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Article type : Original Article

Journal of Diabetes Investigation- Original Article

Falls and fractures associated with type 2 diabetic polyneuropathy; a cross-sectional nationwide questionnaire study

Short running title:

Falls and fractures in polyneuropathy

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Word count: Short running title character count (spaces included): 37, Number of references: 44, Number of tables: 2, Number of figures: 2, Word count abstract: 250, Word limit: 3,302 (max 4,000) including title page, abstract but excluding references.

Abstract

Aim

To examine the prevalence of falls and fractures and the association with symptoms of diabetic polyneuropathy (DPN) in patients with recently diagnosed type 2 diabetes.

Research design and methods

A detailed questionnaire on neuropathy symptoms and falls was sent to 6,726 patients enrolled in the DD2 cohort (median age 65 years, diabetes duration 4.6 years). Complete data on fractures and patient characteristics were ascertained from population-based health registries. We defined possible DPN as a score ≥4 on the Michigan Neuropathy Screening Instruments questionnaire (MNSIq). Using Poisson regression analyses, we estimated the adjusted prevalence ratio (aPR) of falls and fractures, comparing patients with and without DPN.

Results

In total, 5,359 (80%) answered the questions on MNSIq and falls. Within the year preceding questionnaire-response, 17% (n=933) reported at least one fall and 1.4% (n=76) suffered from a fracture. The prevalence ratio of falls was substantially increased in patients with possible DPN compared to those without: aPR: 2.33 (95% confidence interval [CI] 2.06-2.63). The prevalence ratio increased with the number of falls from aPR: 1.51 (95% CI: 1.22-1.89) for one fall to aPR: 5.89 (95% CI: 3.84-9.05) for ≥4 falls within the preceding year. Possible DPN was associated with a slightly although non-significantly increased risk of fractures: aPR: 1.32 (95% CI: 0.75-2.33).

Conclusions

Patients with recently diagnosed type 2 diabetes and symptoms of DPN had a highly increased risk of falling. These results emphasize the need for preventive interventions to reduce fall risk among patients with type 2 diabetes and possible DPN.

Keywords: Diabetic polyneuropathy, Falls, Fractures, Type 2 diabetes.

Introduction

The risk of falls is increased in patients with diabetes (1,2), and falling is a major cause of morbidity and mortality in the elderly (3,4). Patients with type 2 diabetes suffer from more recurrent falls (5), more severe fall-related injuries (6), a higher risk of bone fractures (7), and increased risk of hospitalized fall injury (8) compared to healthy individuals. Delayed fracture healing in diabetes (9) leads to longer hospital stays and more frequent hospital readmissions (10), which poses a great economic burden on the health care system (5). Therefore, knowledge on the causes of falls and fractures and the identification of persons with high fall risk early in the course of type 2 diabetes is of great importance.

Diabetic polyneuropathy (DPN) is a common complication in type 2 diabetes (11) that leads to decreased peripheral sensation (12), unstable gait (13), impaired balance (14), and motor dysfunction (15). A few studies have suggested a positive association of DPN in type 2 diabetes with falls (16–19), fractures (20–23), or both (24,25) but convincing evidence is lacking, as the studies have been limited by either size (≤ 48 patients) (17,23), by not applying validated tools for DPN assessment (18,20,22,24,25), by including mixed diabetes populations (both type 1 and type 2 diabetes) (20), by lacking a comparisons group without DPN (17), or by including older populations (age 70-79 years) (16). We, therefore, examined the prevalence of falls and fractures in a large cohort of patients with recently diagnosed type 2 diabetes in Denmark including both patients with and without DPN. We hypothesized that symptoms of DPN are associated with an increased risk of falls and fractures.

Research Design and Methods

This nationwide cross-sectional questionnaire study was conducted on patients enrolled in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort (https://dd2.dk/). The DD2 cohort includes enrolls recently diagnosed type 2 patients from general practitioners (GPs) and endocrinology clinics in Denmark. Enrolment began in November 2010 and is still ongoing (26). Details on the implementation, enrolment process, data linkage, and patient characteristics of this cohort have been described in detail elsewhere (27).

Study population

On June 7th, 2016, a questionnaire consisting of 41 items was sent to all patients enrolled in the DD2 cohort (N = 6,726). The questionnaire was sent to all non-responders a second time on

September 12th, 2016, and a third time on October 10th, 2016. The questionnaire has been described in detail elsewhere (28). Our study population consisted of the patients who answered both the questions on falls and the Michigan Neuropathy Screening Instrument Questionnaire (MNSIq). Figure S1 illustrates a flowchart of the study population.

DPN

The MNSIq is a self-administered validated screening tool available for DPN assessment. The questionnaire consists of 15 "yes" or "no" questions with a maximal score of 13. We used the MNSIq for the evaluation of symptoms of DPN with a validated cut-off score ≥4 to define DPN at the level of "possible" DPN according to the Toronto Classification of DPN (11).

Falls

In the questionnaire, patients were asked to report whether they had fallen within the preceding year, and if so, how many fall-episodes they had experienced: 0, 1, 2-4, or >4 falls. This method of fall evaluation has been used in previous studies evaluating fall frequency (19) and is the best time frame for obtaining self-reported falls ruling out any seasonal influence (29). Patients were asked whether the fall episode(s) had led them to seek medical attention and to specify whether they contacted their general practitioner (GP) and/or a hospital.

Fractures

As the questionnaire did not contain questions regarding fractures, we extracted data on fractures from the Danish National Patient Register (DNPR) (30). All Danish residents are assigned a unique personal identification number, which allows for accurate individual-level linkage of data across registries (27), including the DNPR. The DNPR (30) includes recorded data regarding all non-psychiatric hospital admissions since 1977, and on outpatient clinic and emergency room visits since 1995. In Denmark, all persons suspected of having a fracture are referred to the hospital for further diagnostic work-up. Fractures are coded according to the International Classification of Diseases, version 10 (ICD-10) from 1994 and onwards, thus the DNPR holds complete fracture history. We extracted data on fractures, including the number and types of fractures for all individuals included in the study (N=5,359). Data on fractures were linked and time-matched to the questionnaire data on the occurrence of falls within the preceding year. Figure 1 illustrates the dates on which the questionnaires were sent out and the corresponding time periods used for the assessment of falls and fractures in the primary analyses. The precise date on

which the questionnaires were filled out was not obtained. Thus, in a sensitivity analysis, we expanded the period from June 7th, 2015, to January 24th, 2017, which was the date the last questionnaire was returned, to also include possible fractures in the period from October 10th, 2016, to January 24th, 2017 as illustrated in Figure 1. Fractures were identified based on pre-specified ICD-10 codes (Table S1). If the same type of fracture occurred within three months from the prior fracture, we assumed that this represented the same fracture and consequently was counted once only (see Table S1 for codes and definitions).

Other characteristics

We obtained information from the questionnaire concerning other patient characteristics that may be associated with falls and fractures, including age, sex, BMI, alcohol consumption, and smoking. Additional data, such as the presence of eye disease and a range of comorbidities included in the Charlson Comorbidity Index (CCI), was extracted from the DNPR. Data on medication use was attained from the DNPR. Diabetes duration was determined by either the first diabetes-related hospital-contact, the first prescription redemption of a glucose-lowering drug, or enrollment in DD2. Codes used for the additional data extraction are presented in Table S2. Based on the overall CCI score excluding diabetes, the comorbidity burden was divided into three categories; no comorbidity (CCI score 0), moderate comorbidity (CCI score 1-2), and high comorbidity (CCI score ≥3) (31).

Ethical considerations

All patients in the DD2 project gave informed written consent, and the project was approved by the National Danish Committee on Health Research Ethics (S-20100082) and registered with the Data Protection Agency (2008-58-0035).

Statistical analyses

Main outcomes were self-reported falls and registry-based fractures within the year preceding DPN assessment. We calculated the prevalence of falls and fractures and used Poisson regression to calculate prevalence ratios (PRs) with 95% confidence intervals (95% CI) of falls and fractures for patients with DPN compared to patients without DPN, adjusting for potential confounders mentioned above. We stratified the analyses according to biological sex. Moreover, we conducted a more extensively adjusted analysis adding use of antihypertensive medication and insulin to the regression model. The adjusted PRs (aPR) of falls comparing patients with DPN to those without,

were evaluated by the number of falls. We further compared the proportions of patients with falls who sought medical attention, and we assessed the subtype and number of fractures.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

Results

Among the 6,726 DD2 patients, who received a questionnaire, 5,359 (80%) answered the questions on falls and the MNSIq (Figure S1). Of these, 17 % (n=933) reported at least one fall within the preceding year. Out of all patients reporting at least one fall, 46% had suffered from 1 fall, 36% had 2-4 falls, and 10% had > 4 falls, whereas 8% did not specify the number of falls. In total, 1.4% (n=76) had suffered at least one fracture within the preceding year.

DPN and falls

In patients with DPN, after adjustment for confounders, the prevalence of falls was substantially higher as compared to those without DPN: aPR: 2.33 (95% confidence interval (CI) 2.06-2.63) (Table 1), which was found for both females and males (Table S3). An additional adjustment for the use of antihypertensive medication and insulin did not change the estimate; aPR: 2.31 (95% CI: 2.04-2.61) (Table S4). The prevalence ratio increased with the number of falls from: aPR: 1.51 (95% CI: 1.22-1.89) for having precisely one fall in patients with DPN compared to those without DPN, aPR: 2.86 (95% CI: 2.32-3.52) for having 2 to 4 falls, and aPR: 5.89 (95% CI: 3.84-9.05) for having 4 or more falls within the preceding year (Table 2).

Among the 933 patients with at least one fall, 36% (n = 336) reported a subsequent contact with their GP and/or a hospital. Patients without DPN sought medical attention to a higher degree than those with DPN, mainly driven by those reporting only one fall (Figure 2).

DPN and fractures

In the year preceding DPN assessment, a total of 87 fractures were identified in 76 patients. Of these 87 fractures, 14 (16%) were fractures of the shoulder and upper arm, 14 (16%) of the forearm, 17 (20%) of the wrist and hand, 13 (15%) of the hip and other femoral fractures, 12 (14%) of the lower leg including ankle, 8 (9%) fractures of foot and toe, except ankle, 5 (6%) spinal fractures, 1 (1%) pelvic fractures, 1 (1%) of the skull and facial bones, and 2 (2%) fractures of the ribs and sternum (Table S5).

Possible DPN was associated with a slightly although non-significantly increased risk of fractures: aPR: 1.32 (95% CI: 0.75-2.33) after adjusting for possible confounders (Table 1). Analyses stratified by sex revealed similar results, although these findings were limited by low statistical power (Table S3). In the sensitivity analysis, extending the fracture assessment time-period further attenuated the association aPR: 1.19 (95% CI: 0.77-1.85) (Table S6). Adding the use of antihypertensive medication use and insulin-use to the regression model did not change the estimate; aPR: 1.30 (95% CI: 0.74-2.30) (Table S4).

Other characteristics

Based on the confounder effect estimates, the following clinical characteristics had a positive correlate indicating confounding, when calculating prevalence ratios for falls in patients with DPN: comorbidity burden (CCI 1-2 vs. 0, aPR: 1.26 (95% CI: 1.11-1.43) and CCI ≥3 vs. 0, aPR: 1.29 (95% CI: 1.07-1.54), higher BMI (per one kg/m^2 increase, aPR: 1.01 (95% CI: 1.00-1.02), higher age (per one year increase, aPR: 1.02 (95% CI: 1.01-1.03), and longer diabetes duration (per one year increase, aPR: 1.03 (95% CI: 1.00-1.05) (Table 1). Whereas male sex had a negative correlate indicating confounding when calculating prevalence ratios for patients with DPN compared to patients without DPN both for falls and fractures; aPR: 0.62 (95% CI: 0.55-0.70) and aPR: 0.50 (95% CI: 0.31-0.80), respectively.

Discussion

In this large nationwide cross-sectional questionnaire study of patients with recently diagnosed type 2 diabetes, we determined the prevalence of falls and fractures and evaluated the association with possible DPN based on the MNSIq.

Our main findings are that patients with recently diagnosed type 2 diabetes and possible DPN had a 2.3 times higher risk of falling compared to those without DPN, and the association gradually increased with a higher number of falls. DPN was associated with a slightly, although non-significantly, increased risk of fractures. One-third sought medical attention after a fall-episode, which may indicate that these falls were severe and injurious. Noteworthy, seeking medical attention seemed less frequent in those with DPN compared to those without DPN, indicating that patients with DPN suffered less injurious falls.

DPN and falls in type 2 diabetes

Our findings demonstrate that possible DPN is strongly associated with falls in patients with

recently diagnosed type 2 diabetes. This is the first study evaluating the association between symptoms of neuropathy and the incidence of falls and fractures by applying validated tools for the assessment of DPN. Our findings corroborate previous studies reporting an association between impaired vibration perception (32), reduced nerve conduction velocities of the peroneal nerve (33), and insensate feet (34) and increased risk of falls in patients with longer type 2 diabetes duration. Other factors that have been associated with falls in diabetes include older age, female sex, increased BMI, polypharmacy, hypoglycemic episodes, insulin use, and macro- and microvascular complications (33,35). However, adjustment for multiple these confounders in our study did not change the association between falls and possible DPN.

DPN and fractures in type 2 diabetes

We found that fractures of upper- and lower limbs were the most commonly reported fracture sites, and these findings are in agreement with other studies in type 2 diabetes (36,37). In our study, DPN was only slightly and non-significantly associated to higher prevalence of fractures. Previous studies have shown that patients with longer type 2 diabetes duration have an increased risk of suffering from a fracture (37–39) when compared to healthy individuals. Higher bone fragility is suggested to be the cause of fractures in chronic type 2 diabetes (38), which can occur due to accumulation of advanced glycation end products in bone collagen, increased urinary calcium excretion due to high blood glucose levels, microvascular damage, and decreased bone turnover (40,41). However, it remains unknown why patients with type 2 diabetes have a higher risk of suffering from fractures. Our population is characterized by a relatively high BMI, young age, and relatively short diabetes duration, all of which are known to protect against bone fractures (38), however adjusting for these potential confounders did not change the estimates. We identified fractures based on diagnosis codes; thus, we can only infer that they were fall-related. However, the most common fracture sites were upper and lower limbs, including the hips, which are commonly injured in fall-episodes, thus indicating that patients were “catching themselves from falling”.

In seek of medical attention

In our study, a significant fraction of patients reported seeking medical attention due to falling, while the number of fractures was relatively small. This suggests that although falling does not necessarily result in a bone fracture, there are many other severe and injurious consequences that require medical attention. Following a fall, patients without DPN did seek medical attention more

frequently than those with DPN, indicating that even though patients with DPN fall more often, the falls might be less severe. The high number of patients seeking medical attention in our study is worrisome as our population is younger and has a shorter duration of diabetes compared to other studies describing similar associations. We did not obtain data on the types of injuries other than fractures.

Strengths and Limitations

Falls were self-reported and recorded retrospectively, which may introduce a possible recall-bias or a misinterpretation of the definition of a fall by patients. Further, the cross-sectional design of the study does not allow for a temporal assessment. In our study, multiple confounders were taken into consideration. Medications such as benzodiazepines or opiates may increase the risk of falling. However, since these medications may also be prescribed due to fracture occurrence and for the treatment of neuropathic pain and sleep disorders, these medications may be a part of the causal pathway and thereby not solely considered as confounders. Therefore, we did not adjust for these medications in our study. Hyperglycemic status may be associated with increased fracture risk (42). We did not adjust for HbA1c as we have obtained data on HbA1c in a minor subpopulation only, thus, we did not include HbA1c in the regression analysis. However, we did include both diabetes duration and comorbidities in the regression model, which may to some degree provide similar information as Hba1c levels. Furthermore, we have attained data on insulin-use, which may be an indicator of the severity in dysregulated diabetes, and a marker of increased risk of hypoglycemia. Adding insulin-use to the regression model did not attenuate the impact of DPN. Because of a low number of total fractures and limitations in the specificity of ICD-10 coding and the fact that the DNPR does not distinguish clearly between osteoporotic and non-osteoporotic fractures, we could not examine osteoporotic and non-osteoporotic fractures separately. This should be considered in future studies..

We used a validated questionnaire to determine the presence of DPN. However, since our DPN diagnosis did not include clinical evaluations and neurophysiological examinations, the diagnosis of DPN is only at the level of "possible" DPN according to the Toronto Classification of DPN (11). The MNSIq has a fairly low sensitivity (40%), and high specificity (92%) (43), which is more important when performing measures of relative risk as described in detail elsewhere (44). As of today, there are still no easily assessable tools available for screening and early identification of type 2 diabetes patients at risk of falling. Interestingly, we found that even in

recently diagnosed diabetes, patients report considerably more falls when having symptoms of DPN. Our study can aid in the development of future fall prevention programs and the identification of patients at risk; however, this needs to be further studied in large scaled prospective studies.

In summary, we found that patients with recently diagnosed type 2 diabetes and possible DPN were 2.3 times more likely to have suffered from a fall than those without possible DPN, whereas possible DPN was only slightly and non-significantly associated with fractures. Identifying patients with possible DPN may help in detecting patients at risk of falling and should be considered in future longitudinal studies on fall prevention.

Declaration of interest

The authors declare no conflicts of interest. Research reported in this publication is part of the International Diabetic Neuropathy Consortium (IDNC) research programme, which is supported by a Novo Nordisk Foundation Challenge Programme grant (Grant number NNF14OC0011633) and Aarhus University. The Danish Centre for Strategic Research in Type 2 Diabetes Project (DD2) is supported by the Danish Agency for Science [grant number 09-067009, 09-075724], the Danish Health and Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S. Project partners are listed on the website www.DD2.nu. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies has any relation to the present study.

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Supporting Information

Figure S1. Flowchart of study population

Abbreviations: CCI: Charlson Comorbidity Index; DD2: Danish Centre for Strategic Research in Type 2 Diabetes; DNPR: Danish National Patient Register; ICD-10: International Classification of Diseases, version 10; MNSIq: Michigan Neuropathy Screening Instrument Questionnaire.

Table S1. ICD-10 codes used for data extraction regarding fractures from the Danish National Patient Register (DNPR).

Legends: †Include all lower level codes

Table S2. ICD-10 and ICD-8 codes used for the data extraction and estimation of the Charlson Comorbidity Index from the Danish National Patient Register.

Table S3. Adjusted prevalence ratio of falls and fractures in patients with possible DPN compared to patients without possible DPN. Stratified analyses according to biological sex. Adjusted for age, sex, BMI, smoking, alcohol consumption, CCI, diabetes duration, and eye disease

Table S4. Adjusted prevalence ratio of fractures in patients with possible DPN compared to patients without possible DPN (more extensive adjustment including antihypertensive medication and insulin).

Abbreviations: CI: Confidence Interval, aPR: adjusted prevalence ratio , CCI: Charlson Comorbidity Index,
Adjusted for age, sex, BMI, smoking, alcohol consumption, CCI, anti-hypertensive medication, insulin, diabetes duration, and eye disease.
†DPN defined as MNSIq score ≥4.

Table S5. The total number of fractures extracted from the Danish National Patient Register (June 7th, 2015 to October 10th, 2016).
Legend: The total number of fractures extracted from the DNPR: Danish National Patient Register for two different periods. Proportions (%) calculated for row totals.

Table S6. Adjusted prevalence ratio of fractures in patients with possible DPN compared to patients without possible DPN (sensitivity analysis for the entire time period from June 7th**,** 2015 to January 24th, 2017).

Abbreviations: CI: Confidence Interval, aPR: adjusted prevalence ratio , CCI: Charlson Comorbidity Index

Adjusted for age, sex, BMI, smoking, alcohol consumption, CCI, diabetes duration, and eye disease.

†DPN defined as MNSIq score ≥4.

Figure legends

Figure 1. Dates for the questionnaire distributions and the corresponding time period used for the assessment of falls and fractures. Orange boxes represent time periods over which falls were assessed in the questionnaire. Blue boxes show the corresponding periods used for data extraction from the registry and represent time period over which fractures were obtained. The sensitivity analysis included the entire time period until January 24th, 2017.

Figure 2. Proportion of patients with one or more falls (n=933) who sought medical attention at hospitals, in primary care, or both in primary care and hospitals.

Filled circles: Patients with possible DPN, Empty circles: Patients without DPN

Table 1.

Abbreviations: CI: Confidence Interval; aPR: Adjusted Prevalence Ratio, DPN: Diabetic Polyneuropathy, BMI: Body Mass Index, CCI: Charlson Comorbidity Index.

Adjusted for all variables listed in the table: age, sex, BMI, smoking, alcohol consumption, diabetes duration, CCI and eye disease. Confounder effect estimates were mutually adjusted.

†Possible DPN defined as MNSIq score ≥4.

‡Data are presented as frequencies and percentages (n (%)) or as mean±SD.

§ All analyses were performed as complete case analyses (N = 5,178) as there were only a few missing variables. Missing data: Possible DPN: 0; Sex: 0; Age: 0; Diabetes duration: 2 (0.0%); CCI: 0; BMI: 93 (1.7%); Alcohol: 78 (1.5%); Smoking: 18 (0.3%); Eye disease: 0.

Table 2.

Abbreviations: CI: Confidence Interval; aPR: Adjusted Prevalence Ratio, DPN: Diabetic Polyneuropathy, BMI: Body Mass Index, CCI: Charlson Comorbidity Index.

Adjusted for: age, sex, BMI, smoking, alcohol consumption, diabetes duration, CCI, and eye disease.

†DPN defined as MNSIq score ≥4. ‡Data are presented as frequencies and percentages (n (%)) or as mean±SD.

§ All analyses were performed as complete case analyses (N = 5,178) as there were only few missing variables. Individuals with missing data: Possible DPN: 0; Sex: 0; Age: 0; Diabetes duration: 2 (0.0%); CCI: 0; BMI: 93 (1.7%); Alcohol: 78 (1.5%); Smoking: 18 (0.3%); Eye disease: 0), and 13 patients (0.2%) did not specify the number of falls.

Tables

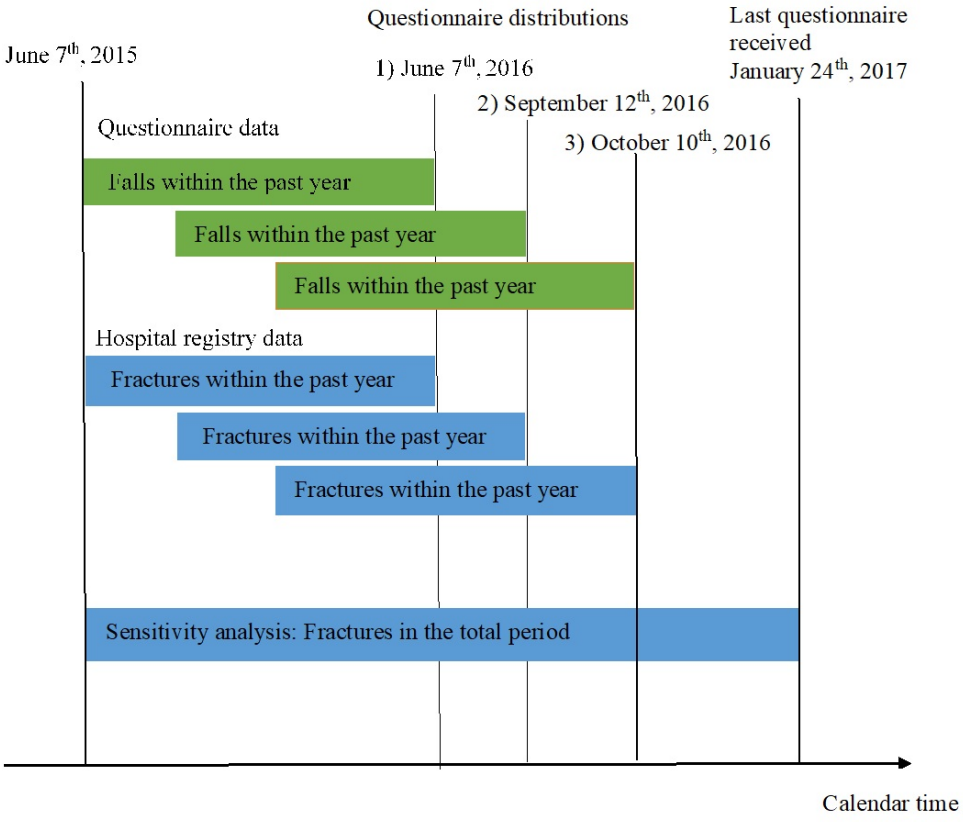
Table 1. Prevalence of falls and fractures in patients with Type 2 diabetes, and the adjusted prevalence ratios of falls and fractures associated with possible DPN and clinical characteristics.

	Falls			Fractures		
	No falls n (%)‡	≥1 fall n (%)‡	≥1 fall aPR (95% CI)§	No fractures n (%)‡	≥1 fracture n (%)‡	≥1 fracture aPR (95% CI)§
Total	4,426 (82.5)	933 (17.4)	-	5,283 (98.6)	76 (1.4)	-
Possible DPN†						
No	3,790 (86.2)	607 (13.8)	Ref.	4,337 (98.6)	60 (1.4)	Ref.
Yes	636 (66.1)	326 (33.9)	2.33 (2.06-2.63)	946 (98.3)	16 (1.7)	1.32 (0.75-2.33)
Sex						
Female	1,759 (77.4)	515 (22.6)	Ref.	2,227 (97.9)	47 (2.1)	Ref.
Male	2,667 (86.5)	418 (13.5)	0.62 (0.55-0.70)	3,056 (99.1)	29 (0.9)	0.50 (0.31-0.80)
Age (unit=1 year)	64±11	66±11	1.02 (1.01-1.03)	64±11	67±10	1.02 (0.99-1.05)
Diabetes duration (unit =1 year)	4.8±2.3	5.1±2.5	1.03 (1.00-1.05)	4.8±2.3	5.1±2.3	1.02 (0.95-1.10)
CCI						
0	2,564 (85.7)	428 (14.3)	Ref.	2,955 (98.8)	37 (1.2)	Ref.
1-2	1,418 (79.3)	370 (20.7)	1.26 (1.11-1.43)	1,759 (98.4)	29 (1.6)	1.25 (0.77-2.05)
≥3	444 (76.7)	135 (23.3)	1.29 (1.07-1.54)	569 (98.3)	10 (1.7)	1.15 (0.51-2.58)
BMI (unit=1 kg/m2)	30.4±5.8	31.0±6.7	1.01 (1.00-1.02)	30.5±5.9	29.4±7.3	0.97 (0.92-1.03)
Units of alcohol/week (F/M)						
≤7/14	3,674 (82.7)	770 (17.3)	Ref.	4,380 (98.6)	64 (1.4)	Ref.
>7/14	697 (83.3)§	140 (16.7)§	1.07 (0.90-1.26)	826 (98.7)	11 (1.3)	1.09 (0.56-2.12)
Current and former history of daily smoking						

No	1,577 (83.0)	324 (17.0)	Ref.	1,870 (98.4)	31 (1.6)	Ref.
Yes	2,837 (82.5)§	603 (17.5)§	0.99 (0.87-1.12)	3,396 (98.7)	44 (1.3)	0.82 (0.50-1.33)
Eye disease						
No	3,810 (83.6)	746 (16.4)	Ref.	4,497 (98.7)	59 (1.3)	Ref.
Yes	616 (76.7)	187 (23.3)	1.15 (0.98-1.33)	786 (97.9)	17 (2.1)	1.28 (0.70-2.32)

Table 2. Adjusted prevalence ratio of falls in type 2 diabetes patients with possible DPN compared to patients without possible DPN by the number of falls.

	Number of falls							
	No falls n (%)‡	No falls aPR (95% CI)§	1 fall n (%)‡	1 fall aPR (95% CI)§	2-4 falls n (%)‡	2-4 falls aPR (95% CI)§	>4 falls n (%)‡	>4 falls aPR (95% CI)§
Total	4,426 (82.6)	-	431 (8.0)	-	393 (7.3)	-	96 (1.8)	-
Possible DPN†								
No	3,790 (86.2)	Ref.	323 (7.3)	Ref.	233 (5.3)	Ref.	40 (0.9)	Ref.
Yes	636 (66.1)	0.78 (0.74-0.82)	108 (11.2)	1.51 (1.22-1.89)	160 (16.6)	2.86 (2.32-3.52)	56 (5.8)	5.89 (3.84-9.05)



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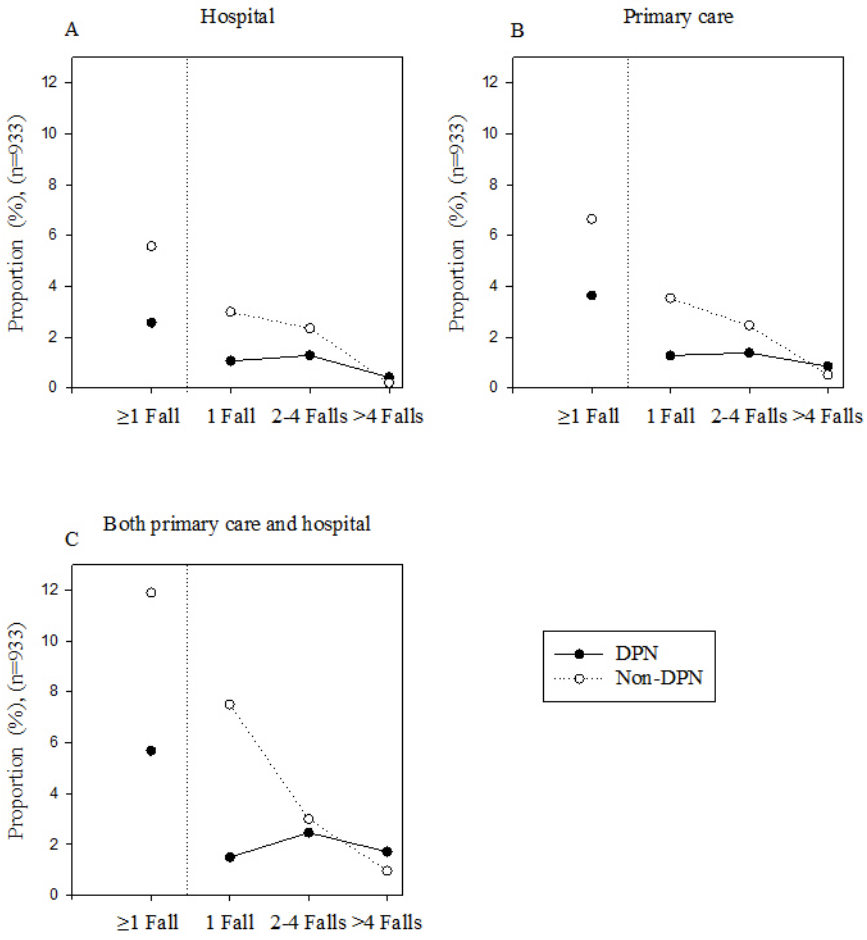

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