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Cardiovascular autonomic dysfunction is associated with central obesity in persons with impaired glucose tolerance

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Abstract

Aims The aim of this study was to investigate the prevalence of cardiovascular autonomic neuropathy in persons with previously diagnosed impaired glucose tolerance and to characterize associations between components of metabolic syndrome and cardiovascular autonomic neuropathy in the Finnish Diabetes Prevention Study cohort.

Methods Two hundred and sixty-eight individuals with impaired glucose tolerance at baseline in the Finnish Diabetes Prevention Study, but not diagnosed with diabetes during follow-up, were studied for cardiovascular autonomic neuropathy. At the second annual follow-up visit after the end of lifestyle intervention, we performed deep-breathing and active orthostatic tests to detect possible parasympathetic and sympathetic dysfunction. To describe metabolic characteristics, anthropometric measurements, an oral glucose tolerance test and assessments for $HbA_{1c,}$ serum lipids and blood pressure were carried out.

Results Prevalence of parasympathetic dysfunction was 25% and prevalence of sympathetic dysfunction was 6%, with no difference between the former intervention and control group participants or between men and women. Subjects with parasympathetic dysfunction were older, more obese (weight, waist circumference, body mass index) and had higher triglyceride concentration compared with those with normal parasympathetic function ($P < 0.01$ for all). Parasympathetic dysfunction was not significantly associated with other characteristics of metabolic syndrome; for example, high cholesterol, glucose and insulin levels or HbA_{1c}. Correlations between the Expiration/Inspiration (E/I) ratio (the longest heart beat duration in expiration divided by the shortest heart beat duration in inspiration) and measures reflecting obesity were statistically significant in the pooled population and in men but not in women.

Conclusions Cardiovascular autonomic neuropathy is common in persons with impaired glucose tolerance. Obesity, especially among men, seems to play an important role in the early pathogenesis of cardiovascular autonomic neuropathy.

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Keywords autonomic nervous system, autonomic neuropathy, impaired glucose tolerance

Abbreviation E/I - ratio, Expiration/Inspiration Ratio

Introduction

Cardiovascular autonomic neuropathy is an overlooked but important disorder related to diabetes mellitus and known to be associated with a disability in coping with daily activities, a wide

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spectrum of cardiovascular problems and predicting cardiovascular mortality [1]. In persons with Type 2 diabetes, the best-known risk factors for cardiovascular autonomic neuropathy are duration of diabetes and poor glycaemic control [2]. The pathogenesis of cardiovascular autonomic neuropathy within the diabetic spectrum is not fully understood and it is likely that cardiovascular autonomic neuropathy is of multifactorial origin [3]. On the one hand, there are data suggesting that autonomic dysfunction is an early defect and can be seen in pre-diabetic conditions [4–6]. On the other hand, cardiovascular autonomic neuropathy is known to be related to insulin resistance and obesity, which are closely involved in the pathogenesis of Type 2 diabetes [7–10]. Based on these observations, it can be hypothesized that cardiovascular autonomic neuropathy and Type 2 diabetes could share common pathophysiological mechanisms. Thus, there is a special interest to investigate cardiovascular autonomic neuropathy in pre-diabetic conditions and in risk groups of Type 2 diabetes, such as in persons with impaired glucose tolerance, most of whom also have the metabolic syndrome [11].

To our knowledge, prevalence of cardiovascular autonomic neuropathy has not been systematically examined in persons with impaired glucose tolerance and only few studies have evaluated autonomic dysfunction or its correlates within this high-risk group. Perciaccante and co-workers demonstrated that persons with impaired glucose tolerance have decreased heart rate variability in 24-h electrocardiograph (ECG) recordings [9]. In the Hoorn Study, several variables reflecting cardiovascular autonomic function tended to be reduced in subjects with impaired glucose tolerance compared with a group with normal glucose tolerance group [12] and cardiovascular autonomic function score was found to be closely related to glucose tolerance [13]. Furthermore, cardiovascular autonomic neuropathy was associated with albuminuria in those with impaired glucose tolerance and Type 2 diabetes. In a recent study by Putz and co-workers, subtle but detectable changes in autonomic function were found in a sample of 46 subjects with impaired glucose tolerance when compared with control subjects [14]. Although previously published data support the concept of impaired glucose tolerance-related early autonomic dysfunction, opposite findings have also been reported. Isak *et al*. failed to show any significant differences between impaired glucose tolerance and control subjects in heart rate variability, heart rate response to deep breathing, Valsalva manoeuvre or in blood pressure response during orthostatic test and hand grip test [15].

We hypothesized that cardiovascular autonomic neuropathy is associated with metabolic disorders related to impaired glucose tolerance and the metabolic syndrome and that cardiovascular autonomic neuropathy could be excessively prevalent in a population with impaired glucose tolerance. The aim of this study was to investigate the prevalence of cardiovascular autonomic neuropathy in persons with impaired glucose tolerance and to characterize association between the metabolic syndrome and cardiovascular autonomic regulation in the Finnish Diabetes Prevention Study cohort.

Patients and methods

Originally, 522 subjects were randomized either to lifestyle intervention or to a control group in the Finnish Diabetes Prevention Study. Details on the design, intervention, subjects, methods used and results of the original trial have been previously reported [16]. Briefly, 40- to 65-year-old overweight or obese individuals with impaired glucose tolerance were eligible. Impaired glucose tolerance was defined as a 2-h plasma glucose of 7.8–11.0 mmol/l after oral glucose (75 g) with a fasting glucose < 7.8 mmol/l [17]. The protocol was approved by the ethics committee of the National Public Health Institute (Helsinki, Finland). All participants gave written informed consent.

Autonomic nervous function tests were performed at the second annual follow-up visit after the end of intervention. Parasympathetic and sympathetic dysfunctions were assessed in 268 subjects who had remained to be without diabetes (148 individuals belonging to the intervention group and 120 individuals belonging to the control group). Any medications were not held for testing.

Parasympathetic (deep-breathing test) and sympathetic (active orthostatic test) tests were performed at approximately 08.00–11.00 h. All subjects were requested to abstain from smoking and beverages with caffeine for 12 h before the experiments. Only a light breakfast was allowed before the cardiovascular autonomic testing with a time interval of at least 2 h to the testing. In the deep-breathing test, the subjects breathed with maximum vital capacity with a respiratory cycle of 10 s (0.1 Hz) while in the supine position. The ECG during 3–4 breathing cycles was analysed and the mean value of the ratios of the longest R-R interval (expiration) to the shortest R-R interval (inspiration) was considered the Expiration/Inspiration (E/I) ratio. In the active orthostatic test, the subjects stood up after 5 min of rest in the supine position. Systolic blood pressure was measured at the end of rest and once at 1 min after change of position from supine to standing. Parasympathetic dysfunction was classified as an E/I ratio of ≤ 1.10. Sympathetic dysfunction was assessed as decrease of systolic blood pressure ≥ 20 mmHg during standing. Other main examinations were anthropometric measurements, oral glucose tolerance test, assessment of plasma glucose, insulin, HbA_{1c}, serum lipids and blood pressure. Updated National Cholesterol Education Program 2005 criteria were used for the definition of the metabolic syndrome [18].

Because the E/I ratio was not normally distributed, the data were analysed using tests for non-parametric distribution. The differences between two independent groups were analysed by the Mann–Whitney *U*-test for unpaired samples or by the χ^2-test when appropriate. Spearman's correlation coefficients were calculated for selected variables. A *P*-value < 0.05 was considered statistically significant. All values are presented as mean ± standard deviation (SD). Analyses were performed with SPSS 14.0 for Windows (SPSS, Chicago, IL, USA).

Table 1 Clinical and demographic data of the whole study group (n = 268) and in subjects with or without parasympathetic dysfunction.

	All subjects	With parasympathetic dysfunction (E/I ≤ 1.10)	Without parasympathetic dysfunction (E/I > 1.10)
Men/women (n)	91/177	26/41	65/136
Age (years)	62 ± 7	64 ± 6†	62 ± 7
Weight (kg)	83 ± 15	89 ± 18†	81 ± 13
BMI (kg/m^2)	30.3 ± 5.4	32.6 ± 6.9†	29.6 ± 4.5
Waist circumference (cm)	101 ± 12	106 ± 15‡	99 ± 11
Waist–hip ratio	0.93 ± 0.07	0.94 ± 0.07	0.92 ± 0.07
Fasting plasma insulin (mU/l)	7.6 ± 6.5	8.1 ± 6.6	7.4 ± 6.5
2-h OGTT plasma insulin (mU/l)	53.3 ± 65.9	52.7 ± 48.9	53.6 ± 70.8
Fasting plasma glucose (mmol/l)	6.1 ± 0.7	6.1 ± 0.7	6.1 ± 0.7
2-h OGTT plasma glucose (mmol/l)	8.2 ± 2.3	8.3 ± 2.2	8.2 ± 2.3
HbA_{1c} (%)	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.5
(mmol/mol)	37 ± 5	37 ± 5	37 ± 5
Fasting serum total cholesterol (mmol/l)	5.4 ± 0.9	5.4 ± 0.9	5.4 ± 0.9
Fasting serum HDL cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
Fasting serum triglycerides (mmol/l)	1.5 ± 0.6	1.7 ± 0.7†	1.4 ± 0.6
Fasting serum triglycerides/HDL cholesterol	1.09 ± 0.65	1.22 ± 0.63*	1.05 ± 0.65
Systolic blood pressure (mmHg)	133 ± 18	135 ± 20	133 ± 17
Diastolic blood pressure (mmHg)	79 ± 10	80 ± 11	78 ± 10

Values are means ± SD.
OGTT, oral glucose tolerance test.
*P < 0.05, †P < 0.01 and ‡P < 0.001 between subjects with and without parasympathetic dysfunction.

Results

Characteristics of the study participants are presented in Table 1. Prevalence of parasympathetic and sympathetic dysfunction was 25 and 6%, respectively.

Age, body composition, blood pressure, glucose, insulin and lipids as well as variables reflecting cardiovascular autonomic function were comparable between the former intervention group participants and former control group participants. Also, prevalence of parasympathetic dysfunction (E/I ≤ 1.10) was comparable between the two groups (27% in the intervention group and 23% in the control group, NS between the groups). Only 11 subjects in the former intervention group and four subjects in the former control group were found to have sympathetic dysfunction (7 vs. 3%, NS between the groups).

Persons with parasympathetic dysfunction were older, heavier, had higher BMI, waist circumference as well as waist–hip ratio than those without parasympathetic dysfunction (Table 1). They also had higher serum triglycerides and triglycerides to HDL ratio. Parasympathetic dysfunction was equally prevalent in men and in women (29 vs. 23%, respectively, NS between groups). E/I ratio correlated inversely with age (r = −0.213, P < 0.001), weight (r = −0.162, P < 0.01), BMI (r = −0.162, P < 0.01), waist circumference (r = −0.162, P < 0.01) and systolic blood pressure (r = −0.153, P < 0.05). However, we did not find significant correlations between E/I ratio and concentrations of plasma glucose, HbA_{1c}, plasma insulin or serum lipoproteins values. Correlations between E/I and age or variables reflecting obesity were statistically significant in men but not in women (Fig. 1).

When we analysed E/I ratio according to the presence of the metabolic syndrome, E/I was not significantly different in persons with and without the metabolic syndrome (1.16 ± 0.12 vs. 1.18 ± 0.12, respectively, NS).

As compared with those without sympathetic dysfunction, subjects with sympathetic dysfunction were older (67 ± 5 vs. 62 ± 7 years, P < 0.05) and tended to have higher 2-h plasma glucose in oral glucose tolerance test (8.9 ± 1.6 vs. 8.2 ± 2.3 mmol/l, P = 0.067), while other differences were not observed. Orthostatic response in systolic blood pressure was not correlated with age or any variables reflecting metabolic disorders except for systolic blood pressure itself (r = 0.140, P < 0.05).

Discussion

The main finding of this study was a high prevalence of cardiovascular autonomic neuropathy as assessed by the heart rate response to deep breathing in persons without diabetes with a history of impaired glucose tolerance. Variables reflecting obesity, elevated serum triglycerides and hypertension were associated with parasympathetic dysfunction. These observations support the concept that cardiovascular autonomic neuropathy and Type 2 diabetes could have common risk factors and/or they may have common underlying pathogenetic mechanisms. Our findings suggest that aging and obesity may contribute to decreased E/I ratio,

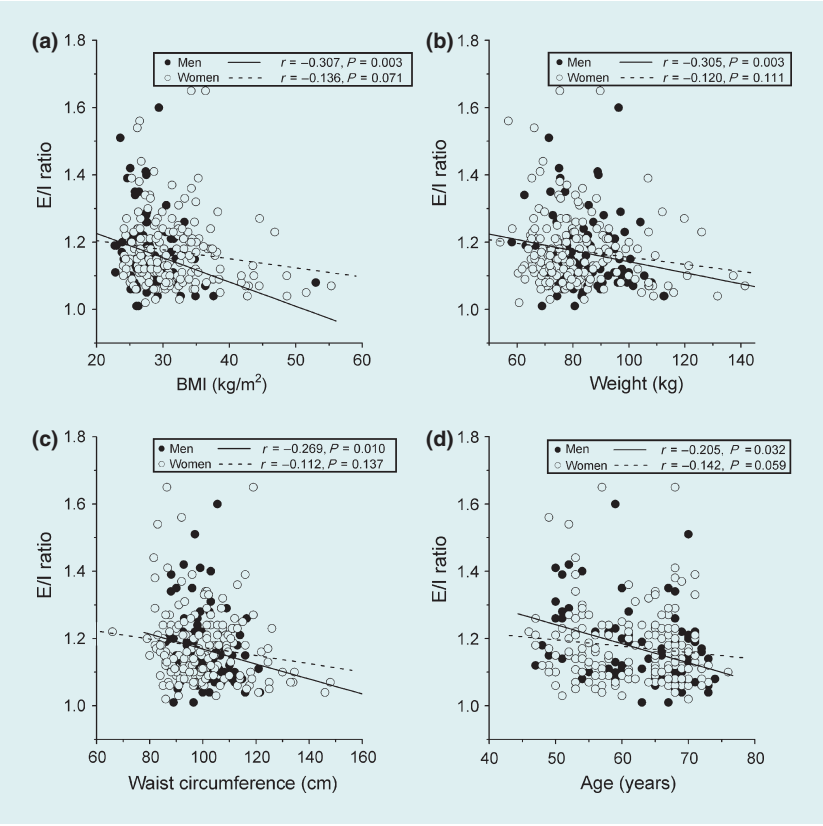

FIGURE 1 Relationships between E/I ratio and (a) BMI, (b) weight, (c) waist circumference and (d) age; $n = 268$. Solid lines represent linear regression lines in men and dashed lines represent linear regression lines in women.

especially in men, while, in women, we could not detect possible clinical determinants of decreased E/I.

Heterogeneous methodology used and differences in the definition of cardiovascular autonomic neuropathy should be taken into consideration when comparing epidemiological cardiovascular autonomic neuropathy results across different studies [1]. Furthermore, variables reflecting cardiovascular autonomic neuropathy are largely age and gender dependent and, thus, the age and gender distribution of the study population obviously contributes to the observed prevalence of cardiovascular autonomic neuropathy. In our study with persons with impaired glucose tolerance, parasympathetic dysfunction was defined according to a depressed E/I ratio in the deep-breathing test, which has been commonly used and considered to be the most informative method for evaluating cardiovascular autonomic neuropathy in diabetes mellitus patients [19]. In this Finnish Diabetes Prevention Study cohort at the second annual follow-up visit after the end of lifestyle intervention, every fourth subject had signs of parasympathetic dysfunction. Interestingly, our finding of 25% prevalence of parasympathetic dysfunction is in line with a smaller study by Eriksson and co-workers in which cardiovascular autonomic neuropathy was excessively found among persons with impaired glucose tolerance compared with control subjects and the prevalence of cardiovascular autonomic neuropathy was 29% when evaluated 12–15 years after the original diagnosis of impaired glucose tolerance [20].

The main characteristics (gender distribution, body composition) of our present study cohort compared well with those of the subjects in our a former study in which occurrence of cardiovascular autonomic neuropathy was evaluated in 133 Finnish subjects with newly diagnosed Type 2 diabetes and control subjects without diabetes at baseline and during a 10-year follow-up [21]. Subjects of the present study were on an average 6 years older than those in the previous study at the time of diagnosis of Type 2 diabetes. Parasympathetic dysfunction was even more prevalent in the present study with subjects with previously diagnosed impaired glucose tolerance than in previously studied persons with Type 2 diabetes and comparable age distribution at the 5-year follow-up (25 vs. 20%, and 9% in control subjects without diabetes). This may be attributable to the fact that, in the present study, impaired glucose tolerance and other pathological characteristics could have been operative for years, but cardiovascular autonomic neuropathy was still surprisingly common in the present study. In our previous study on newly diagnosed Type 2 diabetes, a distinct increase in parasympathetic dysfunction in persons with Type 2 diabetes was observed with increasing duration of diabetes, prevalence of cardiovascular autonomic neuropathy was only 5% at the time of Type 2 diabetes diagnosis, 20% at

5-year follow-up and it increased up to 65% at the 10-year follow-up [2]. Another previous study has shown that heart rate variability in persons with impaired glucose tolerance was lower than in those with normal glucose tolerance, but higher than in persons with newly diagnosed or previously known Type 2 diabetes [12]. Thus, it is likely that the diabetic process, even before the onset of diabetes, is involved in the progression of parasympathetic dysfunction. Our results suggest that, besides glycaemia as such, other pathological changes related to central obesity could also be operative as well. These include a low-grade inflammation process, oxidative stress and putative genetic link between autonomic nervous function and the risk for central obesity.

Although assessment of sympathetic dysfunction based on the orthostatic blood pressure response has been commonly used in previous studies, its sensitivity to detect sympathetic dysfunction may not be optimal. According to a laser perfusion imaging in detection of responses in finger blood flow, abnormal findings reflecting sympathetic dysfunction have been found in over 40% of persons with Type 1 or Type 2 diabetes [22]. This is in contrast to much smaller prevalence of abnormal blood pressure responses seen in orthostatic tests of patients with diabetes. Sympathetic dysfunction according to presence of orthostatic hypotension has been found in 7–24% of persons with Type 2 diabetes, depending on the duration of diabetes [2]. In a few studies evaluating orthostatic blood pressure response in impaired glucose tolerance, abnormal findings have not been more prevalent compared with control subjects [23], and magnitude of systolic blood pressure response has been comparable in persons with impaired glucose tolerance and those with normal glucose tolerance [12]. We found orthostatic hypotension as a sign of sympathetic dysfunction in only 6% of patients with impaired glucose tolerance, which corresponds well with the value of 6% observed in a population of normal Finnish subjects with a quite similar age distribution [2].

We found that, in persons with impaired glucose tolerance, parasympathetic dysfunction was associated with variables reflecting the metabolic syndrome, such as waist–hip ratio and serum triglycerides, and variables reflecting obesity such as weight and BMI, while it was not statistically significantly associated with other characteristics of the metabolic syndrome, including elevated glucose and insulin levels or HbA_{1c}. This is in contrast with an observation of hyperinsulinaemia and hypertension as major correlates of parasympathetic dysfunction with only modest association between BMI and parasympathetic dysfunction seen in persons with Type 2 diabetes [2]. Also, in persons with Type 1 diabetes, cardiovascular autonomic neuropathy has been found to be associated with older age, longer duration of diabetes, female gender, elevated fasting blood glucose and triglycerides, elevated systolic blood pressure as well as urinary albumin excretion [24].

In subjects without diabetes, the metabolic syndrome has been found to be associated with reduced heart rate variability, suggesting adverse effects on cardiac autonomic control [25,26]. We observed that all variables reflecting obesity, and especially central obesity, were inversely correlated with E/I ratio. This is in line with some previous studies that have found an association between obesity and attenuated sympathetic and vagal baroreflexes or decrease in heart rate variability [7,10]. Grassi *et al*. have also reported that central obesity compared with peripheral obesity is characterized by a greater sympathetic activation [27]. These findings emphasize the role of central adiposity, not only in the aetiology of the metabolic syndrome itself, but also as a determinant of cardiovascular autonomic regulation.

One limitation of our study is that this evaluation of cardiovascular autonomic neuropathy was performed at the second annual follow-up visit after the end of the lifestyle intervention in the Diabetes Prevention Study. Unfortunately, cardiovascular autonomic testing was not taken into consideration when planning the original study. Thus, because of the only cross-sectional approach, it was not possible to detect individual changes in autonomic regulation related to lifestyle changes or to perform comparative simultaneous evaluation of intervention on metabolic variables and autonomic function. Furthermore, the present study population does not represent the original randomized groups, as participants with incident diabetes or subsequent post-intervention follow-up, and thus supposedly with higher risk for cardiovascular autonomic neuropathy, had been excluded from the analyses, the majority of them belonging to the former control group. Another limitation related to the original setting is that a control group including subjects with normal glucose tolerance is lacking. Therefore, it is not possible to define the actual increase in prevalence of cardiovascular autonomic neuropathy as a result of impaired glucose tolerance.

We decided to use only two simple field tests for the measurement of cardiovascular autonomic function, which can be considered as a sort of methodological limitation. However, selection of the deep-breathing and passive orthostatic tests has certain rationale. The use of these two methods is based on our previous works with similar testing in other materials. We had published studies with similar methodology; for example, a study in which the prevalence of autonomic dysfunction was described in patients with newly diagnosed Type 2 diabetes [2]. In the assessment of sympathetic dysfunction, we performed only a single standing blood pressure measurement 1 min after standing, which cannot be considered optimal procedure for diagnostics of orthostatic hypotension in which diagnosis is based on a sustained fall in blood pressure within 3 min of standing. Instead of one single measurement, several blood pressure readings could have been carried out to confirm orthostatic hypotension. Individuals with drops in blood pressure between 1 and 3 min may have been missed, leading to under-reporting of this clinical problem in the present study.

In summary, cardiovascular autonomic dysfunction is common among persons with impaired glucose tolerance in the Finnish Diabetes Prevention Study cohort. At the second annual follow-up visit after the end of lifestyle intervention, parasympathetic dysfunction was observed in every fourth subject, both in the intervention and in the control group of the

original Diabetes Prevention Study lifestyle intervention study. While parasympathetic dysfunction was commonly seen, sympathetic dysfunction was not prevalent in this population. Of the major features of the metabolic syndrome, central obesity was especially associated with parasympathetic dysfunction.

Competing interests

Nothing to declare.

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