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## Standing Balance and Trunk Position Sense in Impaired Glucose Tolerance (IGT)-Related Peripheral Neuropathy

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### Abstract

Type 2 diabetes mellitus (T2DM) and pre-diabetes or impaired glucose tolerance (IGT) affects a large segment of the population. Peripheral neuropathy (PN) is a common complication of T2DM, leading to sensory and motor deficits. While T2DM-related PN often results in balance- and mobility-related dysfunction which manifests as gait instability and falls, little is known about balance capabilities in patients who have evidence of PN related to IGT (IGT-PN). We evaluated patients with IGT-PN on commonly-used clinical balance and mobility tests as well as a new test of trunk position sense and balance impairment, trunk repositioning errors (TREs). Eight participants aged 50–72 years with IGT-PN, and eight age and gender matched controls underwent balance, mobility and trunk repositioning accuracy tests at a university neurology clinic and mobility research laboratory. Compared to controls, IGT-PN participants had as much as twice the magnitude of TREs and stood approximately half as long on the single leg balance test. People with IGT-PN exhibit deficits in standing balance and trunk position sense. Furthermore, there was a significant association between performance on commonly-used clinical balance and mobility tests, and electrophysiological and clinical measures of neuropathy in IGT-PN participants. Because IGT-related neuropathy represents the earliest stage of diabetic neuropathy, deficits in IGT-PN participants highlights the importance of early screening in the dysglycemic process for neuropathy and associated balance deficits.

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## Keywords

balance; impaired glucose tolerance; peripheral neuropathy; trunk position sense

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) affects nearly 20 million people in the United States, while pre-diabetes or impaired glucose tolerance (IGT) affects approximately 42 million people [1]. Peripheral neuropathy (PN) is a common complication of T2DM occurring over time in more than half of patients [2,3] leading to lower extremity somatosensory deficits including reductions in ankle position sense, foot cutaneous sensation, and ankle vibratory sense [4]. Laboratory-based studies indicate impairments in postural control in people with T2DM-induced PN; T2DM patients with PN have greater postural instability than both diabetic patients without PN [5,6] and age-matched healthy controls [6,7]. In many cases T2DM diabetic-related deficits result in or are associated with mobility-related dysfunction such as gait instability [8] and falls [9,10]. Studies such as these suggest that T2DM PN plays a key role in the instability observed in patients with diabetes [6].

Recent research in diabetes has focused on a pre-diabetic state known as impaired glucose tolerance (IGT) [11,12]. IGT is diagnosed with a 2-hour oral glucose tolerance test (OGTT) with plasma glucose values of 140–199 mg/dL indicating prediabetes (IGT) [11], and confers increased risk of developing non-insulin dependent diabetes [13]. Nerve conduction studies demonstrate that neuropathy is already present in 10–18% of patients at the time of diabetes diagnosis [14,15], suggesting that peripheral nerve injury occurs at early stages of disease and with milder glycemic dysregulation. Neuropathy occurring early in diabetes is usually characterized by symmetrical sensory symptoms including pain, and autonomic dysfunction [12,16–20]. Nerve fiber density and electrophysiological studies have shown that IGT contributes to small-fiber sensory neuropathy, similar to that observed in diabetes, yet is milder in its clinical phenotype [12,21,22].

Although patients with T2DM and PN may have balance impairments that may lead to problems with gait and falls, little is known about balance capabilities in patients who have IGT and PN. In the present study, we evaluated patients with IGT-related PN on commonly-used clinical balance and gait tests as well as a new test of trunk flexion position sense [trunk repositioning errors (TREs)], the latter a measure of underlying balance impairments in older adults [23]. Our objectives were to compare clinical balance and mobility tests, as well as TREs between two groups: patients with IGT and PN (IGT-PN) and age- and gender matched controls (CON). A second objective was to relate performance on clinical balance and mobility tests, as well as TREs to electrophysiological and clinical measures of neuropathy in IGT-PN participants. We hypothesized that when compared to CON, patients with IGT-PN would show greater deficits in clinical balance and gait tests as well as TREs. We also hypothesized that performance on clinical balance tests would be associated with electrophysiological and clinical measures of neuropathy in IGT-PN participants.

## 2. Materials and Methods

### Participants

Eight participants aged 50–72 years with impaired glucose tolerance (IGT) and peripheral neuropathy (PN), were recruited from the Neurology Clinic at the University of Michigan. Our investigation was approved by the Institutional Review Board of the University of Michigan Medical School, and participants were consented according to the Declaration of Helsinki. The criteria for inclusion within this study cohort were evidence of symptomatic clinical peripheral

neuropathy based on the Michigan Neuropathy Symptom Instrument (MNSI), Michigan Diabetic Neuropathy Score (MDNS) [24–26] and an abnormality in at least one of the following: (1) nerve conduction studies (NCS) of the median motor and sensory responses, tibial and peroneal motor responses and sural sensory response on the left sides, (2) CASE IV quantitative sensory testing (QST) ( $\geq 95^{\text{th}}$  percentile compared to gender and age matched controls for cold detection threshold (CDT) in the dorsal foot or vibration detection threshold (VDT) at the great toe) [27,28] or (3) quantitative sudomotor axon reflex testing (QSART) sweat volume ( $\leq 5^{\text{th}}$  % at one of four sites: medial forearm 75% of the distance from the ulnar epicondyle to the pisiform bone, the proximal leg, medial distal leg, and proximal foot [29, 30]. Participants also required glucose measurements consistent with either IGT or impaired fasting glucose (IFG) on at least two separate tests of IGT or IFG, using current definitions for these disorders of glucose regulation [31]. Subjects were screened for other causes of neuropathy including concurrent use of neuropathy-inducing medications, environmental toxins, hereditary neuropathy, and laboratory screening (thyroid stimulating hormone, serum protein electrophoresis and immunofixation, antinuclear antibody, vitamin B12 levels, folate levels, and erythrocyte sedimentation rate). Participants were excluded from enrollment if they had a history of an unstable, severe, or chronic medical, arthritic or neurological condition, other than impaired glucose regulation, that might be associated with neuropathy, impairment of balance control, cognition, or ability to comply with the testing requirements of the study. Participants were also excluded if they were on concomitant therapy with experimental medications or with medications known to cause IGT or impairment of balance or cognition. Participants were allowed to remain on stable doses of pain medications that did not cause an adverse effect in the participant. Eight healthy community-dwelling age- and gender-matched participants were recruited as non-diabetic controls (CON). Functionally independent community-dwelling volunteers were recruited from a database maintained by the University of Michigan Older Americans Independence Center Human Subjects and Assessment Core and other University of Michigan Hospital and local advertisements. All participants were Caucasian. All participants (IGT-PN and CON) underwent a complete medical history and physical examination. Participants were excluded if they were medically unstable, reported back or lower extremity symptoms that might affect balance and trunk position sense testing, or reported a history of upper motor neuron disease such as stroke or Parkinson's disease that could affect balance. At screening, all IGT-PN participants had clinical symptoms and signs of peripheral neuropathy. Those in the CON group denied a history of diabetes or elevated glucose and had no clinical evidence of PN on history or examination. Both IGT-PN and CON had limited musculoskeletal complaints in the lower extremity (2/8 in each group), but were asymptomatic at the time of testing. Four of the eight IGT-PN complained of difficulty with balance, walking or falls. There were no other relevant active symptoms or diagnoses. Height, weight, and body mass index (BMI) was obtained for all participants. BMI was calculated as  $\text{kg}/\text{m}^2$ .

### Measures of Neuropathy

The methods for performing and interpreting the NCS, QST, QSART, and intraepidermal nerve fiber density (IENFD) have been previously published [21,32,33]. An abnormal sural nerve amplitude is a frequent NCS abnormality in IGT patients (other NCS measures are most often normal) and provides a measure of large myelinated nerve fiber function in a distal leg sensory nerve. An abnormal response is consistent with clinical findings of neuropathy.

The Michigan Diabetic Neuropathy Score (MDNS) provides a quantitative neurological assessment of sensation, strength and reflexes in the extremities, with emphasis on the hands and feet. This instrument is currently in use in the Epidemiology of Diabetes and Complications Trial (EDIC). The MDNS has been administered to over 8,000 patients and has been validated

as an instrument to determine the presence and severity of neuropathy in diabetic patients [25,26]

### Trunk repositioning errors (TREs)

Trunk position sense as indicated by Trunk Repositioning Errors (TREs) was assessed under three visual-surface conditions: eyes opened standing on the floor (EO FLOOR), eyes closed standing on the floor (EC FLOOR), and eyes opened while standing on foam of density 44.85kg/m<sup>3</sup> (EO FOAM) [23]. A hand-held digital inclinometer at the level of the T4 spinous process was used to record trunk flexion angles. With arms folded across the chest, participants flexed the trunk in the sagittal plane, stopping for a count of 3 seconds on the examiner's command at a point that corresponded to approximately 30° of forward bending (position 1). They then returned to the neutral upright position and attempted to duplicate the previously attained trunk flexion angle. Participants indicated when they perceived that they had reached the previously attained angle, and held their position for a count of 3 seconds (position 2). The absolute difference in degrees between positions 1 and 2 was defined as the trunk repositioning error, and represented a measure of trunk position sense. Five trials were performed for each of the three visual-surface conditions, generating five scores for each condition. For each condition the highest and lowest scores were discarded, and the final TRE used in the analysis of each visual-surface condition was mean of the remaining three scores.

### Clinical Balance and Mobility Tests

**Unipedal stance time**—Unipedal stance time (UST) is a commonly-used measure of balance capabilities, and a significant predictor of falls [34], injurious falls [35] and peripheral neuropathy [36]. With the arms folded across the chest, participants stood on their dominant leg and lifted the foot of the other leg approximately 2 inches from the medial malleolus of the stance leg. A practice trial preceded two experimental trials, and UST was recorded as the better of the two trials up to a maximum of 30 seconds.

**Maximum step length**—Maximum step length (MSL) is a test of stepping that correlates with balance and mobility measures, as well as falls in balance-impaired older adults [37,38]. With arms folded across the chest, participants attempted to step forward maximally with their dominant leg and return successfully to the original position. A practice trial preceded five experimental trials, the mean of which was recorded as MSL.

**Timed up and go**—Timed up and go (TUG) is a valid test of mobility and dynamic balance [39] and a predictor of falls [40]. Participants were required to rise from a chair, walk 3 meters at their usual comfortable safe pace, turn around and return to the seated position. Participants performed a practice trial and TUG was scored as the mean time of three subsequent trials.

### Data analysis

Differences between the IGT-PN and CON groups in anthropometric variables (height, weight, BMI), clinical balance and mobility measures (UST, MSL, and TUG), and TREs were evaluated using independent samples t-tests. As UST was not normally distributed, it was further analyzed categorically using Fisher's Exact Test, based on a cut-point of 10 seconds [41]. To evaluate TRE differences between the two groups, while simultaneously accounting for the possible effect of truncal obesity on TREs, BMI was included as a covariate in repeated measures and univariate ANCOVA models. In the repeated measures analysis of covariance (RM-ANCOVA) analysis, TREs measured under the three visual-surface conditions constituted the repeated measures. In order to determine which TREs were different between the groups, separate univariate ANCOVAs for TREs measured under each of the three visual-surface conditions were conducted. The relationships between BMI and TREs, and clinical

balance/mobility tests and TREs were evaluated for each of the groups separately, as well as for the entire sample using Pearson's Correlation Coefficient. Due to the skewed nature of UST in this sample, Spearman's rho statistic was used to evaluate the relationship between UST and TREs. For the IGT-PN group, relationships between measures of neuropathy and clinical balance/mobility tests, as well as TREs were evaluated using Pearson's Correlation Coefficient. Intertrial reliability for TREs measured under each of the three visual-surface conditions was assessed using Cronbach's alpha.

### 3. Results

#### Participant characteristics

Anthropometric characteristics of the age- and gender-matched 16 participants are included in Table 1. Height, weight and BMI tended to be higher in the IGT-PN group than in control participants, although the differences were not significant ( $p=0.14-0.66$ ).

#### Clinical Balance/Mobility Tests and Neuropathy Measures

Clinical balance and mobility tended to be better in CON than in the IGT-PN group (Table 2). For mean UST, CON (28.3 seconds) stood approximately twice as long compared to IGT-PN (15.2 seconds) group ( $p=0.02$ ). Categorical analysis of UST revealed that for the CON group, 100% of participants exceeded the cut-point of 10 seconds [41], yet in the IGT-PN group only 3/8 (39%) were able to stand unipedally for greater than 10 seconds ( $p=0.026$ , two-tailed Fisher's Exact Test). For IGT-PN compared to CON, mean TUG was one second slower while the mean MSL expressed as a percent of body height was reduced by 11%, with neither difference reaching statistical significance ( $p=0.17-0.35$ ).

Measures of neuropathy are presented for the IGT-PN group (Table 2). IENFD, a measurement of "small fiber" peripheral nerve pathology at the distal leg (mean 0.86 fibers/mm, range from 0 through 1.66 fibers/mm) was severely reduced in all participants in the study and a clinical measure of neuropathy, the MDNS, was also abnormal in 90% of participants (mean 13.1, range from 0 through 22). The MDNS was most abnormal for pain and monofilament touch perception. In contrast, the sural nerve amplitude, a measure of large sensory myelinated fiber function was normal in half the participants (mean 4.14 microvolts, range from 0 through 19.6 microvolts). QST was also abnormal in the distal lower extremity. In two participants the VDT and CDT were >99% (completely insensitive). In the remainder of the participants the mean CDT (mainly small fiber function) was  $96.2 \pm 0.6\%$  and the mean VDT (mainly large fiber function) was  $92.2 \pm 4.3\%$ . Overall, this indicates that the IGT-PN cohort have a predominantly distal sensory small fiber neuropathy with some participants exhibiting large fiber abnormality as well.

Performance on clinical balance tests was associated with electrophysiological and clinical measures of neuropathy in IGT-PN participants. MSL correlated significantly with sural nerve amplitude ( $r=0.79$ ,  $p=0.02$ ) and showed a trend toward significant correlation with the MDNS ( $r=-0.69$ ,  $p=0.06$ ). TUG correlated significantly with MDNS ( $r=0.71$ ,  $p=0.05$ ). These correlations suggest a relationship between measures of neuropathy and performance on clinical balance and mobility tests in the IGT-PN group.

#### Trunk Repositioning Errors

Independent samples t-tests demonstrated that TREs were significantly greater in the IGT-PN than in the CON group for each of the three visual-surface conditions ( $p<0.05$ ) (Table 3). In the RM-ANCOVA model, there was a significant difference in TREs between IGT-PN and control participants, even when covarying BMI ( $p=0.004$ ). Univariate ANCOVAs demonstrated that TREs were significantly greater in the IGT-PN than in the CON group, even



when controlling for BMI, for EO FLOOR ( $p=0.02$ ), EC FLOOR ( $p=0.03$ ) and especially for EO FOAM ( $p=0.002$ ) (Table 3). Difference in TREs between the groups was 1.6-fold for EO FLOOR; 1.7-fold for EC FLOOR, and 2.2-fold for EO FOAM. In contrast to the significant main effect for groups, there were no significant main effect for the covariate BMI in either the repeated-measures or univariate ANCOVAs ( $p>0.05$ ). Pearson's Correlations confirmed that there was no significant association between BMI and TREs within either group, or for the groups combined ( $p>0.05$ ).

For the entire sample, TREs assessed as EO FOAM correlated strongly with UST (Pearson's  $r = -0.50$ ;  $p<0.05$ ; Spearman's  $\rho = -0.41$ ;  $p>0.05$ ). For the entire sample, EO FLOOR (Pearson's  $r = -0.27$ ;  $p>0.05$ ; Spearman's  $\rho = -0.21$ ;  $p>0.05$ ) and EC FLOOR (Pearson's  $r = -0.23$ ;  $p>0.05$ ; Spearman's  $\rho = -0.21$ ;  $p>0.05$ ) did not correlate significantly with UST. For the IGT-PN and CON groups considered separately, TREs measured under each of the three visual-surface conditions did not correlate significantly with UST.

There was an association between TREs and electrophysiological measures. For the IGT-PN group, Pearson's correlation coefficient between TREs and IENFD at the proximal thigh ranged from  $-0.36$  (EO FOAM) to  $-0.51$  (EO FLOOR). These values did not reach significance most likely due to the small sample size of IGT-PN subjects.

Intertrial test-retest reliability of TRE measures was excellent for the sample as a whole. Cronbach's alpha for EO FLOOR, EC FLOOR, and EO FOAM was 0.71, 0.81, and 0.90 respectively. In the IGT-PN group, Cronbach's alpha for EO FLOOR, EC FLOOR, and EO FOAM was 0.69, 0.72, and 0.95 respectively. In the CON group, Cronbach's alpha for EO FLOOR, EC FLOOR, and EO FOAM was 0.30, 0.71, and 0.25 respectively.

#### 4. Discussion

To our knowledge, this is the first report demonstrating balance deficits in patients with Impaired Glucose Tolerance (IGT) and peripheral neuropathy (PN), specifically in unipedal stance time (UST) and trunk repositioning errors (TREs). It is also the first report of an association between commonly-used clinical balance and mobility tests such as MSL and TUG, and electrophysiological and clinical measures of neuropathy in IGT-PN participants. As the IGT-PN participants in the study demonstrated distal foot somatosensory deficits on electrophysiological and clinical testing, these results suggest a role for foot somatosensation in single limb stance and trunk positioning ability. The importance of these deficits in IGT-PN participants is highlighted by the recent finding that IGT-PN patients' improved metabolic control following dietary and exercise counseling is associated with early regeneration of peripheral epidermal nerve fibers [21]. This raises the question of whether regeneration of peripheral nerve fibers can also translate to improvement in IGT-induced deficits in balance control. The possibility that early reversal or slowing of PN progression and subsequent balance deficits may be accomplished by interventions including diet and exercise is particularly intriguing.

For the entire sample, we noted a strong and significant relationship between UST and trunk repositioning accuracy assessed as EO FOAM. This relationship between EO FOAM and UST was not observed when considering the two groups individually. Whether this may be due to the relatively small sample sizes of the two group ( $n=8$  each) is unclear. TRE reliability was excellent, with Cronbach's alpha ranging from 0.71–0.90 for the three visual-surface conditions.

Although BMI of the IGT-PN group exceeded that of CON, the differences were not significantly different. Therefore group differences in TREs are unlikely to be due to inter-group BMI differences. We found no significant correlations between BMI and TREs within

each of the groups considered separately, as well as for the groups combined. Furthermore, after controlling for inter-group variation in BMI, there were still significant differences in TREs between the groups. These data suggest a limited role for BMI in influencing TREs, and that the ability to accurately reposition the trunk may be dependent on factors other than BMI.

Previous studies have demonstrated T2DM PN-induced reductions in UST [36] as well as deficits in postural control as indicated by fluctuations in center of pressure and center of mass [7,42]. By contrast, patients with peripheral neuropathy associated with Charcot-Marie-Tooth disease type 1A (CMT1A), exhibit a different postural response compared to the diabetic cohorts. In patients with CMT1A, body sway area under all postural and visual conditions (eyes open or closed; feet together or apart) was within normal limits in the less severely affected patients, and was increased only in the most severely affected patients [43]. This observation is consistent with the notion that loss of the largest afferent fibers (group Ia) such as occurs in CMT1A patients is by itself not detrimental to postural control during quiet stance, and that increased unsteadiness in those with severe neuropathy may be due to both large and small fibers being affected [43]. These studies suggest heterogeneity of responses due to the effects of peripheral neuropathy, and the pattern of increased body sway exhibited by diabetic neuropathy patients may be due to loss or impairment of afferent myelinated fibers of smaller diameter than the large Ia fibers [42], or because, unlike CMT1A where predominantly large myelinated fibers are affected, the population of peripheral nerve fibers affected is very heterogeneous in diabetes mellitus. As IGT-related neuropathy is characterized by involvement of a heterogeneous fiber population in which small nerve fiber injury predominates [12,21], our data showing IGT-PN induced deficits in UST and TREs are consistent with the idea that small fiber injury is associated with deficits in upright equilibrium.

Although our data presented here suggest that the small-fiber injury that occurs during glucose dysmetabolism is associated with deficits in standing balance, the full functional and clinical implications of TRE deficits in IGT-PN or even T2DM-PN patients remains to be determined. Trunk position sense studies to date have largely addressed trunk repositioning accuracy in patients with low back pain [44]. We have recently shown the validity of TREs as a measure of underlying balance impairment in adults 65 years or older; in those individuals, trunk repositioning errors are increased in balance-impaired individuals, and correlate with commonly-used clinical balance measures [23]. This finding is notable given the importance of trunk flexion control in recovering from a stumble in order to avoid a fall [45]. Future prospective studies should address the functional implications of deficits in trunk position sense in patients with IGT-PN, such as the relationship between TREs and falls in those with IGT-PN.

There are limitations associated with this study. First, the controls did not undergo electrophysiological testing to rule out underlying subtle changes in neurological status, although these changes are unlikely given their normal clinical evaluation and functional performance. Second, the small sample size in the IGT-PN group precluded a more in-depth analysis of relationships between neuropathy and clinical balance measures. The findings from this study are not generalizable, and future studies addressing these limitations may be needed to confirm the present results.

IGT-related neuropathy represents the earliest stage of diabetic neuropathy [12,16–21]. The relationship observed here between measures of neuropathy and performance on clinical balance and mobility tests in participants with IGT-PN, together with our finding of postural control and balance deficits in IGT-PN participants versus CON, suggests that people with IGT-PN should be screened early in the dysglycemic process for balance and mobility-related problems. Future studies must be undertaken to validate TREs as a measure of balance impairment and falls risk in this patient population. Should TREs be shown to be associated

with increased falls risk in people with IGT-related neuropathy, appropriate rehabilitation interventions should be instituted in a timely fashion. Future studies should determine whether cutaneous nerve fiber preservation and reinnervation leads to improvements in trunk position sense in people with IGT-related neuropathy. If this turns out to be the case, TREs may be a useful endpoint measure in future neuropathy intervention studies, and TREs may also be a useful and valid measure of underlying clinical progression.

## 5. Conclusions

These data demonstrate balance deficits in participants with IGT-PN, specifically in unipedal stance time and trunk repositioning errors. As IGT-related neuropathy represents the earliest stage of diabetic neuropathy, people with IGT-PN should be screened early in the dysglycemic process for balance and mobility-related problems.

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## References

- Davidson JA. Introductory remarks: diabetes care in America - "a sense of urgency". *Endocr Pract* 2006;12 (Suppl 1):13–5. [PubMed: 16627373]
- Ziegler D, Gries FA, Spuler M, Lessmann F. The epidemiology of diabetic neuropathy. Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. *J Diabetes Complications* 1992;6:49–57. [PubMed: 1562759]
- Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 1993;43:817–24. [PubMed: 8469345]
- Dickstein R, Shupert CL, Horak FB. Fingertip touch improves postural stability in patients with peripheral neuropathy. *Gait Posture* 2001;14:238–47. [PubMed: 11600327]
- Simoneau GG, Ulbrecht JS, Derr JA, Becker MB, Cavanagh PR. Postural instability in patients with diabetic sensory neuropathy. *Diabetes Care* 1994;17:1411–21. [PubMed: 7882810]
- Yamamoto R, Kinoshita T, Momoki T, Arai T, Okamura A, Hirao K, et al. Postural sway and diabetic peripheral neuropathy. *Diabetes Res Clin Pract* 2001;52:213–21. [PubMed: 11323091]
- Corriveau H, Prince F, Hebert R, Raiche M, Tessier D, Maheux P, et al. Evaluation of postural stability in elderly with diabetic neuropathy. *Diabetes Care* 2000;23:1187–91. [PubMed: 10937520]
- Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Arch Phys Med Rehabil* 2004;85:245–52. [PubMed: 14966709]
- 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. [PubMed: 12351472]
- Tilling LM, Darawil K, Britton M. Falls as a complication of diabetes mellitus in older people. *J Diabetes Complications* 2006;20:158–62. [PubMed: 16632235]
- Singleton JR, Smith AG, Russell J, Feldman EL. Polyneuropathy with Impaired Glucose Tolerance: Implications for Diagnosis and Therapy. *Curr Treat Options Neurol* 2005;7:33–42. [PubMed: 15610705]
- Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology* 2003;60:108–11. [PubMed: 12525727]



13. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 1997;46:701–10. [PubMed: 9075814]
14. Lehtinen JM, Niskanen L, Hyvonen K, Siitonen O, Uusitupa M. Nerve function and its determinants in patients with newly-diagnosed type 2 (non-insulin-dependent) diabetes mellitus and in control subjects--a 5-year follow-up. *Diabetologia* 1993;36:68–72. [PubMed: 8436256]
15. Cohen JA, Jeffers BW, Faldut D, Marcoux M, Schrier RW. Risks for sensorimotor peripheral neuropathy and autonomic neuropathy in non-insulin-dependent diabetes mellitus (NIDDM). *Muscle Nerve* 1998;21:72–80. [PubMed: 9427226]
16. Singleton JR, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve* 2001;24:1225–8. [PubMed: 11494277]
17. Russell JW, Feldman EL. Impaired glucose tolerance--does it cause neuropathy? *Muscle Nerve* 2001;24:1109–12. [PubMed: 11494263]
18. Novella SP, Inzucchi SE, Goldstein JM. The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve* 2001;24:1229–31. [PubMed: 11494278]
19. Smith AG, Ramachandran P, Tripp S, Singleton JR. Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. *Neurology* 2001;57:1701–4. [PubMed: 11706115]
20. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. *Diabetes* 2003;52:2867–73. [PubMed: 14633845]
21. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 2006;29:1294–9. [PubMed: 16732011]
22. Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care* 2001;24:1448–53. [PubMed: 11473085]
23. Goldberg A, Hernandez ME, Alexander NB. Trunk repositioning errors are increased in balance-impaired older adults. *J Gerontol A Biol Sci Med Sci* 2005;60:1310–4. [PubMed: 16282565]
24. Feldman EL, Stevens MJ. Clinical testing in diabetic peripheral neuropathy. *Can J Neurol Sci* 1994;21:S3–7. [PubMed: 7874610]
25. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994;17:1281–9. [PubMed: 7821168]
26. Fedele D, Comi G, Coscelli C, Cucinotta D, Feldman EL, Ghirlanda G, et al. A multicenter study on the prevalence of diabetic neuropathy in Italy. Italian Diabetic Neuropathy Committee. *Diabetes Care* 1997;20:836–43. [PubMed: 9135952]
27. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 1997;49:229–39. [PubMed: 9222195]
28. Dyck PJ, O'Brien PC, Kosanke JL, Gillen DA, Karnes JL. A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. *Neurology* 1993;43:1508–12. [PubMed: 8351003]
29. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 1983;14:573–80. [PubMed: 6316835]
30. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. *Muscle Nerve* 1997;20:1561–8. [PubMed: 9390669]
31. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–7. [PubMed: 14578255]
32. Peltier AC, Consens FB, Sheikh K, Wang L, Song Y, Russell JW. Autonomic dysfunction in obstructive sleep apnea is associated with impaired glucose regulation. *Sleep Med* 2007;8:149–55. [PubMed: 17236808]
33. Russell, JW. Quantitative sensory testing. In: Bromberg, MB.; Smith, AG., editors. *Handbook of peripheral neuropathy*. Taylor and Francis LLC; 2005. p. 45-52.
34. Hurvitz EA, Richardson JK, Werner RA, Ruhl AM, Dixon MR. Unipedal stance testing as an indicator of fall risk among older outpatients. *Arch Phys Med Rehabil* 2000;81:587–91. [PubMed: 10807096]

35. Vellas BJ, Wayne SJ, Romero L, Baumgartner RN, Rubenstein LZ, Garry PJ. One-leg balance is an important predictor of injurious falls in older persons. *J Am Geriatr Soc* 1997;45:735–8. [PubMed: 9180669]
36. Hurvitz EA, Richardson JK, Werner RA. Unipedal stance testing in the assessment of peripheral neuropathy. *Arch Phys Med Rehabil* 2001;82:198–204. [PubMed: 11239310]
37. Medell JL, Alexander NB. A clinical measure of maximal and rapid stepping in older women. *J Gerontol A Biol Sci Med Sci* 2000;55:M429–33. [PubMed: 10952364]
38. Cho BL, Scarpace D, Alexander NB. Tests of stepping as indicators of mobility, balance, and fall risk in balance-impaired older adults. *J Am Geriatr Soc* 2004;52:1168–73. [PubMed: 15209657]
39. Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8. [PubMed: 1991946]
40. 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;80:896–903. [PubMed: 10960937]
41. 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:M291–7. [PubMed: 7583799]
42. Nardone A, Schieppati M. Group II spindle fibres and afferent control of stance. Clues from diabetic neuropathy. *Clin Neurophysiol* 2004;115:779–89. [PubMed: 15003757]
43. Nardone A, Tarantola J, Miscio G, Pisano F, Schenone A, Schieppati M. Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. *Exp Brain Res* 2000;135:155–62. [PubMed: 11131499]
44. Gill KP, Callaghan MJ. The measurement of lumbar proprioception in individuals with and without low back pain. *Spine* 1998;23:371–7. [PubMed: 9507628]
45. Grabiner MD, Koh TJ, Lundin TM, Jahnigen DW. Kinematics of recovery from a stumble. *J Gerontol* 1993;48:M97–102. [PubMed: 8482818]

**Table 1**  
 Characteristics of Impaired Glucose Tolerant-Peripheral Neuropathy (IGT-PN)  
 and Non-Diabetic Control (CON) groups

	IGT-PN (n=8)	CON (n=8)	p value
<i>Characteristic</i>			
Age (years)	60.1 ± 2.4 (54.5–65.8)	60.0 ± 2.6 (53.9–66.1)	-
Age range (years)	50–72	51–73	
Height (meters)	1.71 ± 0.03 (1.64–1.78)	1.69 ± 0.03 (1.62–1.77)	.66
Weight (kilograms)	93.71 ± 7.11 (76.89–110.53)	80.47 ± 4.83 (69.04–91.90)	.15
BMI (kg/m <sup>2</sup> )	31.65 ± 1.50 (28.10–35.19)	28.10 ± 1.70 (24.07–32.12)	.14
Sex (male : female)	4:4	4:4	-

*Notes:* Age, height, weight, and body mass index (BMI) values are mean ± standard errors of the mean. Figures in parentheses are the 95% confidence intervals for the mean. In each case the p values are from independent samples t-tests.

**Table 2**  
Clinical Balance/Mobility and Neuropathy Measures for Impaired Glucose Tolerant-Peripheral Neuropathy (IGT-PN) and Non-Diabetic Control (CON) groups

	IGT-PN (n=8)	CON (n=8)	p value
<i>Balance/mobility</i>			
UST (s)	15.2 ± 4.4 (4.9–25.5)	28.3 ± 1.7 (24.4–32.3)	0.02
TUG (s)	10.0 ± 0.7 (8.3–11.6)	9.2 ± 0.2 (8.7–9.8)	0.35
MSL (adjusted)	49.7 ± 3.0 (42.5–56.8)	55.7 ± 2.9 (48.9–62.5)	0.17
<i>Neuropathy</i>			
IENFD distal leg (fibers/mm)	0.86 ± 0.24 (0.27–1.4)	NT	-
IENFD proximal thigh (fibers/mm)	5.37 ± 0.42 (4.3–6.4)	NT	-
Sural nerve amplitude (microvolts)	4.14 ± 2.4 (1.4–9.7)	NT	-
MDNS	13.13 ± 2.5 (7.2–19.0)	NT	-

*Notes:* Values are mean ± standard errors of the mean. Figures in parentheses are the 95% confidence intervals for the mean. UST = unipedal stance time in seconds; TUG = timed up and go in seconds; MSL (adjusted) = maximum step length expressed as a percent of body height; IENFD = intraepidermal nerve fiber density; MDNS = Michigan Diabetic Neuropathy Score; NT=not tested. In each case the p values are from independent samples t-tests.

**Table 3**

Trunk position sense measured as trunk repositioning errors (TREs) for Impaired Glucose Tolerant-Peripheral Neuropathy (IGT-PN) and Non-Diabetic Control (CON) groups

	IGT-PN (n=8)	CON (n=8)	p value
<i>TREs (degrees)</i>			
EO FLOOR	5.4 ± 0.6 (3.9–6.9)	3.4 ± 0.4 (2.4–4.3)	0.018
EO FLOOR (adj.)	5.5 ± 0.6 (4.3–6.7)	3.3 ± 0.6 (2.0–4.5)	0.020
EC FLOOR	6.6 ± 0.7 (5.0–8.2)	3.8 ± 0.7 (2.2–5.5)	0.013
EC FLOOR (adj.)	6.5 ± 0.7 (4.9–8.1)	3.9 ± 0.7 (2.3–5.5)	0.030
EO FOAM	6.9 ± 0.9 (4.8–8.9)	3.1 ± 0.5 (2.1–4.2)	0.002
EO FOAM (adj.)	7.1 ± 0.7 (5.5–8.6)	2.9 ± 0.7 (1.4–4.5)	0.002

*Notes:* Values are mean ± standard errors of the mean. Figures in parentheses are the 95% confidence intervals for the mean. EO FLOOR = trunk repositioning errors measured with eyes opened standing on floor; EC FLOOR = trunk repositioning errors measured with eyes closed standing on floor; EO FOAM = trunk repositioning errors measured with eyes opened standing on foam. (adj.) = trunk repositioning errors measured with body mass index as a covariate. *p* values are from independent samples *t*-tests for EO FLOOR, EC FLOOR, and EO FOAM, or from univariate analysis of variance models with body mass index as a covariate for EO FLOOR (adj.), EC FLOOR (adj.), and EO FOAM (adj.).