Risk factors of sensory and autonomic neuropathy and diminished circadian blood pressure variability in impaired glucose tolerance

Doctoral thesis

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INTRODUCTION

In the past few years not only type 2 diabetes but also the importance of prediabetic stages (IFG: impaired fasting glucose; IGT: impaired glucose tolerance) have been emphasized in public health. By 2035, the number of people with diabetes and prediabetes is expected to increase by 55%, according to the 2014 forcast of the International Diabetes Federation from. In line with increasing prevalence of type 2 diabetes we ought to consider the increase in microvascular and macrovascular complications as well.

The development of type 2 diabetes can be long lasting even going back for years, typically progressing in the background without symptoms. Insulinresistance, hyperinsulinaemia and postprandial hyperglycaemia antedate years before the increase of fasting plasma glucose. Accordingly, it is not surprising that newly diagnosed diabetic patients might already have microvascular and macrovascular complications.

Neuropathy is a severe prognostic complication of diabetes, appearing after a while in more than half of type 2 diabetic patients. Cardiovascular autonomic and sensory neuropathy belong to the progrediating forms of neuropathy and their clinical and prognostic importance has become evident in the recent decades.

Data on the prevalence of diabetic neuropathy (5-100%) in point of cardiovascular autonomic (2.5-50%) such as sensory (8-54%) neuropathy are reported within wild limits. This is probably due to the absence of diagnostic criteria of different types of neuropathy, the diagnostic tests, the heterogenity of the study population, the duration and type of diabetes. Earlier studies have proven that the presence of cardiovascular autonomic neuropathy carries a fivefold risk of mortality to diabetic patients. Sensory neuropathy is the most important reason of diabetic foot, furthermore, in some follow-up studies sensory neuropathy was proven to be an independent predictor of mortality. Lower limb amputations among diabetic patients are 15-45 times more frequent compared to non- diabetic populations.

Over the past decade, several groups have reported association between IGT and neuropathy. Several studies proved association between IGT and idiopathic polyneuropathy, while others could not confirm this. Interesting data, that the prevalence of IGT was confirmed to be 30-50% during oral glucose tolerance test (OGTT) in patients with idiopathic neuropathy. Singleton and Smith found the

prevalence of IGT 27% in subjects suffering from painful neuropathy. Ziegler et al. proved slightly increased prevalence of polyneuropathy in individuals with IGT compared those with normal glucose tolerance (13.0% versus 8.9%). Population-based studies have assessed the prevalence of neuropathy in IGT: the San Luis Valley diabetes study (11.2%) and the AusDiab study (3.9–6.1%).

Diminished circadioan blood pressure in diabetic patients with hypertension caused by cardiovascular autonomic neuropathy was proved by investigating the association between autonomic neuropathy and circadian blood pressure variations. Chen et al. confirmed that in individuals with IGT the sympatho-vagal imbalance leads to the lack of physiological decrease in heart rate and blood pressure during the night.

Several epidemiological studies observed the role of traditional cardiovascular risk factors in the development of neuropathy in diabetes. Hypertension, elevated LDL-cholesterol level and decreased HDL-colesterol level were proven to be independent risk factors of neuropathy in the Pittsburgh study. The EURODIAB IDDM Complication Study has identified age, duartion of diabetes, diastolic blood pressure, cholesterol level, LDL-cholesterol and triglyceride levels, microalbuniuria and smoking as a risk factor for autonomic neuropathy. Peripheral neuropathy was associated with age, duration of diabetes, quality of metabolic control and traditional cardiovascular risk factors. No comprehensive studies have been reported so far on the role of traditional cardiovascular risk factors in the pathogenesis of IGT associated neuropathy.

AIMS OF OUR STUDY

I have been looking for answers for the following questions:

1. What is the prevalence and what are the clinical characteristics of cardiovascular autonomic neuropathy in impaired glucose tolerance?
2. Is there an association between autonomic function and the 24 hour blood pressure parameters in patients with impaired glucose toelarnce?
3. What are the risk factors of cardiovascular autonomic neuropathy in impaired glucose tolerance, are traditional cardiovascular risk factors of importance?
4. What is the the frequency and what are the clinical characteristics of sensory neuropathy in patients with impaired glucose tolerance?
5. What are the risk factors of sensory neuropathy in patients with impaired glucose tolerance, and what are the independent risk factors?

RESEARCH DESIGN AND METHODS

Seventy-five people with IGT (male/female: 34/41, age [mean±SD]: 58.67±11.05 years, fasting plasma glucose: 5.63±0.58 mmol/l, 120 min plasma glucose: 8.74±0.96 mmol/l, HbA1c: 6.03±0.30%) and 40 age and sex-matched healthy volunteers (HV) (male/female: 17/23, age [mean±SD]: 55.13±9.95 years, fasting plasma glucose: 4.67±0.47 mmol/l, 120 min plasma glucose: 4.93±0.45 mmol/l, HbA1c: 5.00±0.47%) with normal glucose tolerance were assessed.

The diagnosis of IGT was based on a 75g oral glucose tolerance test according to the WHO criteria from 1999 (fasting blood glucose < 6.0 mmol/l and 120min value of 7.8 – 11.0 mmol/l). None of the participants had impaired fasting glucose (IFG).

Every participant was asked to refrain from consuming caffeine and alcoholic beverages, and tobacco products 12 hours before autonomic testing.

Autonomic status was assessed by the five standard cardiovascular reflex tests using the Ewing protocol: heart rate responses to deep breathing, standing and Valsalva maneouvre assess mainly parasympathetic function, and blood pressure responses to standing and sustained handgrip assess mainly sympathetic function. The heart rate variability and the circadian rhythm of blood pressure were evaluated. Blood pressure was measured every 20 minutes during daytime and every 30 minutes during night-time.

The 24-hour ambulatory blood pressure and heart rate variability (HRV) were evaluated by Meditech CardioTens-01 ambulatory blood pressure monitoring (ABPM) device using combined ABPM and ECG monitoring system. Analysis of stored data was done by Medibase software. Heart rate variability (HRV) was characterized by the triangular index (ti). The HRVti is an estimate of overall HRV, being a time domain measure of HRV. It is calculated by a conversion of the RR intervals into a geometric pattern and by dividing the integral of the density distribution (that is, the number of all RR intervals) with the maximum of the density distribution. From ABPM parameters the 24-hour systolic and diastolic blood pressure means (RRS, RRD), systolic and diastolic blood pressure means of the daytime period (daytime-RRS, daytime-RRD), the blood pressure means of the night-time period (night-time RRS, night-time RRD) and sistolic and diastolic diurnal indices (DIS, DID) were assessed.

Sensory function was assessed by Neurometer R device, calibrated 128Hz tuning fork and Semmes-Weinstein monofilament. Current perception threshold (CPT) was measured at median and peroneal nerves (digital branches) by the Neurometer at three different frequencies (2 kHz, 250 Hz, 5 Hz) assessing large myelinated, small myelinated and small unmyelinated sensory fibre function, respectively.

Statistical analyses were performed using SPSS version 14.0. Statistical significance was set at $P<0.05$. Data are expressed as mean±SD for normally distributed and median (interquartile range) for skewed data. The latter variables were log-transformed to adjust for skewness. For comparison between groups, $\chi 2$-tests, two sample t-tests were used as required. To prevent overadjustment, analyses were not adjusted for the matching variables.

To investigate whether observed differences between IGT and control participants were independent of obesity and the presence of CAN, multiple logistic regression (categorical outcomes) and multiple linear regression (continuous outcomes) were used with the actual measurement (or its log-transfomed version) as outcome and BMI, CAN, and IGT/Control group as predictors.

To differentiate the effect of IGT from CAN, we run a sensitivity analysis comparing ABPM derived variables between control participants and the IGT with CAN and IGT without CAN groups using one-way ANOVA and predefined contrasts.

The association between sensory neuropathy and IGT was investigated using a logistic regression model with sensory neuropathy 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 glycemic variables individually to models including all other cardiovascular risk factors.

All variables univariately associated ($p<0.1$) with sensory neuropathy were made available for a multiple logistic regression with stepwise backward elimination to determine independent risk factors for sensory neuropathy.

RESULTS

1. The prevalence and clinical characteristics of cardiovascular autonomic neuropathy in people with impaired glucose tolerance

The prevalence of cardiovascular autonomic neuropathy was 57.3%. We observed mild dysfunction in 32, while moderate dysfunction in 11 cases. In 15 cases isolated parasympathetic dysfunction, while in 28 cases both sympathetic and parasympathetic dysfunction were found. There was no cardiovascular autonomic neuropathy in control group.

Significant differences were found between IGT and control subjects in cardiovascular reflex tests regarding the following parameters: beat-to-beat variation (11.7±6.3 [mean±SD] vs. 19.8±4.1 beats/min; p=0.0001), postural heart rate change (1.2±0.1 vs. 1.2±0.2; p=0.04), Valsalva ratio (1.2±0.2 vs. 1.5±0.2; p=0.0001), postural systolic blood pressure change (4.8±6.2 vs. 0.7±2.2 mmHg; p=0.0002), diastolic blood pressure increase during a sustained handgrip (17.8±7.6 vs. 24.0±6.3 Hgmm; p=0.0003).

The triangular index of heart rate variability (HRV_{ti}) was significant lower in people with imapired glucose tolerance compared to healthy controls (27.95±8.42 [mean±SD] vs. 39.5±9.28; p<0.0001).

2. The association between autonomic dysfunction and 24-hour blood pressure parameters in impaired glucose

In spite of no history of hypertension and normal clinic blood pressure values, hypertension (defined as 24-hour mean systolic blood pressure ≥ 125 mmHg) was present in 35 (46.7%) people with impaired glucose tolerance, 25 (33.3%) of them had cardiovascular autonomic neuropathy too, and 9 (22.5%) people of the group of healthy volunteers.

The prevalence of unrecognised hypertension was significantly higher in the group of impaired glucose tolerance with cardiovascular autonomic neuropathy compared to the group of impaired glucose tolerance without cardiovascular autonomic neuropathy (p=0.021) and to control group (p=0.001).

Comparing the 24-hour ambulatory blood pressure parameters between IGT and control groups: the 24-hour mean systolic (MD [Mean Differnce]: -9.4; 95%CI [Confidence Interval]: 1.6-9.0) and diastolic (MD: -4.0; 95%CI: -6.6--1.5) blood pressures were significantly higher, the systolic (MD: 4.1; 95%CI: 1.2-6.9) and diastolic (MD: 3.9; 95%CI: 0.4-7.4) diurnal indices and 24-hour mean heart rate (MD: 5.3; 95%CI: 1.6-9.0) were significantly lower, and the presence of non-dippers (MD: 0.2; 95%CI: 0.09-0.5) were significantly oftener in patients with impaired glucose tolerance compared to healthy volunteers.

After BMI adjustment most of the differences between the IGT and control groups remained statistically significant except for systolic and diastolic diurnal indices.

Further adjustment for CAN mostly decreased effect sizes and the difference lost significance for systolic blood pressure and nigh-time diastolic blood pressure.

3. Risk factors in the pathogenesis of autonomic neuropathy in impaired glucose tolerance, the potential etiological role of traditional cardiovascular risk factors

Comparing the HRVti and ABPM parameters between IGT group without cardiovascular autonomic neuropathy and control group: the 24-hour mean diastolic blood pressure (75±6 [mean±SD] vs. 71±6 mmHg; p=0.045) and the presence of non-dipping phenomenon (22/32 vs. 12/40; p=0.003) were significantly. Similar, but more pronounced associations were found between the IGT group with cardiovascular autonomic neuropathy and the control group. Furthermore the systolic (8.5±8.7 vs. 13.2±5.4; p=0.007) and diastolic (13.8±10.0 vs. 18.4±7.1; p=0.043) diurnal indices were significantly lower, while 24-hour mean systolic blood pressure (129±13 vs. 117±10 mmHg; p<0.0001) was significantly higher in IGT peolpe with cardiovascular autonomic neuropathy compared to healthy volunteers.

There were no significant associations in some traditional cardiovascular risk factors, such as total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels and smoking neither between individuals with IGT and control group, nor between IGT groups with and without cardiovascular autonomic neuropathy.

4. The frequency and clinical characteristics of sensory neuropathy in impaired glucose tolerance

The prevalence of sensory neuropathy was 58.3% in people with impaired glucose tolerance, while 10.3 % in the control gourp. In 5 cases isolated hyperaesthesia, 21 cases isolated hypaesthesia and 16 cases both hyperaesthesia and hypaesthesia were measured in IGT group.

5. The risk factors of sensory neuropathy in impaired glucose tolerance

The prevalnece of cardiovascular autonomic (43/74 vs. 0/40; p<0.0001) and sensory (42/75 vs. 4/40; p<0.0001) neuropathy were significantly higher in patients with impaired glucose tolerance compared to healthy volunteers. The major demographic data and clinical characteristics of IGT and control group: HbA_{1c} (6.03±0.30 [mean±SD] vs. 5.00±0.47 mmol/l; p<0.0001), fasting glucose level (5.63±0.58 vs. 4.67±0.47 mmol/l; p<0.0001), 120 min glucose level (8.74±0.96 vs. 4.93±0.45 mmol/l; p<0.0001), weight (84.09±15.38 vs. 72.03±12.42 kg; p<0.0001), BMI (29.94±4.71 vs. 25.05±3.97 kg/m^2; p<0.0001), 24-hour mean systolic (126.14±11.81 vs. 116.69±10.22 mmHg; p<0.0001) and diastolic (75.14±6.78 vs. 71.10±6.04 mmHg; p=0.002) blood pressure and 24-hour mean heart rate (72.63±9.67 vs. 77.97±8.92 beats/min; p=0.005) were significantly higher in patients with IGT compared to healthy volunteers.

The association between sensory neuropathy and IGT was investigated using a logistic regression model The prevalence of sensory neuropathy was at a rate eleven times higher among people with impaired glucose tolerance OR /Odds Ratio/: 11.23 (CI /95% Confidence Intervals/: 3.57-35.35) compared to healthy controls. This association was hardly explained by obesity (BMI) (OR: 12.97, 95%CI: 3.65-46.00), or further adjustment for systolic and diastolic blood pressure and heart rate (OR: 17.10, 95%CI: 4.28-68.28), or autonomic neuropathy (OR: 13.87, 95%CI: 3.18-60.58), while further adjustment for glycaemic measures abolished the association (OR: 1.58, 95%CI: 0.07-35.68). In contrast to HbA1c that had no major effect on the association between sensory neuropathy and IGT association (OR: 13.94, 95%CI: 1.84-105.5), fasting plasma glucose substantially attenuated it (6.75, 1.33-34.27) and the association lost

significance when 120-min postload glucose level was used in the model (OR: 3.76, 95%CI: 0.26-54.10).

After dividing the entire study population to two groups with (n=46) and without (n=65) sensory neuropathy, we compared demographic data and clinical characteristics between them: age (61.00±10.61 [mean±SD] vs. 54.95±10.39 years; p=0.003), BMI (29.33±4.41 vs. 27.36±5.34 kg/m^2; p=0.003), weight (85.62±14.3 vs. 76.10±15.40 kg; p=0.001), height (170.50±8.00 vs. 166.90±8.96 cm; p=0.033), a HbA_{1c} (5.91±0.38 vs. 5.47±0.67 mmol/l; p<0.0001), fasting glucose level (5.63±0.58 vs. 5.05±0.71 mmol/l; p<0.0001), a 120 min glucose level (8.44±1.50 vs. 6.70±2.02 mmol/l; p<0.0001) were significant higher, while total cholesterol (4.78±0.90 vs. 5.20±1.12 mmol/l; p=0.031) and LDL-cholesterol (2.88±0.72 vs. 3.29±0.96 mmol/l; p=0.027) levels were significant lower in the group with sensory neuropathy. Cardiovascular autonomic neuropathy (26/65 vs. 16/46; p<0.0001), IGT (42/65 vs. 30/46; p<0.0001) and male gender (26/65 vs. 24/46; p=0.053) were more frequent in subjects with sensory neuropathy compared to the group without sensory neuropathy. There were no significant correlation between the two groups in smoking habits, 24-hour mean systolic and diastolic blood pressure, triglyceride and HDL-cholesterol level.

Independent determinants of sensory neuropathy were: older age (OR: 1.06, 95%CI 1.00-1.12/year), cardiovascular autonomic neuropathy (OR: 3.28, 95%CI: 0.99-10.90), 120 min glucose level (OR: 1.87, 95%CI: 1.20-2.63/mmol/l), and higher height (OR: 1.12, 95%CI: 1.04-1.21/cm) in the pooled population.

CONCLUSION

1. Cardiovascular autonomic neuropathy may be present in patients with impaired glucose tolerance, can be moderate, and can affect both parasympathetic and sympathetic nervous system.
2. In patients with impaired glucose tolerance with no history of hypertension, the prevalence of unrecognized hypertension diagnosed by 24-hour ambulatory blood pressure monitoring is twice as many in those with cardiovascular autonomic neuroapthy compared to those normal autonomic function. Our data suggest patients with impaired glucose tolerance suffering from autonomic neuropathy should be screened for hypertension using 24-hour ambulatory blood pressure monitoring and vica versa, hypertensive patients with IGT should be screened for autonomic neuropathy as well.
3. Hypertension, as a traditional cardiovascular risk factor, might have a role in the pathogenesis of autonomic neuropathy in patinets with impaired glucose tolerance.
4. Diminished circadian blood pressure variability can be detected even in people with IGT. Our data suggest, that the sympatho-vagal imbalance leads to the development of diminished circadian blood pressure variability in IGT.
5. Obesity might have a key role in the development of autonomic dysfunction and diminished circadian blood pressure variability in impaired glucose tolerance.
6. Sensory neuropathy may be present in patients with IGT, and glycaemia per se is the major driver of IGT associated sensory neuropathy.
7. Cardiovascular autonomic neuropathy, 120-min glucose, older age, and taller height are independent determinants of sensory neuropathy in non-diabetic people.
8. These results prove an early neuropathic dysfunction in patients with impaired glucose tolerance. The association with hypertension, obesity and glucose intolerance draw attention to the prevention of neuropathy with lifestyle intervention.

PUBLICATIONS

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