12 (1.52-6.41)**
Fear of Falling	46 (48.4)	69 (66.3)	.014	66 (49.6)	48 (75.0)	3.05 (1.57-5.89)**
Previous Falls	24 (26.1)	53 (52.5)	<.001	35 (27.1)	42 (66.7)	5.37 (2.80-10.31)**
Vibration Perception Threshold *(V)*	30.37 ± 11.15	39.60 ± 10.37	<.001	34.1 ± 12.0	37.2 ± 10.8	1.31 (0.96-1.77) ^
Muscle Strength						
Grip Strength *(kg)*	19.84 ± 12.09	14.97 ± 8.78	.002	19.4 ± 11.2	15.3 ± 9.8	0.72 (0.52-1.00)*

Table 2.1 Continued

Risk Factor	Controls (N = 95)	Diabetes (N = 104)	*p* Value	Nonfallers (N = 133)	Fallers (N = 64)	Odds Ratio (95% CI)
Gait						
Gait Speed *(cm/s)*	90.57 ± 37.70	68.52 ± 29.27	<.001	85.0 ± 35.5	72.2 ± 34.4	0.68 (0.49-0.94)*
Stride Length *(cm)*	105.45 ± 33.65	85.22 ± 28.91	<.001	100.7 ± 32.4	88.5 ± 32.9	0.68 (0.49-0.93)*
CV Stride Length *(%)*	4.068 ± 3.345	5.959 ± 4.247	.001	4.46 ± 3.33	5.74 ± 4.58	1.41 (1.04-1.91)*
Balance						
Medio-lateral LOS *(cm)*	15.46 ± 7.48	13.24 ± 6.15	.029	15.5 ± 6.9	12.8 ± 6.7	0.67 (0.48-0.94)*
Antero-posterior LOS *(cm)*	9.72 ± 4.17	9.20 ± 4.00	.389	9.58 ± 3.99	9.05 ± 4.13	0.88 (0.64-1.20)
LOS area *(cm^2)*	1.52 ± 1.19	1.24 ± 1.07	.091	1.46 ± 1.12	1.19 ± 1.14	0.78 (0.55-1.08)
Cognitive						
MMSE	26.73 ± 4.13	24.29 ± 4.33	<.001	26.3 ± 3.6	24.7 ± 5.1	0.71 (0.53-0.95)*
CDT	5.18 ± 2.10	4.50 ± 2.30	.034	5.2 ± 2.1	4.5 ± 2.5	0.75 (0.56-1.01) ^
MMSE-CDT	7.09 ± 2.72	5.48 ± 2.88	<.001	6.8 ± 2.7	5.7 ± 3.2	0.71 (0.53-0.95)*
MMSE-CDT < 7	24 (25.3)	62 (62.0)	<.001	49 (37.7)	35 (55.6)	2.07 (1.12-3.81)

Notes: Data are M ± SD or n (%). ^P≤.10, *P≤.05, ** P≤.01.
CV = Coefficient of Variation; LOS = Limits of Stability; CI = Confidence Interval; MMSE = Mini-Mental State Examination; CDT = Clock Drawing Test.

Explanatory covariates ($p<.1$) were separately entered with diabetes into stepwise multivariate logistic regression models. The association between diabetes and falls remained significant, even after adjusting for CDT (OR=2.13, 95%CI 1.13-4.00), age (OR=2.08, 95%CI 1.11-3.90), MMSE (OR=2.08, 95%CI 1.09-3.95), Vibration Perception Threshold (OR=2.04, 95%CI 1.04-3.97), medio-lateral LOS (OR=2.03, 95%CI 1.06-3.88) and MMSE-CDT (OR=2.02, 95%CI 1.06-3.85). The percentage reduction of the diabetes/falls odds ratio from the logistic regression analyses was less than 10% when controlling for these covariates. Parameters that caused a substantial reduction of the diabetes/falls relationship and therefore could be considered mediators, were number of medications (20.7%, OR=1.79, 95%CI 0.82-3.90), stride length (14.9%, OR=1.92, 95%CI 0.99-3.72), gait velocity (14.7%, OR=1.92, 95%CI 0.99-3.72), MMSE-CDT categorization (13.8%, OR=1.94, 95%CI 1.00-3.78), grip strength (11.0%, OR=2.01, 95%CI 1.06-3.79) and stride length variability (10.8%, OR=2.01, 95%CI 1.05-3.85).

In a final stepwise logistic regression analysis all explanatory covariates ($p\leq.1$) were entered together. The multivariate model identified diabetes (OR=2.03, 95%CI 1.06-3.88) and medio-lateral LOS displacement (OR=0.70, 95%CI 0.49-0.99) as the best predictors of future falls. Therefore, the presence of diabetes and smaller limits of stability in the medio-lateral plane are independent predictors of falls in our sample.

Discussion

This study confirmed that diabetes mellitus is a strong predictor of falls in a mixed cohort of older adults with and without diabetes. About 41% (n=42) of the participants with diabetes were classified as fallers (35.9% experienced multiple falls and 4.9% experienced a single injurious fall). Compared to healthy controls, older adults with diabetes perform worse on physical and cognitive tests. Diabetes remained an independent risk factor of future falls, even after controlling for poor balance.

Older adults with diabetes often develop a range of long-term complications, which can explain why diabetes participants in our sample performed worse on all physical and cognitive measures. Our results confirm previous findings which commonly report more medication use, reduced peripheral nerve function, and poorer grip strength [25], gait performance [26] and balance [27] in older adults with diabetes. Similarly, the worse performance on cognitive screening measures in diabetes participants is in accordance with previous studies [28]. Older adults with diabetes also suffered more falls in the previous year and reported higher levels of fear of falling than healthy controls. We further demonstrated that older adults with diabetes

were at increased risk of suffering injurious or multiple falls, even after adjusting for medical, physical and cognitive covariates.

Poor balance has previously been identified as a major risk factor for falling in older adults [7]. Accurate balance performance relies on visual, vestibular and somatosensory systems [7]. Deficiencies in these systems have proven to occur with ageing [29] and might thus lead to a loss of balance, possibly resulting in a fall. Older adults with diabetes show greater postural sways but there are many conflicting findings concerning the underlying mechanisms [30]. Our final regression model suggested that diabetes and poor balance were independently associated with falls.

In this experiment, a substantial proportion of the relationship between diabetes and future falls could be explained by more medication use, slowed walking speed and reduced cognitive performance, each of which are established risk factors for falls in older adults. First, number of medications was the strongest mediator in the diabetes/falls relationship (20.7% reduction). Previous research has consistently associated number of medications with an increased fall risk in older adults [31]. Given the multiple complications of the disease, older adults with diabetes often take a high number of medications. This was confirmed by our results; older adults with diabetes took about nine medications on average compared to four medications in older adults without diabetes. Even without medications for diabetes treatment (data not shown), the number of medications was still significantly higher for older adults with diabetes with an average of about seven medications. Second, walking performance mediated the diabetes/falls relationship in this trial and reduced the odds ratio by nearly 15 percent. Older adults with diabetes walked slower, took shorter strides and had greater stride length variability compared to controls, which confirms previous research [26]. Slowed gait can predict falls in healthy older adults [32]. Walking velocity reflects overall health and functional status and has been recommended as a potentially useful clinical indicator of well-being among older adults. The final mediator of the diabetes/falls relationship was poor cognitive performance reducing the odds ratio by 14 percent. During the past decade, researchers have provided a large body of evidence suggesting that walking performance relies on cognitive processing, executive functions and attention [33], thereby countering the former assumption of an automated human gait. Older adults with mild cognitive impairment or low cognitive reserves indeed show gait abnormalities [34,35] and also an increased fall risk [14]. The suggested cognitive decline in patients with diabetes [36] might therefore explain why the diabetes/falls relationship is partly mediated by reduced cognitive performance. Clinicians should be aware that these factors might predispose older patients with diabetes to falling. Future research in larger samples should establish whether diabetes patients who use more medications, walk slower

and show reduced cognitive performance are more prone to falling compared to diabetes patients who do not suffer from these conditions.

Current guidelines and recommendations on the management of type 2 diabetes in the general practice setting include nutrition management and increasing physical activity levels, with primary goals of controlling weight and improving metabolic control. Additionally, insulin and/or oral anti-diabetic agents are prescribed for optimizing glycemic control. Considering our finding that older adults with diabetes perform worse on physical and cognitive tests when compared to healthy controls, a comprehensive fall risk assessment, involving tests of balance, gait and cognitive functioning, should be incorporated into the clinical management of diabetes patients. Second, older adults with type 2 diabetes should be encouraged to take part in exercise programs that focus on improving balance and gait, in addition to the recommended cardiovascular fitness and resistance training. It has been shown that a challenging balance training program of adequate intensity and duration can successfully reduce fall rates in older adults [37]. Low level aerobic exercise (e.g. brisk walking for half an hour per day) is often recommended. Targeted training including gait, balance and functional strength exercises has been shown to improve gait speed, balance, muscle strength and joint mobility in patients with diabetes [38].

Limitations

The main limitation of this study relates to a possible selection bias of the study population. Participants were recruited through advertisements or by access to patient files at the Endocrinology Clinic. Also, we acknowledge that we excluded people with severe diabetic complications that would make them unable to complete the assessments. Nevertheless, we feel that our sample does reflect the heterogeneous nature of the older adults with diabetes seen in routine practice. Also, certain potential mediators were not assessed as part of this trial. For example, poor vision has clearly been proven to adversely affect gait [39] and postural control, consequently increasing fall risk [11]. Decreased foot strength and foot pain have also independently been associated with falls [40]. Future multifactorial prospective studies should therefore include more comprehensive assessments to further enhance our understanding of the relationship between diabetes and falls.

Conclusions

This study demonstrated that diabetes is an independent risk factor for falling, even after controlling for poor balance. Taking higher numbers of medications, poor walking performance and reduced cognitive functioning were mediators of the

relationship between diabetes and faller status. These physical and cognitive measures were significantly worse in older adults with diabetes compared to older adults without diabetes. Preventive programs including systematic medication reviews, specific balance exercises and cognitive training might be beneficial in reducing fall risk in older adults suffering from diabetes.

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PART TWO

Additional screening as part of fall prevention strategies

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Chapter 3

Vibration Perception Threshold in Relation to Postural Control and Fall Risk Assessment in Elderly

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Abstract

Purpose The present study investigates (i) the potential discriminative role of a clinical measure of PN in assessing postural performance and fall risk and (ii) whether the integration of a simple screening (VPT) for PN in any physical (fall risk) assessment among elderly should be recommended, even if they do not suffer from DM.

Methods 195 elderly were entered in a 4-group-model: DM with PN (D+; n=75), DM without PN (D-; n=28), non-diabetic elderly with idiopathic PN (C+; n=31) and non-diabetic elderly without PN (C-; n=61). Posturographic sway parameters were captured during different static balance conditions (AMTI® AccuGait). Vibration Perception Threshold, fall data, Mini-Mental State Examination and Clock Drawing Test were registered. Multivariate repeated-measures ANOVA was used to compare between groups and across balance conditions.

Results The groups with PN demonstrated a strikingly comparable though bigger sway and a higher prospective fall incidence than their peers without PN.

Conclusions The indication of PN, irrespective of its cause, interferes with postural control and fall incidence. The integration of a simple screening for PN (like Bio-Thesiometry) in any fall risk assessment among elderly is highly recommended.

Key words Vibration Perception Threshold; Falls; Postural Control; Peripheral Neuropathy; Diabetes Mellitus; Elderly

Introduction

Impaired postural control is perhaps the most hazardous common denominator for falls in elderly people. It therefore draws with every right and reason explicit attention of rehabilitative researchers and clinicians for fall risk assessment and prevention purposes. Postural control is an overall generic construct seen as an essential prerequisite for most daily life activities at any age. It maintains, achieves or restores a state of balance while a person is stationary, preparing to move, in motion or preparing to stop moving. Notwithstanding the given attention it remains one of the most complex human abilities to fully embrace its consequences in case of impairment. Afferent input from the visual, vestibular and proprioceptive systems has to be interpreted, integrated and analyzed by central cognitive processes in view of the mandatory appropriate motor responses. Due to this multifaceted nature postural control can be undermined at any respective level. Deterioration in vision, vestibular input, muscle strength, flexibility, cognitive abilities, … are potential threats for a good working balance system and embody fall inducing risks.

These decrements may occur due to age- or disease-related changes of physical functions or inner body processes. As approximately 50% of all patients with diabetes suffer from peripheral neuropathy [1], the postural control of these patients might partially be hampered due to losses of somatosensory feedback and appropriate motor responses. In older adults with DM the observed increased fall rate has indeed repeatedly been shown not to be based on DM as a whole per se but to the existence of PN [2-5]. PN describes damage to the peripheral nervous system that results in a wide array of afferent symptoms, varying from paresthesia, autonomic deficits, sensitivity to touch, burning pain (especially at night) or efferent characteristics like muscle weakness and paralysis. Interestingly, structural and functional changes in peripheral nerves seem to occur quite commonly in the oldest elderly as a phenomenon of aging without any causative mechanism (like in DM), known as 'idiopathic PN' [6-9]. This ascertainment turns PN into a potential contributing factor to disturbed balance and falls in the elderly as such [10-13].

Assessing the presence of PN and, in a subsequent phase, the implementation of somatosensory stimulation in postural rehabilitation seems therefore justified. The efferent part may be assessed by motor performance tests or muscle testing, but results are often inconclusive due to the wide array of putative underlying mechanisms for bad performance for that matter. The afferent part should ideally be assessed by nerve conduction and tissue biopsies. However, as suggested by Garrow *et al.* [14], these methods are impractical for routine screening and should be substituted by useful clinical alternatives, such as vibration perception threshold (VPT) determination.

Although loss of vibratory sensation is commonly accepted as a major clinical somatosensory indicative expression of PN in DM, Lord *et al.* are to our knowledge one of the very few researchers proposing to implement peripheral sensation tests in fall risk assessment by a measure of joint position sense [15].

We hypothesize that detection of VPT, which has proven to be a useful [14] and reliable [16] clinical measure, can play an important role in assessing postural performance and fall risk detection. This study investigates (i) the potential discriminative role of a clinical measure of PN in assessing postural performance and fall risk and (ii) whether the integration of a simple screening (VPT) for PN in any physical (fall risk) assessment among elderly should be recommended, even if they do not suffer from DM.

Methods

Participants

195 elderly were included in this study and entered in a 4-group-model: type 2 DM with PN (D+; n=75), type 2 DM without PN (D-; n=28), non-DM elderly controls with (idiopathic) PN (C+, n=31) and non-DM elderly controls without PN (C-; n=61). Participants comprised both community-dwelling elderly and elderly living in a residential care setting and were recruited through online advertising, flyer distribution and by word of mouth. Subjects suffering from additional major (gait and cognitive) disabling illnesses (e.g. stroke, Parkinson's disease, …) or musculoskeletal disorders that may affect their postural control in a more or less predictable way (foot ulcerations, amputations, major rheumatic conditions in the lower extremity, …), were excluded. Inclusion criteria were age ≥ 60 years, being able to understand instructions and stand independently. The Ethical Committee of the Ghent University Hospital gave approval to this study and all participants signed an informed consent.

Personal and medical history

Medical and fall history of the past year were registered. A fall was defined as "an event, which results in a person coming unintentionally to rest on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard" [17]. In addition, a follow-up of 8-months for falling took place by collecting monthly fall calendars. The attending general practitioners or treating specialists were responsible for the medical diagnosis of the presence or absence of DM (fasting glucose levels) and in case of DM also for the presence of PN. PN should have been established by electromyography or any other kind of nerve conduction examination.

Physical measurements

Besides the general practitioners' diagnosis, the presence of PN in DM was objectified by a vibration perception threshold (VPT) of ≥ 25 Volt [18] which is considered as a standard for clinical diagnostic indication of diabetic peripheral neuropathy [19]. This threshold was the recorded voltage the participant indicated when he or she first felt the vibration [20]. It was determined by three measurements on four distinctive points (medial malleolus and dorsal side of the big toe on both feet) using a Bio-Thesiometer® (Bio Medical Instrument co, Ohio, USA). For each location the mean of the three values was calculated to one VPT. Based on its qualities in DM the VPT was also used to clinically indicate the presence of idiopathic PN in the non-diabetic elderly rendering the formation of a specific group (C+). With respect to postural control the Center of Pressure (COP) measurements during quiet standing were captured using an AMTI® AccuGait (Advanced Mechanical Technology Inc., Watertown, MA, USA) portable force platform. All data were collected using a sampling rate of 50Hz and exported to MATLAB (version 7.12) for calculation of the following parameters: medio-lateral (ML) sway, anterior-posterior (AP) sway, sway velocity and sway area. ML and AP sway represent the mean sway path length of the ML and AP movement of the COP, while sway velocity is the mean speed of the COP displacement. The sway area is the elliptic surface in which 95% of the COP samples are predicted to be enclosed (95% confidence ellipse). Data were filtered with a cut-off frequency of 5Hz by a 4-th order low-pass Butterworth filter. Subjects were instructed to stand quietly on the force plate looking straight ahead with the arms comfortably alongside the body. Subjects were asked to perform posturography wearing close fitted shoes without heels. The maintenance of the upright position was challenged by changing the base of support and/or visual feedback. Postural control was measured during following randomly ordered conditions: (1) feet at pelvis width (wide base), eyes open (EO), (2) feet at pelvis width (wide base), eyes closed (EC), (3) feet together (narrow base) EO, (4) feet together (narrow base) EC, (5) semi-tandem EO, (6) semi-tandem EC. Each trial took 25 s, with the initial 10 s and last 5 s removed to avoid initial transient and anticipatory effects.

Neuropsychological measurements

Given the fact that DM is a risk factor for cognitive decline [21] and derangement of peripheral nerves may coincide with deterioration in the central nervous system, as such rendering an additional hazard for disturbed postural control, measurement of cognitive state was entered in this assay to assess the eventual relationship in elderly without DM and with PN. The Mini-Mental State Examination (MMSE) was used as cognitive screening instrument [22,23] and to complementary highlight executive functioning [24], the Clock Drawing Test (CDT) was performed. The item score proposed by Thalmann *et al.* was selected to score the CDT (with a maximum of 7) as well as their combined 'MMSE and CDT'-single score with a maximum of 9 [25].

Statistical analyses

All data were analyzed using SPSS version 20 for Windows (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) and statistical significance was assumed at $P < .05$. Descriptive statistics were used to describe the general characteristics (Table 3.1). Multivariate repeated-measures ANOVA was used in order to compare each sway parameter between the groups and across the six experimental static balance conditions. The normality and sphericity assumptions were verified. Pairwise comparisons with Bonferroni adjustment for multiple comparisons were performed between different experimental conditions. In the case of interaction effects between the experimental conditions and the groups, pairwise comparison of conditions was produced within each group. As mean age significantly differed between some groups, age was introduced as a co-variable.

Results

Demographic characteristics, fall data and neuropsychological performance of the subjects are presented in Table 3.1. The mean age of the elderly with PN (idiopathic

Table 3.1 Characteristics of the Subjects

	C- (n=61)	C+ (n=31)	D- (n=28)	D+ (n=75)
Age *(yrs)*	71.3 ± 8.9**	82.5 ± 7.1††	74.3 ± 8.6§§	79.8 ± 8.3#
Male : Female *(%)*	34.4 : 65.6	35.5 : 64.5	32.1 : 67.9	40.0 : 60.0
BMI	27.4 ± 4.3	27.7 ± 4.5	31.0 ± 6.7¶§	28.9 ± 5.2
Fall incidence (retrospective)	0.35 ± 0.76**	0.54 ± 0.84	1.26 ± 2.26¶	1.33 ± 2.35
Fall incidence (prospective)	0.37 ± 0.90**	1.07± 1.51†	1.33± 1.73¶¶	1.74± 2.61
MMSE	27.0 ± 4.1**	26.1 ± 4.1‡	25.3 ± 4.3¶¶	24.1 ± 4.2
CDT	5.5 ± 2.0**	4.5 ± 1.9†	5.2 ± 2.3§	4.3 ± 2.2#
MMSE-CDT	7.6 ± 2.5**	6.1 ± 2.7††	6.6 ± 2.9	5.1 ± 2.7#

C- = non-DM elderly controls without PN; C+ = non-DM elderly controls with PN; D- = DM elderly without PN; D+ = DM elderly with PN; BMI = Body Mass Index; MMSE = Mini-Mental State Examination; CDT = Clock Drawing Test; MMSE-CDT = combined MMSE and CDT single score
**p≤0,001 between C- and D+
†p<0,05 and ††p≤0,001 between C- and C+
‡p<0,05 between C+ and D+
§p<0,05 and §§p≤0,001 between C+ and D-
¶p<0,05 and ¶¶p≤0,001 between C- and D-
#p<0,05 between D- and D+

and diabetic) was significantly higher than in elderly without PN. All groups were gender matched. Prospective fall incidence in C- was significantly lower in comparison with all three other groups. Concerning the cognitive state it could be ascertained that on average of all 4 groups D+ scored the lowest on every cognitive score. Subjects diagnosed with PN (C+ and D+) scored significantly lower on the CDT and the joined MMSE-CDT compared to the subjects without PN.

As this study was part of a greater fall risk assessment, not all participants completed the whole assessment battery. One C-, two D- and four D+ subjects did not complete sway analysis due to illness or absence at the time of sway assessment. Furthermore, some sway variables could not be calculated by the software system.

Table 3.2 contains the absolute sway values (mean ± SD) during each experimental quiet standing condition. As in depth analysis revealed an interaction effect between groups and different standing conditions, results are presented for the separate groups. In general, each quiet standing of the PN groups was characterized by larger ML and AP sways and higher sway velocities and areas.

Comparison between the different quiet standing conditions revealed that provocation by decreasing the base of support and/or removing visual supervision or feedback, adversely influenced postural control. The most significant changes in sway parameters occurred when the most challenging condition (semi-tandem, EC) was compared to the least challenging condition (wide base, EO).

Comparisons between the four respective groups were made in Table 3.3. *Between-subjects* interactions revealed that sway parameters between the groups without PN (C- vs. D-) were not significantly different as this was also the case in comparing the two groups with PN (C+ vs. D+) (Table 3.3, rectangles). Between C- and C+ AP sway, sway velocity and sway area were significantly different. For discrimination between the two DM groups ML sway, sway velocity and sway area yielded significant different scores.

Table 3.2 Balance Outcomes for C-, C+, D- and D+ during the Six Static Balance Conditions. *Within-Task* Comparisons for C-, C+, D- and D+

	C-	C+	D-	D+
Wide base, EO (1)				
ML sway *(cm)*	5.4 ± 2.9	8.3 ± 4.7	7.7 ± 5.2	9.7 ± 5.8
AP sway *(cm)*	9.3 ± 4.0	15.7 ± 7.8	12.8 ± 7.3	17.2 ± 9.1
Sway velocity *(cm/s)*	1.2 ± 0.5	1.9 ± 1.0	1.7 ± 0.9	2.2 ± 1.1
Sway area *(cm^2)*	1.5 ± 1.2	3.7 ± 3.1	3.2 ± 2.1	4.9 ± 3.9
Wide base, EC (2)				
ML sway *(cm)*	6.8 ± 3.2*	12.5 ± 10.4	7.7 ± 3.9	14.4 ± 9.1**
AP sway *(cm)*	15.0 ± 8.2**	24.9 ± 14.3**	17.2 ± 9.2	26.7 ± 13.1**
Sway velocity *(cm/s)*	1.8 ± 0.9**	3.0 ± 1.8*	2.0 ± 1.0	3.3 ± 1.6**
Sway area *(cm^2)*	2.8 ± 2.2*	8.9 ± 15.2	4.4 ± 4.2	9.8 ± 8.5*
Narrow base, EO (3)				
ML sway *(cm)*	12.7 ± 5.2††	17.9 ± 9.3††	15.9 ± 6.6†	20.1 ± 9.4††
AP sway *(cm)*	12.0 ± 5.9†	19.7 ± 11.0	15.6 ± 6.3	20.9 ± 11.3†
Sway velocity *(cm/s)*	2.0 ± 0.8††	3.0 ± 1.5††	2.5 ± 1.0†	3.2 ± 1.5††
Sway area *(cm^2)*	4.6 ± 3.2††	10.7 ± 13.5	6.8 ± 5.3†	10.4 ± 12.1††
Narrow base, EC (4)				
ML sway *(cm)*	22.1 ± 11.6**††	30.4 ± 18.9**††	23.3 ± 11.2††	32.9 ± 13.4**††
AP sway *(cm)*	20.3 ± 10.5**††	31.9 ± 19.7*	24.0 ± 12.1	33.3 ± 16.3**†
Sway velocity *(cm/s)*	3.4 ± 1.6**††	4.9 ± 2.9*†	3.7 ± 1.7††	5.2 ± 2.2**††
Sway area *(cm^2)*	11.5 ± 10.4**††	19.9 ± 14.9	15.5 ± 20.7*††	22.6 ± 16.0**††
Semi-Tandem, EO (5)				
ML sway *(cm)*	15.9 ± 7.9‡‡§	19.6 ± 7.9‡‡	17.5 ± 5.6‡‡	23.1 ± 9.9‡‡
AP sway *(cm)*	14.4 ± 6.7‡‡§	21.7 ± 13.3	16.8 ± 5.1	23.5 ± 10.4‡‡
Sway velocity *(cm/s)*	2.4 ± 1.1‡‡§	3.2 ± 1.5‡‡	2.7 ± 0.8‡‡	3.7 ± 1.5‡‡
Sway area *(cm^2)*	5.0 ± 4.0‡‡	8.1 ± 6.0	6.0 ± 3.8	9.9 ± 6.9‡‡
Semi-Tandem, EC (6)				
ML sway *(cm)*	27.8 ± 12.3**‡‡	34.4 ± 14.3**‡‡	32.2 ± 13.9**‡‡	36.4 ± 15.8**‡‡
AP sway *(cm)*	25.3 ± 11.8**‡‡§	34.0 ± 17.8**‡	29.4 ± 13.0**‡	39.2 ± 17.3**‡‡§
Sway velocity *(cm/s)*	4.1 ± 1.8**‡‡§	5.3 ± 2.4**‡‡	4.8 ± 2.0**‡‡	6.0 ± 2.5**‡‡
Sway area *(cm^2)*	14.6 ± 13.1**‡‡	18.8 ± 13.3*‡	17.5 ± 12.0*‡‡	24.3 ± 14.7**‡‡

C- = non-DM elderly controls without PN; C+ = non-DM elderly controls with PN; D- = DM elderly without PN; D+ = DM elderly with PN; ML sway = medio-lateral sway; AP sway = anterior-posterior sway; EO = eyes open; EC = eyes closed

*$p<0.05$ and **$p\leq0.001$ between EO and EC condition. same foot position (effect of visual feedback)

† $p<0.05$ and ††$p\leq0.001$ between wide and narrow base. same visual feedback (effect of foot position)

‡$p<0.05$ and ‡‡$p\leq0.001$ between wide base and semi-tandem. same visual feedback (effect of foot position)

§$p<0.05$ between narrow base and semi-tandem. same visual feedback (effect of foot position)

Table 3.3 Significance of the *Between-Subjects* Interactions, Corrected for Age (P-values)

	C- vs. C+	C- vs. D-	C- vs. D+	C+ vs. D-	C+ vs. D+	D- vs. D+
ML sway *(cm)*	0.056	1.000	**< 0.001**	0.749	1.000	**0.023**
AP sway *(cm)*	**0.031**	1.000	**< 0.001**	0.858	1.000	0.067
Sway velocity *(cm/s)*	**0.026**	1.000	**< 0.001**	0.799	1.000	**0.026**
Sway area *(cm^2)*	**0.011**	1.000	**< 0.001**	0.101	1.000	**0.003**

C- = non-DM elderly controls without PN; C+ = non-DM elderly controls with PN; D- = DM elderly without PN; D+ = DM elderly with PN; ML sway = medio-lateral sway; AP sway = anterior-posterior sway

Discussion

Unhampered input of all participating afferent systems for postural control is essential for sound static and dynamic postural and motor performance of human beings. Any impairment of any participating system can therefore be estimated as potentially interfering in the maintenance of the upright position and consequently the occurrence of falls. For the informative flow of somatosensation, derangement of peripheral nerves like in PN is detrimental. This is the case in DM. The presence of PN in this population is generally accepted to be a major complication and a potential aggravating risk for falls. In the absence of diabetes, PN is in general not considered as a routine entity in daily clinical practice in elderly. This is undoubtedly based on the fact that establishment of the presence of PN is labor intensive, highly specialized (nerve conduction analysis) and expensive. As the presence of PN might be debilitating and its idiopathic form is known to be a widely underestimated problem in older people, a quest for alternatives that may be less intensive, easy to use and inexpensive, but nevertheless encompass a valid indication of problems seems highly justified.

Therefore this study entered the VPT as an indicative measure of PN in diabetic and non-diabetic elderly and revealed that one third of the non-diabetic population could be indicated as (potentially) confronted with idiopathic PN. The study enrolled four groups of elderly (C-, C+, D- and D+) in an assessment of postural control during different quiet standing conditions in conjunction with an 8-month follow-up of fall incidents. The overall finding is that the postural control of the groups without PN (C- and D-) is similar during all conditions. The same is true for the groups with PN, albeit that these both groups (C+ and D+) have a less stable postural control than the two

groups without PN (C- and D-). Therefore, this study demonstrates that debilitated postural control ability in elderly might partially but nevertheless substantially be attributed to the existence of PN. The indication of existence of PN seems to go hand in hand with increasing age. As sensory functions, such as vibration threshold, decline with age [26-28], it is not surprising that the groups with a high VPT are older than the groups with a low VPT.

Static postural control seems to be provoked most in the semi-tandem stance position with the eyes closed (condition 6). The removal of *vision* seems to hamper postural control in all groups during all conditions. This is in line with previous results [2,4,29-31].

It was striking to note that the less postural performing PN groups also have significantly worse MMSE-CDT scores than the groups without PN. This ascertainment renders an additional interesting discussion concerning the issue that elderly with peripheral nerve damage also may struggle with problems in the central nervous system. Attention for assessment of these abilities seems therefore also appropriate.

According to previous research, the ML sway should be able to provide valuable information in predicting future falls [32,33] and recurrent fallers [33]. In this study, a significant correlation between the ML sway (condition 1) and the retrospective and prospective fall incidences could be observed (retrospective: $Rs^2=25,8$ and $p=0,001$; prospective: $Rs^2=29,4$ and $p<0,001$). A dominant shift of COP in the sagittal plane (AP) represents use of ankle strategy whereas a dominating shift in the frontal plane (ML) implies use of hip strategy [34]. Simmons *et al.* found that in the most challenging conditions DM used hip strategy significantly more than healthy controls [35]. They suggested a diminished sensation at the feet as a putative reason [35]. In this study, where participants were also matched for PN, this ML shift could be noticed when comparing the wide base EO (condition 1) with the semi-tandem EO (condition 5) (Table 3.2). Remarkably, the changes are manifest greater in the PN groups (C+ and D+). A diminished sensation at the feet might in fact be responsible for the use of a different postural control system (hip strategy). Inversely, enhancing somatosensory input by (soft) textured insole surface has recently been proven to significantly reduce AP and ML sway and effectively may ameliorate age-related deficits in somatosensory function [36]. After identification of somatosensory disturbances in fall risk assessment, it might therefore be useful to integrate somatosensory stimulation in rehabilitation programs designed for fall prevention. The promising results of Qiu *et al.* [36] should however be confirmed by prospective designs implementing this somatosensory stimulation in fall prevention rehabilitation programs in high risk populations like DM with PN.

It is surprising that in former research in DM in relation to PN most designs comprised only two or three groups lacking a control group with an estimated PN. This may imply that the used control groups are probably a mixture of elderly with and without (idiopathic) PN entering a bias in discussing comparative sway parameters.

The fact that the peripheral nerves were only tested on mere one characteristic, vibratory sensation, can be assessed as methodological limitation. The assessment of other sensory modalities seems appropriate to use the overall-encompassing term of "peripheral neuropathy". Also the lack of formal nerve conductive diagnostics in controls can be seen as a flaw. Although based on relationship between diagnosis in DM and the VPT and the aim to search for potential routine alternatives for mere indicating the presence of eventual problems, this lack can be put in perspective.

Nevertheless, from these results it can be concluded that the indication of PN based on VPT, irrespective of its cause, interferes with postural control. As impaired postural control mechanisms are known to generally result in an increased fall risk, which was confirmed by fall incidence data in this study, one should aim to assess all potentially interfering factors. We therefore agree not only with the importance of early determination of abnormal VPT's in DM patients for its inherent clinical risks [14,37], but also like to extend this practice for screening in non-diabetic elderly. The significantly higher prospective fall incidence in elderly with indicated PN underpins this advice. We suggest that the indication of sensory disturbances based on peripheral neuropathies should be assessed in fall risk assessments like Lord *et al.* proposed in their Physiological Profile Assessment [15]. This aim could be established with a simple device as a Bio-Thesiometer® as demonstrated in this trial. This portable valuable [14] and reliable [16] quantitative measurement is not time-consuming, inexpensive and requires minimal training of the assessor. The implementation of a simple screening for indication of PN (like Bio-Thesiometry) in fall risk assessments among elderly is therefore recommended.

Implications for Rehabilitation

- The indication of Peripheral Neuropathy, *irrespective of its cause*, interferes with postural control and fall incidence.
- Therefore, the integration of a simple screening for Peripheral Neuropathy (like Bio-Thesiometry) in any fall risk assessment among elderly is highly recommended.
- It might be useful to integrate somatosensory stimulation in rehabilitation programs designed for fall prevention.

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none.

Declaration of interest

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Chapter 4

The Impact of Peripheral Neuropathy and Cognitive Decrements on Gait in Older Adults with Type 2 Diabetes Mellitus

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Abstract

Objective Peripheral neuropathy is a common complication of diabetes mellitus. In addition, diabetes has been linked to an increased risk of cognitive impairment in older adults. Changes in peripheral neuromuscular transmission and cognitive abilities have been associated with impaired motor performance. This study investigated the relationship between neuropathy and cognition on gait performance in older adults with diabetes.

Design Cross-sectional study.

Setting Community and residential aged care.

Participants 101 older adults (56 diabetics, 28 with peripheral neuropathy and 28 without peripheral neuropathy; 45 matched controls).

Interventions Not applicable.

Main Outcome Measures Spatiotemporal gait parameters were recorded under three conditions: simple, counting backwards by 3 from 40, and reciting animal names. Mini-Mental State Examination and Clock Drawing Test were used to estimate cognitive impairment levels.

Results Compared to controls, older adults with diabetes walked slower, took shorter strides during all walking conditions, and showed more gait variability especially during dual task conditions. Gait patterns did not differ between diabetic participants with and without neuropathy. Compared to normal walking, dual task conditions affected all gait parameters similarly in all groups. Backward counting affected gait more than animal naming in participants with diabetes but not in healthy controls. Additional analyses in older adults with diabetes showed that participants with impaired cognitive function walked slower, took shorter strides, had shorter double support time and increased gait variability when compared to participants with intact cognitive function.

Conclusions This study showed that gait parameters are affected in older adults suffering from type 2 Diabetes Mellitus. Gait was further affected by reduced cognitive function, irrespective of the presence of neuropathy.

Key Words Cognition; Gait speed; Vibration Perception Threshold; Dual Tasking.

Introduction

Diabetes Mellitus is a common problem in older adults worldwide. According to the American Diabetes Association 26.9% of people aged 65 years or older are currently living with diabetes [1], with over 90% suffering from type 2 diabetes [2]. Increasing age is a major risk factor for the development of type 2 diabetes but also of more severe diabetes-related complications. Diabetes in old age has been associated with vision problems, depression, urinary incontinence, dehydration, cerebrovascular accidents and with an increased risk of falls. Recurrent episodes of severe hypoglycemia and/or chronic hyperglycemia have been associated with more severe and accelerated diabetic complications [3]. This might be due to poor disease management or delayed diagnosis of the disease.

Painful peripheral neuropathy is a common and disabling complication, which affects approximately 50% of all patients with diabetes [4]. Initially, diabetic neuropathy presents with sensory disturbances, resulting in loss of tactile and proprioceptive function and slowed reaction times. This can cause inappropriate stepping responses following a balance perturbation [5]. At later stages, peripheral neuropathy has been associated with weakness of the muscles of the lower leg and foot, resulting in impaired motor and gait performance [6]. Diabetes has been associated with slowed gait speed, shorter steps, prolonged double support time, increased step width and gait variability [7].

In recent years, cognitive deficits have been identified in patients with diabetes [3,8-10], even at early stages of the disease [11]. The metabolic syndrome and cardiovascular burden caused by the disease have been associated with reduced cognitive function and structural brain abnormalities [12]. Affected cognitive domains are reduced psychomotor speed [9,13], and impaired memory, executive function [13-16] and attention [14,17]. Executive functioning has been associated with increased gait variability and postural instability while walking in healthy community-living older people, especially under dual tasking conditions. The presence of cognitive deficits might therefore reduce availability of cognitive resources to compensate for diabetic gait disturbances by compromising motor planning in complex everyday environments.

The cognitive demand of gait control is commonly explored using a dual task paradigm. A number of studies have shown that the effects of a concurrent cognitive task on gait are much larger in patients with mild cognitive impairments and in frail older adults [18]. The purpose of this study was to explore the effect of peripheral neuropathy and reduced cognitive functioning on gait under simple and dual task

conditions in diabetic patients. We hypothesized that (i) the presence of diabetes affects gait under single task conditions in older adults, (ii) dual task conditions affect gait more in older adults with diabetes compared to older adults without diabetes, and (iii) reduced cognitive function affects gait in older adults with diabetes.

Methods

Participants

101 older adults were enrolled in this study: 56 diabetes patients (28 with neuropathy, 28 without neuropathy) and 45 age and gender matched controls. Diabetes patients were recruited through online advertising, flyer distribution, by word of mouth and from the Endocrinology Clinic at the Ghent University Hospital, Belgium. Inclusion criteria were: (i) aged 60 years and above, (ii) living in the community or residential aged care setting, (iii) able to understand instructions, (iv) able to walk independently with or without walking aids, (v) absence of stroke, Parkinson's disease or other major neurological conditions, and (vi) absence of musculoskeletal disorders that may affect their gait in a predictable way (e.g. amputations, major rheumatic conditions in the lower extremity). The 45 age and gender matched control participants were recruited through online advertising, flyer distribution and by word of mouth. Inclusion criteria were: (i) aged 60 years and above, (ii) living in the community or residential aged care setting, (iii) Vibration Perception Threshold < 25V, and (iv) absence of diabetes and meeting the inclusion criteria required for the diabetes participants. The Ethical Committee of the Ghent University Hospital gave approval to this study and all participants signed an informed consent.

Personal and medical history

Socio-demographic data, medical history and falls in the past year were recorded by means of a questionnaire. The general practitioner or medical specialist of each participant confirmed the presence or absence of diabetes (fasting glucose and HbA1c levels) and peripheral neuropathy (based on electromyography, nerve conduction studies and/or clinical assessments).

Physical measurements

Peripheral nerve function was assessed by determination of the Vibration Perception Threshold, which has proven reliability and validity towards assessment of neural dysfunction in people with diabetes [19,20]. It was determined using a Bio-Thesiometer® (Bio Medical Instrument co, Ohio, USA) by three measurements on four distinct points (medial malleolus and big toe on both feet). For each location the mean of three values was calculated. Peripheral neuropathy was defined as calculated

thresholds of ≥ 25V in one or more locations [21,22]. The Diabetic Neuropathy Symptom Score includes four yes/no questions on (1) unsteadiness in walking, (2) pain, burning or aching in legs or feet, (3) prickling sensations in legs or feet, (4) numbness in legs or feet [23]. Meijer *et al.* have validated the Diabetic Neuropathy Symptom Score and have proven that a total score of 1-4 has high predictive value in screening for diabetic polyneuropathy [23]. Diabetes participants were classified as having peripheral neuropathy based on two positive criteria: diagnosis by general practitioner, a Vibration Perception Threshold score of ≥ 25V, and/or a Diabetic Neuropathy Symptom Score of 1-4. In cases where Diabetic Neuropathy Symptom Score was missing or general practitioners could not be reached or give a decisive answer concerning the existence of peripheral neuropathy, categorization was based on Vibration Perception Threshold measurement. This was the case for 11 participants.

Spatiotemporal gait analysis was performed using the portable electronic GAITRite® walkway system (8.3m x 0.89m; CIR Systems Inc., Havertown, PA, USA) with proven validity [24]. The GAITRite® System calculates a number of spatiotemporal gait parameters based on footfall data. The following spatiotemporal gait parameters were selected for this study: stride velocity (cm/s), stride length (cm), double support time (s) and coefficient of variation (CoV) of stride length (%). The CoV is a measure of variability and is expressed as the percentage of the ratio of the standard deviation to the mean. Participants were asked to walk at a self-selected normal walking speed wearing comfortable footwear with a low and wide heel and a thin, grooved and moderately hard sole. They were allowed to use their usual walking aid such as crutches, walkers or canes. Three gait conditions were assessed: (i) single task walking, (ii) walking while counting backwards by 3 from 40 (arithmetic dual task), and (iii) walking while reciting animal names (verbal fluency dual task). Before the participant started walking, they were instructed to concentrate equally on walking and the cognitive task. The three different walking conditions were offered in a randomized order and a two minute rest period was provided between each walk. Participants were instructed to start walking two meters before the GAITRite® mat and keep walking for two meters beyond the mat to minimize acceleration and deceleration effects.

Cognitive measurements

The Mini-Mental State Examination (MMSE) was used as a general cognitive screening instrument [25]. The Clock Drawing Test (CDT) was done to estimate executive functioning. Four items as proposed by Thalmann *et al.* were selected: item 2 (12 numbers are present), item 5 (number '12' correctly placed), item 25 (hands have correct proportions) and item 34 (subject reads time correctly) [26]. The scores of the MMSE and the CDT (maximum scores of 30 and 7 respectively) were then

combined into a single score (MMSE-CDT) with a maximum of 9 [26]. A cut-off score of <7 was used to classify people as having reduced cognitive functioning [26].

Statistical analyses

First, a $Group_{(DM)}$ (3) × Condition (3) linear mixed model analysis with random intercept was conducted to compare each spatiotemporal gait parameter between the three groups (diabetes with neuropathy (n=28), diabetes without neuropathy (n=28), matched controls (n=45)) and within the three experimental walking conditions. Normality and linearity assumptions were verified and Bonferroni adjustment for pairwise comparisons was performed. Second, an additional $Group_{(VPT)}$ (2) × $Group_{(MMSE\text{-}CDT)}$ (2) × Condition (3) linear mixed model analysis with random intercept was conducted in the diabetes group only to investigate the impact of reduced cognitive function on gait performance. Spatiotemporal gait parameters were compared between participants with MMSE-CDT score <7 (n=28) and participants with MMSE-CDT score ≥ 7 (n=26) and within the three experimental walking conditions. This analysis was not performed in the control group as subdivision resulted in an unequal distribution among groups (only a few participants scored below the cut-off).

Five participants (3 healthy controls and 2 diabetics) had incomplete gait data, of which two did not complete any gait condition and three participants completed only one or two gait conditions. In the verbal fluency dual task condition, a score of three standard deviations above the mean was given for one outlier in stride length variability.

Results

The demographic and medical characteristics of all participants are shown in Table 4.1. Participants with diabetes had a higher BMI, reported more previous falls, used more walking aids and were more likely to live in residential aged care compared to the matched healthy controls. There was no significant difference between the groups for age or gender. Within the diabetes groups, participants with neuropathy complications showed worse cognitive functioning compared to participants without neuropathy.

Table 4.2 reports on the spatiotemporal gait parameters under the three conditions between diabetes participants with neuropathy, diabetes participants without neuropathy and matched controls. There was a significant main effect of $Group_{(DM)}$ for all gait parameters (Table 4.3). Participants with diabetes walked slower, took shorter strides, had a longer double support phase and walked with increased stride length

Table 4.1 Clinical characteristics of the subjects

	diabetes with neuropathy (n=28)	diabetes without neuropathy (n=28)	healthy controls (n=45)
Age *(yrs)*	74.8 ± 7.5	74.1 ± 8.2	71.3 ± 8.1
Male : Female *(n, (%))*	15:13 (53.6:46.4)	10:18 (35.7:64.3)	20:25 (44.4:55.6)
BMI *(kg/m²)*	31.3 ± 6.3*	30.6 ± 6.9	27.6 ± 4.3
HbA1c *(%)*	7.7 ± 2.0	7.0 ± 1.0	-
HbA1c *(mmol/mol)*	60.4 ± 22.3	53.2 ± 10.8	-
Insulin use *(n (%))*	14 (50.0)	13 (46.4)	-
Walking aids *(%)* Community-dwelling *(%)*	51.9* 28.6*	35.7† 50.0	9.1 64.4
Fall history			
Number of falls	1.81 ± 3.09**	1.25 ± 2.22†	0.30 ± 0.77
Faller : Non-faller *(%)*	63.0 : 37.0**	50.0 : 50.0†	15.9 : 84.1
MMSE	25.5 ± 3.2*	25.1 ± 4.2††	27.0 ± 3.8
CDT	4.2 ± 1.9**‡	5.2 ± 2.4	5.6 ± 2.0
MMSE-CDT	5.5 ± 2.7**	6.3 ± 3.1†	7.6 ± 2.5

BMI, Body Mass Index; HbA1C, glycated haemoglobin;
*$p<0,05$ and **$p\leq0,001$ between DM with PN and healthy controls
†$p<0,05$ and ††$p\leq0,001$ between DM without PN and healthy controls
‡$p<0,05$ between DM with PN and DM without PN

variability compared to controls. There were no significant differences in gait parameters between diabetes participants with neuropathy and diabetes participants without neuropathy. Participants with neuropathy walked slower than diabetes participants without neuropathy, however this was not statistically significant ($p=0.057$). There was a significant main effect of Condition for all gait parameters (Table 4.2 and 4.3). All participants walked slower, took shorter strides, and had increased stride length variability while counting backwards and while reciting animal names compared to the simple gait condition (Table 4.2). There was a significant $Group_{(DM)} \times$ Condition interaction effect for stride velocity and borderline significant interaction effects for the other mean spatiotemporal gait parameters. When comparing the arithmetic task to the verbal fluency task, stride velocity was affected

Table 4.2 Comparison of spatiotemporal gait parameters (Means ± Standard Errors) between gait conditions for diabetes participants with neuropathy (n=28), diabetes participants without neuropathy (n=28), and healthy controls (n=43). Comparisons (P-values) of spatiotemporal gait parameters between participants with diabetes (n=56) and healthy controls (n=43)

Spatiotemporal parameters	Normal Walking			
	diabetes with neuropathy	diabetes without neuropathy	healthy controls	(All) diabetes vs. healthy controls
stride velocity *(cm/s)*	62.4 ± 5.7**††	82.5 ± 5.7**††	103.4 ± 4.6**††	***p*<0.001**
stride length *(cm)*	81.5 ± 5.5*††	96.8 ± 5.5**††	118.0 ± 4.5**††	***p*<0.001**
double support time *(s)*	0.97 ± 0.32	0.60 ± 0.32**††	0.38 ± 0.26	*p*=0.239
CoV stride length *(%)*	5.68 ± 0.80**††	4.94 ± 0.80*	3.05 ± 0.65*†	***p*=0.010**
	Walking + Verbal Fluency Task			
	diabetes with neuropathy	diabetes without neuropathy	healthy controls	
stride velocity *(cm/s)*	48.2 ± 5.7†	65.7 ± 5.7†	79.6 ± 4.6	***p*<0.001**
stride length *(cm)*	75.3 ± 5.5†	90.2 ± 5.5	110.2 ± 4.6	***p*<0.001**
double support time *(s)*	1.27 ± 0.32	1.71 ± 0.32	0.51 ± 0.26	***p*=0.005**
CoV stride length *(%)*	9.17 ± 0.80	7.37 ± 0.80	5.14 ± 0.65	***p*<0.001**
	Walking + Arithmetic Task			
	diabetes with neuropathy	diabetes without neuropathy	healthy controls	
stride velocity *(cm/s)*	41.1 ± 5.7	58.2 ± 5.7	82.0 ± 4.6	***p*<0.001**
stride length *(cm)*	69.8 ± 5.5	87.1 ± 5.5	111.8 ± 4.5	***p*<0.001**
double support time *(s)*	1.39 ± 0.32	1.55 ± 0.32	0.53 ± 0.26	***p*=0.007**
CoV stride length *(%)*	9.00 ± 0.81	6.45 ± 0.81	4.90 ± 0.65	***p*=0.001**

*$p<0.05$ and **$p\leq0.001$ compared to walking + verbal fluency task
†$p<0.05$ and ††$p\leq0.001$ compared to walking + arithmetic task

Table 4.3 Main and interaction effects of linear mixed model with $Group_{(DM)}$, Condition and $Group_{(DM)}$ × Condition as Fixed factors. Main and interaction effects of linear mixed model with addition of $Group_{(MMSE\text{-}CDT)}$

	All Participants (N=101)			Diabetes participants (n=56)	
	$Group_{(DM)}$	Condition	$Group_{(DM)}$ × Condition	$Group_{(MMSE\text{-}CDT)}$	$Group_{(MMSE\text{-}CDT)}$ × $Group_{(VPT)}$
Stride Velocity	$F_{2, 96}=15.06$, $\mathbf{p<0.001}$	$F_{2, 189}=101.94$, $\mathbf{p<0.001}$	$F_{4,189}=2.64$, $\mathbf{p=0.035}$	$F_{1, 50}=16.80$, $\mathbf{p<0.001}$	$F_{1,50}=1.67$, $p=0.202$
Stride Length	$F_{2, 96}=15.48$, $\mathbf{p<0.001}$	$F_{2, 189}=36.88$, $\mathbf{p<0.001}$	$F_{4,189}=2.23$, $p=0.068$	$F_{1, 50}=20.64$, $\mathbf{p<0.001}$	$F_{1,50}=0.65$, $p=0.424$
Double Support Time	$F_{2, 93}=3.45$, $\mathbf{p=0.036}$	$F_{2, 187}=7.61$, $\mathbf{p= 0.001}$	$F_{4,187}=2.26$, $p=0.065$	$F_{1, 49}=4.28$, $\mathbf{p=0.044}$	$F_{1,49}=1.46$, $p=0.232$
CoV Stride Length	$F_{2, 90}=10.15$, $\mathbf{p<0.001}$	$F_{2, 184}=18.05$, $\mathbf{p<0.001}$	$F_{4,184}=0.75$, $p=0.558$	$F_{1,45}=10.87$, $\mathbf{p=0.002}$	$F_{1,45}=0.31$, $p=0.579$

$Group_{(DM)}$, healthy controls – diabetes without neuropathy – diabetes with neuropathy; Condition, single task – verbal fluency dual task – arithmetic dual task; $Group_{(MMSE\text{-}CDT)}$, MMSE-CDT ≥ 7/9 – MMSE-CDT < 7/9; $Group_{(VPT)}$, diabetes without neuropathy – diabetes with neuropathy

Table 4.4 Pairwise comparisons of spatiotemporal gait parameters (Means ± Standard Errors) between normal (MMSE-CDT ≥ 7/9) and impaired (MMSE-CDT < 7/9) cognitive function for diabetes participants during the three walking conditions

	Stride Velocity *(cm/s)*	Stride Length *(cm)*	Double Support Time *(s)*	CoV Stride Length *(%)*
Normal walking				
MMSE-CDT < 7/9	60.7 ± 4.4	75.8 ± 4.3	1.33 ± 0.39	6.72 ± 0.75
MMSE-CDT ≥ 7/9	85.5 ± 4.5	103.4 ± 4.5	0.26 ± 0.41	3.70 ± 0.78
p-value	**<0.001**	**<0.001**	**0.044**	**0.002**
Verbal fluency dual-task				
MMSE-CDT < 7/9	45.0 ± 4.4	69.0 ± 4.3	2.07 ± 0.39	9.72 ± 0.75
MMSE-CDT ≥ 7/9	69.8 ± 4.5	96.7 ± 4.5	0.99 ± 0.41	6.69 ± 0.78
p-value	**<0.001**	**<0.001**	**0.044**	**0.002**
Arithmetic dual-task				
MMSE-CDT < 7/9	37.9 ± 4.4	65.0 ± 4.3	1.95 ± 0.39	8.86 ± 0.77
MMSE-CDT ≥ 7/9	62.8 ± 4.5	92.7 ± 4.5	0.87 ± 0.41	5.83 ± 0.78
p-value	**<0.001**	**<0.001**	**0.044**	**0.002**

more while counting backwards in participants with diabetes (DM-PN: $p=0.016$ and DM+PN: $p=0.022$) but not in controls ($p=0.343$).

Table 4.3 reports on the spatiotemporal gait parameters under the three conditions in the subsample of older adults with diabetes between participants with neuropathy and without neuropathy ($Group_{(VPT)}$) and between participants with a MMSE-CDT score of 7 or above and below 7 ($Group_{(MMSE\text{-}CDT)}$). Pairwise comparisons of this linear mixed model are presented in Table 4.4. Participants with impaired cognitive function walked slower, took shorter strides, had a shorter double support time and an increased gait variability compared to participants with intact cognitive function during all walking conditions (Table 4.4). There was no significant $Group_{(MMSE\text{-}CDT)} \times Group_{(VPT)}$ interaction effect for any of the gait parameters (Table 4.3), suggesting that reduced cognitive function affects gait in older adults with diabetes, irrespective of the presence of neuropathy. There was no significant 2-way or 3-way interaction effect between conditions × groups for any of the gait variables, suggesting that gait was not affected more in the dual task conditions compared to the simple gait condition.

Figure 4.1 illustrates the effect of diabetes mellitus and impaired cognitive function on stride length during walking while backward counting. This trend is similar for the other gait parameters and conditions.

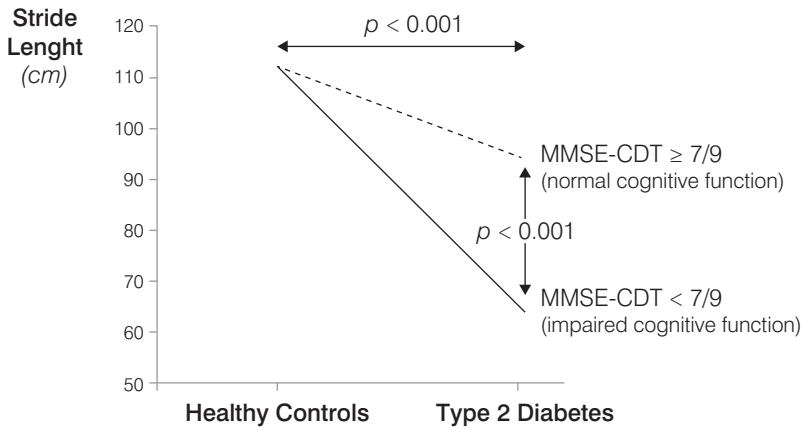

Figure 4.1 The effect of diabetes mellitus and impaired cognitive function on stride length during walking while backward counting

Discussion

his study showed that the presence of diabetes affected gait in older adults and that dual task conditions relying on attentional resources affected gait more in older adults with diabetes compared to older adults without diabetes. Within our sample of diabetes participants, reduced cognitive function adversely affected gait, irrespective of the presence of neuropathy.

Previous studies have reported that older adults suffering from diabetes mellitus have an altered gait pattern. Diabetes has most commonly been associated with reduced gait speed and shorter step and/or stride length under simple gait conditions [27-31]. Reduced cadence and increased step time, single or double support time and stance time have also been reported [7,27,29,31]. The current experiment confirmed these previous findings, supporting the hypothesis of a 'more conservative' gait pattern in older adults with diabetes. The altered gait pattern can be seen as a clinical manifestation of the disease. However, as suggested by Stegemoller *et al.* [32], it might also be a well-considered choice of the patient to adopt a compensatory strategy to improve or maintain safe dynamic stability during more demanding gait conditions. By using a conservative gait, people with diabetes might compensate for reduced sensory information about the position and movement of their body and limbs [31,33,34]. Gait variability has also been a useful parameter to provide better insights of motor control during walking [35] and has been associated with future falls [36] and cognitive decline in healthy older adults [37]. An increased gait variability has also been identified in patients with diabetes suffering from peripheral neuropathy [7,29,33,38], which could be partially explained by a compensatory reduced self-selected walking speed [38]. Similar to Allet *et al.* [39] and Sawacha *et al.* [30], we did not find any differences in gait parameters between diabetic participants with and without peripheral neuropathy complications. However, a trend ($p=0.057$) of slower stride velocity for diabetic participants with peripheral neuropathy compared to without could be noticed. Further research in larger samples is needed to understand the impact of peripheral neuropathy on gait in older adults with (and without?) diabetes.

Dual task conditions relying on attentional resources have been shown to adversely affect gait in older adults. However, this has not been commonly investigated in older adults suffering from type 2 Diabetes Mellitus. Overall, both backward counting and reciting animal names while walking affected gait equally in all participants. In participants with diabetes, the arithmetic dual task affected gait more than the verbal fluency task, whereas there was no difference between the two dual task conditions in the control group. The verbal fluency task depends on semantic memory, while the

arithmetic task and gait itself both rely on working memory [40]. Choosing a dual task that relies on the same memory as gait may therefore be important to elucidate an effect [40]. There is ample evidence indicating that gait utilizes higher cognitive processing. Our results suggest that an attentional cognitive dual task can further affect gait in older adults with diabetes mellitus.

There is controversy regarding the degree to which cerebral effects of type 2 diabetes contribute to slower walking speed, lack of balance and increased fall incidence [41]. Reijmer *et al.* have recently suggested that diabetes is associated with subtle cognitive decrements [42], which was confirmed in our study by a worse performance on MMSE and the CDT in participants with diabetes compared to controls. The present study showed that, in our sample of diabetes participants, based on a simple clinical categorization, impaired cognitive functioning was associated with decreased gait speed, shortened strides, prolonged double support time and increased gait variability, irrespective of the presence of neuropathy. Peripheral and central nerve damage partly go hand in hand [10,15,17], which complicates their relation with gait. Further research is required to investigate this association in more detail and in larger samples.

Study Limitations and future research

Diagnosing peripheral neuropathy in clinical practice is often a lengthy process, including laboratory testing, electromyography, and nerve conduction studies. In the present study, we have relied solely on clinical measures to identify and categorize people with peripheral neuropathy in combination with GP reports without access to the primary data. The Diabetic Neuropathy Symptom Score correlates well with nerve conduction studies [23] and has previously been able to discriminate between patients with and without diabetic polyneuropathy [43]. Evidence-based clinical guidelines have suggested that combined use of the Diabetic Neuropathy Symptom Score and Vibration Perception Threshold is sufficient for screening, prevention and instruction purposes in clinical practice [43,44]. Future studies should explore potential mediating pathways of neuropathy on gait performance, i.e. through joint mobility, muscle strength, or other comorbidities. In order to get better insights into the subdomains of cognitive functioning that mediate the relationship between diabetes and gait, a more extensive neuropsychological screening should also be considered.

Conclusions

This study confirmed that gait parameters are affected in older adults suffering from type 2 Diabetes Mellitus, especially under dual task conditions. We showed that

irrespective of the well-known diabetes-related complication peripheral neuropathy, reduced cognitive function further affects gait in older adults with diabetes.

Conflicts of interest

Nothing to declare.

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4

Chapter 5

Does Footwear matter in Spatiotemporal Gait Analysis among Older Women?

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Abstract

Background and Purpose Although the shoe type may influence gait performance and is considered to be an extrinsic fall risk factor, little or no attention is paid to it when conducting research in this field. Therefore, this study aims to assess the effect of various types of footwear under single- and dual-task conditions on spatiotemporal gait characteristics in older women.

Methods Fifty-seven community-dwelling women (68.0±4.6 years) were enrolled in this study. Spatiotemporal gait analysis using the GAITRite® walkway was performed under 4 footwear conditions (barefoot, slippers, high heels, standard shoes) and 3 task conditions (single-task, motor dual-task, cognitive dual-task). Multivariate repeated-measures ANOVA was conducted. Primary outcomes were velocity, cadence, stride time, stride length, and stride length variability.

Results Irrespective of task condition, walking barefoot resulted in a significantly slower gait pattern with decreased cadence and stride length, and increased stride time and stride length variability compared to walking with the standard shoe. These significant gait alterations were also observed when adding a cognitive task to normal walking. The effects of footwear were most obvious during the cognitive dual-task condition and for the spatiotemporal parameters velocity and stride length.

Conclusions Footwear matters when analyzing gait in older women. It should be described in greater detail by gait researchers. Footwear should also be considered by clinicians in light of the study findings and its effects on gait. Older women are strongly discouraged to walk barefoot since barefoot walking adversely affects gait patterns. A well-fitting standard shoe with laces, a low and wide heel, firm heel collar and a grooved, moderately hard sole is recommended in research, rehabilitation and daily use.

Key words Aged; Gait; Walking; Footwear; Dual Tasking

Introduction

One of the major complaints and challenges when growing older is the decline in the ability to perform activities of daily living. A lot of these activities are mobility related and often depend on a safe and appropriate performance of gait. Especially with respect to this gait-related-mobility requirement, it is generally accepted that age induces important and often limiting alterations in locomotion undermining personal and social independence [1-4]. The altered gait pattern of healthy older adults is generally characterized by reduced gait speed [5-7], shorter step and/or stride lengths [5,6] and increased gait variability [8]. In addition to age- or disease-related intrinsic risk factors, gait might supplementary be affected by an essential extrinsic risk factor: i.e. footwear. Unless studies are specifically designed to assess the effects of footwear, shoes often seem to be overlooked when conducting mobility-related research in older adults.

Depending on task conditions or personal preferences, walking occurs with or without shoes. Shoes are available in all weights and sizes since they are designed for different purposes (activities) and terrains and affected by fashion. Older adults who live in the community preferably wear slippers, socks, or no shoes at home [9]. In residential settings, as well as with increasing age, the 'slipper-mania' is even greater [10]. However, these types of footwear (or no footwear) have previously been identified as fall risk factors [11-13] and have even been associated with increased injurious falls [14,15]. Poorly fitting shoes have been shown to cause foot problems, foot ulcerations and pain, consequently increasing indirectly the risk of falling [10,16-18] based on altered somatosensory input to the foot and ankle influencing postural control and creating instability [10].

In the context of gait analyses, numerical and statistical differences are often based on marginal differences within the frame of cut-off scores. As such, walking speed has been used to make critical judgments about an individual in terms of responsive measure for short-term rehabilitation [19], risk of adverse outcome [20], functional decline [21], fall prediction [22] and survival [23,24]. Since footwear is hypothesized to affect gait (speed), it may also interfere with these outcomes in a decisive way.

The cognitive demand of gait is commonly explored using dual-task paradigms. Walking while performing a cognitive task has been shown to cause gait alterations not only in older adults with cognitive impairments [25-27] but also in non-disabled older adults [7,28]. The introduction of dual-task conditions in gait analysis might be useful to reveal more subtle gait alterations and has previously been suggested to become a part of routine evaluations of gait abnormalities and fall risk [29]. The type

of footwear worn may complicate gait when walking occurs under conditions of increased task complexity brought on by the need to perform two tasks simultaneously.

Based on foregoing facts, clarification regarding the effects of footwear worn by older adults on gait is necessary for clinical as well as scientific purposes. Understanding the effects of footwear on gait might increase the awareness concerning proper footwear of scientists and clinicians on the one hand and older adults and their caregivers on the other hand. Therefore, this study aimed (i) to investigate the effect of various types of footwear on spatiotemporal gait in older women, (ii) to look into these characteristics while walking without and with a dual-task, and (iii) to provide recommendations to researchers, health-care workers and older women concerning optimal types of footwear in relation to gait performance.

Methods

Participants

Sixty older women between 60 and 75 years volunteered to participate in this study. Individuals older than 75 were not enrolled since women aged 60-75 are more likely to wear high-heeled shoes. Other inclusion criteria were (i) living independently in the community, (ii) being able to understand instructions (according to clinical diagnosis of dementia or other severe cognitive impairment (Mini Mental State Exam score <24) [30], (iii) being able to walk independently without walking aids, (iv) absence of stroke, Parkinson's disease or other major neurological conditions, and (v) absence of musculoskeletal disorders that may affect their gait in a predictable way (e.g., amputations, major rheumatic conditions in the lower extremity). Three participants did not meet the inclusion criteria. The Ethical Committee of the Ghent University Hospital gave approval to this study and all participants signed an informed consent.

Experimental design

Gait analysis was performed using the portable and reliable electronic GAITRite® walkway system (8.3m x 0.89m; CIR Systems Inc., Havertown, PA, USA) [31]. The following clinically relevant spatiotemporal gait parameters were considered in this study: velocity, cadence, stride time, stride length, and coefficient of variation (CV) of stride length. The CV is a measure of variability and is expressed as the percentage of the ratio of the standard deviation to the mean. Gait variability has been shown to be a useful parameter to provide better insights of motor control during walking [32] and has been associated with future falls [33]. Cadence and stride length were selected since minimal detectable changes (MDC) have previously been determined for these parameters [34]. Participants were asked to walk across the walkway under

4 conditions: barefoot, wearing their own open heel slippers, wearing their own high heeled (min 3.5cm) shoes, and wearing a standard shoe offered by the investigators. The standard shoe was a walking shoe with laces, a low (<2.5cm) slightly rounded heel and firm heel collar (6.5cm), a shock-absorbing ethylene vinyl acetate (EVA) foam midsole and grooved outsole (Figure 5.1) and was provided by Decathlon Belgium. The standard shoes were available in different sizes and the investigators fitted each subject into the standard shoes by palpating a thumb's width of space (10-20mm) between the end of the hallux and the end of the shoe [35].

Figure 5.1 The standard shoe

Participants were instructed "to walk at their normal speed" and perform each footwear condition in 3 randomly offered task conditions: as a single-task, while carrying a tray with a cup of pearls (motor dual-task) and while counting backwards by 3's starting from 50 (cognitive dual-task). The dual-tasks were introduced to distract the focus of the single walking task in order to obtain gait patterns similar to real life. Before the participants started walking, they were instructed to concentrate equally on walking and the dual-task. The different walking conditions were offered in a randomized order, and a 2-minute rest period was provided between each walk. Participants were instructed to start walking 2 m before the GAITRite® walkway and keep walking for 2 meters beyond the walkway to minimize acceleration and deceleration effects. In order to avoid practice bias with regard to the dual-tasks, only one trial per walking condition was performed. Before the beginning of gait analyses, participants were asked to freely walk for 2-3 minutes in the laboratory to realize adaptation to the standard shoe and to the laboratory environment.

Statistical analysis

Spatiotemporal gait parameters were calculated by the GAITRite® software and statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Normality assumptions were verified by Kolmogorov-Smirnov goodness-of-fit test. For each gait parameter, multivariate repeated-measures ANOVA models were conducted to compare spatiotemporal gait parameters between the 4 different types of footwear and across the 3 experimental walking conditions. Since Mauchly's Test of Sphericity was violated, Greenhouse-Geisser adjustment was applied. Finally, pairwise comparisons with Bonferroni adjustment for multiple comparisons were performed. If interaction effects were present, pairwise comparisons between the conditions were performed within each group.

Results

Mean age and body mass index (BMI) of the older women (N=57) were 68.0 (SD 4.6) and 27.9 (SD 4.5) respectively. Pairwise comparisons were made between types of footwear (irrespective of task conditions) and between task conditions (irrespective of types of footwear) for velocity, cadence, stride time, stride length and CV stride length (Table 5.1). Mean values of the spatiotemporal gait parameters for each type of footwear and each task condition are presented in Table 5.2 whereas Table 5.3 contains the pairwise comparisons of types of footwear within each task condition.

Effects of footwear

There was a statistical significant main effect of footwear for all gait parameters: velocity $F(3,430) = 145.24$, $p < 0.001$; cadence $F(3,428) = 14.37$, $p < 0.001$; stride time $F(2,410) = 11.67$, $p < 0.001$; stride length $F(3,465) = 281.88$, $p < 0.001$; CV stride length $F(3,486) = 14.86$, $p < 0.001$. Therefore, only the results of pairwise comparisons are included in Table 5.1. Pairwise comparisons between all types of footwear resulted in significantly different gait velocities. Compared to shod walking, walking barefoot revealed a significantly slower gait velocity with decreased stride lengths and increased stride-to-stride variability. All gait parameters were significantly different when walking with the standard shoe compared to barefoot walking.

Effects of task condition

There was a statistical significant main effect of task condition for velocity $F(2,168) = 8.26$, $p < 0.001$; cadence $F(2,168) = 18.60$, $p < 0.001$; stride time $F(2,168) = 19.70$, $p < 0.001$, and CV stride length $F(2,168) = 22.12$, $p < 0.001$. The cognitive dual-task resulted in a significantly slower gait pattern with decreased cadence, increased

Table 5.1 Statistically Significant Pairwise Comparisons (P-values) of Differences in Temporal and Distance Gait Parameters for the Main Effects of Footwear and Task Conditions*

Footwear comparisons and task comparisons	Velocity	Cadence	Stride Time	Stride Length	CV Stride length
Barefoot vs. Slippers	**<0.001**	0.149	0.751	**<0.001**	**<0.001**
Barefoot vs. High heels	**<0.001**	1.000	0.850	**<0.001**	**<0.001**
Barefoot vs. Standard	**<0.001**	**0.001**	**0.001**	**<0.001**	**<0.001**
Slippers vs. High heels	**0.002**	**0.014**	**0.025**	0.104	1.000
Slippers vs. Standard	**<0.001**	**<0.001**	**<0.001**	**<0.001**	1.000
High heels vs. Standard	**<0.001**	0.405	**0.007**	**<0.001**	1.000
Single-task vs. motor dual-task	1.000	0.339	0.505	1.000	1.000
Single-task vs. cognitive dual-task	**0.005**	**<0.001**	**<0.001**	0.781	**<0.001**
Motor vs. cognitive dual-task	**0.001**	**<0.001**	**<0.001**	1.000	**<0.001**

*Note: For the footwear pairwise comparisons, the three task conditions were collapsed and for the task condition pairwise comparisons, the four types of footwear were collapsed.

stride time, and increased stride-to-stride variability compared to the motor dual-task or to the single-task. No significant differences in gait parameters between single-task walking and walking while performing the motor dual-task were found (Table 5.1).

Interaction effects

Significant interaction effects (footwear × task) were found for velocity $F(5,430) = 5.23$, $p < 0.001$; cadence $F(6,428) = 6.73$, $p < 0.001$; stride time $F(6,410) = 6.08$, $p < 0.001$, and CV stride length $F(6,486) = 3.41$, $p = 0.003$. Therefore, spatiotemporal gait parameters obtained for the separate kinds of footwear are presented for the 3 task conditions (Table 5.2) and the *p*-values for the pairwise footwear comparisons are reported in Table 5.3. Pairwise task comparisons for each footwear type were not listed in a table but described below.

Pairwise footwear comparisons per task condition

Under the single-task condition, gait velocity was significantly slower ($p<0.001$) and stride lengths were significantly decreased ($p<0.001$) when walking barefoot compared to shod walking. Compared to all other footwear types, walking with the standard shoe resulted in a significantly faster gait pattern with higher cadence, increased stride lengths and decreased stride times. No differences in spatiotemporal gait parameters were noted between walking with high heels and walking with slippers.

Table 5.2 Means (SD) of the Spatiotemporal Gait Parameters for each Type of Footwear under the Single- and Dual-Task Conditions

Footwear per task condition	Velocity *(cm/s)*	Cadence *(steps/min)*	Stride Time *(s)*	Stride Length *(cm)*	CV Stride Length *(%)*
Single-Task					
Barefoot	114.6 (17.7)	115.9 (9.3)	1.041 (.085)	118.5 (13.0)	0.021 (0.010)
Slippers	122.1 (15.8)	116.1 (8.1)	1.037 (.073)	126.1 (11.8)	0.018 (0.006)
High heels	123.0 (17.0)	116.4 (8.2)	1.035 (.073)	126.7 (13.0)	0.018 (0.008)
Standard	128.5 (18.9)	118.3 (8.6)	1.018 (.073)	130.2 (14.1)	0.018 (0.008)
Motor Dual-Task					
Barefoot	119.0 (17.1)	120.9 (8.9)	0.997 (0.075)	118.2 (12.8)	0.020 (0.008)
Slippers	123.6 (16.1)	118.4 (8.4)	1.018 (0.073)	125.3 (11.9)	0.017 (0.007)
High heels	123.9 (17.3)	118.2 (8.6)	1.019 (0.073)	125.7 (12.7)	0.018 (0.008)
Standard	129.1 (17.7)	120.2 (8.4)	1.002 (0.071)	128.9 (13.1)	0.017 (0.007)
Cognitive Dual-Task					
Barefoot	102.7 (19.0)	107.5 (13.1)	1.133 (0.152)	114.7 (13.8)	0.033 (0.017)
Slippers	110.0 (19.6)	107.4 (12.5)	1.134 (0.156)	123.0 (14.4)	0.025 (0.013)
High heels	115.3 (19.0)	110.7 (10.5)	1.095 (0.112)	124.9 (14.3)	0.022 (0.009)
Standard	119.2 (19.4)	111.6 (11.2)	1.087 (0.123)	128.1 (14.4)	0.023 (0.013)

Adding a dual-task, regardless of the type, did not significantly alter spatiotemporal gait parameters based on footwear worn. Again, velocity and stride length significantly decreased when walking barefoot compared to shod walking. The standard shoe yielded a faster gait pattern with increased stride lengths compared to the other kinds of footwear or no footwear. Similar to the findings during single-task walking, the gait pattern while performing a motor dual-task wearing slippers could not be differentiated from that wearing high heels. The addition of a cognitive dual-task, however, induced a significantly faster gait pattern with increased cadence and decreased stride times when walking with high heels compared to walking with slippers ($p=0.001$, $p=0.002$, and $p=0.011$ respectively). Furthermore, the cognitive dual-task condition was the only condition in which barefoot walking could be differentiated from high-heeled walking and walking with the standard shoe based on *all* spatiotemporal gait parameters.

Table 5.3 Significances (*p*-values) of the Footwear Pairwise Comparisons for Spatiotemporal Gait Parameters within each Task Condition

Task condition	Footwear comparisons	Velocity	Cadence	Stride Time	Stride Length	CV Stride Length
Single-Task	Barefoot vs. Slippers	**<0.001**	1.000	1.000	**<0.001**	0.077
	Barefoot vs. High heels	**<0.001**	1.000	1.000	**<0.001**	0.255
	Barefoot vs. Standard	**<0.001**	**0.035**	**0.021**	**<0.001**	0.143
	Slippers vs. High heels	1.000	1.000	1.000	1.000	1.000
	Slippers vs. Standard	**<0.001**	**0.002**	**0.001**	**<0.001**	1.000
	High heels vs. Standard	**<0.001**	**0.017**	**0.017**	**<0.001**	1.000
Motor Dual-Task	Barefoot vs. Slippers	**<0.001**	**<0.001**	**0.001**	**<0.001**	0.216
	Barefoot vs. High heels	**0.001**	**0.001**	**0.001**	**<0.001**	1.000
	Barefoot vs. Standard	**<0.001**	1.000	1.000	**<0.001**	0.330
	Slippers vs. High heels	1.000	1.000	1.000	1.000	1.000
	Slippers vs. Standard	**<0.001**	**0.019**	**0.010**	**<0.001**	1.000
	High heels vs. Standard	**<0.001**	**0.005**	**0.001**	**<0.001**	1.000
Cognitive Dual-Task	Barefoot vs. Slippers	**<0.001**	1.000	1.000	**<0.001**	**0.008**
	Barefoot vs. High heels	**<0.001**	**0.010**	**0.010**	**<0.001**	**<0.001**
	Barefoot vs. Standard	**<0.001**	**0.002**	**0.011**	**<0.001**	**0.001**
	Slippers vs. High heels	**0.001**	**0.002**	**0.011**	0.159	0.647
	Slippers vs. Standard	**<0.001**	**0.001**	**0.021**	**<0.001**	1.000
	High heels vs. Standard	**0.009**	1.000	1.000	**0.001**	1.000

Pairwise task condition comparisons per footwear type

For each separate type of footwear (within footwear), cognitive dual-task walking revealed different spatiotemporal gait parameters compared to motor dual-task walking or single-task walking. The differences were statistically significant for velocity, cadence, stride time, and stride-to-stride variability but not for stride length. Single-task gait patterns could not be differentiated from motor task gait patterns.

Overall, it can be concluded that walking with the standard shoe resulted in a significantly different gait pattern compared to the other types of footwear or no footwear. The addition of a dual-task, irrespective of its characteristic (motor or cognitive), did not alter footwear effects on gait. Nevertheless, the effects of the footwear types could be discriminated the best during the cognitive dual-task

condition. Conversely, irrespective of the type of footwear, cognitive dual-task walking revealed a significantly different gait pattern (i.e. slower velocity, decreased cadence, increased stride time, and increased stride-to-stride variability) compared to motor dual-task walking or walking as a single-task.

Discussion

The results of this study indicate that footwear has a definite influence on gait patterns in a healthy older female cohort. First of all, not wearing any kind of footwear caused the most unstable gait pattern (highest stride-to-stride variability). Barefoot walking also resulted in a significantly slower gait with decreased stride lengths compared to walking with slippers and high heels. Walking with the standard shoe was obviously characterized by the fastest gait speed, most decreased stride time and most increased stride length compared to any other type of footwear or barefoot walking.

Since small changes in spatiotemporal gait parameters might be attributed to measurement error or random variability, some researchers have established minimal detectable change (MDC) values. Changes in spatiotemporal gait parameters that are equal to or greater than the MDC can be considered 'real' changes [34]. Youdas *et al.* performed GAITRite® analyses at comfortable self-selected walking speed in older adults and determined a MDC of 12.6 cm/s for walking speed, 8.4 steps/min for cadence and 7.0 cm for stride length [34]. Although a lot of statistically significant differences could be found when comparing the shoe types with each other, MDC values were not always reached. All shoe type induced differences of cadence were smaller than the MDC of 8.4 steps/min, irrespective of task condition. As for velocity, differences between barefoot walking and walking with the standard shoe were greater than the MDC of 12.6 cm/s during single-task walking. Walking while counting backward revealed a slower velocity for barefoot walking compared to high-heeled walking or walking with the standard shoe, which was respectively equal and greater than the MDC. The stride lengths while barefoot walking compared to any other shoe type exceeded the MDC value of 7.0 cm/s, irrespective of the task condition. According to the MDC theory, clinically meaningful differences could thus be retained for barefoot walking compared to walking with the standard shoe. It should however be noticed that previous MDC calculations were primarily based on changes over time. MDC values in the context of different types of footwear have not been established so far.

Considering the effects of dual-tasks on gait, it can be concluded that the addition of a cognitive dual-task affects gait resulting in a slower gait pattern, with decreased cadence, increased stride times and increased stride-to-stride variability

compared to single-task walking and to walking while carrying a tray. Stride lengths decreased but did not reach significance level of 0.05. The appearance of adverse gait alterations in healthy older individuals when walking while performing a cognitive dual-task is a well-documented phenomenon [7,29,36-39]. As cognitive dual-tasks are used to assess the influence of attention on gait performance and normal ageing is known to be accompanied by a subtle decline of some components of executive functioning, such as attention [29], the affected gait pattern during walking while backward counting in these healthy older women is not surprising. The CV of stride length was significantly higher when barefoot walking was compared to shod walking during cognitive dual-task walking but not during single-task or motor dual-task walking. Executive functions have previously been associated with stride length variability [40] which might explain this finding.

To the contrary, gait abilities were not altered when a motor dual-task was added to normal walking. The self-selected gait speed even slightly increased when carrying a tray filled with pearls compared to walking as a single-task. Hsiang *et al.* found that wearing a weight with both hands, resulted in a forward movement of the center of gravity and a passive increase in the forward pulse generation during the push-off phase [41]. A forward shift of the center of gravity, possibly provoked by the tray, might thus have led to an increase in velocity. Alternatively, it might be that the participants attempted to terminate the task as fast as possible, before the cup with pearls would fall and the task should appear to be failed.

Footwear types altered gait parameters most obviously during cognitive dual-task walking. In each task condition and compared to all other types of footwear, however, barefoot walking resulted in a significantly slower gait with decreased stride lengths, whereas walking with the standard shoe yielded a significantly faster gait with increased stride lengths. Barefoot walking has previously been associated with an increased fall risk in older adults [11,13]. As plantar pressures are higher when walking barefoot [42], the slower velocities and shorter stride lengths might be explained by the application of a compensatory strategy to decrease local stress (pain sensation) underneath the heel [43]. Inversely, according to Arnadottir *et al.* walking shoes provide a shock absorption allowing people to walk faster without increasing the impact loading of the body [44]. When task conditions were compared to each other, it could be concluded that cognitive dual-task walking consistently (i.e. irrespective of the type of footwear) resulted in a slower gait pattern with decreased cadence, increased stride times and increased stride-to-stride variability compared to motor dual-task walking or walking as a single-task.

The finding of a more conservative gait pattern (slower walking speed, decreased cadence, increased stride time and decreased stride length) when single-task walking with high heels compared to walking with the flat standard shoe is also in line

with the existing literature [44-47]. Menant *et al.* showed that walking with a high-heeled shoe can lead to lateral instability [46], consequently reducing velocity, step and stride length. Another suitable explanation was suggested by Snow *et al.* They showed that wearing high heels results in a shifting of the total body center of mass in anterior direction, thereby modifying plantar pressure distribution and increasing tissue stress [48]. Contrary to our findings, Arnadottir *et al.* [44] and Lord *et al.* [47] found that dress shoes (high heels) yielded slower walking speeds than barefoot walking. All 35 older women included in the study of Arnadottir *et al.* were living in assisted living facilities [44] and 25 out of the 30 women of Lord's cohort were recruited in a residential care setting [47], whereas our older women were living independently in the community. Furthermore, compared to the two aforementioned studies the older individuals of this study were at least 10 years younger on average, which may also have some consequences with regard to footwear habituation in daily life. The differences in residence and age might represent different states of health and/or habits, including fashion preferences. Possibly, the women who participated in our study were habituated to wearing high heels, elucidating their better performance wearing this type of shoes in comparison with barefoot walking. As habituation to wearing high heels was not registered in this study, we will consider this in future research.

Based on the clearly adverse effects of barefoot walking on the spatiotemporal gait parameters, we recommend older women to wear shoes rather than no shoes and to prefer a type of shoe with similar characteristics as the standard shoe used in this study. The features of the standard shoe seem generally to be consistent with the shoe characteristics recommended as safe footwear for older adults in existing scientific literature: a low heel with large contact area, comfortably fitting, with laces and an anti-slip moderately hard sole [10,13,15,45,49,50]. Furthermore, walking without shoes or with socks has been shown by Menz *et al.* to increase fall risk (indoors) [13]. Similarly, high heels have been associated with an increased risk of falling [50]. As this type of shoes in our study indeed induced some significant adverse gait alterations, we prefer the standard shoe above all else. The fact that the slippers and high heeled shoes were brought by the participants, potentially provided good generalizability of habitual daily living performance. However, characteristics of these footwear types lacked standardization, which can be considered a limitation. Another limitation of this study lies in the fact that the arithmetic cognitive task was not measured as a single-task. This might have allowed the investigators to assess which task was prioritized by the participants during dual-task walking.

Conclusions

Gait alterations occur depending on the type of footwear and are most pronounced when walking barefoot. Footwear effects are similar when dual-task walking compared to walking as a single-task. We advise healthy older women to wear shoes rather than no shoes and if possible to choose for a well-fitting standard shoe with laces, a low and wide heel, firm heel collar and a grooved, moderately hard sole. Researchers evaluating gait in older individuals should provide a precise description of the participants' shoes. The use of a more uniform shoe may serve standardization of any research protocol, even if participants are not immediately familiar with this kind of shoe. This accounts also for clinicians who clinically assess gait on a regular basis and for them it is recommended to at least assess gait always wearing the same shoes as diversity implies different outcome measures.

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Chapter 6

General discussion

6

SUMMARY

The major purpose of this doctoral thesis was to contribute to the understanding of falling among older adults with T2DM. Part One identified fall risk factors among a mixed cohort of older adults with and without T2DM and assessed factors that mediated the relationship between T2DM and falls. In Part Two intriguing and potentially interfering factors in gait, balance and fall risk assessments were elucidated.

Part One: Fall risk factors

Chapter 2 showed that the fall incidence among T2DM was nearly twice that of controls (Answer Research Question 1a). Older adults with T2DM were found to have more than a two-fold higher risk for experiencing multiple falls or at least one injurious fall compared to older adults without T2DM (Answer Research Question 1a). Apart from T2DM, univariate risk factors for falling among a mixed cohort of older adults with and without T2DM can be summarized as increasing age, using walking aids, increasing number of medications, urinary incontinence, fear of falling, previous falls, lower grip strength, poor gait and balance performance and cognitive decrements (Answer Research Question 1b). A higher vibration perception threshold and lower CDT score were borderline significant. All these risk factors, except for urinary incontinence, appeared significantly worse in older adults with T2DM compared to controls (Answer Research Question 1c).

Beyond identifying individual risk factors, it is important to understand the underlying mechanisms that are responsible for cause-effect relationships. Therefore, we applied mediational analyses in our prospective study. Explanatory variables that mediated (reduced) the relationship between T2DM and falls the most were the increased number of medications, a poor gait performance and a reduced cognitive functioning (Answer Research Question 1d). As illustrated in Figure 6.1, a mediational model hypothesizes that the independent variable (here T2DM) influences the mediator variable (here number of medications, gait and cognition), which in turn influences the dependent variable (here falls). The relationship between the independent and dependent variable is then no longer significant. Thus, the mediators serve to clarify the nature of the relationship between the independent and dependent variables. Multivariate logistic regression considering all covariates that reduced the T2DM/falls relationship, retained T2DM and poor balance as independent risk factors for falling among older adults.

In this experiment, a substantial proportion of the relationship between diabetes and future falls could be explained by more medication intake, slowed walking speed and reduced cognitive performance. Previous research and our own results have clearly demonstrated that older adults with T2DM take a higher number of medications

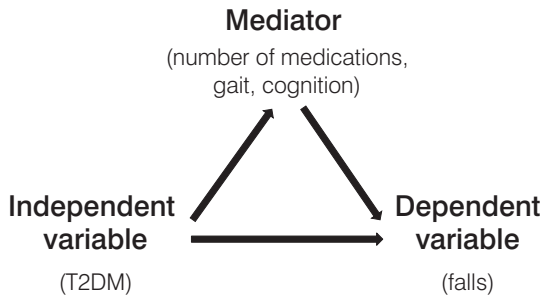

Figure 6.1 Statistical mediatonal model

(even when diabetic agents are ignored), show greater gait alterations and cognitive decrements. As number of medications [1], poor walking [2] and poor cognitive performance [3] have previously been associated with an increased fall risk in healthy older adults, it might not be surprising that these variables mediate the relationship between diabetes and the faller status. Based on the findings of this study, it is recommended that these mediators should be addressed in assessments and preventive strategies among older adults with T2DM.

Part Two: Intriguing interfering factors for assessments

The role of diabetic peripheral neuropathy in gait and balance performance and in fall risk is very controversial. *Chapter 3* investigated peripheral nerve function by measuring vibration perception threshold in both older adults with and without T2DM. Based on this outcome participants were categorized as T2DM with peripheral neuropathy, T2DM without peripheral neuropathy, no-T2DM with peripheral neuropathy and no-T2DM without peripheral neuropathy. Not only diabetic subjects with peripheral nerve dysfunction ("diabetic neuropathy") but also non-diabetic subjects with peripheral nerve dysfunction ("idiopathic neuropathy") showed greater sways during quiet standing assessments compared to their peers without peripheral neuropathy. It can thus be concluded that peripheral neuropathy (based on an indicative measurement) interferes with postural control (quiet standing performance) (Answer Research Question 2a). Furthermore, these "neuropathic" subjects had a higher prospective fall incidence (Answer Research Question 2a).

In the absence of diabetes, peripheral neuropathy is generally not considered as a routine entity in daily geriatric clinical practice or in mobility-related research. This study found that the presence of peripheral neuropathy, irrespective of its cause, interferes with postural control. These results support the idea that idiopathic neuropathy is a widely underestimated problem in older people. The implementation of a simple screening for indication of peripheral neuropathy (such as determining

the vibration perception threshold) in fall risk assessments among older adults is therefore highly recommended (Answer Research Question 2b).

Chapter 4 demonstrated that gait was affected in T2DM (Answer Research Question 3a) but this was not majorly based on the well-known diabetic complication, peripheral neuropathy (Answer Research Question 3b). However, reduced cognitive function, an often unrecognized and denied diabetes-related complication, significantly worsened gait in older adults with T2DM (Answer Research Question 4a). Dual task conditions resulted in altered gait patterns among all participants (Answer Research Question 4b). The type of dual task mattered in older adults with T2DM but not in healthy controls (Answer Research Question 4c).

The altered gait pattern of older adults with T2DM can be seen as a clinical manifestation of the disease. However, it might also be a well-considered choice of the patient to adopt a compensatory strategy for interfering comorbidities such as reduced sensory information. In our study, no significant differences in gait parameters between diabetes participants with and without neuropathy could be noticed. However, a trend of slower stride velocity for diabetic participants with peripheral neuropathy compared to without could be noticed. Reduced cognitive performance (based on a simple clinical categorization) clearly affected gait among older adults with T2DM, irrespective of peripheral neuropathy. There is some evidence that peripheral and central nerve damage partly go hand in hand [4-6], which complicates their relation with gait. Further research in larger samples is needed to understand these potential interrelationships and their impact on gait. From this study could be concluded that cognitive screenings and dual task conditions should be implemented in gait analyses and fall risk assessments, especially in older adults suffering from T2DM.

In contrast to the gait study *(Chapter 4)*, the indication of peripheral neuropathy, whether associated with diabetes or not, clearly interfered with postural control and fall incidence *(Chapter 3)*. This discrepancy might be explained by several factors. At first, the different categorization criteria in both studies might have led to different results. In the gait study *(Chapter 4)* diabetes participants were classified as having peripheral neuropathy based on a minimum of two positive criteria: diagnosis by general practitioner, Vibration Perception Threshold score of ≥ 25V, and/or Diabetic Neuropathy Symptom score of ≥ 1/4. Only subjects with an intact vibratory perception (< 25V) were allocated to the control (no T2DM) group. On the contrary, the postural control study *(Chapter 3)* considered an additional fourth group, which included subjects without T2DM but with a hampered Vibration Perception Threshold (≥ 25V). Classification was based on one clinical measure, i.e. Vibration Perception Threshold. Therefore, this study mainly focussed on large fiber dysfunction whereas in the gait study *(Chapter 4)* also subjects with small fiber dysfunctions might have been

included. Postural control analysis is intrinsically more focused on the contribution of proprioception (and somatosensation in general) to the given attribute than this is the case for analysis of gait performance. As explained in the General Introduction *(Chapter 1)* somatosensory (mainly proprioceptive) feedback accounts for 70% of the input for accurate postural control [7-9]. Furthermore, it should be noticed that the sample size (N=101) of the gait study *(Chapter 4)* was smaller than the sample size (N=195) of the postural control study *(Chapter 3)*. Still, a trend for adverse effects of peripheral neuropathy on gait could be seen in *Chapter 4*. Future research is needed to elucidate the effects of (different types of) peripheral nerve dysfunction on gait and balance in older adults with and without T2DM.

Previous clinical research taught us that differing opinions concerning the impact of (sub)optimal footwear on walking (dis)abilities and safety feelings exist among older adults. Although generally accepted as an extrinsic fall risk factor, a lot of studies pay little or no attention to the type of footwear during gait or balance assessments as such or as part of fall risk assessments. However, classifications and predictions are often based on marginal differences within the frame of gait velocity cut-off scores as mentioned earlier. From *Chapter 5* it could be concluded that the type of footwear indeed significantly influences gait performance (Answer Research Question 5a). From the four types of footwear (barefoot, slippers, high heels and a standard shoe), gait patterns were most altered when wearing no shoes (barefoot walking). The standard shoe (a well-fitting shoe with laces, a low and wide heel, firm heel collar and a grooved, moderately hard sole) yielded the most fluent gait pattern characterized by a faster walking speed, increased cadence and stride length and decreased stride time and stride length variability (Answer Research Question 5a). Footwear effects were similar in motor (carrying a tray with a cup of pearls) or cognitive (backward counting) dual task walking compared to walking as a single task (Answer Research Question 5c). The cognitive dual task resulted in a significantly worse gait pattern compared to the motor dual task or the single task (Answer Research Question 5b). No significant differences in gait parameters between single task walking and walking while performing the motor dual task could be retained (Answer Research Question 5b). The self-selected gait speed even slightly increased when carrying a tray filled with pearls compared to walking as a single task (Answer Research Question 5b).

The effects of the motor and cognitive dual tasks on gait performance might be explained by forward movement of the center of gravity induced by carrying the tray with pearls (increasing gait speed) and the age-related structural changes of the brain (decreasing gait speed) [10] respectively. Gait speed is a crucial determinative and prognostic feature for development of disabilities and general health problems, which highlights the importance of (accurate) gait (speed) analysis. Researchers often omit descriptions of footwear used during mobility analyses whereas they

should describe more accurately the used shoes because (i) different types of shoes (or no shoes) may substantially influence gait performance, and (ii) risk profiles use cut-off levels for gait variables and are based on small differences, which may render abusive categorization of older adults as (not) being at risk. As changes in gait could be masked when different types of shoes are used in consecutive measurements it is advisable to monitor the used type during assessment and re-assessment. With respect to the most stable, fluent and less risky gait, a standard shoe with a low and wide heel and a grooved, moderately hard sole is recommended in research as well as in daily use among healthy older women.

It should, however, be emphasized that this study considered a different research population (healthy older women) than the previous studies from *Chapter 2, 3* and *4* and that these specific results can therefore not be generalized to male or female older adults with T2DM. Nevertheless, the generalizability of the concept, i.e. the role of shoes in assessing and interpreting gait assessment, may be seen as of common importance.

Conclusions

Older adults:

- Poor balance and T2DM are both independent fall risk factors
- Peripheral neuropathy affects static postural control performance
- The type of shoe influences gait patterns
- Older women should be discouraged to walk barefoot

Older adults with T2DM:

- The relationship between T2DM and falling can partly be explained by (i) number of medications, (ii) cognitive decrements and (iii) poor walking performance
- Peripheral neuropathy affects static postural control performance
- Gait alterations are more manifest if a semantic cognitive dual task is added to single walking
- Impaired cognitive functions further affect gait patterns

CLINICAL IMPLICATIONS

The overall objective of scientific research is not only to contribute to unravel unexplained observations but also and perhaps even the ultimate aim for society; to implement the findings into clinical practice. The clinical implications of this doctoral thesis will be outlined below.

Suggestions for fall risk assessment

More than 400 potential risk factors for falling have been identified in the past [11] and albeit that in this context the saying "the more (investigated), the better" probably holds true, this is not a realistic message for the physiotherapist in everyday clinical practice. Still, since the risk of falling has proven to linearly increase with the number of risk factors [12], fall risk assessments should be multifactorial. In an attempt to stimulate the clinician in tackling the difficult clinical challenge of fall prevention, a flowchart for fall risk detection in older adults will be introduced at the end of this section.

Older adults

About ten years ago, Lord *et al.* developed the Physiological Profile Assessment (PPA) [13]. The PPA consists of simple tests of vision, vestibular function, peripheral sensation, muscle strength, reaction time and balance [13]. *Chapter 2* of this doctoral thesis confirmed that balance is an independent risk factor for falling. As balance relies on visual, vestibular and somatosensory systems, we completely agree with the assessments included in the PPA. Furthermore, the tests of the PPA have proven to be valid and reliable and can be administered quickly and with portable equipment [13]. However, another independent risk factor was identified in *Chapter 2*: T2DM. Also, previous falls and fear of falling were strong univariate risk factors for falling *(Chapter 2)*, which is in line with previous research. From *Chapter 3*, it could be concluded that the integration of a simple screening for peripheral neuropathy (like biothesiometry) should not be limited to older adults with T2DM but could also be useful to measure in the so-called "healthy" older adults as consequences (impaired balance) were similar in both populations. Apart from that, the finding that a substantial proportion of "healthy" non-diabetic controls appeared to have hampered vibration sense, illustrates that peripheral nerve dysfunction is not necessarily a complication of the older adult with T2DM. The significantly older age of non-diabetic participants with peripheral neuropathy compared to non-diabetic participants without peripheral neuropathy confirmed the age-related trend of idiopathic neuropathies, which has previously been proven by Verghese *et al.* [14]. We therefore suggest to minimally

administer the following items in fall risk assessments among the aged population: balance, vibration perception, T2DM, previous falls and fear of falling.

Older adults with Type 2 Diabetes Mellitus

All physical (muscle strength, gait, balance) and cognitive measures that were identified as risk factors for falling in our prospective study, indeed appeared to be significantly worse in older adults with T2DM compared to controls *(Chapter 2)*. Walking slower and with shorter strides, performing worse on cognitive tests and taking more medications substantially mediated the relationship between T2DM and faller status *(Chapter 2)*.

Older adults with T2DM had an increased vibration perception threshold compared to controls but this parameter was only borderline significantly associated with an increased fall risk among older adults with and without T2DM *(Chapter 2)*. *Chapter 4* revealed that gait performance in T2DM was further affected by reduced cognitive function but not by peripheral neuropathy. To the contrary, a hampered vibration perception significantly interfered with postural control in older adults with and without T2DM *(Chapter 3)*.

For older adults with T2DM we therefore suggest to extend "regular" fall risk assessment by analyzing gait and cognitive performance and recording the number of medications. Although the role of peripheral neuropathy in fall risk remains unclear, we nevertheless suggest to measure peripheral nerve function if possible (e.g. by a simple screening instrument like the Bio-Thesiometer®).

Flowchart fall risk detection

Inspired by the suggestions of Ganz *et al.* [15] and the results of this doctoral thesis, we developed a flowchart for fall risk detection in older adults (Figure 6.2). We thereby hope to provide the clinician with an easy tool to narrow the gap between the numerous existing guidelines and everyday clinical practice and take the first step to fall preventive initiatives and strategies.

We suggest to start risk detection by asking two simple questions: (i) "Have you had any falls in the past year?" and (ii) "Do you suffer from T2DM?".

If both questions are answered negatively, a short screening of gait and balance should be performed. An impaired mobility and balance can be objectified by the Timed Up & Go (TUG) Test. If the older individual is able to fluently complete this test in less than 14 seconds and no other pre-existent fall inducing pathologies are present, an increased fall risk based on physical performance might be ruled out. If more than 14 seconds are

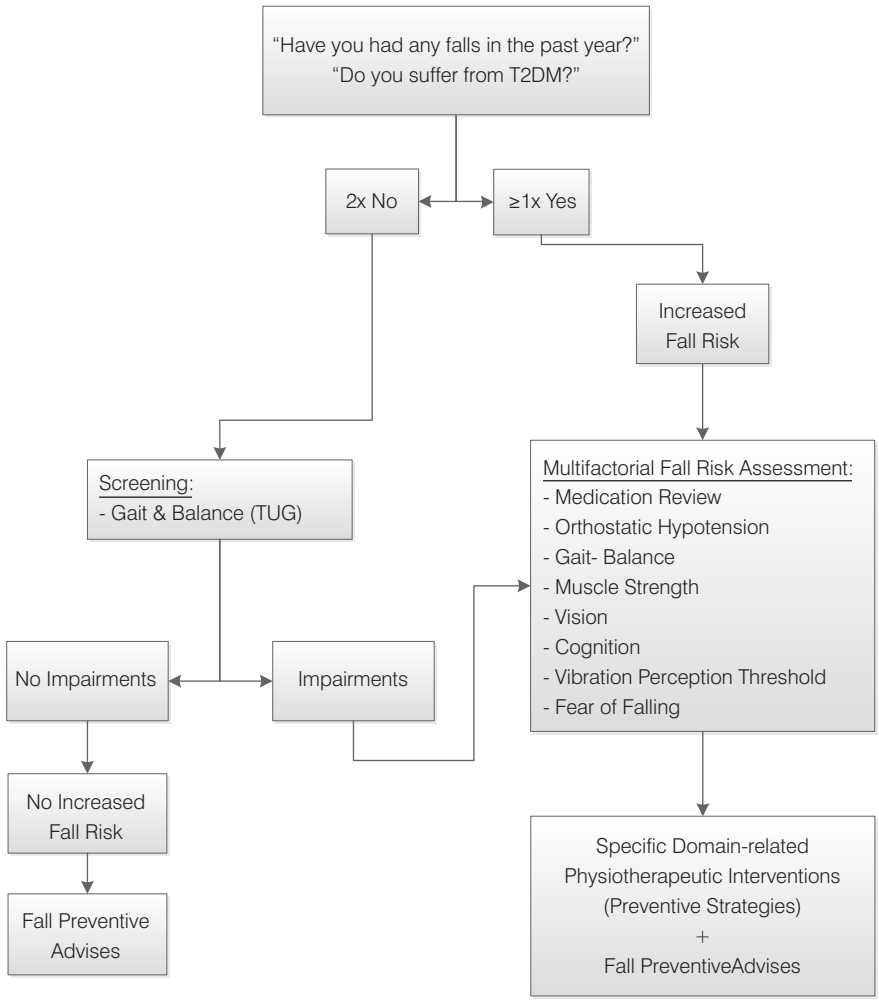

Figure 6.2 Suggested flowchart for fall risk detection in older adults

needed to complete the test or an irregular/unstable gait pattern can be observed or the older individual cannot execute this test due to cognitive or physical reasons, a multifactorial fall risk assessment is recommended. This screening is in line with the practical guidelines for fall prevention in community-dwelling older adults developed by the "Expertisecentrum Val- en fractuurpreventie Vlaanderen (EVV)" [16].

An older individual who experienced one or more previous falls and/or suffers from T2DM, needs a more extended multifactorial fall risk assessment including medication reviews, evaluation of orthostatic hypotension and testing of gait, balance, muscle strength, vision, cognition, vibration perception threshold and fear of falling. Assessing these fall risk factors will supply clinicians with specific treatment goals. As mentioned earlier, medications can increase fall risk when a large number (≥5) or specific types of medications (i.e. psychotropic medications and antihypertensive agents [17]) are used. In these cases, reconsideration of medication schemes in consultation with the general practitioner is recommended. The prevalence of orthostatic hypotension is significantly higher in older adults with compared to older adults without T2DM and orthostatic complaints have been associated with an increased fall risk [18]. We therefore recommend to evaluate orthostatic hypotension conform the instructions included in the Appendix. Besides the TUG Test, gait can be assessed by the Tinetti-Test (Gait Evaluation) or by introducing dual tasks while walking ("Stops Walking When Talking Test") [19]. Balance can be evaluated by the Tinetti-Test (Balance Evaluation), Four Test Balance Scale or Functional Reach Test whereas the Timed Chair Stand-Test or measuring grip strength can be used for assessing muscle strength. Visual acuity can be measured using a letter chart. The assessment of other visual abilities (contrast sensitivity, depth perception, …) are described elsewhere [20]. The MMSE and CDT can be used to obtain an idea of general cognitive performance. However, as the load in former testing is carried by the CDT and dual tasking is a crucial issue the Montreal Cognitive Assessment (MoCa) might be a good alternative since this test focuses even more on executive functioning, which is suggested to play a key role in gait and dual tasking. Furthermore, T2DM has repeatedly been associated with impaired executive functioning [21-23]. The MoCa is available in Dutch and also takes into account the educational level. Before measuring vibration perception (e.g. using the Bio-Thesiometer®), footwear and feet should be inspected. In our studies major neurological or musculoskeletal disorders that may have interfered on gait in a predictable way (such as amputations or major ulcers), were excluded. Podiatry assessment (foot deformations, ulcers, ingrown nails, …) and treatment is however important in fall risk assessment of older adults with T2DM. Fear of falling and related activity restriction should be recorded. The older adult can immediately be provided by advises concerning proper footwear and fear of falling. As explained earlier in this doctoral thesis clinicians are strongly advised to carefully inspect footwear in view of accurate mobility assessment and reassessment.

The clinical tests that were proposed for fall risk assessment (TUG Test, evaluation of orthostatic hypotension, Tinetti Test, Four Test Balance Scale, Functional Reach Test, Timed Chair Stand-Test, MMSE, CDT, MoCa) are generally in accordance with the suggested tests of the EVV [16], except for the cognitive tests. In our studies gait and

balance were assessed by means of expensive electronic devices such as the GAITRite® System and AMTI® force platform. These instruments are preferable for research as they provide more objective and very detailed data which are essential for understanding and determining the impact of diseases or challenging conditions on physical performance. However, they are not suitable for clinical practice. We therefore proposed tests that are relatively inexpensive, not time-consuming and easy to administer and interpret for daily practice. The tests with description and interpretation are appended at the end of this doctoral thesis.
Ideally, the two screening questions at the top of this flowchart are embedded in an initial anamnesis. In the case of previous fall(s), further details should be obtained concerning the circumstances of the fall(s). This may reveal important information for future interventions and preventive advises. Also, urinary incontinence should be asked. Activities of daily living and fear of falling are not included in the flowchart by means of the existing B-ADL, I-ADL and FES-(I) instruments since some of these questions are not applicable for older adults living in residential care settings and our aim was to develop a flowchart that can be used for all older adults. Nevertheless, these items can sharpen the picture of the older individual and his/her behavior. It is therefore advised to obtain this information in the anamnesis or whenever the opportunity presents itself.

In view of specific and individual rehabilitation/preventive exercises, it is recommended that physiotherapists evaluate fall risk factors such as gait, balance, muscle strength and fear of falling. While other fall risk factors may require other areas of competence, other health care workers may become essential in a congruent and complementary fall risk assessment. The multifactorial nature of fall risk detection and prevention demands an inter- and transdisciplinary approach, especially in cases of T2DM where multiple bodily systems and functions are involved. However, one should realize that this ideal theoretical framework is not always achieved due to various reasons. We therefore aimed to select clinical tests that are valid and relevant but nevertheless quite simple to administer for a variety of health care workers. If other disciplines cannot be involved in the multifactorial fall risk assessment, a short training period should be sufficient for the physiotherapist to adequately administer all suggested tests and gain information that outreaches his/her familiar domains but may reveal important insights.

Nomenclature for Type 2 Diabetes Mellitus?

About 800 000 people in Belgium suffer from T2DM [24]. It is likely that global trends will be followed also in Belgium and that this number will only increase in the future. As stated in the general introduction of this doctoral thesis, the Belgian RIZIV-nomenclature [25] for physiotherapists is not specifically suitable to older adults suffering from T2DM due to its rather generic character, thereby being less sensitive for the specific disease-related challenges. It renders undoubtedly generic potential but this may nevertheless be insufficient for the given population.

This doctoral thesis clearly demonstrated that older adults with T2DM have a significantly increased fall incidence compared to older adults without T2DM *(Chapter 2)*. Also, the hypothesized increased fall risk of older adults with T2DM [26-30] was confirmed and mediating factors were identified *(Chapter 2)*. Taking a high number of medications *(Chapter 2)*, poor gait performance *(Chapter 2 and 4)*, poor balance *(Chapter 2 and 3)*, impaired vibration perception *(Chapter 2 and 3)* and poor cognitive performance *(Chapter 2 and 4)* were associated with T2DM and with an increased fall risk.

Because of its major eye-catching comorbidities, the increased fall risk of older adults with T2DM is perhaps considered of minor attention demanding importance. However, based on (i) the epidemic challenge, (ii) the multiple drastic fall consequences, and (iii) the results of this doctoral thesis, we think that for this matter T2DM perhaps deserves more specific attention in treatment strategies and as a consequence in the Belgian nomenclature for physiotherapists. By doing so an increasing amount of correct fall risk profiled older adults may be retrieved rendering the potential of specific preventive care to tackle growing costs when injuries have to be treated or residential care becomes necessary. Further research is needed to prove this hypothesis and to determine clinical cut-points for number of medications, vibration perception threshold, and performance of gait, balance and cognition. Suggesting specific adaptations to the nomenclature lies beyond the scope of this doctoral thesis. Whether T2DM should be added to the list of E-pathologies or whether the criteria for meeting F-pathology should be adapted based on the aforementioned risk factor for falls, can however be considered in the future.

STRENGTHS AND LIMITATIONS

The major aim of this doctoral thesis was to gain better insights into the hypothesized increased risk of falling among older adults suffering from T2DM *(Chapter 2)*. Also, we investigated some often overlooked though potentially interfering aspects in clinical gait, balance and fall risk assessments *(Chapter 3, 4, 5)*.

To our knowledge, we were the first to conduct an extensive fall risk study among older adults, focusing on T2DM and using mediational models *(Chapter 2)*. In addition to the prospective design of this study, this might be considered the main strength of this doctoral thesis. Previous studies considering fall risk factors in T2DM included only older adults with T2DM without a non-diabetic control group [30-33], only women [28,29,34], only older adults living in residential settings [35], only older adults living in the community [27-31,34], or had no prospective design [27,32,33].

We have tried to match participants with and without T2DM for age and sex. If matching was lost due to classification of the participants into different categories, corrections were applied in statistical analyses to avoid potential confounding bias *(Chapter 3)*. We only imposed an inclusion criterion for minimum age (60 years old) in *Chapter 2, 3 and 4*, which yielded (very) wide age ranges (up to 94 years old). This factor complicated age-matching during the recruitment process but resulted in a representative sample of older adults as such, allowing extrapolation of the results to the broader population. The unequal distribution of participants living in a residential care setting versus in the community (a greater proportion of T2DM lived in residential care settings compared to controls), can be seen as limitation. However, this is a realistic reflection of dwelling in the aged, which favors extrapolation.

Although a lot of scientific research has focused on T2DM in relation to peripheral neuropathy, we were surprised to notice that nearly all designs comprised only two or three groups, lacking a control group with peripheral neuropathy. To our opinion this is a remarkable observation as one could imagine that this lacking group is essential when aiming to assess whether either T2DM or peripheral neuropathy causes alterations in physical performance. The addition of a fourth group in our postural control study *(Chapter 3)*, can therefore be seen as a strength.

Another strength of the research in this doctoral thesis is that simple screening measures that were used, appeared to be of clinical importance. As such, performance of the MMSE and CDT, two widespread and well-known cognitive screening instruments, was associated with gait *(Chapter 4)* and fall risk *(Chapter 2)*. Similarly, using a portable Bio-Thesiometer® could distinguish balance performance

and fall incidence among older adults with or without T2DM *(Chapter 3)*. Furthermore, this outcome measure (vibration perception) was identified as univariate risk factor for falling, albeit that the significance was borderline *(Chapter 2)*. Finally, the type of footwear has proven to affect gait in healthy older women *(Chapter 5)*. This is a very easy adjustable though often ignored item for both researchers and health care workers to pay attention to. The above described examinations are not only of clinical importance but they are also relatively inexpensive, easy to administer, not time-consuming and therefore applicable in everyday practice.

At the same time, the simple screenings of peripheral and central nervous function (vibration perception and MMSE/CDT respectively) are limitative in what they (do not) measure. As illustrated by Figure 1.6, the peripheral nervous systems comprises a spectrum of fiber types and functions. By determining vibration perception threshold only sensory nerves with large, myelinated fibers were measured. We did not measure any small fibers or motor nerves. By measuring vibration, however, the same large (myelinated) sensory fibers that are responsible for proprioception (position sense) are measured. This is an important remark because postural control mainly depends on the somatosensory system and particularly on the proprioceptive input, as explained in the introduction. Similarly, the MMSE is a measure for global cognitive functioning and the CDT for visuospatial and executive functioning and attention. However, a lot of other cognitive domains could have been assessed by available screening instruments. Also educational level should have been registered as this might influence cognitive test scores. Furthermore, neuropsychological tests are unable to provide specific information about the neural structures responsible for any dysfunction identified [36]. In an attempt to get better insights in the type of nerves and cognitive domains that are affected, more extensive screenings should have been applied. However, Nilsson *et al.* concluded that cognitive deficits associated with diabetes in very old age may be detected with the MMSE [37]. Furthermore, as mentioned in the previous paragraph, the simple screenings that were used in this doctoral thesis (VPT, MMSE, CDT) appeared to have enough discriminative value for our purposes.

Although the visual system is considered to be a less important input for the postural control system than the vestibular and somatosensory (proprioceptive) system, the major limitation of the research in this doctoral thesis probably lies in the lack of screenings of the visual abilities. Some studies failed to find associations between visual impairments and falls [15,27,35] but other studies clearly related visual deficits [20,38], especially poor visual acuity [13,39], decreased depth perception [20,40,41] and lessened contrast sensitivity [20,40] to falls. About 30% of people with diabetes suffers from retinopathy [42,43]. In our postural control study *(Chapter 3)*, we have

tried to imitate visual dysfunction by asking participants to close their eyes during the different quiet standing conditions. The removal of vision significantly hampered postural control. Nevertheless, we have to admit that visual screenings should have been applied in order to better understand the impact on the postural control system.

Another important covariate that was not implemented in our studies is the duration of the (T2DM) disease or the year wherein T2DM was diagnosed. Per definition, chronic complications progressively develop over time. A longer disease duration might therefore interfere in clinical outcomes. Due to the large proportion of missing values (particularly of participants living in residential settings), it was statistically unwarranted to include this parameter in our analyses.

A final limitation lies in the recruitment method. Participants were recruited through online advertising, flyer distribution, by word of mouth and from the Endocrinology Clinic at the Ghent University Hospital. This may have led to a potential volunteer bias related to the fact that only those participants who were actually willing to participate, entered the studies. Also, there may have been an under-reporting of falls due to recall bias. Poorer recall of falls is hypothesized to more likely occur in cases of less severe (non-injurious) falls and among older adults with cognitive impairments. However, these hazards are hard to avoid and monthly fall records are recommended by the ProFaNE [44].

FUTURE RESEARCH DIRECTIONS

Although during the last decades an incredible amount of studies has been accomplished in the area of fall risk detection and prevention strategies among healthy older individuals, further research is needed in older adults suffering from T2DM. The mediating factors of the diabetes/falls relationship should be confirmed and extra attention should be paid to visual functioning. Additionally, as suggested earlier, future research should be elaborated to determine clinical cut-points for these mediating factors (i.e. number of medications, gait and cognition). This would allow researchers to formulate specific and applicable proposals for adjusting the Belgian nomenclature for physiotherapists, thereby making it more convenient for older adults with T2DM.

Our findings concerning the role of peripheral nerve dysfunction were somewhat inconsistent *(Chapter 3 vs. Chapter 4)* and inconclusive *(Chapter 2)*. This might be due to fact that only one objective measure for peripheral neuropathy was used in our trials. Therefore, it would be of interest to further investigate the potential relationship between peripheral neuropathy and gait, balance and falls. An extensive assessment of peripheral neuropathy, preferably with the inclusion of specialized tools (electrodiagnostic methods) is suggested in order to differentiate between different types of peripheral nerve dysfunctions. Aiming to (cor)relate specific peripheral nerve dysfunctions to functional outcomes (e.g. gait, balance, falls) would be of clinical importance. Taking into account the feasibility of measuring vibration perception, it would also be of interest to validate this test to more complex nerve conduction analysis on a large scale. Some researchers hypothesized that peripheral and central nerve damage may partly go hand in hand. Unraveling this putative interrelationship, although potentially challenging, would be very interesting. The potential impact of limited joint mobility in T2DM on gait, balance and/or falls has never been investigated so far and could form another intriguing research focus.

Further, it would be of interest to find out more about the cognitive decrements in older adults with T2DM and their impact on physical abilities. Discovering the affected domains and functions is crucial for early pharmacological and rehabilitation regimens. In a next step, the effect of different (specific) intervention strategies on physical and cognitive performance should be evaluated. Again, a four-group design could be applied; (i) no intervention, (ii) physical training, (iii) cognitive training, (iv) physical and cognitive training. Similar intervention studies have been suggested [45] previously in healthy older adults. However, it might be the case that older adults with T2DM benefit more from other modalities (e.g. higher intensities) to compensate for the increased physical and cognitive deprivation due to diabetes-related complications.

As exemplified in the General Introduction *(Chapter 1)*, certain types of medications have been proven to increase fall risk among older adults. In older adults with T2DM renal function might be affected (nephropathy), which in turn may influence the effects of medications in these individuals. It would therefore be of great interest to assess the effects of certain groups of medications on fall risk among older adults with T2DM and compare the results to those among older adults without T2DM. Renal function should then be incorporated in the assessments since it might be a potential mediating factor in the medication/faller status.

FINAL CONCLUSIONS

This doctoral thesis demonstrated that older adults with T2DM have a two-fold increased fall incidence and fall risk compared to older adults without T2DM. T2DM, increased age, walking aids, higher number of medications, urinary incontinence, fear of falling, previous falls, increased vibration perception thresholds, lower grip strength, poorer gait, balance and cognitive performance are risk factors for falling in older people. Clinicians must be aware that all the aforementioned risk factors, except for urinary incontinence, are significantly worse in older adults with T2DM compared to controls. Although we cannot conclude whether T2DM itself on the one hand or T2DM-related complications on the other hand are responsible for the increased fall rates in this older subpopulation, it is likely that the same major fall risk factors as found in older adults without T2DM (i.e. gait and balance impairments) are affected, albeit to a greater extent.

Some clinical implications can be derived from our findings. At first, we wish to issue some points of interest regarding fall risk assessment. Our results justify the implementation of peripheral neuropathy assessment in any balance or fall risk assessment. In everyday clinical practice the use of a simple screening instrument such as a biothesiometer might be sufficient to give an indication of peripheral nerve dysfunction, prompting to be cautious in terms of impaired mobility and increased fall risk. Although large amounts of evidence suggest that older adults with dementia are at increased fall risk and cognitive performance is related to gait and falls, cognitive screenings are generally not a primarily part of fall risk profiles. This doctoral thesis showed that impaired cognitive performance was a risk factor for falling and further affected gait in older adults with T2DM. Furthermore, the diabetic participants in our studies had poorer cognitive performance compared to controls. Cognitive deterioration has previously been shown to be a chronic complication of T2DM. We therefore suggest to include cognitive screening(s) in fall risk assessment, especially in older adults suffering from T2DM. A final recommendation for researchers and health care workers is to pay attention to the type of shoes the older adult wears during physical assessments and in daily life. Poor footwear (slippers, high heels or walking barefoot) causes gait alterations and older adults should be advised to wear a good fitting shoe with a low and wide heel and a thin, grooved and moderately hard sole.

Besides these clinical implications, adaptation of the Belgian nomenclature for physiotherapists for the benefit of older adults with T2DM might be useful. Further research is however needed to formulate specific suggestions for adaptation.

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Chapter 7

Nederlandstalige samenvatting

7

Volgens de Verenigde Naties zal rond 2050 het aantal ouderen in de wereld het aantal kinderen voor het eerst in de geschiedenis overstijgen. In de ontwikkelde landen is deze wijziging van de bevolkingssamenstelling nu reeds aan de gang. Hoewel de levenskwaliteit van ouderen over het algemeen aanzienlijk is verbeterd, neemt met de leeftijd ook het aantal ouderdomsgerelateerde ziektes en verschijnselen toe.

Vallen is één van die verschijnselen en wordt, gezien de impact op diverse domeinen, terecht bestempeld als een groot geriatrisch probleem of een zogenaamde "geriatric giant". Deze problematiek wordt meestal veroorzaakt door een combinatie van multipele omgevings- en/of persoonsgebonden factoren. Een dergelijke val kan dramatische gevolgen hebben voor het oudere individu, variërend van lichamelijke letsels (schaafwonden, kneuzingen, fracturen, hoofdletsels, …) tot psychosociale (depressie, valvrees, vermijdingsgedrag, sociale isolatie, …) en socio-economische (immobilisatie, medische kosten, ziekenhuisopname, vroegtijdige institutionalisering, …) consequenties. Ernstige valpartijen kunnen leiden tot blijvende invaliditeit of zelfs overlijden. Ondanks de verbluffende feiten en cijfers en de veelheid aan wetenschappelijk bewijsmateriaal, wordt het belang van valpreventie nog al te vaak onderschat. In het licht van de preventieve mogelijkheden die vandaag zijn aangetoond en redelijk toegankelijk zijn, wordt er overeenkomstig nog steeds ontoereikend aandacht aan gegeven door zowel zorgverstrekkers als de ouderen zelf. Zo is het potentieel van oefenen en oefentherapie als één van de meest afdoende strategieën waarbij de kinesitherapeut een cruciale rol kan vervullen, vandaag nog onvoldoende geëxploiteerd. Sensibilisering van alle betrokkenen is vandaag echter op kruissnelheid aan het komen, waardoor promotie en verfijning van de kennis en inzichten essentieel is geworden.

Hoewel elke oudere moet worden gesensibiliseerd om door eigen initiatief (aandacht, voorzorg en gedrag) verantwoordelijkheid te nemen voor valpreventie, moeten structurele en georkestreerde preventiemaatregelen minimaal worden voorzien voor de ouderen met een verhoogd valrisico. Factoren die bijdragen aan een dergelijk verhoogd risicoprofiel zijn de aanwezigheid van een valhistoriek, schrik om te vallen, toenemende leeftijd, fysieke zwakte ("prefraile" en "fraile" ouderen), alsook de aanwezigheid van bepaalde aandoeningen zoals onder andere een beroerte, de Ziekte van Parkinson en dementie. Bij zwakke ouderen en ouderen met specifieke ziektebeelden neemt de kans op vallen meestal toe door de sterk valbevorderende aanwezigheid van spierzwakte of stoornissen in gang en/of evenwicht. In de regel hebben deze mensen gestructureerde ondersteuning nodig om het vallen het hoofd te bieden.

Hoewel gangbaar minder courant als risicofactor opgenomen in diverse overzichten, wordt Diabetes Mellitus type 2 (T2DM) ook beschouwd als een aandoening waarbij het risico op vallen is verhoogd. Deze geringe focus is mogelijk toe te schrijven aan

het feit dat andere complicaties bij deze aandoening meer de aandacht trekken of als ernstiger worden beschouwd. Feit is echter ook dat er nog veel onduidelijkheden heersen betreffende de onderliggende mechanismen van het verhoogd valrisico binnen deze specifieke deelpopulatie. Dit maakt dat vandaag zowel generiek als specifiek naar de valproblematiek in de kinesitherapeutische regelgeving geen gewag wordt gemaakt van deze aandoening en haar specifieke karakteristieken.

De criteria voor valpreventie tegen regulier terugbetalingstarief voorzien door de Belgische nomenclatuur voor kinesitherapie van het Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV) zijn vrij generiek en als dusdanig gericht naar de oudere populatie zonder specifieke risicobeïnvloedende morbiditeiten. De afwezigheid van morbiditeiten en hun rol naar het vallen wordt mogelijk voor een aantal van hen opgevangen door hun aanwezigheid in andere secties van de nomenclatuur (bv. beroerte en Ziekte van Parkinson in E-nomenclatuur). Voor de epidemiologisch steeds wilder om zich heen grijpende aandoening T2DM is dit vandaag echter nog niet het geval. Op zich, kan dit worden beschouwd als een confirmatie van het niet (er)kennen van bovenstaand probleem.

Met dit doctoraal proefschrift werd de aandacht gevestigd op de valproblematiek bij ouderen met T2DM teneinde betere inzichten te verschaffen in de mechanismen die ten grondslag liggen aan deze perfide relatie. Vooreerst werden daartoe de valrisicofactoren bij ouderen zonder en met T2DM geïdentificeerd en onderzocht (Deel Een). Verder werden een aantal potentieel interfererende doch systematisch onvoldoende gewaardeerde factoren in screenings van gang, evenwicht en vallen, op gecontroleerde wijze onderzocht (Deel Twee).

Deel Een omvat een prospectieve studie waarin een groep van 199 ouderen na het doorlopen van een uitgebreide testbatterij gedurende 1 jaar werd opgevolgd naar valincidenten *(Hoofdstuk 2)*. Iets meer dan de helft van deze ouderen hadden T2DM. Uit deze studie kon worden weerhouden dat ouderen die lijden aan T2DM bijna dubbel zo vaak vallen dan ouderen zonder T2DM. Opvallend was dat alle onderzochte parameters (met uitzondering van urinaire incontinentie) die werden geïdentificeerd als univariate risicofactoren voor vallen, significant slechter bleken te zijn bij de ouderen met T2DM in vergelijking met de ouderen zonder T2DM. Wanneer deze univariate risicofactoren afzonderlijk werden toegevoegd aan een T2DM/val-model, konden 3 factoren worden weerhouden die deze relatie (T2DM~vallen) “afzwakten” en dus beschouwd konden worden als verklarende factoren of onderliggende mechanismen van deze relatie. Het betrof een verhoogd medicatiegebruik en geringer performante gang en cognitie. Hieruit kon dus worden afgeleid dat bij ouderen met T2DM in het kader van valrisicodetectie systematisch nazicht van

medicijnen (met het oog op eventuele aanpassingen inzake gebruik of dosis van medicijnen die bijvoorbeeld niet meer noodzakelijk zijn) en onderzoek van gang en cognitie zinvol zijn. Uit multifactoriële analyses konden de aanwezigheid van T2DM op zich alsook een zwak evenwicht worden weerhouden als onafhankelijke risicofactoren voor vallen.

Gezien de demografische wijzigingen werd gedurende de afgelopen decennia terecht veel wetenschappelijk onderzoek verricht rond de valproblematiek in al zijn facetten. Heel wat intrisieke (persoonsgebonden) en extrinsieke (omgevingsgebonden) risicofactoren werden daarbij bepaald en tal van nuttige instrumenten werden daartoe ontwikkeld. Toch viel het op dat bepaalde weliswaar vaak aangehaalde risicofactoren systematisch over het hoofd worden gezien bij evaluatie, en dit zowel door onderzoekers als door clinici. Deel Twee trachtte daarom na te gaan of deze factoren al dan niet terecht minder aandacht krijgen.

In een eerste studie werd aandacht gegeven aan een mediërende dimensie van de somatosensoriek op het evenwicht van de oudere *(Hoofdstuk 3)*. Hiertoe werden proefpersonen op basis van een gekende cut-off voor vibratiezin ingedeeld in vier groepen: T2DM met perifere neuropathie, T2DM zonder perifere neuropathie, niet-T2DM met perifere neuropathie (een minder logische groep gezien het ontbreken van een manifeste pathologische factor) en niet-T2DM zonder neuropathie (waarbij men er vaak vanuit gaat dat hierin alle ouderen zonder T2DM zouden zitten). Niet alleen de groep T2DM met perifere neuropathie ("diabetische neuropathie"), maar ook de minder courant omschreven groep *niet*-T2DM met perifere neuropathie ("idiopathische neuropathie") vertoonde gelijkaardige, significant grotere afwijkingen tijdens statische evenwichtsanalyses in vergelijking met de respectieve groepen zonder perifere neuropathie. Hieruit kon bijgevolg worden afgeleid dat niet diabetes per se, maar wel het aanwezig zijn van perifere neuropathie cruciaal is voor evenwichtsprestaties. Bovendien hadden de groepen met perifere neuropathie een hogere prospectieve valincidentie. Het onderzoeken van perifere zenuwfuncties lijkt in deze context dus niet alleen zinvol bij ouderen met T2DM maar ook bij de "gezonde" ouderen (zonder T2DM).

De rol van diabetische perifere neuropathie op gang- en evenwichtsprestaties is zeer controversieel. Uit de studie in *Hoofdstuk 4* bleek dat niet de bekendste complicatie van T2DM (perifere neuropathie) maar wel één van de minst gekende complicaties, zijnde een verminderde cognitieve functie, het gangpatroon van ouderen met T2DM verder aantast. Stappen met een cognitieve dubbeltaak leidde tot significante veranderingen in het gangpatroon van alle ouderen waarbij het type cognitieve dubbeltaak niet van belang was bij ouderen zonder T2DM maar wel bij ouderen met

T2DM. Cognitieve deterioratie kan zijn weerslag hebben op het stappatroon van ouderen met T2DM en cognitieve screenings en/of dubbeltaak condities zouden dus deel moeten uitmaken van ganganalyses en onderzoeken in het kader van valrisico-detectie.

In een laatste studie werd de invloed van de extrinsieke risicofactor 'schoeisel' op het stappen onderzocht in een groep gezonde oudere vrouwen (*Hoofdstuk 5)*. Schoeisel wordt vaak als een compromitterende valrisicofactor gezien, maar globaal wordt hier -zowel in de kliniek als in het onderzoek- bijvoorbeeld bij screenings relatief weinig of geen aandacht aan gegeven. Het type schoeisel beïnvloedde echter overduidelijk het gangpatroon. Van de vier types 'schoeisel' (blootsvoets, pantoffels, schoenen met hakje en een standaardschoen) werd het gangpatroon het meest beïnvloed indien geen schoenen werden gedragen. Stappen met een standaard-schoen leverde het meest vloeiende en derhalve veiligste gangpatroon op, en dit zowel tijdens het stappen als enkeltaak, stappen met motorische dubbeltaak (een dienblad met een tas vol parels dragen) als stappen met cognitieve dubbeltaak (achterwaarts tellen). Onderzoekers moeten dus rekening houden met het type schoen dat proefpersonen dragen, te meer gezien sommige risicoprofielen cut-off waarden gebruiken die veelal zijn gebaseerd op minimale verschillen. Het al dan niet dragen van een bepaalde schoen zou er dus voor kunnen zorgen dat een oudere net boven of net onder zo'n waarde valt en aldus verkeerdelijk wordt gecategoriseerd. In deze context is voorzichtigheid ook geboden in het kader van herevaluaties. Zowel voor onderzoeksdoeleinden als voor dagelijks gebruik wordt zonder tegenindicatie een standaardschoen met lage en brede hiel en dunne, matig harde en gegroefde zool aanbevolen. Blootsvoets stappen, in andere wetenschappelijke studies reeds meermaals geassocieerd met een verhoogd valrisico, lijkt ook op basis van de resultaten uit deze studie te moeten worden afgeraden (aan oudere dames).

Conclusies

Oudere populatie:

- Een zwak evenwicht alsook de aanwezigheid van T2DM zijn beide onafhankelijke valrisicofactoren
- De aanwezigheid van perifere neuropathie tast statische evenwichtsprestaties aan
- Het type schoen beïnvloedt het gangpatroon
- Vrouwen moeten worden afgeraden om blootvoets te stappen

Oudere populatie met T2DM:

- Het aantal medicaties, alsook prestaties van cognitie en gang verklaren deels de relatie tussen T2DM en vallen
- De aanwezigheid van perifere neuropathie tast statische evenwichtsprestaties aan
- Afwijkingen van het gangpatroon worden manifester bij toevoeging van een semantische cognitieve dubbeltaak
- Verminderde cognitieve functies tasten het gangpatroon verder aan

Chapter 8

Appendix

8

Valkalender

Voorzijde

Gelieve een **V** te schrijven naast de dag dat U gevallen bent en een **N** indien U niet gevallen bent. Wij zullen telefonisch met U contact opnemen voor verdere informatie. Dank U.

SEPTEMBER 2011													
ma		**di**		**woe**		**do**		**vrij**		**zat**		**zon**	
						1		2		3		4	
5		6		7		8		9		10		11	
12		13		14		15		16		17		18	
19		20		21		22		23		24		25	
26		27		28		29		30					
Post de briefkaart vandaag a.u.b.													

Opmerkingen:……

Wijziging telefoonnummer:…….....

Achterzijde

ONNODIG
TE FRANKEREN

Naam en adres afzender:

.....

.....

.....

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hogeschool

REVAKI GENT
t.a.v. Prof. D. Cambier

Testen Flowchart

Timed Up & Go (TUG) Test

1. Instructies

Afname: De te onderzoeken patiënt zit op een stoel met een rugleuning en de armen steunen op de armleuningen. Hij wordt verzocht recht te staan, drie meter te wandelen tot aan een lijn of een merkteken, zich 180° om te draaien, terug te komen naar de stoel en te gaan zitten. Het gebruik van een hulpmiddel (bijvoorbeeld een wandelstok of een looprek) is toegestaan. De patiënt mag dat hulpmiddel met de handen vasthouden bij het begin van de test. De test begint op het startsein van de onderzoeker en de tijd wordt stopgezet wanneer de patiënt terug met de rug tegen de rugleuning van de stoel zit.

Scoring: De test is positief indien de oudere 14 seconden of langer doet over de test (verhoogd valrisico) of een afwijkend gangpatroon vertoont tijdens de test. Het gangpatroon wordt als afwijkend beschouwd wanneer de oudere een ongelijkmatig/onevenwichtig gangpatroon vertoont; slentert, schuifelt of sloft; van de lijn afwijkt; onvaste, wankele stappen neemt. Bij ouderen die omwille van cognitieve of fysieke redenen de test niet kunnen uitvoeren, wordt de test automatisch als positief beoordeeld.

- **www.riziv.be**
- **www.valpreventie.be**
- Podsiadlo D, Richardson S. The timed “up and go”: A test of basic functional mobility for frail elderly persons. *JAGS* 1991; **39**:142-148
- Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000; **80**(9):896-903

Evaluatie van orthostatische hypotensie

1. Instructies

Screenende vragen:

- *"Heeft u soms last van duizeligheid of draaierigheid?"*
- *"Heeft u dit bij het rechtstaan uit bed, stoel of zetel, of bij het bukken?"*
- *"Heeft u dit al gehad binnen het uur na een maaltijd?"* (postprandiale hypotensie)

Afname: Meet de bloeddruk en pols na een liggende houding van minimaal 5 (liefst 10) minuten, bij voorkeur 's morgens of na de middagrust. Laat de oudere vervolgens rechtstaan. Meet de bloeddruk en pols opnieuw onmiddellijk na het rechtstaan en na drie minuten rechtstaan. Bevraag de aanwezigheid van eventuele symptomen.

Scoring: De test is positief indien een systolische bloeddrukdaling van ≥ 20 mmHg of een diastolische bloeddrukdaling van ≥ 10 mmHg wordt vastgesteld onmiddellijk na het rechtstaan of na drie minuten.

- **www.valpreventie.be**
- Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996; **46**(5):1470.
- Gupta V & Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; **120**(10):841-847
- Irvin DJ & White M. The importance of accurately assessing orthostatic hypotension. *Geriatr Nurs* 2004; **25**(2):99-101

Tinetti-test BALANS

1. Instructies, afname en scoring

De proefpersoon zit op een harde stoel zonder leuningen.

Taak	Beschrijving	Score
1) Zitbalans	0 = hangt in de stoel of glijdt weg 1 = veilige, stabiele houding	
2) Rechtstaan	0 = onmogelijk zonder hulp 1 = mogelijk met hulp van armen 2 = mogelijk zonder hulp van armen	
3) Pogingen om recht te staan	0 = onmogelijk zonder hulp 1 = mogelijk in meer dan 1 poging 2 = mogelijk in 1 poging	
4) Evenwicht in stand onmiddellijk na het rechtstaan (eerste 5 sec)	0 = onstabiel (wankelt, voet- en/of rompbewegingen) 1 = stabiel, met gebruik van steun (rollator, stok, …) 2 = stabiel, zonder extra steun	
5) Evenwicht in stand	0 = onstabiel 1 = stabiel, met voeten > 10 cm uit elkaar of armsteun 2 = voeten gesloten, zonder steun	
6) Drie keer duwen met de handpalm op het sternum met voeten tegen elkaar	0 = begint te wankelen 1 = wankelt, maar herstelt zichzelf 2 = stabiel	
7) Ogen dicht met de voeten tegen elkaar	0 = onstabiel 1 = stabiel	
8) 360° graden draaien	0 = beweging niet vloeiend (onregelmatige stapjes) 1 = vloeiende beweging (regelmatige stapjes) 0 = onstabiel (wankelt) 1 = stabiel	
9) Gaan zitten	0 = onveilig (valt in stoel, afstand mis ingeschat) 1 = veilig en vlot mits gebruik van armen 2 = veilig en vlot zonder extra steun	
Evenwichtsscore (max. 16)		**/16**

Tinetti-Test GANG

1. Instructies, afname en scoring

De proefpersoon staat samen met de onderzoeker; hij/zij stapt in de gang of in de kamer, eerst aan een gewoon tempo, dan op de terugweg in een snellere maar veilige pas (hij/zij gebruikt eigen hulpmiddelen zoals een stok of een looprek).

Taak	Beschrijving	Score
1) Initiatie gang na *"start"*	0 = aarzeling of verschillende pogingen 1 = zonder aarzeling	
2) Staplengte en -hoogte	0 = rechter 'zwaaivoet' passeert linker 'standvoet' niet 1 = rechter 'zwaaivoet' passeert linker 'standvoet'	
	0 = rechtervoet komt niet volledig los van de vloer 1 = rechtervoet komt volledig los van de vloer	
	0 = linker 'zwaaivoet' passeert linker 'standvoet' niet 1 = linkervoet 'zwaaivoet' passeert linker 'standvoet'	
	0 = linkervoet komt niet volledig los van de vloer 1 = linkervoet komt volledig los van de vloer	
3) Stapsymmetrie	0 = linker- en rechter staplengte zijn niet gelijk 1 = linker- en rechter staplengte zijn gelijk	
4) Continuïteit van de stap	0 = haltes (stoppen) of discontinuïteit tussen stappen 1 = stappen lijken continu (vloeiend)	
5) Afwijkende gang	0 = opvallende afwijking 1 = middelmatige afwijking of gebruik van hulpmiddel 2 = rechtuit zonder hulpmiddel	
6) Romp	0 = uitgesproken rompbeweging of gebruik van hulpmiddel 1 = geen rompbeweging maar flexie van knieën of rug, of spreiden van de armen tijdens stappen 2 = rechtop zonder hulpmiddel	
7) Walking distance (voetafstand)	0 = hielen uit elkaar 1 = hielen raken elkaar bijna tijdens stappen	
Gangscore (max. 12)		/12
TOTAALSCORE = Evenwicht + Gangscore (max. 28)		/28

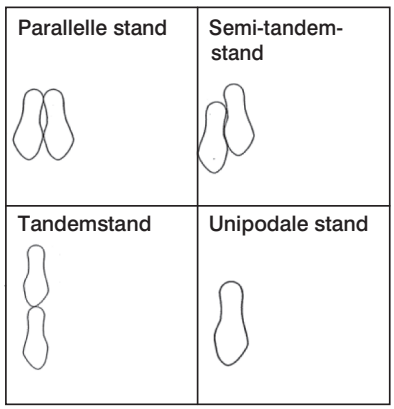
Totaalscore < 20/28: valrisico x5

- Tinetti M. Performance oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc* 1986; **34**:119-126

Four Test Balance (FTB) Scale

1. Instructies

Afname: Vraag aan de oudere om elk van de vier posities van de Four Test Balance Scale gedurende 10 seconden aan te nemen (zie onderstaande figuur). Voor de vierde positie mag de oudere kiezen op welk been hij zal staan.



Deze test wordt uitgevoerd zonder hulpmiddel of schoeisel. De onderzoeker mag de oudere helpen om de juiste positie aan te nemen. Vervolgens moet de oudere aangeven wanneer hij klaar is om de test zonder hulp uit te voeren. Oefenen is niet toegelaten. Plaats een stoel achter de oudere. De vier condities worden aangeboden in de volgorde van toenemende moeilijkheidsgraad.

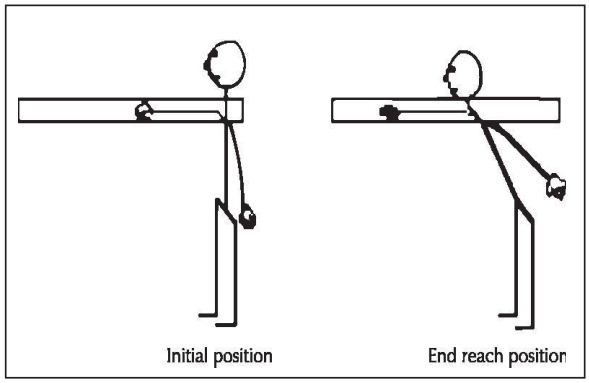
Scoring: De test eindigt en is positief van zodra men een van de vier posities geen 10 seconden kan aannemen, bijvoorbeeld: de oudere beweegt zijn voeten, de hulpverlener moet de oudere vastnemen om een val te voorkomen, of de oudere raakt de muur, tafel of stoel om het evenwicht te behouden.

- **www.valpreventie.be**
- Gardner MM, Buchner DM, Robertson MC, Campbell AJ. Practical implementation of an exercise-based falls prevention programme. *Age Ageing* 2001; **30**(1):77-83
- Rossiter-Fornoff JE, Wolf SL, Wolfson LI, Buchner DM. A cross-sectional validation study of the FICSIT common data base static balance measures. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *J Gerontol A Biol Sci Med Sci* 1995; **50**(6):M291-297

Functional Reach Test (FRT)

1. Instructies

Afname: De oudere neemt met de voeten op schouderbreedte plaats naast de lintmeter en houdt de dominante arm het dichtst tegen de muur met gebalde vuist horizontaal met de lintmeter. De oudere reikt zo ver mogelijk voorwaarts zonder het evenwicht te verliezen. De voeten mogen niet worden verplaatst, de hielen moeten op de grond blijven en de romp mag niet draaien. De reikafstand (de afstand tussen de begin- en eindpositie van metacarpaal 3) wordt gemeten en bepaalt de testscore. Deze test wordt uitgevoerd zonder hulpmiddel of schoeisel.



Scoring: De test is positief indien de reikafstand ≤ 25 cm bedraagt;

> 25 cm:	geen verhoogd valrisico
15-25 cm:	verhoogd valrisico
≤ 15 cm:	sterk verhoogd valrisico

- **www.valpreventie.be**
- Duncan PW, Studenski S, Chandler J, Prescott B. Functional reach: predictive validity in a sample of elderly male veterans. *J Gerontol* 1992; **47**(3):M93-98

Timed Chair Stand (TCS) Test

1. Instructies

Afname: De te onderzoeken oudere zit met de armen gekruist over de borstkas op een stoel met een rugleuning en zonder armleuningen. Om veiligheidsredenen wordt de rugleuning van de stoel tegen een muur geplaatst. De oudere wordt verzocht vijfmaal na elkaar zo snel mogelijk recht te staan en te gaan zitten zonder de armen te gebruiken. Het gebruik van een hulpmiddel is niet toegestaan. De test begint op het startsein van de onderzoeker en de tijd wordt stopgezet bij de vijfde keer dat de oudere rechtop staat.

Scoring: De test is positief indien de oudere hiervoor 14 seconden of meer nodig heeft of indien hij niet in staat is de test uit te voeren.

- **www.riziv.be**
- Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med* 1995; **332**(9):598-599

Mini-Mental State Examination (MMSE)

1. Instructies en Test

(i) Oriëntatie in tijd en ruimte

In welk jaar zijn we?	☐ Jaar
In welk seizoen zijn we?	☐ Seizoen
De hoeveelste zijn we vandaag?	☐ Datum
Welke dag is het vadaag?	☐ Dag
In welke maand zijn we?	☐ Maand
In welk land leven wij?	☐ Land
In welke provincie zijn we?	☐ Provincie
In welk dorp zijn we?	☐ Dorp
In welk centrum bent u?	☐ Centrum
Op welke verdieping bent u?	☐ Verdieping

(ii) Inprentingsvermogen

Ik noem u drie woorden. Als ik ze gezegd heb, moet u ze alledrie herhalen.

☐ Sigaar
☐ Bloem
☐ Deur

Lees de woorden voor aan 1 woord per seconde.
Laat ze daarna herhalen en noteer elk correct woord.
Als de patiënt ze niet correct herhaalt,
lees ze dan opnieuw voor en herhaal eventueel tot 6 maal toe.

Onthoud deze woorden goed, want ik ga ze u straks nog eens vragen.

(iii) Aandacht

Wilt u van het getal 100 zeven aftrekken? Van de uitkomst trekt u dan telkens weer zeven af en zo verder tot wanneer ik 'stop' zeg.

Elke juiste aftrekking levert 1 punt op.

☐ 93
☐ 86 of -7
☐ 79 of –7
☐ 72 of –7
☐ 65 of –7

Wilt u het woord kamer van achteren naar voren spellen?

☐ R
☐ E
☐ M
☐ A
☐ K

Vergelijk de twee vorige testen. Weerhoud enkel de test met de hoogste score.
Schrap de andere en tel die niet mee in de eindscore.

(iv) Geheugen

Welk waren de drie woorden die u moest onthouden?

- ☐ Sigaar
- ☐ Bloem
- ☐ Deur

(v) Taal

Wat is dit? *Wijs een horloge aan.*	☐ Horloge
Wat is dit? *Wijs een potlood aan.*	☐ Potlood
Wilt u de volgende zin herhalen: Geen als, en of maar.	☐ Correct
Neem dit papier met de rechterhand,	☐ Neemt papier
vouw het in twee en leg het op uw schoot.	☐ Vouwt papier
	☐ Legt op schoot
Lees wat op dit papier staat en doe wat gevraagd wordt.	☐ Sluit ogen

Hou het papier omhoog, waarop staat 'sluit uw ogen'.

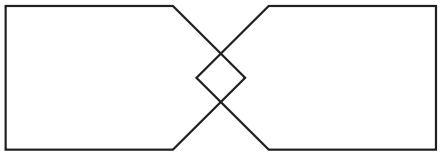
Kan u voor mij een zin opschrijven. ☐ Zin

De zin moet een onderwerp en werkwoord bevatten en betekenis hebben.

(vi) Constructieve vaardigheid

Kan u deze figuur natekenen? ☐ Figuur

Toon de twee vijfhoeken. Voor een correct antwoord moeten er 10 hoeken zijn, waarvan er 2 kruisen.



TOTAALSCORE MMSE: ……/ 30

Interpretatie:

- $>$ 26/30: geen cognitieve beperking
- 24-26/30: milde cognitieve deficieten
- $<$ 24/30: matige tot ernstige cognitieve beperkingen

• Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**(3):189-198

SLUIT UW OGEN

Clock Drawing Test (CDT)

1. Instructies

Afname: *"Wilt u een klok tekenen alstublieft? Vul alle getallen en wijzers in.*
Proefpersonen mogen zelf kiezen welke tijd de klok aangeeft.
Als de proefpersoon aangeeft klaar te zijn met het tekenen van de klok, zeg dan:
"Schrijf hieronder de tijd neer die uw klok aangeeft."

Scoring CDT:

- Item 2: 12 nummers zijn aanwezig	ja: 1 punt	neen: 0
- Item 5: nummer '12' is correct gepositioneerd	ja: 2 punten	neen: 0
- Item 25: wijzers hebben juiste proportie	ja: 2 punten	neen: 0
- Item 34: proefpersoon kan de tijd correct aflezen	ja: 2 punten	neen: 0

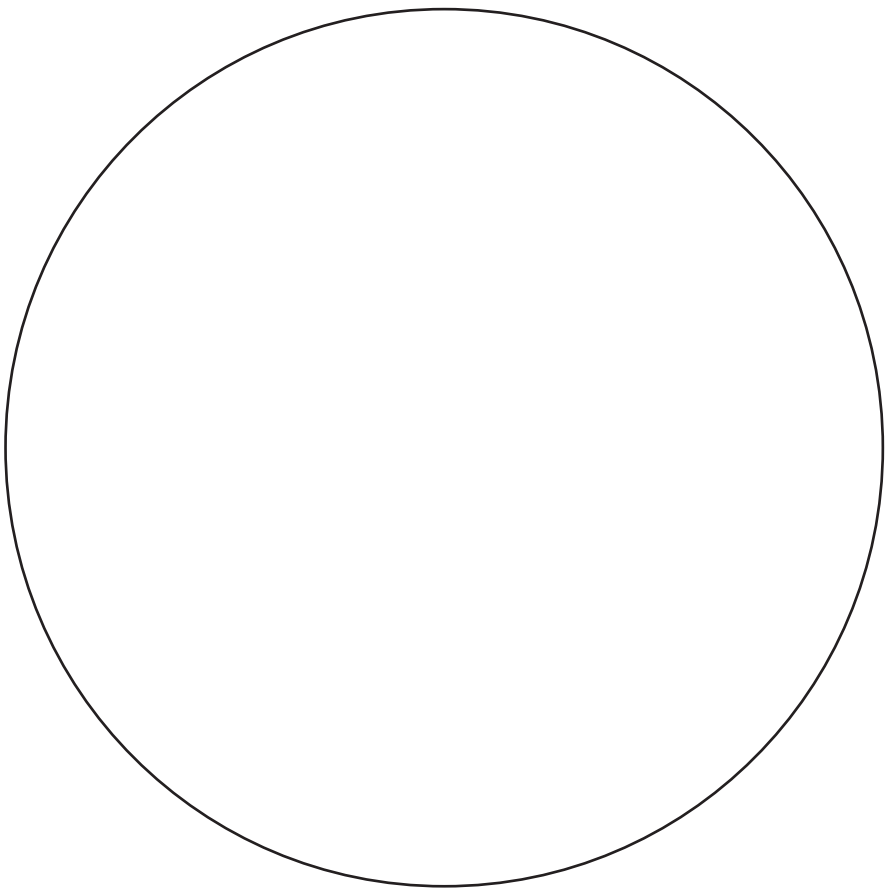
Scoring gecombineerde MMSE-CDT:

Test	MMSE	CDT	MMSE-CDT
Scoring	≥ 27		3
	< 27		0
		Item 2	
		0	0
		1	1
		Item 5	
		0	0
		2	3
		Item 25	
		0	0
		2	1
		Item 34	
		0	0
		2	1
Max. score	30	7	9
Cut-off score	<24	< 6	< 7

- Thalmann B, Spiegel R, Stähelin HB, Brubachner D, Ermini-Fünfschilling D, Bläsi S, Monsch AU. Dementia screening in general practice: Optimised scoring for the Clock Drawing Test. *Brain Aging* 2002; **2**(2):36-43

2. Test

Wilt U een klok tekenen? Vul alle cijfers in, alsook de wijzers van de klok.



Schrijf hieronder de tijd neer die uw klok aangeeft

Montreal Cognitive Assessment (MoCa)

1. Instructies

(i) Alternerende Trail Making:
Afname: *"Teken een lijn, van een cijfer naar een letter en in oplopende volgorde. Begin hier (wijs naar 1) en teken een lijn van 1 naar A, dan naar 2 en zo verder. Stop hier (wijs naar E)."*
Scoring: 1 punt wordt toegekend indien de proefpersoon het volgende patroon correct tekent: 1-A-2-B-3-C-4-D-5-E, zonder dat de lijnen elkaar kruisen. Een fout die de proefpersoon niet direct zelf verbetert, krijgt een score 0.

(ii) Visuo-constructieve vaardigheden (Kubus):
Afname: *"Teken deze figuur zo nauwkeurig mogelijk na, in de ruimte hieronder".*
Scoring: Er wordt 1 punt toegekend voor een correcte tekening. De tekening moet driedimensionaal zijn, alle lijnen moeten zijn getekend, er mag geen extra lijn worden toegevoegd en de lijnen moeten relatief parallel lopen en van gelijke lengte zijn (rechthoekige prisma's worden geaccepteerd). Indien aan één van bovenstaande criteria niet wordt voldaan, is de score 0.

(iii) Visuo-constructieve vaardigheden (Klok):
Afname: *"Teken een klok. Plaats er alle cijfers in en zet de wijzers op 10 over 11".*
Scoring: Er wordt één punt toegekend voor elk van de volgende 3 criteria:
- Omtrek (1 pt.): de omtrek van de klok moet een cirkel zijn. Hooguit een kleine afwijking is acceptabel (b.v., een kleine onvolkomenheid bij het sluiten van de cirkel);
- Cijfers (1 pt.): alle cijfers van de klok zijn aanwezig, zonder toevoeging van extra cijfers; de cijfers staan in de juiste volgorde en moeten ongeveer in de kwadranten van de klok geplaatst zijn; Romeinse cijfers zijn toegestaan; de cijfers mogen aan de buitenkant van de cirkel worden geplaatst;
- Wijzers (1 pt.): er moeten twee wijzers zijn die samen de correcte tijd aangeven; de uurwijzer moet duidelijk korter zijn dan de minutenwijzer; de wijzers moeten in de klok worden getekend en elkaar ongeveer in het midden van de cirkel kruisen.

Er wordt geen punt toegekend voor een element indien aan de bovenstaande criteria niet wordt voldaan.

(iv) Benoemen:
Afname: Wijs vanaf links ieder figuur aan en zeg: *"Hoe heet dit dier?".*
Scoring: Voor elk van de volgende antwoorden wordt 1 punt gegeven: (1) leeuw, (2) neushoorn, (3) kameel of dromedaris.

(v) Geheugen:

Afname: Onderzoeker leest een rij van 5 woorden voor met een snelheid van één woord per seconde en geeft hierbij de volgende instructies*: "Dit is een geheugentest. Ik ga een rij woorden voorlezen die u moet onthouden, nu maar ook straks. Luister goed. Als ik klaar ben, vertelt u me alle woorden die u hebt onthouden. Het maakt niet uit in welke volgorde u ze opnoemt".* Zet een kruisje in de aangegeven ruimte voor ieder woord dat de proefpersoon tijdens deze eerste aanbieding reproduceert. Wanneer de proefpersoon aangeeft dat hij/zij klaar is (alle woorden heeft herinnerd), of zich geen woorden meer weet te herinneren, lees dan de lijst met woorden een tweede keer voor met de volgende instructie: *"Ik ga dezelfde lijst een tweede keer voorlezen. Probeer zo veel mogelijk woorden te onthouden en vertel ze me, ook de woorden die u de eerste keer hebt opgenoemd."* Zet een vinkje in de aangegeven ruimte voor ieder woord dat de proefpersoon zich herinnert na de tweede aanbieding. Vertel de proefpersoon aan het einde van de tweede aanbieding dat later nogmaals naar de woorden gevraagd zal worden, door te zeggen: *"Ik zal u aan het eind van deze test opnieuw vragen welke woorden u zich nog weet te herinneren."*

Scoring: Er worden géén punten gegeven voor aanbiedingen één en twee.

(vi) Aandacht:

Afname Cijferreeksen vooruit: *"Ik ga een aantal cijfers opnoemen en als ik klaar ben, moet u ze in dezelfde volgorde nazeggen als ik ze heb gezegd".* Lees de vijf-cijfer reeks met een snelheid van één cijfer per seconde.

Afname Cijferreeksen achteruit: *"Nu ga ik weer cijfers opnoemen, maar zodra ik klaar ben, moet u ze in omgekeerde volgorde nazeggen."* Lees de drie-cijfer reeks met een snelheid van één cijfer per seconde.

Scoring: Er wordt 1 punt gegeven voor elke correct nagezegde reeks, (N.B.: het correcte antwoord voor cijferreeksen achteruit is 2-4-7).

Afname Volgehouden aandacht: De onderzoeker leest de rij letters voor met een snelheid van één letter per seconde. *"Ik ga u een reeks letters voorlezen. Iedere keer dat ik de letter A noem, tikt u eenmaal met uw hand op tafel. Wanneer ik een andere letter noem, tikt u niet met uw hand op tafel".*

Scoring: Geef 1 punt bij nul of één fout (een fout is een tik bij de verkeerde letter of geen tik bij de letter A).

Afname Seriële 7's: *"Wilt u van 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg?"* Geef deze instructie zo nodig tweemaal.

Scoring: Op dit item zijn maximaal 3 punten te behalen. Geef geen (0) punten indien geen enkele correct is, 1 punt voor één correcte aftreksom, 2 punten voor twee of drie correcte aftreksommen, en 3 punten indien vier of vijf aftreksommen juist zijn gemaakt. Tel iedere juiste aftrekking van 7, beginnend bij 100. Iedere aftreksom wordt individueel beoordeeld; dit houdt in dat indien een proefpersoon met een foutief getal

antwoordt, maar vervolgens correct doorgaat met hier 7 van af te trekken, er een punt voor iedere correcte som wordt gegeven. Een proefpersoon kan bijvoorbeeld antwoorden: *"92 – 85 – 78 – 71 – 64"* waarbij de "92" fout is, maar alle volgende getallen correct zijn afgetrokken. Dit is één fout en het item krijgt een score van 3.

(vii) Zinnen nazeggen:

Afname: *"Ik ga u een zin voorlezen. Zeg deze na zodra ik klaar ben, precies zoals ik hem heb gezegd [pauze]: Ik weet alleen dat Jan vandaag geholpen zou worden."* Na het antwoord zegt u: *"Nu ga ik u een andere zin voorlezen. Zeg deze na, precies zoals ik hem heb gezegd [pauze]: De kat verstopte zich altijd onder de bank als er honden in de kamer waren."*

Scoring: Ken 1 punt toe voor iedere correct herhaalde zin. De herhaling moet precies hetzelfde zijn. Wees alert voor omissies (b.v., "alleen", "altijd" vergeten) en vervangingen of toevoegingen (b.v., "Jan is degene die vandaag heeft geholpen"; "verstopte" vervangen door "verstopt", meervoud veranderen, etc.).

(viii) Verbale fluency:

Afname: *"Noem zo veel mogelijk woorden als u kunt bedenken die beginnen met een bepaalde letter van het alfabet. Ik zal u de letters straks vertellen. U mag ieder woord noemen dat u wilt, behalve namen, cijfers, of woorden die met hetzelfde voorstukje (voorvoegsel) beginnen, zoals bijvoorbeeld lief, liefde, liefdevol. Na één minuut vraag ik u te stoppen. Bent u er klaar voor? [pauze] Noem zo veel mogelijk woorden als u kunt bedenken die beginnen met de letter D. [tel 60 sec af]. Stop."*

Scoring: Ken 1 punt toe indien de proefpersoon 11 woorden of meer kan opnoemen in 60 seconden. Noteer de antwoorden onderaan het blad, of in de kantlijn.

(ix) Abstractie:

Afname: De onderzoeker vraagt de proefpersoon uit te leggen wat ieder woordpaar gemeenschappelijk heeft. Begin met het voorbeeld: *"Kunt u mij vertellen in welke opzicht een sinaasappel en een banaan aan elkaar gelijk zijn, wat is de overeenkomst tussen beide?"*. Wanneer de proefpersoon een concreet antwoord geeft, zeg dan slechts één keer extra: *"Weet u nog een andere overeenkomst?"*. Indien de proefpersoon niet het correcte antwoord geeft (fruit), zeg dan, *"Ja, en het is beide fruit."* Geef geen extra instructies of verduidelijking.

Na de oefenafname, zegt u: *"In welk opzicht zijn een trein en een fiets aan elkaar gelijk?"*. Nadat het antwoord gegevens is, stelt u een tweede vraag: *"Vertel me nu in welk opzicht een liniaal en een horloge aan elkaar gelijk zijn"*. Geef geen extra instructies of aanmoedigingen.

Scoring: Alleen de laatste twee itemparen worden gescoord. Geef 1 punt voor ieder correct beantwoord itempaar. Deze antwoorden worden goedgekeurd:

Trein-fiets = vervoermiddelen, manieren om te reizen, je kunt met beide tochten maken;
Liniaal-horloge = meetinstrumenten, worden gebruikt om te meten.
De volgende antwoorden worden niet goedgekeurd: Trein-fiets = zij hebben wielen; Liniaal-horloge = zij hebben cijfers.

(x) Uitgestelde recall:
Afname: *"Ik heb u eerder een rij met woorden voorgelezen, en ik vroeg u ze te onthouden. Vertel me zo veel mogelijk woorden die u zich kunt herinneren."* Zet een vinkje in de daarvoor bestemde ruimte (√) voor ieder correct woord dat de proefpersoon zich spontaan, zonder aanwijzingen, heeft weten te herinneren.
Scoring: Ken 1 punt toe voor ieder woord dat spontaan wordt herinnerd zonder aanwijzingen.

(xi) Oriëntatie:
Afname: *"Vertel me de datum van vandaag".* Indien de proefpersoon een onvolledig antwoord geeft, moedig hem dan aan door te zeggen: *"Vertel me het [jaar, maand, precieze datum, en dag van de week]."* Zeg vervolgens: *"Vertel nu: hoe heet dit gebouw en in welke stad/plaats zijn we nu?"*
Scoring: Geef 1 punt voor ieder correct beantwoord item. De proefpersoon moet de exacte datum en het exacte gebouw noemen (naam van het ziekenhuis, kliniek, kantoor). Er worden geen punten toegekend als de proefpersoon er één dag naast zit wat betreft de dag van de week en de datum (dag van de maand).

TOTALE SCORE: Tel alle subtestscores die aan de rechterkant staan bij elkaar op. Tel er 1 punt bij op voor personen die 12 jaar of minder formele opleiding hebben gehad (gerekend vanaf leeftijd 6 jaar), zodat een maximum van 30 punten mogelijk is. Een uiteindelijke score van 26 of hoger wordt beschouwd als normaal.

- **www.mocatest.org**
- Nasreddine ZS, Philips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**(4):695-699

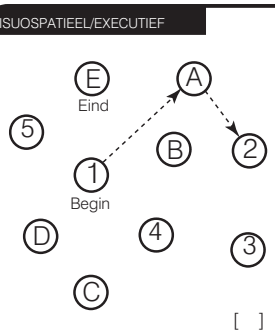
2. Test

Nederlandse versie

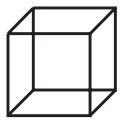
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Geboortedatum:
Jaren opleiding:
Geslacht:
Naam:
Datum:

VISUOSPATIEEL/EXECUTIEF — PUNTEN



Kopieer de kubus

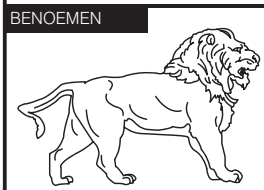


[ ] [ ]

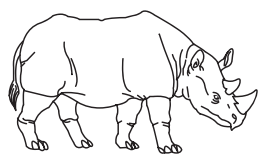
Teken een klok (tien over elf) (3 punten)

[ ] Omtrek [ ] Cijfers [ ] Wijzers __/5

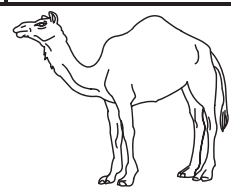
BENOEMEN



[ ]



[ ]



[ ] __/3

GEHEUGEN

Lees de woorden op, proefpersoon moet ze nazeggen. Neem 2 maal af. Laat ze na 5 min. opnieuw opnoemen.

	GEZICHT	FLUWEEL	KERK	MADELIEF	ROOD
1e afname					
2e afname					

Geen punten

AANDACHT

Lees de rij cijfers op (1 cijfer/sec). Proefpersoon moet ze in dezelfde volgorde nazeggen **[ ] 2 1 8 5 4**
Proefpersoon moet ze in omgekeerde volgorde nazeggen **[ ] 7 4 2** __/2

Lees de rij letters op. De proefpersoon moet bij iedere letter A met zijn hand op de tafel tikken Geen punten bij ≥ 2 ft
[ ] **F B A C M N A A J K L B A F A K D E A A A J A M O F A A B** __/1

Serieel 7 aftrekken, beginnend bij 100 **[ ] 93** **[ ] 86** **[ ] 79** **[ ] 72** **[ ] 65**
4 of 5 goed: **3 pt**, 2 of 3 goed: **2 pt**, 1 goed: **1 pt**, 0 goed: **0 pt** __/3

TAAL

Zeg na: Ik weet alleen dat Jan vandaag geholpen zou worden. [ ]
De kat verstopte zich altijd onder de bank als er honden in de kamer waren. [ ] __/2

Fluency: Noem binnen één minuut zo veel mogelijk woorden die beginnen met de letter D [ ] (N ≥ 11 woorden) __/1

ABSTRACTIE

Overeenkomst tussen bijv. banaan en sinaasappel = fruit [ ] trein-fiets [ ] horloge-liniaal __/2

UITGESTELDE RECALL

	Woorden moeten herinnerd worden **zonder cue**	GEZICHT [ ]	FLUWEEL [ ]	KERK [ ]	MADELIEF [ ]	ROOD [ ]
Optioneel	Categoriecue					
	Meerkeuzecue					

Punten alleen voor recall zonder cue __/5

ORIËNTATIE

[ ] Datum [ ] Maand [ ] Jaar [ ] Dag [ ] Locatie [ ] Plaats __/6

www.mocatest.org

Normaal ≥ 26 / 30

TOTAAL __/30
Tel er 1 pt bij op indien ≤ 12 jr opleiding

Acknowledgements
List of abbreviations

Acknowledgements

In a sense, going through a PhD project is similar to fall risk management. A lot of intrinsic, extrinsic and situational risk factors can make you fall and get hurt quite seriously. Fall prevention should be targeted but some slips or trips just cannot be avoided. Fortunately, appropriate rehabilitation programs, reducing fatal fall accidents, are available these days and make you forget the incident and enjoy your regained mobility even more. It is my pleasure to thank the people who contributed to my personal fall risk detection, prevention and treatment.

It is difficult to overstate my gratitude to my supervisor, Prof. Dr. Dirk Cambier, who was not only a very supportive mentor but became a true friend. Dirk, throughout my doctoral thesis period and even before, you have always had faith in me. Thank you for giving me the opportunity to do this PhD, for sharing your scientific insights, your professionalism, for your as quick as lightning feedback and for always being there for me. I really enjoyed working with such a *lusus naturae*… Thanks a lot for everything!

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I would like to express my deep gratitude to my parents for always being willing to help, providing a loving environment for me, for being proud of me and substantially contributing to realize my dreams. I really believe that these favorable conditions were essential for me to successfully accomplish this doctoral thesis. Dear brothers, let's go on holidays now and play "Pass the Pigs" till we drop!

Most of all I would like to express my special appreciation and thanks to my dearest husband and very best friend, Koen. Boelietje, for almost 10 years now, your unequalled support, understanding and love form the cornerstone of my being and doing. Thank you for making me smile through my tears and for making me laugh till I cry. You are my everything and definitely the best thing that ever happened to me.

List of abbreviations

ANOVA:	Analysis of Variance
AP:	Anterior-Posterior
B-ADL:	Basic Activities of Daily Living
BMI:	Body Mass Index
BOF:	Bijzonder Onderzoeks Fonds
CDT:	Clock Drawing Test
COP:	Center of Pressure
CoV:	Coefficient of Variation
CV:	Coefficient of Variation
DM:	Diabetes Mellitus
DNE:	Diabetic Neuropathy Examination
DNS:	Diabetic Neuropathy Symptom score
EMG:	Electromyography
EC:	Eyes Closed
EO:	Eyes Open
EVA:	Etylene Vinyl Acetate
EVV:	Expertisecentrum Val- en fractuurpreventie Vlaanderen
FES:	Falls Efficacy Scale
FES-I:	Falls Efficacy Scale International
FoF:	Fear of Falling
FPG:	Fasting Plasma Glucose
FRT:	Functional Reach Test
GI:	Glycemic Index
GP:	General Practitioner
HbA1c:	Glycated Haemoglobin
I-ADL:	Instrumental Activities of Daily Living
LJM:	Limited Joint Mobility
MCI:	Mild Cognitive Impairment
MDC:	Minimal Detectable Change
ML:	Medio-Lateral
MMSE:	Mini-Mental State Examination
MoCa:	Montreal Cognitive Assessment
OGTT:	Oral Glucose Tolerance Test
OR:	Odds Ratio
PN:	Peripheral Neuropathy
PPA:	Physiological Profile Assessment
ProFaNE:	Prevention of Falls Network Europe
RIZIV:	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
ROS:	Reactive Oxygen Species
SD:	Standard Deviation
SPSS:	Statistical Package for the Social Sciences
T2DM:	Type 2 Diabetes Mellitus
TCS:	Timed Chair Stand test
TUG:	Timed Up & Go test
VPT:	Vibration Perception Threshold
WHO:	World Health Organization

Scenes so lovely must have been gazed upon by angels in their flight
Dr. Livingstone discovering the Victoria Falls