Falls and Fractures in Diabetes—More than Bone Fragility

Nicklas Højgaard Rasmussen[1] · Jakob Dal[2]

Abstract

Purpose of Review Based on a systematic literature search, we performed a comprehensive review of risk factors for falls and fractures in patients with diabetes.

Recent Findings Patients with diabetes have an increased risk of fractures partly explained by increased bone fragility. Several risk factors as altered body composition including sarcopenia and obesity, impaired postural control, gait deficits, neuropathy, cardiovascular disease, and other co-morbidities are considered to increase the risk of falling.

Summary Diabetes and bone fragility is well studied, but new thresholds for fracture assessment should be considered. In general, the risk factors for falls in patients with diabetes are well documented in several studies. However, the fall mechanisms among diabetic patients have only been assessed in few studies. Thus, a gab of knowledge exits and may influence the current understanding and treatment, in order to reduce the risk of falling and thereby prevent fractures.

Keywords Type 1 diabetes · Type 2 diabetes · Falls · Fractures · Bone fragility · Sarcopenia

Introduction

Diabetes mellitus is a growing healthcare problem and affects more than 450 million people with an expected increase to 629 million by the year 2045 [1–3]. Fractures are a major health issue in the global population with an estimate of 9 million fractures annually attributed to osteoporosis and associated with high morbidity and mortality [4–6]. In recent years, awareness of the adverse effects of diabetes on bone fragility and fracture risk has advanced and may thus represent a hitherto overlooked complication to diabetes as, e.g., retinopathy, nephropathy, or cardiovascular disease [7]. Therefore, it is important to identify and modify risk factors for fractures such as bone fragility, and non-skeletal factors, i.e., altered body composition and risk of falls (Fig. 1). The *aim* of this review is to explore the risk of fractures in diabetic patients and to gain knowledge of the potential risk factors for fractures and falls as bone fragility, altered body composition, impaired postural control, gait deficits, neuropathy, cardiovascular disease, and other co-morbidities.

Method

To identify all articles associated with diabetes, falls, and fractures, we performed a systematic literature search in October 2018. We searched Embase from January 2002 to October 2018 using the Mesh terms "fractures, incidental fractures in diabetes," "falling," "risk factors," and "Sarcopenia and Altered Body Composition." PubMed was searched from January 2002 to October 2018 using the search string below. We followed the PRISMA guidelines (www.prisma-statement.org, Figure Fig. 2).

"(((("Accidental Falls"[Mesh]) AND ((((("Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR diabet*[tw] OR tdm2[tw] OR dm2[tw] OR dm1[tw] OR tdm1[tw] OR t1dm[tw] OR t2dm[tw])))))) OR ((((("Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR diabet*[tw] OR tdm2[tw] OR dm2[tw] OR dm1[tw] OR tdm1[tw] OR t1dm[tw] OR t2dm[tw])) AND (((((("Accidental Falls"[Mesh]) OR fall[tw]) OR falls[tw]) OR falling[tw]) OR faller[tw]) OR fallers[tw]))) NOT medline[sb])."
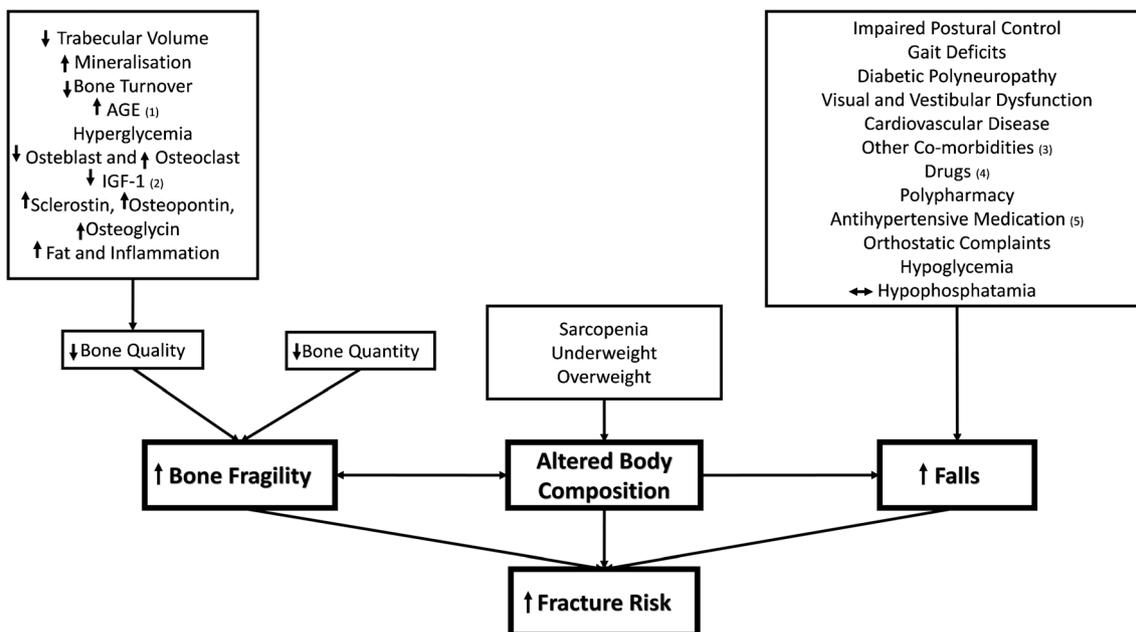

✉ Nicklas Højgaard Rasmussen
nicklas.rasmussen@rn.dk

1   Steno Diabetes Center North Jutland, Aalborg University Hospital, Aalborg, Denmark

2   Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark

Overview of Risk Factors for Falls and Fractures in Diabetes

Fig. 1 A schematic overview of risk factors for falls and fractures in diabetes. Different mediators decrease bone quality and quantity, which increases the bone fragility. Over time, a fragile bone is more susceptible for micro-cracks, which increases the risk of fractures. Increased falls or alteration in the fall mechanism contribute to the increased fracture risk by several mediators but is also influenced by an alteration in body composition such as sarcopenia, underweight and overweight, and fat infiltration in bone or muscles. Altered body composition intervenes with both falls and bone fragility. Arrow pointing up: "increases." Arrow pointing down: "decreases." Arrow horizontal: "inconclusive data." AGE: advanced glycation end-product. IGF-1: insulin-like growth factor 1. Other co-morbidities: osteoarthritis and arthritis. Drugs: Benzodiazepines and opioids. Antihypertensive medication: The use of antihypertensive medication seems to be a protective factor against the risk of falling

The Pubmed and Embase search yielded 568 and 1.005 potentially relevant records, respectively (Fig. Fig. 2). After initial screening, 1.461 studies were excluded. Reasons for exclusion were unrelated topics and review articles and studies older than 2002. We assessed 112 full-text articles for eligibility. We excluded 59 studies due to duplicate data, in vitro/vivo or animal studies. Thus, 53 studies were included in the literature review.

Risk of Fracture

The overall incidence of any fracture in type 1 diabetes (T1D) is increased in the vast majority of studies [8–11]. A meta-analysis showed an increased relative risk (RR) of any fracture with T1D of 3.16 (95% confidence interval (CI) 1.51–6.63) and a RR of hip fracture of 3.78 (95% CI 2.05–6.98) [10]. These findings are supported by two earlier meta-analyses from 2007 by Vestergaard and Janghorbani et al. that confirms an increased risk of hip fracture in T1D patients of 6.94 (95% CI 3.25–14.78) and 6.3 (95% CI 2.6–15.1) [8, 12]. T1D is often diagnosed in childhood, which could influence the peak bone mass. Most studies have been conducted in individuals aged 40 years or older. Few studies have addressed the incidence rate ratio (IRR) of fractures in the younger population. However, studies by Weber et al. and Hothersall et al. found a modest increase of any fracture in T1D patients aged 0–19 years and hip fractures in patients aged with T1D, respectively [13, 14].

In most studies, the RR of any fracture is also increased in type 2 diabetes (T2D), although lower than in T1D [7, 8, 12, 15–17, 18••, 19, 20]. A proposed estimate by Vestergaard for any fracture yielded a RR of 1.19 (95% CI 1.11–1.27) [8]. Data from the Rotterdam Study observed a higher RR of any fracture in those with inadequately controlled diabetes of 1.31 (95% CI 1.00–1.71) but not in patients who were adequately treated [RR 0.85 (95% CI 0.63–1.15)] [15]. Numerous studies have reported an increase in hip fractures in patients with T2D [21]. A new meta-analysis observed a RR of hip fractures in patients with T2D of 1.34 (95% CI 1.19–1.51) [11].

Bone Fragility

Increased bone fragility consists of decreased bone quality and quantity (Fig. 1). Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) is diagnostic for osteoporosis and predicts fracture risk [22]. Loss of bone quantity and to some degree bone quality can be estimated by a decrease in BMD. In most studies, patients with T1D have decrease in BMD at the spine, hip, and whole body compared
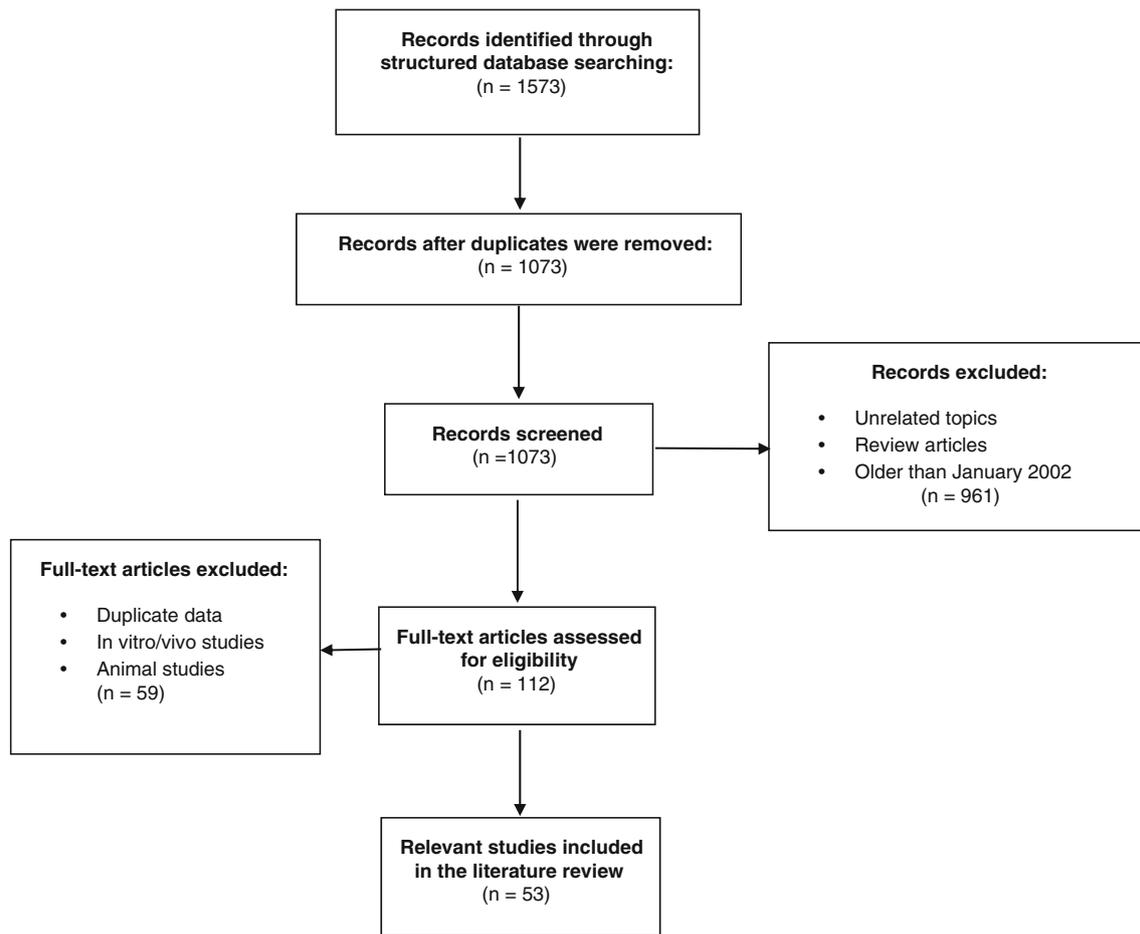
Fig. 2 *PRISMA flow diagram* of the literature search for diabetes, falls, and fractures based on predefined inclusion criteria. The Pubmed and Embase search yielded 568 and 1.005 potentially relevant records, respectively. After initial screening, 1.461 studies were excluded.

Reasons for exclusion were unrelated topics and review articles and studies older than 2002. We assessed 112 full-text articles for eligibility. We excluded 59 studies due to duplicate data, in vitro/vivo or animal studies. Thus, 53 studies were included in the literature review

to healthy subjects [23–25]. In patients with T2D, BMD tends to be normal or even higher compared to healthy individuals and in patients with T1D, the BMD is not decreased to a level that explains the observed fracture risk [26]. Therefore, BMD measures tend to underestimate the fracture risk in T1D and T2D [27]. Although BMD does not explain the difference in fracture risk, bone quantity may still be a predictor, but with another threshold.

Changes in bone quality are suggested to be a risk factor for fractures in several studies [28–31] (see Fig. 1). A recent bone-biopsy study showed an increase in mineralization and non-enzymatic collagen cross-links in type 1 diabetics, suggesting a low bone turnover [32]. Chronic hyperglycemia can induce non-enzymatic glycation of collagen that leads to increased levels of advanced glycation end products (AGEs). The build-up of AGEs within the bone matrix alters the biomechanical properties of the bone and increases the stiffness of the bone, resulting in a poor bone quality, immeasurable by DXA. Both hyperglycemia and AGEs decrease the bone resorption. A recent study have suggested that the low bone turnover is caused by osteocyte dysfunction and increased sclerostin levels, which results in bone micro-cracks and fractures in patients with T2D [18••]. Furthermore, high levels of osteopontin and osteoglycin are also associated with a low bone turnover and have been associated with increased fractures in both types of diabetics [33, 34]. In addition, decreased levels of insulin-like growth factor-1 have been reported in patients with T1D and T2D and may be associated with an increased risk of fractures [35, 36]. Finally, an increased infiltration of fat in the bone marrow and low-grade inflammation may contribute to alterations in the bone quality, thus increasing the risk of fractures [37].

Altered Body Composition

Alterations in body composition are changes in bone quantity, muscle mass, and fatty tissue, which may influence the bodyweight. The age-related decrease in muscle mass and function is often referred to as sarcopenia [38•]. Currently, different definitions for sarcopenia exists [39–41]. A revised

version of The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) has defined diagnostic criteria and cut-off thresholds for sarcopenia [42•]. It is defined as a muscle disease with a decline in skeletal muscle mass, muscle strength, and physical performance [42•]. Sarcopenia is considered to be primary or age-related when no other specific cause is evident, while sarcopenia is considered to be secondary when causal factors as disease, inactivity, or malnutrition are present. Muscle mass can be measured by DXA, which is the preferred method for clinical use. Muscle strength can be measured by handgrip strength with a hand dynamometer. Physical performance is measured by gait speed and dynamic stability, often done by *timed up-and-go (TUG)* test.

The association between sarcopenia and the risk of falls and fractures has been studied in the general population, but few studies have examined this association among diabetic patients [43•]. Kim et al. observed a higher risk of sarcopenia in patients with T2D [OR of 3.06, (95% CI 1.42–6.62)] compared to healthy subjects [38•]. However, the diagnosis of sarcopenia was based on a skeleton muscle index measured by DXA, and the EWGSOP2 criteria were not met. Other studies have reported a decrease in muscle mass, strength, and function when comparing healthy subjects and T2D patients [44, 45]. In these two studies, the EWGSOP2 criteria of sarcopenia were met. Different mechanisms have been suggested to induce sarcopenia as hyperglycemia and insulin resistance, which decreases muscle mass and strength [46, 47]. Insulin resistance is associated with an increased intramuscular fat (IMF), which induces sarcopenia by low-grade inflammation and decreases muscles function [48–50]. Also, sarcopenia increases with high age where type 2 muscle fibers are replaced by type 1 fibers resulting in decreased gait speed and instability [51, 52]. If loss of balance occurs, preventing a fall may become challenging due to an inadequate muscle response and fall-related injuries could increase due to an altered fall mechanism. A meta-analysis by Chapman et al. found that exercise interventions focusing on balance and lower-limb strength reduced fall-related injuries in diabetic patients [53•].

In general, underweight is thought to increase the risk of falls and fractures, due to sarcopenia, a low BMD, fatigue, malnutrition, and less soft tissue padding [42•, 54]. Weight loss often occurs in type 1 diabetics, especially prior to diagnosis [55]. One meta-analysis reported an increased risk of hip fractures in underweight older women, whereas another meta-analysis found no association between underweight and the risk of fractures in healthy subjects [56, 57]. The risk of fractures in underweight T1D patients is unclear and few studies exist on the risk of falls. The effect of overweight on falls and fractures in diabetics have yielded inverse results. A meta-analysis on

non-diabetics showed a reduced risk of hip fractures in obese persons compared to persons with normal weight [RR 0.66 (95% CI 0.57–0.77)], possibly because protection of a greater soft tissue padding [58]. It is likely that this effect also applies for diabetic patients. On the contrary, Volpato et al. showed that diabetic women suffering from overweight were more likely to fall compared to healthy subjects [OR 3.5 (95% CI 1.21–10.10)] [58, 59]. Furthermore, men with diabetes are known to have an even higher frequency of falls, which could be attributed to an increase in abdominal fat and change in the center of gravity [60–62]. The optimal weight in diabetics in order to avoid falls and fractures is unclear. However, diabetics should strive to maintain a normal weight, which reduces the risk of complications of diabetes.

Falls

Falls are a tremendous burden to patients and associated with severe injuries, such as fractures and hemorrhages [63]. Falling also affects the mental health by inducing fear of falling, confusion, and depression [64]. The outcome is often an impaired quality of life, immobility, inactivity, and institutionalization [63]. A recent meta-analysis by Yang et al. found an increased RR of falls of 1.64 (95% CI 1.27–2.11) in older diabetic patients compared to non-diabetics, whereas the Maastricht Study reported similar fall rates in young and well-treated T2D patients compared to healthy subjects [65•, 66•]. Patients with diabetes have a higher risk of fall-related injuries than subjects without diabetes [67]. Different fall mechanisms among diabetes patients have been proposed as contributors to the increased fracture risk [68]. Some patients may be able to use their forearms to prevent a fall, thereby leading to an increased risk of fracture of the forearm whereas other patients do not fend with their arms and may thus fracture the hips. However, to our knowledge, the association between fracture location and fall mechanism in diabetes patients has not been assessed. Most studies have mainly explored the risk of falling in patients with T2D, although most mechanisms should apply to T1D patients. Few exceptions exit, which have been outlined in the text.

Postural Control and Gait

Postural control is the automatic sequences of events to maintain balance and posture involving dynamic and static stability, whereas gait is the locomotion achieved through the movement of the limbs [69]. Postural control and gait are complex mechanisms that involve sensory-motoric, cognitive, and cardiovascular control [70]. In diabetics, impaired mechanisms of postural control and

altered gait patterns are common and associated with an increased risk of falls [71]. A study of patients with T1D and T2D showed an increase in amount of steps when walking in a linear path and during turns, which indicates an unstable gait due to an impaired dynamic stability [72]. Another study found that T2D patients were associated with impaired dynamic stability measured by TUG [OR 1.59 (95% CI 1.16–2.17)] compared to healthy subjects [73]. In addition, alterations in gait and postural control seem to occur at an early stage of diabetes. A recent study with pre-diabetic patients (T2D) found a more pronounced dynamic support sway during walking, which supports the theory of early changes in postural control and gait [74].

Older adults with diabetes might be more susceptible to cognitive impairment, which can result in altered gait and increased risk for falling. A study found that mild cognitive impairment was associated to falls in older non-diabetics [75]. Another study showed that cognitive function measured by mini-mental state examination and clock drawing test was decreased in diabetics when compared to healthy subjects [OR 0.71 (95% CI 0.53–0.95)] [67]. To which extent cognitive impairments result in altered gait patterns and increased risk of falls in diabetes is uncertain.

Diabetic Polyneuropathy

Diabetic polyneuropathy (DPN) affects the muscular skeletal and motor sensory systems which reduce the ability to detect instabilities and make appropriate adjustments to avoid falling [76, 77]. A study found that DPN in patients with T2D was associated with an increased risk of falls (OR = 1.37, $p = 0.01$), which correlated with the degree of neuropathy judged by a 5.07/10-g Semmes Weinstein Monofilament Examination [78]. A meta-analysis by Abunesh Hazari et al. found a reduced gait speed and a decreased range of the knee joint flexion in T2D patients with DPN compared to non-diabetics, which indicated an impaired dynamic stability [79]. DPN also causes loss of muscle mass and strength in the small muscles of the foot [79]. These changes are thought to induce a higher peak plantar pressure at the forefoot, which contributes to gait and postural control instability. Type 2 diabetics with DPN also exhibit shorter stride lengths and slower hand and foot reaction times, which have been linked to increased risk for falling [80]. The same mechanisms might also apply for patients with T1D.

The Visual and Vestibular System

The visual system is affected both by short-term (edema of the lens) and long-term hyperglycemia, which can lead to diabetic retinopathy (DR) resulting in reduced vision.

Reduced vision can decrease the sensory-motoric response, important for the postural stability. Gupta P et al. found that both type 1 and type 2 diabetic patients with reduced vision from DR have an increased risk of falling compared to non-diabetic patients [OR, 1.31 (95% CI 1.07–1.60)] [81]. In addition, mild or moderate DR were associated with a higher risk of falling when compared with diabetics without DR [OR 1.81 (95% CI 1.23–2.67)] [OR 1.89 (95% CI 1.16–3.07)], respectively.

Vestibular disorder is a well-recognized complication to T2D and may contribute to increased incidences of falling. Agrawl et al. found that vestibular disorder increases the risk of falls among type 2 diabetics, even when adjusted for DPN and DR [OR 2.3 (95% CI 1.1–5.1)] [82]. Specific types of vestibular disorders such as benign paroxysmal positional vertigo (BPPV) and morbus meniere disease (MD) are more prevalent in patients with T1D and T2D [83, 84]. Several studies have suggested that hyperglycemia and hyperinsulinemia are risk factors for the recurrence of BPPV and MD [85, 86]. This indicates that poorly regulated diabetes is associated with vertigo that could lead to falls.

Cardiovascular Disease

Cardiovascular diseases such as cardiac arrhythmia, atherosclerosis, and stroke are common co-morbidities in diabetes that increases the risk of collapse and falls [87, 88]. Diabetic patients with atherosclerosis in, e.g., the central nervous system might suffer from impaired cognition or reduced sensory-motoric reflexes, which alters the postural control and increases the risk of falls. Sequelae to a stroke are associated with changes in the postural control and gait deficits. Changes in postural control reduce static stability during standing and delay the response of dynamic stability in case of imbalances. Gait deficits include reduced force at push-off, decreased joint flexion during the swing phase, and reduced stability during the stance phase [89]. It is reasonable to suggest that the same mechanisms apply in type 1 and type 2 diabetic patients.

Co-Morbidities and Drugs

Diabetic patients often have more than one co-morbidity as hypertension, atherosclerosis, or dyslipidemia, which increases the risk of falling [OR 2.29 (95% CI 1.29–4.08)] [90]. Other morbidities as osteoarthritis [OR 2.13 (95% CI 1.11–4.10)], arthritis [OR 1.45 (95% CI 1.08–1.95)], and coronary heart disease [OR 1.43 (95% CI 1.11–1.99)] additionally increases the risk of falling in patients with T2D [91, 92].

Orthostatic hypotension and orthostatic symptoms are more common in type 2 diabetics when compared to

subjects without diabetes [93, 94•]. J Wu et al. showed that the risk of orthostatic hypotension in T2D diabetics compared to non-diabetic patients was increased [OR 1.68 (95 CI 1.02–2.79)] [93]. However, Hateren et al. found no clear relation between the presence of orthostatic hypotension and falls while orthostatic symptoms as feelings of dizziness, light-headedness, or faintness during the standing period were associated with a high risk of falling [OR 8.21 (95% CI 4.17 to 16.19) [94•].

In the general population, the use of antihypertensive medication seems to be a protective factor against the risk of falling [95]. A study found a decreased risk of falling in subjects using angiotensin-converting enzyme inhibitors [OR 0.62 (95% CI 0.39–0.96)] and calcium channel blockers [OR 0.62 (95% CI 0.42–0.91)] to treat hypertension compared to subjects not taking these drugs [95]. Furthermore, subjects using calcium channel blockers had a higher cerebral blood flow, suggesting a better vascular response to compensate, in case of falling [95]. The ACCORD trial found that intensive antihypertensive treatment that lowered mean systolic blood pressure to below 120 mmHg was not associated with an increased risk of falling in T2D patients aged 40 to 79 years [96].

Drugs as benzodiazepines and opioids may increase the risk of falling due to the occurrence of drowsiness, muscle weakness, change in stability, vertigo, and hypotension. Polypharmacy is a potential contributing factor to the increased risk of falling in patients with T2D. Huang et al. showed that regimens including four or more prescribed medications were significantly associated with an increased risk of falling [4–5 medications, hazard ratio (HR) 1.22 (95% CI 1.04, 1.43)], [6–7 medications, 1.33 (95% CI 1.12, 1.58), [> 7 medications, 1.59 (95% CI 1.34, 1.89)] [97]. T2D patients take on average nine prescription drugs compared to four prescription drugs in non-diabetic patients [67]. Thus, polypharmacy might be an indication of intensified treatment due to a worsening of the diabetes condition.

Hypoglycemia

Diabetic patients have an increased risk of developing hypoglycemia, which is associated with an increased risk of falls in case of collapse or neurological dispute. A retrospective study by Chiba et al. found that hypoglycemia was correlated with an increased risk of falls in T2D patients compared to healthy subjects [OR 3.62 (95% CI 1.24–10.53) [98•]. Furthermore, the number of falls seemed to increase as the frequency of hypoglycemia increased. Sumesh et al. found an increased risk of falls, when comparing T2D patients with or without episodes of hypoglycemia [OR = 1.95 (95% CI = 1.70–2.24)] [99]. Regarding the use of insulin, Schwartz et al. reported an increased risk of falls in women using insulin compared to non-insulin-treated diabetic patients [OR 2.76 (95% CI 1.52–5.01)] [92]. No data was available on the frequency of hypoglycemia, which might explain a part of the increased risk of falls. Although, insulin treatment is a sign of intensified treatment and may represent a worsening of the diabetes condition.

Hypophosphatemia

In diabetes, hyperglycemia and insulin treatment can lead to hypophosphatemia by increased renal clearance or shifts of extracellular phosphate into cells, respectively [100]. In addition, diuretics and bisphosphonates have shown to increase the urinary excretion of phosphate [101]. Both drugs are commonly used in the treatment of diabetic complications. Patients with hypophosphatemia can suffer neuromuscular and hematologic dysfunction and cardiac decompensation [102]. Diabetic patients have an increased risk of developing hypophosphatemia. Therefore, it has been speculated that these mechanisms can affect the risk of falling, possibly by collapse, vertigo, or hypoxia.

Conclusion

In conclusion, an increased risk of fractures in T1D and T2D patients exits. However, in patients with T2D, BMD tends to be normal or even higher compared to healthy individuals. In patients with T1D, BMD underestimates the observed fracture risk. Hence, a new threshold to predict the risk of fractures by DXA in diabetic patients is needed. In diabetes, the bone quality is impaired due to changes in the bone microstructure, alterations of the bone composition, and a low bone turnover leading to increased bone fragility, which increases the risk of fractures. In addition, falls have been suggested to increase the risk of fractures. Several risk factors for falls in diabetic patients exits and seems to affect the postural control, which includes an altered body composition, DPN, cardiovascular disease, other co-morbidities, and the use of medication. Exercise interventions that focus on improving postural control could reduce fall-related injuries in diabetic patients with known risk factors for falls and should be considered by clinicians. The long-term effects of optimal treatment of diabetes should be emphasized in order to reduce complications as DPN, DR, atherosclerosis, and foot ulcer and might prevent the progression of sarcopenia. Additionally, awareness of vestibular disorders as BPPV and MD in T2D might be considered and treatment provided if needed. Adequate treatment of hypertension is important, and clinicians should therefore be careful not to restrain optimal treatment of hypertension in

an effort to prevent falls. Polypharmacy is associated with increased risk of falls in patients with T2D. However, optimal treatment of diabetes is eminent to reduce diabetic complications and polypharmacy might rather be a sign of a worsening of the diabetes condition. Finally, side effects from the use of drugs as insulin, benzodiazepines, and opioids might increase the risk of falls and should be administrated with caution.

The fall mechanisms among diabetic patients have only been assessed in few studies. Thus, a gab of knowledge exits and may influence the current understanding and treatment, in order to reduce the risk of falling and thereby prevent fractures. We need new tools that easily assess risk factors for falls to improve the treatment and prognosis for patients with diabetes and thereby prevent fractures.

Compliance with Ethical Standards

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Federation ID (2017) IDF Diabetes Atlas.
2. Yu OHY, Suissa S. Identifying causes for excess mortality in patients with diabetes: closer but not there yet. Diabetes Care. 2016;39:1851–3.
3. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
4. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos. 2013;8:136.
5. Westberg-Rasmussen S, Starup-Linde J, Gregersen S, Vestergaard P. Predictors of mortality subsequent to a fracture in diabetes mellitus patients. Front Endocrinol (Lausanne). 2015;6:46.
6. Vestergaard P, Rejnmark L, Mosekilde L. Loss of life years after a hip fracture: effects of age and sex. Acta Orthop. 2009;80:525–30.
7. Hamann C, Kirschner S, Günther K-P, Hofbauer LC. Bone, sweet bone—osteoporotic fractures in diabetes mellitus. Nat Rev Endocrinol. 2012;8:297–305.
8. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. Osteoporos Int. 2007;18:427–44.
9. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48:1292–9.
10. Shah VN, Shah CS, Snell-Bergeon JK. Type 1 diabetes and risk of fracture: meta-analysis and review of the literature. Diabet Med. 2015;32:1134–42.
11. Fan Y, Wei F, Lang Y, Liu Y. Diabetes mellitus and risk of hip fractures: a meta-analysis. Osteoporos Int. 2016;27:219–28.
12. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol. 2007;166:495–505.
13. Weber DR, Haynes K, Leonard MB, Willi SM, Denburg MR. Type 1 diabetes is associated with an increased risk of fracture across the life span: a population-based cohort study using the health improvement network (THIN). Diabetes Care. 2015;38:1913–20.
14. Hothersall EJ, Livingstone SJ, Looker HC, Ahmed SF, Cleland S, Leese GP, et al. Contemporary risk of hip fracture in type 1 and type 2 diabetes: a National Registry Study from Scotland. J Bone Miner Res. 2014;29:1054–60.
15. Oei L, Zillikens MC, Dehghan A, Buitendijk GHS, Castano-Betancourt MC, Estrada K, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam study. Diabetes Care. 2013;36:1619–28.
16. Wändell PE, Carlsson AC. Gender differences and time trends in incidence and prevalence of type 2 diabetes in Sweden—a model explaining the diabetes epidemic worldwide today? Diabetes Res Clin Pract. 2014;106:e90–2.
17. Jia P, Bao L, Chen H, Yuan J, Liu W, Feng F, et al. Risk of low-energy fracture in type 2 diabetes patients: a meta-analysis of observational studies. Osteoporos Int. 2017;28:3113–21.
18.•• Starup-Linde J, Hygum K, Langdahl BL. Skeletal fragility in type 2 diabetes mellitus. Endocrinol Metab. 2018;33:339. **This article proposes that the pathogenesis of increased fracture risk in patients with T2D is due to a low bone turnover caused by osteocyte dysfunction and increased sclerostin levels resulting in bone micro-cracks and fractures.**
19. Sellmeyer DE, Civitelli R, Hofbauer LC, Khosla S, Lecka-Czernik B, Schwartz AV. Skeletal metabolism, fracture risk, and fracture outcomes in type 1 and type 2 diabetes. Diabetes. 2016;65:1757–66.
20. Moayeri A, Mohamadpour M, Mousavi SF, Shirzadpour E, Mohamadpour S, Amraei M. Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis. Ther Clin Risk Manag. 2017;13:455–68.
21. Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. Osteoporos Int. 2007;18:1583–93.
22. Blake GM, Fogelman I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgrad Med J. 2007;83:509–17.
23. Eller-Vainicher C, Zhukouskaya VV, Tolkachev YV, Koritko SS, Cairoli E, Grossi E, et al. Low bone mineral density and its predictors in type 1 diabetic patients evaluated by the classic statistics and artificial neural network analysis. Diabetes Care. 2011;34:2186–91.
24. Heilman K, Zilmer M, Zilmer K, Tillmann V. Lower bone mineral density in children with type 1 diabetes is associated with poor glycemic control and higher serum ICAM-1 and urinary isoprostane levels. J Bone Miner Metab. 2009;27:598–604.

25. Kemink SAG, Hermus ARMM, Swinkels LMJW, Lutterman JA, Smals AGH. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. J Endocrinol Investig. 2000;23:295–303.

26. Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol. 2012;27:319–32.

27. de Waard EAC, van Geel TACM, Savelberg HHCM, Koster A, Geusens PPMM, van den Bergh JPW. Increased fracture risk in patients with type 2 diabetes mellitus: an overview of the underlying mechanisms and the usefulness of imaging modalities and fracture risk assessment tools. Maturitas. 2014;79:265–74.

28. Starup-Linde J, Vestergaard P. Management of endocrine disease: diabetes and osteoporosis: cause for concern? Eur J Endocrinol. 2015;173:R93–9.

29. Bullard KM, Cowie CC, Lessem SE, Saydah SH, Menke A, Geiss LS, et al. Prevalence of diagnosed diabetes in adults by diabetes type—United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67:359–61.

30. Leslie WD, Johansson H, McCloskey EV, Harvey NC, Kanis JA, Hans D. Comparison of methods for improving fracture risk assessment in diabetes: the Manitoba BMD registry. J Bone Miner Res. 2018;33:1923–30. https://doi.org/10.1002/jbmr.3538.

31. Tebé C, Martinez-Laguna D, Moreno V, Cooper C, Diez-Perez A, Collins GS, et al. Differential mortality and the excess rates of hip fracture associated with type 2 diabetes: accounting for competing risks in fracture prediction matters. J Bone Miner Res. 2018;33:1417–21.

32. Farlay D, Armas LA, Gineyts E, Akhter MP, Recker RR, Boivin G. Nonenzymatic glycation and degree of mineralization are higher in bone from fractured patients with type 1 diabetes mellitus. J Bone Miner Res. 2016;31:190–5.

33. Filardi T, Carnevale V, Massoud R, Russo C, Nieddu L, Tavaglione F, et al. High serum osteopontin levels are associated with prevalent fractures and worse lipid profile in postmenopausal women with type 2 diabetes. J Endocrinol Investig. 2018;42:295–301. https://doi.org/10.1007/s40618-018-0914-0.

34. Tanaka K, Kanazawa I, Kaji H, Sugimoto T. Association of osteoglycin and FAM5C with bone turnover markers, bone mineral density, and vertebral fractures in postmenopausal women with type 2 diabetes mellitus. Bone. 2017;95:5–10.

35. Miyake H, Kanazawa I, Sugimoto T. Decreased serum insulin-like growth factor-I is a risk factor for non-vertebral fractures in diabetic postmenopausal women. Intern Med. 2017;56:269–73.

36. Ardawi M-SM, Akhbar DH, AlShaikh A, Ahmed MM, Qari MH, Rouzi AA, et al. Increased serum sclerostin and decreased serum IGF-1 are associated with vertebral fractures among postmenopausal women with type-2 diabetes. Bone. 2013;56:355–62.

37. Diascro DD, Vogel RL, Johnson TE, Witherup KM, Pitzenberger SM, Rutledge SJ, et al. High fatty acid content in rabbit serum is responsible for the differentiation of osteoblasts into adipocyte-like cells. J Bone Miner Res. 1998;13:96–106.

38.• Kim TN, Park MS, Yang SJ, et al. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care. 2010;33:1497–9. **This study compares the prevalence of sarcopenia in patients with T2D and controls. T2D was independently associated with sarcopenia.**

39. McLean RR, Shardell MD, Alley DE, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the Foundation for the National Institutes of Health (FNIH) sarcopenia project. J Gerontol Ser A. 2014;69:576–83.

40. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults.

41. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing. 2010;39:412–23.

42.• Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16–31. **This study redefines sarcopneia and provides the newest recommadations. Sarcopenia is a muscle disease and can also occur early in life due to other diseases, inactivity and malnutrition.**

43.• Sarodnik C, Bours SPG, Schaper NC, van den Bergh JP, van Geel TACM. The risks of sarcopenia, falls and fractures in patients with type 2 diabetes mellitus. Maturitas. 2018;109:70–7. **An extensive review, that sum up the existing knowledge on diabetes and falls, suggesting sarcopenia as a significant factor for increased fall risk.**

44. Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes Care. 2007;30:1507–12.

45. Guerrero N, Bunout D, Hirsch S, Barrera G, Leiva L, Henríquez S, et al. Premature loss of muscle mass and function in type 2 diabetes. Diabetes Res Clin Pract. 2016;117:32–8.

46. Umegaki H. Sarcopenia and diabetes: hyperglycemia is a risk factor for age-associated muscle mass and functional reduction. J Diabetes Investig. 2015;6:623–4.

47. Jang HC. Sarcopenia, frailty, and diabetes in older adults. Diabetes Metab J. 2016;40:182–9.

48. Miljkovic-Gacic I, Wang X, Kammerer CM, Gordon CL, Bunker CH, Kuller LH, et al. Fat infiltration in muscle: new evidence for familial clustering and associations with diabetes. Obesity (Silver Spring). 2008;16:1854–60.

49. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. In: Compr. Physiol. Wiley; 2018. p. 1–58.

50. Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. Diabetes. 2002;51:2005–11.

51. Thompson LV. Age-related muscle dysfunction. Exp Gerontol. 2009;44:106–11.

52. Waters DL, Hale L, Grant AM, Herbison P, Goulding A. Osteoporosis and gait and balance disturbances in older sarcopenic obese New Zealanders. Osteoporos Int. 2010;21:351–7.

53.• Chapman A, Meyer C, Renehan E, Hill KD, Browning CJ. Exercise interventions for the improvement of falls-related outcomes among older adults with diabetes mellitus: a systematic review and meta-analyses. J Diabetes Complicat. 2017;31:631–45. **This study found that exercise improves postural control, lower-limb strength and gait among older adults with DM.**

54. Nielson CM, Srikanth P, Orwoll ES. Obesity and fracture in men and women: an epidemiologic perspective. J Bone Miner Res. 2012;27:1–10.

55. Maffeis C, Birkebaek NH, Konstantinova M, Schwandt A, Vazeou A, Casteels K, et al. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: data from the international SWEET registry. Pediatr Diabetes. 2018;19:1211–20.

56. Johansson H, Kanis JA, Odén A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the Association of Fracture Risk and Body Mass Index in women. J Bone Miner Res. 2014;29:223–33.

Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12:249–56.

57. Xiang B-Y, Huang W, Zhou G-Q, Hu N, Chen H, Chen C. Body mass index and the risk of low bone mass–related fractures in women compared with men. Medicine (Baltimore). 2017;96: e5290.

58. Tang X, Liu G, Kang J, Hou Y, Jiang F, Yuan W, et al. Obesity and risk of hip fracture in adults: a meta-analysis of prospective cohort studies. PLoS One. 2013;8:e55077.

59. Volpato S, Leveille SG, Blaum C, Fried LP, Guralnik JM. Risk factors for falls in older disabled women with diabetes: the women's health and aging study. J Gerontol A Biol Sci Med Sci. 2005;60:1539–45.

60. Gravesande J, Richardson J. Identifying non-pharmacological risk factors for falling in older adults with type 2 diabetes mellitus: a systematic review. Disabil Rehabil. 2017;39:1459–65.

61. Heshka S, Ruggiero A, Bray GA, Foreyt J, Kahn SE, Lewis CE, et al. Altered body composition in type 2 diabetes mellitus. Int J Obes. 2008;32:780–7.

62. Herrera-Rangel AB, Aranda-Moreno C, Mantilla-Ochoa T, Zainos-Saucedo L, Jáuregui-Renaud K. Influence of the body mass index on the occurrence of falls in patients with type 2 diabetes mellitus. Obes Res Clin Pract. 2015;9:522–6.

63. Timsina LR, Willetts JL, Brennan MJ, Marucci-Wellman H, Lombardi DA, Courtney TK, et al. Circumstances of fall-related injuries by age and gender among community-dwelling adults in the United States. PLoS One. 2017;12:e0176561.

64. Blackwood J (2018) Cognitive function and falls in older adults with type 2 diabetes mellitus. J Geriatr Phys Ther 1.

65.• Yang Y, Hu X, Zhang Q, Zou R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. Age Ageing. 2016;45:761–7. **In this study with well-treated and young diabetic patients no differences were found in fall and fracture risk when compared to healthy subjects**.

66.• de Waard EAC, Koster A, Melai T, et al. The association between glucose metabolism status, diabetes severity and a history of fractures and recent falls in participants of 50 years and older—the Maastricht Study. Osteoporos Int. 2016;27:3207–16. **In this study with well-treated and young diabetic patients no differences were found in fall and fracture risk when compared to healthy subjects.**

67. Roman de Mettelinge T, Cambier D, Calders P, Van Den Noortgate N, Delbaere K. Understanding the relationship between type 2 diabetes mellitus and falls in older adults: a prospective cohort study. PLoS One. 2013;8:e67055.

68. Patricia Hewston MScOT and Nandini Deshpande PhD (2016) Falls and balance impairments in older adults with type 2 diabetes: thinking beyond diabetic peripheral neuropathy—ClinicalKey.

69. Ivanenko Y, Gurfinkel VS. Human postural control. Front Neurosci. 2018;12:171.

70. Takakusaki K. Functional neuroanatomy for posture and gait control. J Mov Disord. 2017;10:1–17.

71. Hewston P, Deshpande N. Falls and balance impairments in older adults with type 2 diabetes: thinking beyond diabetic peripheral neuropathy. Can J Diabetes. 2016;40:6–9.

72. Petrofsky J, Lee S, Macnider M, Navarro E. Autonomic, endothelial function and the analysis of gait in patients with type 1 and type 2 diabetes. Acta Diabetol. 2005;42:7–15.

73. Kukidome D, Nishikawa T, Sato M, Nishi Y, Shimamura R, Kawashima J, et al. Impaired balance is related to the progression of diabetic complications in both young and older adults. J Diabetes Complicat. 2017;31:1275–82.

74. Almurdhi MM, Brown SJ, Bowling FL, Boulton AJM, Jeziorska M, Malik RA, et al. Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and type 2 diabetes relates to small-fibre neuropathy but not vitamin D deficiency. Diabet Med. 2017;34:839–45.

75. Delbaere K, Kochan NA, Close JCT, Menant JC, Sturnieks DL, Brodaty H, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. Am J Geriat Psychiatry. 2012;20:845–53.

76. Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98:267–80.

77. MacGilchrist C, Paul L, Ellis BM, Howe TE, Kennon B, Godwin J. Lower-limb risk factors for falls in people with diabetes mellitus. Diabet Med. 2010;27:162–8.

78. Bokan-Mirković V, Škarić-Karanikić Ž, Nejkov S, Vuković M, Ćirović D. Diabetic polyneuropathy and risk of falls: fear of falling and other factors. Acta Clin Croat. 2017;56:721–7.

79. Hazari A, Maiya AG, Shivashankara KN, Agouris I, Monteiro A, Jadhav R, et al. Kinetics and kinematics of diabetic foot in type 2 diabetes mellitus with and without peripheral neuropathy: a systematic review and meta-analysis. Springerplus. 2016;5:1819.

80. Morrison S, Colberg SR, Parson HK, Vinik AI. Exercise improves gait, reaction time and postural stability in older adults with type 2 diabetes and neuropathy. J Diabetes Complicat. 2014;28:715–22.

81. Gupta P, Aravindhan A, Gan ATL, Man REK, Fenwick EK, Mitchell P, et al. Association between the severity of diabetic retinopathy and falls in an Asian population with diabetes. JAMA Ophthalmol. 2017;135:1410–6.

82. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Diabetes, vestibular dysfunction, and falls. Otol Neurotol. 2010;31:1.

83. D Silva LJ, Staecker H, Lin J, Maddux C, Ferraro J, Dai H, et al. Otolith dysfunction in persons with both diabetes and benign paroxysmal positional vertigo. Otol Neurotol. 2017;38:379–85.

84. Pieskä T, Kotimäki J, Männikkö M, Sorri M, Hietikko E. Concomitant diseases and their effect on disease prognosis in Meniere's disease: diabetes mellitus identified as a negative prognostic factor. Acta Otolaryngol. 2018;138:36–40.

85. Yoda S, Cureoglu S, Yildirim-Baylan M, Morita N, Fukushima H, Harada T, et al. Association between type 1 diabetes mellitus and deposits in the semicircular canals. Otolaryngol Neck Surg. 2011;145:458–62.

86. Webster G, Sens PM, Salmito MC, Cavalcante JDR, dos Santos PRB, da Silva ALM, et al. Hyperinsulinemia and hyperglycemia: risk factors for recurrence of benign paroxysmal positional vertigo. Braz J Otorhinolaryngol. 2015;81:347–51.

87. Batchelor FA, Mackintosh SF, Said CM, Hill KD. Falls after stroke. Int J Stroke. 2012;7:482–90.

88. Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndr. 2017;9:25.

89. Weerdesteyn V, de Niet M, van Duijnhoven HJR, Geurts ACH. Falls in individuals with stroke. J Rehabil Res Dev. 2008;45: 1195–213.

90. Conner-Kerr T, Templeton MS. Chronic fall risk among aged individuals with type 2 diabetes. Ostomy Wound Manage. 2002;48(28–34):35.

91. Lee KM, Chung CY, Kwon S-S, Lee SY, Kim TG, Choi Y, et al. Factors associated with bone mineral density and risk of fall in Korean adults with type 2 diabetes mellitus aged 50 years and older. J Clin Endocrinol Metab. 2014;99:4206–13.

92. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care. 2002;25:1749–54.

93. Wu J-S, Yang Y-C, Lu F-H, Wu C-H, Wang R-H, Chang C-J. Population-based study on the prevalence and risk factors of orthostatic hypotension in subjects with pre-diabetes and diabetes. Diabetes Care. 2009;32:69–74.

94.• van Hateren KJ, Kleefstra N, Blanker MH, Ubink-Veltmaat LJ, Groenier KH, Houweling ST, et al. Orthostatic hypotension, diabetes, and falling in older patients: a cross-sectional study. Br J

Gen Pract. 2012;62:e696–702. **This study found no clear relation between the presence of orthostatic hypotension and falls in diabetes while orthostatic symptoms during the standing period were associated with a high risk of falling.**

95. Lipsitz LA, Habtemariam D, Gagnon M, Iloputaife I, Sorond F, Tchalla AE, et al. Reexamining the effect of antihypertensive medications on falls in old age. Hypertension. 2015;66:183–9.

96. Margolis KL, Palermo L, Vittinghoff E, Evans GW, Atkinson HH, Hamilton BP, et al. Intensive blood pressure control, falls, and fractures in patients with type 2 diabetes: the ACCORD trial. J Gen Intern Med. 2014;29:1599–606.

97. Huang ES, Karter AJ, Danielson KK, Warton EM, Ahmed AT. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. J Gen Intern Med. 2010;25:141–6.

98.• Chiba Y, Kimbara Y, Kodera R, Tsuboi Y, Sato K, Tamura Y, et al. Risk factors associated with falls in elderly patients with type 2 diabetes. J Diabetes Complicat. 2015;29:898–

902. **In this study, the presence of hypoglycemia was correlated with the risk of falls in Type 2 diabetic patients.**

99. Kachroo S, Kawabata H, Colilla S, Shi L, Zhao Y, Mukherjee J, et al. Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: analysis of a U.S. commercial database. J Manag Care Spec Pharm. 2015;21:243–53.

100. Tenenhouse HS. Phosphate transport: molecular basis, regulation and pathophysiology. J Steroid Biochem Mol Biol. 2007;103: 572–7.

101. Liamis G, Milionis HJ, Elisaf M. Medication-induced hypophosphatemia: a review. QJM. 2010;103:449–59.

102. Padelli M, Leven C, Sakka M, Plée-Gautier E, Carré J-L. Causes, conséquences et traitement de l'hypophosphorémie : une revue systématique de la littérature. Presse Med. 2017;46:987–99.