# Is there a connection between postprandial hyperglycemia and IGT related sensory nerve dysfunction?

Short title: Risk factor of sensory nerve dysfunction in IGT

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**Abbreviations:** ABPM-ambulatory blood pressure monitoring, CPT-current perception threshold, HV-healthy volunteers, IGT-impaired glucose tolerance, IENFD-intraepidermal nerve fibre density, NC-nerve conduction

**Background and Aims**: To assess the risk factors for sensory nerve dysfunction in subjects with isolated impaired glucose tolerance (IGT).

**Methods and Results**: Seventy-two people with isolated IGT (WHO 1999 criteria) and 39 gender and age-matched healthy volunteers underwent detailed clinical and neurological assessment including quantitative sensory testing using the Neurometer device (current perception threshold measurement on four limbs at three different frequencies). Sensory nerve dysfunction was defined as at least two abnormalities on any frequencies on the upper or lower limbs.

Sensory nerve dysfunction was more prevalent among subjects with IGT compared to controls (58.3 vs. 10.3%, OR: 11.23, 95%CI: 3.57-35.35). This association was not influenced by BMI, systolic and diastolic blood pressure, heart rate and autonomic neuropathy (multiple adjusted OR: 13.87, 95%CI: 3.18-60.58), but further adjustment for glycaemic measures abolished the association (OR: 1.58, 95%CI: 0.07-35.68). Assessing the components of glycaemic measures separately, the association between sensory nerve dysfunction and IGT was not affected by HbA1c (OR: 13.94, 95%CI: 1.84-105.5). It was, however, substantially attenuated by fasting plasma glucose (OR: 6.75, 95%CI: 1.33-34.27) while the significance was lost after adjustment for 120-min postload glucose level (OR: 3.76, 95%CI: 0.26-54.10). In the pooled population assessed, independent determinants of sensory nerve dysfunction were older age, 120-min glucose, higher height and cardiovascular autonomic neuropathy **at near significance.**

**Conclusions**: Sensory nerve dysfunction amongst subjects with IGT was not explained by cardiovascular covariates, only by glycaemic measures. In addition to 120-min glucose, cardiovascular autonomic neuropathy **at borderline significance**, age, and height were the independent determinants of sensory nerve dysfunction.

## Introduction

The clinical and prognostic importance of sensory nerve dysfunction has become evident in recent decades. Elucidating the potential risk factors for the development of nerve dysfunction is important, as it is already clear nowadays that even somatic nerve dysfunction should be considered as a significant risk factor for cardiovascular disease[1,2].

Over the past decade, impaired glucose tolerance (IGT) was frequently observed among subjects with idiopatic neuropathy [3-6]. However, this association could not be confirmed in one case-control study after adjustment for age and gender [7], and the role of IGT in the development of idiopathic neuropathy needs further investigation. Nonetheless, in population based studies, the prevalence of sensory nerve dysfunction was higher among people with IGT compared to healthy control subjects [8,9].

Distal sensory neuropathy is considered the most important pathogenetic factor for the development of diabetic foot complications [10]. Whilst the role of traditional cardiovascular risk factors in the pathogenesis of diabetic neuropathy is well recognised [1,2,11-12], the relationship between cardiovascular risk factors and sensory nerve dysfunction in subjects with IGT is still unclear. We have previously reported that subjects with IGT and cardiovascular autonomic neuropathy have higher diastolic blood pressure and higher frequency of the non-dipping phenomenon compared to healthy controls [13].

The present study was undertaken to (I) evaluate whether there is an association between IGT and sensory nerve dysfunction in a larger cohort than previously examined, and if this association exists, (II) to characterize the independent risk factors of sensory nerve dysfunction.

## Methods

Individuals diagnosed with isolated IGT in primary care during a screening program were referred to our department and recruited for the present study. Healthy volunteers working at our Department, as well as their relatives served as healthy controls. Those giving written informed consent underwent a 75g oral glucose tolerance test according to the WHO recommendation to confirm the diagnosis of isolated IGT (fasting blood glucose <6.0 mmol/l and 120 min value of 7.8–11.0 mmol/l) or normoglycaemia, respectively. Seventy-two people with isolated IGT and 39 healthy volunteers (HV) comparable for age and gender were assessed. Our study involved 33 men and 39 women with IGT (mean age: 58.72 years), and 17 men and 22 women with normoglycaemia (mean age: 55.13 years). The study protocol was approved by the local ethics committee and all participants gave written informed consent.

All subjects underwent a detailed neurological assessment to exclude subjects with carpal tunnel syndrome, **and to detect symptoms and signs suggestive of neurological impairment**. A general medical examination was performed with attention to distal muscle atrophy and skin changes. Sensory nerve function was assessed by the Neurometer R device (Baltimore, USA). Current perception threshold (CPT) was measured at median and peroneal nerves (digital branches) by the Neurometer device at three different frequencies (2 kHz, 250 Hz, 5 Hz) assessing large myelinated, small myelinated, and small unmyelinated sensory nerve fibre function respectively [14-16]. The examiner was blinded to IGT status of the participants. Our main outcome measure, sensory nerve dysfunction was defined at least as two abnormal measures either on the upper or on the lower limb at any frequencies. The normal values for the three different frequency measurements of the peroneal and the median nerve were established by Evans et al [17].

Body weight and height were measured in light clothing without shoes on a calibrated digital scale. Current smoking was defined as consuming ≥1 cigarette/day). Serum fasting and 120-

min postload glucose as well as total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels were measured on an AU 680 Beckman Chemistry System (Beckman Coulter Hungary Ltd., Budapest, Hungary), HbA1c with high-performance liquid chromatography (Bio-Rad Hungary Ltd., Budapest Hungary).

Cardiovascular autonomic neuropathy was detected by standard cardiovascular reflex tests: heart rate responses to deep breathing, standing (30/15 ratio) and Valsalva maneouvre (Valsalva ratio) assessing mainly parasympathetic function, and blood pressure responses to standing and sustained handgrip assessing mainly sympathetic function. According to the Toronto Consensus Panel, blood pressure response to sustained handgrip is no longer regarded as an established clinical test but as an investigational test [18]. All reflex-tests were performed using Cardiosys H-01 12-lead portable ECG and non-invasive blood pressure monitoring system with analytical software developed by MDE Ltd., Hungary. The presence of autonomic neuropathy was defined as at least one abnormal cardiovascular reflex test [13,16,19].

24-hour blood pressure was evaluated by ambulatory blood pressure monitoring (ABPM, Meditech CardioTens-01) device [20]. Blood pressure was measured every 20 minutes during daytime and every 30 minutes during night-time. The mean values from the 24-hour recordings of systolic and diastolic blood pressure and heart rate parameters were used during the analysis.

Participants were encouraged to avoid consuming caffeine and alcoholic beverages as well as tobacco products 12 hours preceding autonomic testing**.** They were asked to fast for 10 h overnight and to avoid heavy physical activity on the day before the examination. None of the participants were taking any drugs that could affect blood pressure or heart rate.

***Statistical methods***

Data were expressed as mean±SD for normally distributed and median (interquartile range) for not normally distributed data (triglycerides, HDL-cholesterol, systolic blood pressure). The latter variables were log-transformed to adjust for skewness. For comparison between groups (IGT vs. control and subjects with vs. without sensory nerve dysfunction), either $\chi 2$-test, 2 sample t-test or Mann-Whitney U test were used as required.

The association between sensory nerve dysfunction and IGT was assessed using a logistic regression model with sensory nerve dysfunction as the dependent and IGT as the independent variable. To explore the potential explanatory variables, this model was further adjusted in a stepwise manner for groups of cardiovascular risk factors. As the final step of our analysis, we added individual glycemic variables, fasting and 120 min postprandial glucose values and HbA1c to models including all other cardiovascular risk factors.

All variables univariately associated ($p<0.1$) with sensory nerve dysfunction were made available for a multiple logistic regression with stepwise backward elimination to determine independent risk factors for sensory nerve dysfunction. All analyses were performed using SPSS version 14.0, a two-side p-value $<0.05$ was considered as statistically significant.

**Results**

Baseline characteristics as well as the frequency of autonomic and sensory nerve dysfunction of participants with IGT and healthy volunteers are shown in Table 1. IGT subjects had significantly higher $HbA_{1c}$, fasting plasma glucose concentrations, 120 min plasma glucose concentrations, weight, BMI, systolic and diastolic blood pressures and heart rate compared to controls. Both cardiovascular autonomic and sensory nerve dysfunction were significantly more prevalent among IGT subjects compared to the control group. The prevalence of sensory nerve dysfunction was 58.3% among subjects with IGT compared to 10% in the healthy

volunteers. Cardiovascular autonomic neuropathy was found in 42 IGT subjects (58.3%), while all healthy controls had normal autonomic function.

Potential explanatory variables for the association between sensory nerve dysfunction and IGT are summarized in Table 2. The risk of sensory nerve dysfunction was eleven times higher among people with IGT compared to healthy controls (OR: 11.23, 95%CI: 3.57-35.35). This association was neither explained by BMI (OR after adjustment for BMI remained 12.97, 95%CI: 3.65-46.00), nor by systolic and diastolic blood pressure and heart rate (OR after adjustment: 17.10, 95%CI: 4.28-68.28). Moreover, adjustment for autonomic neuropathy had no major effect on the OR (OR: 13.87, 95%CI: 3.18-60.58), while further adjustment for all glycaemic measures abolished the association (OR: 1.58, 95%CI: 0.07-35.68). When evaluating the glycaemic components separately, HbA1c had no major effect on the association between sensory nerve dysfunction and IGT (OR: 13.94, 95%CI: 1.84-105.5), while it was substantially attenuated by fasting plasma glucose (OR: 6.75, 95%CI: 1.33-34.27). Significance of the association was lost when 120-min postload glucose level was added to the model (OR: 3.76, 95%CI: 0.26-54.10).

Data of participants with and without sensory nerve dysfunction are presented in Table 3. Significant differences between those with and without sensory nerve dysfunction were detected for the following variables: age ($p<0.003$), gender ($p<0.053$), BMI ($p<0.043$), weight ($p<0.001$), height ($p<0.033$), $HbA_{1c}$ ($p<0.0001$), fasting plasma glucose ($p<0.0001$), 120 min plasma glucose ($p<0.0001$), cholesterol ($p<0.031$), LDL-cholesterol ($p<0.027$), cardiovascular autonomic neuropathy ($p<0.0001$), and IGT ($p<0.0001$). No differences were observed for smoking prevalence, triglyceride and HDL-cholesterol levels, systolic and diastolic blood pressure and heart rate.

As 10% of healthy controls had also sensory nerve dysfunction, we have looked at the potential risk factors in the pooled population assessed hypothesis-generating analysis. The

presence of sensory nerve dysfunction was independently related to age, 120 min plasma glucose and height, and with cardiovascular autonomic neuropathy at borderline siginificance (**Table 4**).

**Discussion**

There are limited data on the prevalence of sensory nerve dysfunction in IGT. Some epidemiological studies have reported higher prevalence of neuropathy in people with IGT [8,9], while others could not confirm these results [21]. The association between IGT and sensory nerve dysfunction is not clear. While several uncontrolled observational studies have found an increased prevalence of IGT among individuals with idiopathic neuropathy [3,4-6], the only study using an appropriate control group was unable to demonstrate any association between IGT and idiopathic neuropathy after adjustment for age and gender. In this study patients with chronic idiopathic neuropathy had significantly higher serum triglyceride levels compared to controls [7]. In our study sensory nerve dysfunction was significantly more prevalent among people with IGT, while we couldn't confirm any association with serum triglyceride levels.

In some of the studies patients with painful sensory or idiopathic sensory neuropathy [6,7,22] were assessed. Importantly, all these patients had symptomatic neuropathy. However, this could be considered somewhat as the "tip of an iceberg", as neuropathy in the majority of IGT patients is asymptomatic [9,23], as confirmed in our previous studies as well [13,16].

In our study, there was an eleven times higher odds ratio for sensory nerve dysfunction among people with IGT compared to healthy volunteers. Traditional cardiovascular risk factors did not explain this association. In the multiple logistic regression model, fasting glycaemia still had some effects on the association between sensory nerve dysfunction and IGT, but 120 min postload plasma glucose levels seem to be the major determinant of sensory impairment in

subjects with isolated IGT. Sensory nerve dysfunction was also present in 10% of healthy controls. Evaluating our pooled study population, including patients and controls, age, 120 min plasma glucose, height and cardiovascular autonomic neuropathy –although only at borderline significance- were independently related to sensory nerve dysfunction.

The KORA F4 population-based study showed a relationship between 2-hour postload glucose and the presence of clinical distal sensory motor polyneuropathy in participants with combined impaired fasting glucose and IGT, as well as in those with known diabetes. No association were seen with fasting glucose and $HbA_{1c}$ levels [23]. Our results confirm and also extend these findings, as we found that both fasting and 2-hour postload glucose levels were associated with the presence of sensory impairment.

Cross-sectional studies have suggested that traditional cardiovascular risk factors may play a role in the pathogenesis of neuropathy in patients with diabetes mellitus [2,24,25]. Moreover, the EURODIAB Prospective Complication Study showed that apart from glyacemic control, the incidence of neuropathy was associated with higher triglyceride levels and body-mass index, smoking and hypertension [1]. Metabolic syndrome components seemed to be significantly associated with distal symmetrical polyneuropathy independent of glycemic status, although this effect was less pronounced than that of the presence of diabetes [26]. Obesity seemed to be an important mediator in the development of abnormal autonomic function and diminished diurnal indices in people with IGT [13]. In another study the presence of peripheral neuropathy and the severity of nerve dysfunction was independently associated with prediabetes, but not with metabolic syndrome [27]. Similarly, in our present study, 120 min plasma glucose level was independently associated with sensory nerve dysfunction, while obesity had no effect on the presence of sensory nerve dysfunction in our pooled population.Height is an independent risk factor for peripheral sensory neuropathy in patients with diabetes mellitus [28]. The adverse effect of height on nerve fibre function may

be attributed to the increasing length of nerve fibres as they lose their function distally with progression of diabetic polyneuropathy. A similar pathophysiological mechanism should be supposed in our population.

Cardiovascular autonomic neuropathy has been documented to be associated with the presence of peripheral polyneuropathy [11,29]. Although at borderline siginificance cardiovascular autonomic neuropathy was independently related to sensory nerve dysfunction in our pooled population as well.

In a cohort study of IGT subjects, baseline distal intraepidermal nerve fibre density (IENFD) was strongly related to fasting and 2-hour glucose during OGTT. After 1 year of lifestyle intervention of both fasting and postload glucose levels and proximal IENFD significant improvement was documented [30]. These observations suggest that, at least in the early stages, improvements in dysglycaemia could be helpful in ameliorating or even reversing nerve fibre damage in patients with IGT [30].

The strength of our study is that subjects with isolated IGT have been recruited while autonomic neuropathy was included in the statistical analysis when searching the potential explanatory factors of sensory nerve dysfunction. In addition, 24-hour mean blood pressure values were assessed beside office blood pressure values.

The relatively small sample size should be considered as weakness of the study. Further limitation is the definition of sensory nerve dysfunction as defined by two abnormal CPT parameters either on the upper or on the lower limb at any frequencies measured by the Neurometer. Indeed, it is not a widely used definition of sensory neuropathy. In the recent guideline, confirmed diagnosis of diabetic sensorimotor polyneuropathy was defined as any abnormality on nerve conduction (NC) studies and presence of symptom(s) or sign(s) of neuropathy. If no NC abnormality is present, a validated measure of small-fibre neuropathy (such as skin biopsy) had to be used [31]. However, the Toronto Consensus Panel [18,31]

refers to patients with diabetic neuropathy, while the aim of our study was to identify risk factors of sensory nerve dysfunction among IGT subjects. This way, we had to use a measure detecting early abnormalities rather than definite damage. The Neurometer device has been demonstrated as a sensitive, reproducible and, most importantly, a non-invasive method for the assessment of sensory nerve fibre function. It is able to detect functional abnormalities of all types of sensory nerve fibre [14,15,16]. The Neurometer has been used in studies in order to detect early subclinical sensory abnormalities among diabetic children and adolescents as well [32,33], thus in another group of patients having subclinical neural damage. Small-fibre damage is considered the earliest alteration in the course of diabetic neuropathy and is the most common feature of IGT associated neuropathy as well, and, according to our previous data, CPT 5 Hz frequency stimulation seems to be appropriate for the detection of small-fibre impairment in patients with IGT [16]. Finally, the Neurometer is able to distinguish between normoaesthesia, hypo- and hyperaesthesia, while the latter is considered as a feature of early sensory involvement.

Due to the cross-sectional design of our study, we were unable to investigate the temporal relationship between sensory nerve dysunction and its determinants.

In summary, our data do not support the role of traditional cardiovascular risk factors in the development of neural dysfunction among IGT subjects. Two-hour postprandial plasma glucose level might be the major determinant of early sensory impairment among IGT subjects. This observation might be also relevant to the development of risk reduction strategies. Cardiovascular autonomic neuropathy, age, 120 min plasma glucose and height were independent covariates of sensory nerve dysfunction in the pooled study population.

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The authors declare no conflict of interest concerning the content of this manuscript**.**

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**Table 1** Demographic data and clinical characteristics of participants with IGT and healthy volunteers.

| | Participants with IGT n=72 | Healthy Volunteers n=39 | p |
|---|---|---|---|
| Age (years) | 58.72±11.11 | 55.13±10.08 | 0.096 |
| Male# | 33 (45.8) | 17 (43.6) | 0.844 |
| Smoking rate# | 15 (21.1) | 8 (20.5) | 1.000 |
| Cardiovascular autonomic neuropathy# | 42 (58.3) | 0 (0.0) | <0.0001 |
| Sensory nerve dysfunction# | 42 (58.3) | 4 (10.3) | <0.0001 |
| $HbA_{1c}$ ( %) | 6.02±0.30 | 5.01±0.47 | <0.0001 |
| HbA1c (mmol/mol) | 42.30±3.29 | 31.29±5.11 | <0.0001 |
| Height (cm) | 167.59±8.52 | 169.86±9.10 | 0.196 |
| Weight (kg) | 84.17±15.55 | 72.08±12.58 | <0.0001 |
| BMI (kg/ $m^2$ ) | 29.91±4.72 | 24.97±3.99 | <0.0001 |
| Fasting plasma glucose (mmol/l) | 5.63±0.59 | 4.68±0.48 | <0.0001 |
| 120 min plasma glucose (mmol/l) | 8.76±0.97 | 4.95±0.44 | <0.0001 |
| Cholesterol (mmol/l) | 5.04±1.09 | 5.03±0.97 | 0.957 |
| Triglyceride (mmol/l) | 1.30 [0.99; 1.67] | 1.30 [1.02; 1.80] | 0.476 |
| LDL-cholesterol (mmol/l) | 3.13±0.88 | 3.10±0.91 | 0.912 |
| HDL-cholesterol (mmol/l) | 1.33 [1.16; 1.62] | 1.28 [0.98; 1.70] | 0.849 |
| Systolic blood pressure (mmHg) | 124 [118; 131] | 120 [106; 124] | <0.0001 |
| Diastolic blood pressure (mmHg) | 75.23±6.82 | 70.95±6.04 | 0.002 |
| Heart rate (/min) | 72.72±9.77 | 77.61±8.73 | 0.011 |

Data are reported as mean±SD or median [IQR]. Between group differences are reported according to 2-sample t-tests or Mann-Whitney U-tests and $\chi 2$-tests as indicated.

# Categorical variables are reported as n (%)

**Table 2** Potential explanatory variables of the association between sensory nerve dysfunction and impaired glucose tolerance.

| | Odds Ratio | 95% CIs | p |
|---|---|---|---|
| Model 1 = IGT | 11.23 | 3.57-35.35 | <0.0001 |
| Model 2 = Model 1 + BMI | 12.97 | 3.65-46.00 | <0.0001 |
| Model 3 = Model 2 + RRS;RRD;HR | 17.10 | 4.28-68.28 | <0.0001 |
| Model 4 = Model 3 + Autonomic neuropathy | 13.87 | 3.18-60.58 | <0.0001 |
| Model 5 = Model4 + HbA1c; Fasting plasma glucose; 120 min plasma glucose | 1.58 | 0.07-35.68 | 0.77 |
| Model 6 = Model 4 + HbA1c | 13.94 | 1.84-105.50 | <0.0001 |
| Model 7 = Model 4 + Fasting plasma glucose | 6.75 | 1.33-34.27 | 0.021 |
| Model 8 = Model 4 + 120 min plasma glucose | 3.76 | 0.26-54.10 | 0.33 |

Logistic regression with sensory nerve dysfunction as outcome
RRS: 24-hour systolic blood pressure mean, RRD: 24-hour diastolic blood pressure mean
HR: 24-hour mean heart rate

**Table 3** Demographic data and clinical characteristics in participants with and without sensory nerve dysfunction

| | Participants without sensory nerve dysfunction n=65 | Participants with sensory nerve dysfunction n=46 | p |
|---|---|---|---|
| Age (years) | 54.95±10.39 | 61.00±10.61 | 0.003 |
| Male# | 24 (36.9%) | 26 (56.5%) | 0.053 |
| Smoking rate# | 15 (23.4%) | 8 (17.4%) | 0.485 |
| Cardiovascular autonomic neuropathy# | 16 (24.6%) | 26 (56.5%) | 0.001 |
| Impaired glucose tolerance# | 30 (46.2%) | 42 (91.3%) | <0.0001 |
| $HbA_{1c}$ ( %) | 5.47±0.67 | 5.91±0.38 | <0.0001 |
| HbA1c (mmol/mol) | 36.23±7.32 | 41.14±4.24 | <0.0001 |
| Height (cm) | 166.90±8.96 | 170.50±8.00 | 0.033 |
| Weight (kg) | 76.10±15.40 | 85.62±14.36 | 0.001 |
| BMI (kg/ $m^2$ ) | 27.36±5.34 | 29.33±4.41 | 0.043 |
| Fasting plasma glucose (mmol/l) | 5.05±0.71 | 5.63±0,58 | <0.0001 |
| 120 min plasma glucose (mmol/l) | 6.70±2.02 | 8.44±1.50 | <0.0001 |
| Cholesterol (mmol/l) | 5.20±1.12 | 4.78±0.90 | 0.031 |
| Triglyceride (mmol/l) | 1.30 [0.93; 1.70] | 1.30 [1.00; 1.70] | 0.793 |
| LDL-cholesterol (mmol/l) | 3.29±0.96 | 2.88±0.72 | 0.027 |
| HDL-cholesterol (mmol/l) | 1.35 [1.10; 1.62] | 1.31 [1.15; 1.38] | 0.573 |
| Systolic blood pressure (mmHg) | 122 [116; 129] | 121 [116; 130] | 0.398 |
| Diastolic blood pressure (mmHg) | 72.86±6.17 | 74.98±7.61 | 0.112 |
| Heart rate (/min) | 75.22±9.15 | 73.29±10.35 | 0.307 |

Data are reported as mean±SD or median [IQR]. Between group differences are reported according to 2-sample t-tests or Mann-Whitney U-tests and $\chi 2$-tests as indicated.

**Table 4** Independent determinants of sensory nerve dysfunction in the pooled population based on logistic regression with stepwise elimination. Other variables available for the model (p<0,1) from Table 3

| | Odds Ratio | 95% CIs | p |
|---|---|---|---|
| Cardiovascular autonomic neuropathy | 3.28 | 0.99-10.90 | 0.052 |
| Age (1/years) | 1.06 | 1.00-1.12 | 0.037 |
| 120 min plasma glucose (1/mmol/l) | 1.78 | 1.20-2.63 | 0.004 |
| Height (1/cm) | 1.12 | 1.04-1.21 | 0.004 |