Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and type 2 diabetes relates to small fiber neuropathy but not vitamin D deficiency

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Word Count of Abstract: 246

Word Count: 2,978

Number of Tables: 2

Number of Figures: 1

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Abstract

Objective: Alterations in walking strategy and increased fall risk are recognised in people with Type 2 diabetes mellitus (T2DM), but the underlying basis and natural history are not clear. This study investigated alterations in walking strategy and dynamic sway (unsteadiness) in participants with impaired glucose tolerance (IGT) and T2DM in relation to the severity of neuropathy and vitamin D levels.

Methods: 20 people with T2DM, 20 participants with IGT and 20 controls underwent gait analysis using a motion analysis system and force platforms, detailed assessment of neuropathy and serum 25 hydroxy-vitamin D (25(OH)D) levels.

Results: Ankle strength (P=0.01) and power (P=0.003) during walking and walking speed (P=0.008) were preserved in participants with IGT but significantly lower in people with T2DM compared to controls. However, step width (P=0.005) and dynamic medio-lateral sway (P=0.007) were significantly higher and posterior maximal movement (P=0.000) was lower in participants with IGT, but preserved in T2DM compared to controls. Dynamic medio-lateral sway correlated with corneal nerve fiber length (P=0.001) and corneal nerve branch density (P=0.001), but not vibration perception threshold (P=0.19). 25(OH)D did not differ significantly between groups (P=0.10) and did not correlate with any walking variables or measures of dynamic sway.

Conclusions: Early abnormalities in walking strategy and dynamic sway were evident in participants with IGT, whilst there was a reduction in ankle strength, power and walking speed in T2DM. Unsteadiness correlated with small, but not large fiber neuropathy and there was no relationship between vitamin D levels and walking variables.

Key words: Impaired glucose tolerance, diabetes, gait analysis, balance, neuropathy, Vitamin D.

Novelty Statements

- There are no studies comparing alterations in walking strategy and dynamic sway during walking in people with IGT and T2DM.
- Distal muscle power and speed during walking were lower in people with T2DM compared to controls.
- People with IGT but not T2DM had a significantly higher dynamic medio-lateral sway during walking.
- Early alterations in dynamic sway during walking were associated with small but not large fiber neuropathy.
- Vitamin D levels were not associated with alterations in walking strategy and dynamic sway in people with IGT or T2DM.

Introduction

Walking impairment is perceived to be a late complication of diabetes, as it has been described primarily in patients with established neuropathy [1, 2]. However, a number of studies have shown walking impairment in people with diabetes before the onset of a large fiber neuropathy [3-6]. This suggests that either neuropathy may not be the only contributor to this abnormality, or that small rather than large fiber neuropathy may be a contributing factor.

Peripheral neuropathy may result in biomechanical alterations in walking and balance, with an increased risk of falls [1-3]. People with diabetes have reduced ankle and knee joint strength and power during walking as a result of distal muscular weakness [1]. Muscle weakness and alterations to muscle structure may lead to altered walking ability even in people without diabetic neuropathy [3]. Slower walking speed, shorter step length and wider step width have all been demonstrated, in people without diabetic neuropathy [4-6] and we have recently shown reduced lower limb strength and altered muscle structure in people with T2DM and minimal neuropathy [7].

Increased dynamic medio-lateral sway leading to unsteadiness has been reported in people with diabetic neuropathy [8]. Neuropathy can impair lower extremity function [9] and loss of vibration perception correlates with impaired dynamic medio-lateral sway in people with diabetes [8].

Impaired glucose tolerance (IGT) may result in a small fiber neuropathy [10] and impaired standing balance and trunk position sense [11]. Furthermore, we have recently shown that distal lower limb muscle strength is reduced in participants with IGT, which could impact on gait and stability during normal walking [12].

Muscle weakness, impairment of balance and an increased risk of falls have been associated with vitamin D deficiency during upright quiet standing and walking in healthy elderly participants [13]. Vitamin D deficiency can cause proximal muscle weakness, impaired dynamic sway during walking and an increased risk of falls [14] and of course reduced daily activity may lead to obesity and vitamin D deficiency [15].

The objectives of this study were:

1. To investigate differences in walking characteristics and dynamic sway between people with IGT, T2DM and controls.

2. To quantify the relationship between walking characteristics, neuropathy and vitamin D levels.

Methods

Participants

20 people with Type 2 diabetes (8 with mild neuropathy and 12 without neuropathy) with a median and range of duration of diabetes 14 and 36 years, respectively; 20 participants with IGT (10 with and 10 without neuropathy) and 20 participants without IGT or diabetes (controls) underwent assessment at the gait laboratory of the Manchester Metropolitan University. The study was approved by the UK National Health Service (NHS) ethics committee, local Research Ethics Committees at the University of Manchester and the Manchester Metropolitan University. Written informed consent was obtained from all participants.

Assessment of Neuropathy

Symptoms of DPN were assessed using the Neuropathy Symptom Profile. Neurological deficits were evaluated using the simplified neuropathy disability score (NDS), comprised of assessing vibration perception threshold (VPT), pin-prick, temperature sensation and ankle reflexes. Diabetic sensorimotor polyneuropathy (DSPN) was defined according to the Toronto criteria [16]. Controls underwent assessment of VPT and NDS to confirm the absence of neuropathy.

Small fibre neuropathy was evaluated by quantifying corneal nerve fiber density (CNFD); corneal nerve branch density (CNBD); corneal nerve fiber length (CNFL), corneal nerve fiber tortuosity (CNFT) and intraepidermal nerve fiber density (IENFD) in skin biopsies from the dorsum of the foot [17].

Gait analysis

Participants walked at their self-selected speed over a 10-m level ground walkway, stepping onto two of the three ground-embedded force platforms (Kistler, Winterthur, Switzerland), sampling at 1000Hz. Participant's movement was assessed using a 10-camera motion-capture system (Vicon, Oxford, UK), sampling at 100Hz. Using a full-body modified Helen-Hayes marker set, 52 reflective markers were firmly fixed onto specific anatomical landmarks of the participant's body (upper and lower body segments). Participants walked in standardised shoes appropriate for people with diabetes (MedSurg; Darco, Raisting, Germany) to control footwear condition and ensure that patients with diabetes walked with appropriate footwear. The mean data from four walking trials containing two force platform strikes with the left and two with the right foot was selected for analysis.

Gait measurements

Ankle joint strength and power (peak values) during walking and temporal-spatial measurements (walking speed, step width and step length) were quantified for each participant using Visual 3D software (C-motion Inc., MD, USA) by combining the force and motion data.

Dynamic Sway during Walking

Dynamic sway is a term, which is used from this point on in the manuscript to define the separation distance between the body centre of mass (COM) and centre of pressure (COP) during walking in two planes: a frontal plane (medio-lateral dynamic sway) and a sagittal plane (anterior-posterior dynamic sway) (Figure 1).

Statistical Analysis

A one-way analysis of variance (ANOVA) with post-hoc Bonferroni was used to test the differences between the three independent study groups (T2DM, IGT and controls) for the measured variables. An independent samples Student's *t*-test was used to assess differences between two groups for specific categories of variables: differences in walking and dynamic sway variables between people with and without neuropathy and with lower and higher values of vitamin D (25(OH)D < 25nmol/L vs > 25nmol/L). A Pearson's correlation coefficient was used to assess the correlation between walking and dynamic sway variables. All the data are expressed as mean ± SD unless otherwise stated.

The statistical power for the majority of walking and dynamic sway measurements in participants with IGT and T2DM was 0.80-1.00 (Table 2), which is very high considering an optimal recommendation is 0.8 [18]. We performed an a-priori power calculation based on ankle joint strength (torque) from a previous study [19]. The

power analysis indicated that we needed 14 subjects in each group to detect a difference of 22 Nm between groups (~20% difference between groups), with an alpha level of 0.05 and a beta level of 0.9 (i.e., power of 90%). To account for dropouts we recruited 20 participants into each group and also we adopted a more stringent alpha level ($P<0.01$).

Results

Clinical assessment

20 healthy control participants (13 men and 7 women, 2 Asian and 18 European), 20 participants with IGT (16 men and 4 women, 5 Asian and 15 European) and 20 participants with T2DM (15 men and 5 women, 9 Asian & 11 European) were assessed. Participants were well matched for age and height, but body mass ($P=0.006$) and BMI ($P=0.01$) were significantly higher in participants with IGT compared to controls. HbA1c was significantly higher in participants with IGT and T2DM compared to controls. 25(OH)D did not differ significantly between groups (Table 1).

Neuropathy assessments (Table 1)

Vibration perception threshold (VPT) was significantly higher in participants with IGT ($P=0.001$) but not in T2DM ($P=0.02$) compared to controls. Neuropathy disability score (NDS) did not differ significantly between participants with IGT ($P=0.02$) and T2DM ($P=0.04$), but was higher compared to controls. Peroneal and sural nerve conduction velocity and amplitudes did not differ between groups. Corneal nerve fiber density (CNFD) was significantly lower in participants with IGT ($P=0.004$) and T2DM

(P=0.004) compared to controls. Corneal nerve branch density (CNBD) was significantly lower only in participants with IGT (P=0.002) compared to controls. Corneal nerve fiber length (CNFL), corneal nerve fiber tortuosity (CNFT) and intraepidermal nerve fiber density (IENFD) did not differ between groups.

Peak ankle joint strength and power during walking (Table 2)

During walking, peak ankle plantar flexion strength (P=0.01) and power (P=0.003) were significantly lower in people with T2DM compared to controls.

Temporal-spatial gait measurements (Table 2)

People with T2DM had a significantly slower walking speed (P=0.008) compared to controls. There was no difference in step length between either group, but there was a significantly greater step width (P=0.005) in participants with IGT compared to controls.

Dynamic sway (Table 2)

During walking, dynamic medio-lateral sway (P=0.007) was higher and posterior maximal movement (P=0.000) was lower in participants with IGT compared to controls.

Peripheral neuropathy vs no peripheral neuropathy

There were no significant differences in ankle plantar flexion strength (1.1±0.1 vs 1.2±0.1 Nm/kg; P=0.87) and power (2.5±0.6 vs 2.6±0.7 W/kg; P=0.54), walking speed (1.3±0.2 vs 1.3±0.2 m/s; P=0.77), step width (13.0±2.8 vs 11.7±2.6 cm; P=0.11), step length (148.4±17.9 vs 140.1±19.9 cm; P=0.11) and dynamic medio-lateral sway

(14.9±8.0 vs 13.4±4.3 cm; P=0.46) in participants with (n=19) compared to participants without (n=41) peripheral neuropathy, respectively.

Low (<25nmol/L) vs normal vitamin D (>25nmol/L)

During walking, there was no significant difference in ankle plantar flexion strength (1.1±0.1 vs 1.2±0.1 Nm/kg; P=0.22) and power (2.3±0.5 vs 2.6±0.74 W/kg; P=0.12), walking speed (1.4±0.2 vs 1.3±0.2 m/s; P=0.13), step width (12.1±1.8 vs 12.1±2.8 cm; P=0.92) and dynamic medio-lateral sway (9.7±3.9 vs 8.4±3.8 cm; P=0.36), but step length (70.5±10.3 vs 75.1±5.9 cm; P=0.05) was reduced in participants with a 25(OH)D level <25nmol/L vs. >25nmol/L. Dynamic medio-lateral sway was higher in people with T2DM (12.5±1.9 vs 8.1±2.4 cm; P=0.01) but not participants with IGT (8.2±4.9 vs 9.7±5.0 cm; P=0.62) comparing those with 25(OH)D levels <25nmol/L compared to >25nmol/L, respectively.

Correlations

There were low-to-moderate correlations between dynamic medio-lateral sway with CNFL (r=0.406; P=0.001) and CNBD (r=0.436; P=0.001), but no significant correlation with VPT (r=0.17; P=0.19).

Discussion

This is the first study to show an early alteration in the natural walking strategy and dynamic sway in participants with IGT, which is comparable to people with T2DM. This challenges the belief that balance impairment during walking only occurs in people with diabetes and advanced large fiber neuropathy [8]. Furthermore, we show that

small rather than large fiber abnormalities are more strongly associated with balance impairment.

Whilst we confirm previous findings of a reduction in ankle joint strength and power during walking in people with T2DM [20, 21], we also show that participants with IGT display a reduction in ankle joint power during walking. These findings are supported by our recent data showing a significant weakness of the distal ankle plantar flexors in people with T2DM [7] and participants with IGT [12].

It has previously been shown that people with diabetic neuropathy have a slower self-selected walking speed, smaller step length and greater step width compared to controls [3, 20]. In the present study whilst walking velocity, stride length and step length were preserved; the step width was greater in participants with IGT, suggesting that this may be an early defect. Previously we have observed a greater step width in people with severe diabetic neuropathy compared to controls [8]. This was not found in people with diabetes in the present study as they had only mild neuropathy. However, the IGT group with an equivalent severity of neuropathy had adopted an increased step width, which may be attributed to the greater BMI in this group. Indeed, whilst a greater step width has been traditionally regarded as a way for people with diabetes to increase their base of support [22], we recently reported a positive correlation between step width and medio-lateral dynamic sway [8]. Thus increased step width may be an early sign of walking impairment in participants with IGT representing a more ‘cautious’ walking strategy commonly observed in people with diabetic neuropathy [5, 20].

The lower ankle strength and power observed during walking in participants with IGT and diabetes may be one of the main underlying factors explaining the slower walking

speed, particularly ankle power which reflects aspects of both force and speed [2, 8, 20, 23-25]. The slower walking speed observed in participants with IGT and T2DM may well be a compensatory strategy to lower the strength demands of walking as reported in previous studies in people with diabetes [26]. Furthermore, the reduced step length observed in participants with IGT and T2DM in the present study constitutes a 'biomechanical strategy' that helps to reduce the strength required from knee and ankle muscles by reducing the flexion (and therefore the required torque) of these joints.

Reduced ankle strength and power during walking may play a role in unsteadiness, which can be quantified by measuring dynamic medio-lateral sway. Indeed, we have found that dynamic medio-lateral sway was already higher in participants with IGT during walking indicating greater unsteadiness, in agreement with our recent findings in people with diabetic neuropathy [8]. This is in line with previous findings of impaired postural sway during upright standing balance tests in participants with IGT [11]. In the present study we found a higher mean dynamic medio-lateral sway, in participants with IGT which means on average they demonstrated more side-to-side sway, whereas people with T2DM showed a greater range of dynamic medio-lateral sway, indicating that they periodically allowed greater side-to-side sway and more variability creating a more 'dangerous' situation in terms of the risk of falling for the T2DM group. Diabetic neuropathy may negatively impact on balance during walking [8, 25, 27] and indeed, a recent study has shown that people with diabetic neuropathy have a disturbance in postural sway during upright standing [28]. The presence of peripheral neuropathy may be a potential explanation for the increased medio-lateral sway observed in participants with IGT in the present study, however, our patients had evidence of minimal large fiber neuropathy. Traditionally it has been suggested that

quite marked impairment in sensation and proprioception is required to cause walking alterations [2, 20, 23, 25, 29], however, we now show significant alterations with minimal evidence of large fiber neuropathy.

We have previously shown an association between loss of vibration perception and dynamic medio-lateral sway during walking in people with diabetes [8], however, in the present study we have found no correlation between VPT and medio-lateral sway, possibly because the majority of people with diabetes had very minimal large fiber neuropathy. However, a novel finding in the present study is the much stronger association between dynamic sway and small fiber neuropathy determined using corneal confocal microscopy. The mechanistic basis for the association between dynamic sway and small fiber pathology requires further study, especially as there was no association with IENFD in the foot. We have also shown that participants with IGT have smaller dynamic anterior-posterior sway, which reflects the shorter step length taken by participants with IGT, comparable to previous studies in people with diabetes [5, 8, 20]. The smaller posterior maximum anterior-posterior sway is likely explained by participants with IGT not allowing their body centre of mass to remain as far back compared to the controls and T2DM groups when transferring over to the leading leg during walking, this is likely because the joint moments (strength) associated with keeping the centre of mass any further back would be very high due to the flexed joints and high body mass of the IGT group.

Severe vitamin D deficiency is related to postural instability during quiet standing and an increased risk of falls in elderly participants [30]. However, in the present study our participants did not have severe vitamin D deficiency, and we therefore compared low to relatively normal levels of vitamin D and found no relationship with walking strategy or unsteadiness. This finding is in agreement with our recent finding showing that

people with T2DM had a significantly reduced lower limb muscle strength, which was related to the severity of neuropathy but not to the level of vitamin D [7]. Although, in people with IGT we have recently shown a significant reduction in distal muscle strength, which was associated with increased intramuscular non-contractile tissue, small fiber neuropathy and vitamin D deficiency [12].

Vitamin D deficiency affects proximal more than distal muscles of the lower limb [13, 20]. The present study found that people with T2DM and low vitamin D had significantly higher dynamic medio-lateral sway compared to those with adequate levels of vitamin D, suggesting that vitamin D deficiency may have a role in balance impairment in T2DM. Previously healthy participants with severe vitamin D deficiency (<25nmol/L) have been shown to have decreased proximal muscle strength, increased postural sway during quiet standing and an increased risk of falls [31].

We acknowledge the present study was undertaken with a small sample of subjects with a relative imbalance of ethnicities and did not include people with severe diabetic neuropathy or vitamin D deficiency, which may limit translation to the general population of subjects with IGT and T2DM. Furthermore, the assessment of walking strategy in a more challenging environment such as on stairs may have enhanced the clinical relevance of our findings.

Conclusion

Biomechanical changes to the natural walking strategy and balance control during walking occur in people with IGT and T2DM, and are related to small fiber neuropathy but not vitamin D deficiency. Larger, longitudinal studies are required to better understand the evolution and consequences of these abnormalities.

Funding

This study was funded by both the National Institute of Health (NIH) Grant 5RO1 NS46259-03 NINDS and the Juvenile Diabetes Research Foundation (JDRF) Grant 5-2002-185.

Conflicts of Interest

The authors declare that there are no conflicts of interest associated with this manuscript.

Authors Contributions

M.M.A. researched data, performed statistical analysis and wrote the manuscript.

S.J.B. reviewed and revised the manuscript.

F.L.B. reviewed and revised the manuscript.

A.J.M.B. reviewed and revised the manuscript.

M.J. reviewed and revised the manuscript.

R.A.M. Designed the study, reviewed and revised the manuscript.

N.D.R. Designed the study, reviewed and revised the manuscript.

N.D.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

We thank the staff at the musculoskeletal laboratory in Manchester Metropolitan University and NIHR/Wellcome Trust Clinical Research Facility in Central Manchester

University Hospitals NHS Foundation Trust for providing a high quality service and their state-of-the-art facilities to carry out the research. We gratefully acknowledge the following for undertaking neuropathy and corneal confocal assessment: Ferdousi M, Azmi S, Petropoulos IN, Fadavi H, Ponirakis G, Marshall A, Tavakoli M, Asghar O, Alam U (Centre for Endocrinology and Diabetes, Institute of Human Development, University of Manchester and the Manchester Royal Infirmary, Central Manchester Hospital Foundation Trust, Manchester, UK.)

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Table 1. Clinical and neuropathy measures in controls and participants with IGT and T2DM.

Measurements	Control n=20	IGT n=20	T2DM n=20	P-value
Age (years)	61.5±6.0	62.7±11.1	63.1±10.8	0.86
Body mass (kg)	78.1±11.5	**94.9±18.7**$^{(0.006)}$	82.6±18.2	**0.006**
BMI (kg/m^2)	27.2±3.8	**31.5±5.5**$^{(0.01)}$	29.4±4.1	**0.01**
HbA1c (mmol/mol)	38.0±2.1	**42.4±6.3**$^{(0.007)}$	**53.8±10.6**$^{(0.000)}$	**0.000**
HbA1c (%)	5.6±0.1	**6.0±0.6**$^{(0.007)}$	**7. 3±1.5**$^{(0.000)}$	**0.000**
25(OH)D (nmol/L)	78.9±48.8	50.8±34.8	72.6±43.5	0.10
NDS (0-10)	1.1±1.2	3.3±3.4$^{(0.02)}$	3.1±2.5$^{(0.04)}$	0.014
VPT(Hz)	6.4±3.0	**16.5±11.6**$^{(0.001)}$	13.7±8.6$^{(0.02)}$	**0.001**
SNCV (m/s)	48.6±4.5	45.8±13.6	47.4±4.4	0.58
SNAP (µV)	13.7±7.2	14.5±14.8	11.6±5.6	0.62
PMNCV (m/s)	46.6±4.7	41.4±10.7	42.2±7.05	0.08
PMNAP (mV)	5.3±1.8	3.8±1.8	4.15±2.5	0.07
CNFD (no/mm^2)	35.9±5.1	**27.6±8.2**$^{(0.004)}$	**27.7±9.1**$^{(0.004)}$	**0.001**
CNBD (no/mm^2)	94.9±33.6	**55.7±35.8**$^{(0.005)}$	93.9±41.5	**0.002**
CNFL (mm/mm^2)	26.7±3.8	21.8±6.5	23.1±8.6	0.06
CNFT (TC)	16.4±2.7	18.6±6.5	20.2±4.3	0.05
IENFD (no/mm)	7.7±2.0	6.7±3.4	7.6±5.4	0.70

IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; IFCC: International Federation of Clinical Chemistry; DCC: Diabetes Control and Complications Trial; 25(OH)D: 25 hydroxy-vitamin D; NDS: Neuropathy disability score; VPT: Vibration perception threshold; SNVC: Sural sensory nerve conduction velocity; SNAP: Sural sensory nerve amplitude; PMNCV: Peroneal motor nerve conduction velocity; PMNAP: Peroneal motor nerve amplitude; CNFD: Corneal nerve fiber density; CNBD: Corneal nerve branch density; CNFL: Corneal nerve fiber length;

CNFT: Corneal nerve fiber tortuosity; IENFD: Intraepidermal nerve fiber density. Significant differences between groups as a result of ANOVA (final column) and as a result of Bonferroni post-hoc (p value in superscript) compared to controls are indicated in bold. Values are expressed as mean±SD.

Table 2. Walking measurements in controls and participants with IGT and T2DM.

Measurements	Controls	IGT	T2DM	P-value	Statistical power (IGT)	Statistical power (T2DM)
Peak ankle strength (Nm/kg)	1.2±0.2	1.1±0.2	**1.1±0.2**$^{(0.01)}$	**0.01**	0.82	0.89
Peak ankle power (W/kg)	3.0±0.8	2.4±0.6	**2.2±0.6**$^{(0.003)}$	**0.002**	0.99	1.00
Temporal-spatial gait measurements						
Walking speed (m/s)	1.4±0.2	1.3±0.3	**1.2±0.2**$^{(0.008)}$	**0.008**	0.65	1.00
Step Length (cm)	74.7±6.8	70.4±12.8	69.0±8.2	0.15	0.62	0.96
Step width (cm)	10.9±2.5	**13.5±2.4**$^{(0.005)}$	12.0±2.6	**0.006**	1.00	0.61
Dynamic Sway (cm)						
Post. Max	28.0±2.8	**17.7±5.5**$^{(0.000)}$	25.7±2.8	**0.000**	1.00	0.98
ML mean	5.0±2.5	**8.1±3.7**$^{(0.007)}$	6.4±2.3	**0.009**	1.00	0.78

IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus; W: Watt; Post: Posterior; ML: Medio-lateral; Max: Maximum. Significant differences between groups as a result of ANOVA and as a result of Bonferroni post-hoc (p value in superscript) compared to controls are indicated in bold. Statistical power for each group is indicated. Values are expressed as mean±SD.

Figure 1. Calculation of dynamic sway

Figure legend

Dynamic sway (S), defined as the separation of the body centre-of-mass (grey circle) and the centre-of-pressure (grey triangle). Dynamic sway is shown in the sagittal (left image) and frontal (right image) planes, illustrating the separation in the anterior-posterior direction and medial-lateral directions, respectively. Also highlighted in the sagittal plane image is the resultant ground reaction force vector (grey arrow) and the ankle joint centre position (black cross): joint moments (strength) were calculated based on the relative position and magnitude of the ground reaction force from the joint centre, as well as taking into account the mass and acceleration of the relevant body segments.