Microalbuminuria and cardiovascular risk factors in type 2 diabetes mellitus

Smulders, Y.M.

Publication date
1999

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Cardiovascular Autonomic Function is Associated with (Micro-)Albuminuria in Elderly Caucasian Subjects with Impaired Glucose Tolerance or NIDDM: The Hoorn Study

Yvo M. Smulders, Agnes Jager, Jeanet Gerritsen, Jacqueline M. Dekker, Giel Nijpels, Robert J. Heine, Lex M. Bouter, Coen D.A. Stehouwer

From the Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, and the Institute for Research in Extramural Medicine, Department of Clinical Physics and Informatics, Department of Internal Medicine, and the Department of Epidemiology and Biostatistics, Vrije Universiteit, Amsterdam, The Netherlands

Submitted for publication
Objective: In patients with NIDDM, (micro-)albuminuria is a risk indicator for cardiovascular morbidity and mortality. Studies in IDDM have shown that impaired cardiovascular autonomic function is associated with (micro-)albuminuria. Our objective was to determine whether the same association is found in an age-, sex-, and glucose-tolerance-stratified sample of an elderly (50-75 year old) Caucasian population, and whether this association is independent of other determinants of (micro-)albuminuria.

Methods: We studied 536 subjects: 256 with normal glucose tolerance, 143 with impaired glucose tolerance, and 137 with NIDDM. (Micro-)albuminuria was defined as an albumin-to-creatinine ratio of ≥3.0 mg/mmol in an early morning spot urine sample. Using the deep breathing test and the lying-to-standing test, four measures of cardiovascular autonomic function were recorded: 1- the heart rate variability during deep breathing, 2- the maximum heart rate within 15 sec after standing up minus the mean heart rate before standing, 3- the maximum RR interval between 15 and 30 sec after standing up divided by the minimum RR interval within 15 sec after standing up, and 4- the systolic blood pressure response to standing up. These 4 measures of autonomic function were summarised in a single 'cardiovascular autonomic function score' (CAFS, range: 0 to 12, indicating good to poor autonomic function).

Results: Forty-one subjects with (micro-)albuminuria were identified. In bivariate analyses, (micro-)albuminuria was associated with age, waist-to-hip ratio, systolic and diastolic blood pressure, and glucose tolerance status. The mean CAFS was significantly higher in subjects with versus without (micro-)albuminuria: 7.5 versus 5.9 (p<0.001). Multiple logistic regression analyses revealed that the CAFS was independently associated with (micro-)albuminuria in subjects with impaired glucose tolerance or NIDDM: multivariate odds ratio (OR, 95% confidence interval): 1.19 (1.02 - 1.39) per point increase in the CAFS.

Conclusions: Impaired cardiovascular autonomic function is independently associated with and thus a possible contributor to the presence of (micro-)albuminuria in subjects with impaired glucose tolerance or NIDDM.
INTRODUCTION

Increased urinary albumin excretion is a strong predictor of cardiovascular disease and mortality in patients with NIDDM (1,2), as well as in non-diabetic subjects (3,4). The pathophysiological mechanism behind this association is not entirely clear, but it has been shown that (micro-)albuminuria is associated with the presence of several cardiovascular risk factors, including hypertension, dyslipidaemia, poor glycaemic control, a pro-thrombotic state, and generalised endothelial dysfunction (5).

Several studies in IDDM have suggested that impaired cardiovascular autonomic function and increased urinary albumin excretion are related (6-10). The commonly proposed explanation for this phenomenon is a reduced nightly drop in systemic blood pressure, which is a characteristic of autonomic failure (11,12). Higher nocturnal blood pressure is believed to result in an increase in albuminuria. In addition, renal autoregulation of glomerular arterioles may be disturbed in autonomic neuropathy, causing glomerular hypertension resulting in increased urinary albumin excretion.

The majority of studies addressing the association between cardiovascular autonomic function and albuminuria have been done in IDDM subjects. Most of the studies in NIDDM subjects were relatively small, and did not include normal-glucose-tolerant and impaired-glucose-tolerant subjects for comparison with NIDDM. In the present study, we investigated the relation between cardiovascular autonomic function and albuminuria, using data from a large population-based study including subjects with normal and impaired glucose tolerance and NIDDM subjects. We were specifically interested in determining whether autonomic cardiovascular function is related to albuminuria independently of other factors that are known to be associated with albuminuria, including glucose intolerance and hypertension.

METHODS

Subjects:

The Hoorn Study comprises a cross-sectional investigation of glucose tolerance and other cardiovascular risk factors in a Caucasian population, which was conducted from 1989 to 1992. A random sample of all men and women aged 50-75 years was drawn from the municipal population registry of the town of Hoorn, The Netherlands. A total of 2484 subjects participated (response rate: 71%). An extensive cardiovascular
Chapter 6

Investigation was performed in an age-, sex-, and glucose-tolerance-stratified random subsample (n=631, response rate 89%), as described in detail elsewhere (13). The Hoorn Study was approved by the Ethical Review Committee of the University Hospital Vrije Universiteit. Informed consent was obtained from all participants.

Measurements:

Height and weight were measured barefoot wearing light clothes only. Double readings of systolic and diastolic (Korotkoff V) blood pressure were obtained on two separate occasions on the right arm with the subject in a sitting position. ‘Actual’ hypertension was defined as a mean systolic blood pressure of ≥160 mmHg and/or a mean diastolic pressure of ≥95 mmHg, with or without anti-hypertensive medication. Impaired glucose tolerance and NIDDM were diagnosed according to the 1985 World Health Organisation criteria applied to the mean of two standard oral glucose tolerance tests (14). Fasting and 2-hour post-load venous plasma glucose levels were determined with a glucose dehydrogenase method. Subjects with previously diagnosed NIDDM treated with oral blood-glucose-lowering medication or insulin did not undergo a glucose tolerance test. In addition, we measured fasting serum levels of total cholesterol, high-density-lipoprotein (HDL) cholesterol and triglycerides (enzymatic techniques), creatinine (modified Jaffé method), total homocysteine (free plus protein bound; high-performance liquid chromatography), and HbAlc (ion exchange high-performance liquid chromatography). Urinary albumin excretion was measured in an early morning, first voided urine sample. The presence of leukocytes was tested by light microscopy and scored as positive if >5 leukocytes per high powerfield were found. Urinary albumin concentration was measured by rate nephelometry (Array protein system, Beckman, Ireland), with a detection threshold of 6.2 mg/l and intra- and inter-assay coefficients of variation of 5% and 8%, respectively. Urinary creatinine was measured with a modified Jaffé method. A urinary albumin-to-creatinine ratio of ≥3.0 mg/mmol was considered indicative of (micro-)albuminuria. Urine samples were available for a total of 607 subjects. Duplicate measurements were available for a representative sample of 176 subjects. The albumin-to-creatinine ratio in these subjects was based on the average of these two measurements. Subjects using an angiotensin converting enzyme inhibitor (n=32) were excluded from the analyses in order to avoid misclassification of the dependent variable, leaving 575 subjects for further analysis.

A detailed medical history was obtained from all subjects. Cardiovascular disease was defined as coronary artery, cerebrovascular or peripheral artery disease. Coronary artery
disease was defined as a history of myocardial infarction, angina pectoris, coronary bypass surgery and/or Minnesota codes 1-1 or 1-2 on the 12-lead electrocardiogram (available in 625 subjects). Cerebrovascular disease was defined as a history of transient ischaemic attack or stroke. Peripheral artery disease was defined as a history of intermittent claudication, peripheral arterial reconstruction, limb amputation and/or an ankle-brachial pressure index of ≤0.50. The cardiovascular history was obtained by a self-administered questionnaire and, if positive, accepted only when confirmed by written information from the subject’s general practitioner. All subjects fulfilling the above criteria for cardiovascular disease, plus the subjects who reported using drugs affecting the cardiovascular system (including anti-hypertensive and anti-arrhythmic drugs, β-blockers, diuretics, and vasodilators) were classified as positive for cardiovascular disease and/or drugs (CVD&D). Protein intake was calculated using a self-administered validated semi-quantitative food frequency questionnaire (15).

**Cardiovascular autonomic function tests:**

Both the deep breathing test and the lying-to-standing test were performed by the same investigator. Subjects refrained from smoking and drinking coffee for at least two hours prior to the tests. A light meal >1 hour before the measurements was allowed. The tests were done in quiet surroundings, with a room temperature between 19 and 22°C, according to a fixed protocol. After 10 minutes of rest in a supine position, the deep-breathing test was performed by asking the study subjects to breath deeply for 1 minute at a frequency of 6 breaths per minute (5 sec in, 5 sec out). After 5 minutes of rest, the lying-to-standing test was performed. The subjects stood up as quickly as possible, and remained standing for 2 minutes. During both tests, heart rate and blood pressure were registered using a computer-based data acquisition system. An electrocardiographic registration was obtained from bipolar chest leads. Beat-to-beat systolic and diastolic blood pressure were measured non-invasively on the right middle finger with the Finapress (Type BP2300, Ohmeda, Englewood, CO, USA).

The following measures of cardiovascular autonomic function were used for this study:

1. the EIHR-diff (beats/min): the difference between intra-breath maximum and minimum heart rate (HR), averaged over 6 breaths,
2. the L→SAHRmax (beats/min): the maximum heart rate within 15 sec after standing up minus the mean heart rate during 1 minute before standing,
3. the L→Smax/min-ratio (dimensionless): the maximum RR interval between 15 and
30 sec after standing up divided by the minimum RR interval within 15 sec after standing up, and

4- the $L \rightarrow SABP_{sys}$ (mmHg): the systolic blood pressure after standing up (mean between 1.5 and 2.0 minutes after standing) minus the supine systolic blood pressure (mean of 30 sec).

The ELHR-diff and the $L \rightarrow SAHR_{max}$ predominantly reflect parasympathetic function, the $L \rightarrow S_{max/min}$-ratio is the result of a vagal reflex to sympathetically mediated vasoconstriction, and the $L \rightarrow SABP_{sys}$ is thought to reflect mainly peripheral sympathetic function (16,17).

Results were discarded if multiple non-sinus beats occurred during testing, if standing up took more than 10 sec, or if the recordings were technically unsuccessful for more than one of the four measures (n=30). Subjects with a history of neurological diseases or using drugs known to influence autonomic nerve function (anti-Parkinson drugs, phenytoin, antihistamines, parasympatholytic, sympathicomimetic and parasympathicomimetic drugs) were also excluded from the analysis (n=9), leaving 536 subjects for final inclusion.

Statistical methods:

Routine parametric and non-parametric bivariate tests were used, as appropriate, to test for group differences between subjects with and without (micro-)albuminuria. Correlations between the four autonomic function measures were calculated using Pearson's correlation coefficients, if required after logarithmic transformation. Based on the four measures of cardiovascular autonomic function, a summary 'cardiovascular autonomic function score' (CAFS) was constructed as follows: the results of each measurement were divided into quartiles. A subject was assigned 0 points if the result was in the most normal quartile (lowest values for the $L \rightarrow SABP_{sys}$ test, highest values for the other 3 measures), 1 point if in the second quartile, 2 points if in the third quartile, and 3 points if the test outcome was in the most abnormal quartile (highest values for the $L \rightarrow SABP_{sys}$, lowest values for the other measures). If all 4 measures were completed successfully, the scores of each were added together. If one result was missing (44 of 536 subjects), it was replaced by the median score for this measurement (1.5 points). The result is an CAFS ranging from 0 (good) to 12 (poor). Multiple logistic regression analysis was used to identify independent determinants of (micro-)albuminuria. The presence of interaction effects was studied by entering product terms into the model. A two-sided $p$-value of $<0.05$ was considered statistically significant.
RESULTS

Of the 536 subjects included in the analyses, 256 had normal glucose tolerance, 143 impaired glucose tolerance, and 137 NIDDM. Demographic and clinical data are given separately for those with and without (micro-)albuminuria in Table 1. Age, waist-to-hip

<table>
<thead>
<tr>
<th></th>
<th>normoalbuminuria (n=495)</th>
<th>(micro-)albuminuria (n=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (y)</td>
<td>63.7 (7.1)</td>
<td>66.7 (6.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>sex (% males)</td>
<td>47</td>
<td>54</td>
<td>0.40</td>
</tr>
<tr>
<td>waist-to-hip ratio</td>
<td>0.91 (0.09)</td>
<td>0.95 (0.06)</td>
<td>0.002</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)</td>
<td>136.7 (18.2)</td>
<td>152.4 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>81.9 (9.5)</td>
<td>87.4 (12.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>mean arterial blood pressure (mmHg)</td>
<td>100.2 (11.3)</td>
<td>109.0 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>'actual' hypertension (%)</td>
<td>14</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGT/IGT/NIDDM (%)</td>
<td>50/27/23</td>
<td>24/24/52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbAlc (%)</td>
<td>5.5 (2.7 - 15.2)</td>
<td>6.0 (4.5 - 12.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>total cholesterol (mmol/l)</td>
<td>6.7 (1.2)</td>
<td>6.6 (1.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.25 (0.56 - 3.43)</td>
<td>1.10 (0.57 - 2.29)</td>
<td>0.08</td>
</tr>
<tr>
<td>triglycerides (mmol/l)</td>
<td>1.5 (0.4 - 14.0)</td>
<td>1.8 (0.7 - 13.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>current smoking (% yes)</td>
<td>28</td>
<td>27</td>
<td>0.84</td>
</tr>
<tr>
<td>protein intake (g/kg/day)</td>
<td>0.95 (0.29 - 2.38)</td>
<td>0.90 (0.31 - 1.80)</td>
<td>0.56</td>
</tr>
<tr>
<td>homocysteine (µmol/l)</td>
<td>11.3 (4.9 - 49.6)</td>
<td>12.4 (6.1 - 77.5)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 1: Demographic and clinical data of subjects without and with (micro-)albuminuria.

Data are presented as mean (SD), with p-value calculated by unpaired t-test, or by median (range), with p-value calculated by Mann-Whitney U-test, or by % of subjects. P-values for nominal variables are calculated with the Chi-square test (for glucose tolerance categories: Chi-square test for trend). (micro-)albuminuria = albumin-to-creatinine ratio ≥3.0 mg/mmol in early morning spot urine sample, mean arterial blood pressure = diastolic blood pressure + (0.33×pulse pressure), 'actual' hypertension = systolic blood pressure ≥160mmHg and/or diastolic blood pressure ≥95mmHg, NGT = normal glucose tolerance, IGT = impaired glucose tolerance, NIDDM = non-insulin-dependent diabetes mellitus, HDL = high-density-lipoprotein. For explanation of autonomic function tests: see methods section.

Ratio, blood pressure, and glucose tolerance were significantly related to the presence of (micro-)albuminuria in bivariate tests. All four measures of cardiovascular autonomic function showed less favourable results in subjects with (micro-)albuminuria.

Table 2 displays the difference in CAFS between subjects with and without (micro-)albuminuria, with separate results given for substrata of glucose tolerance and 'actual' hypertension. In the whole group, the CAFS was significantly related to the presence of
Table 2: Mean cardiovascular autonomic function score (CAFS) in subjects without and with (micro-)albuminuria.

<table>
<thead>
<tr>
<th></th>
<th>(normo-)albuminuria (n)</th>
<th>(micro-)albuminuria (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>5.9 (495)</td>
<td>7.5 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGT</td>
<td>5.4 (246)</td>
<td>6.4 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>IGT</td>
<td>6.0 (133)</td>
<td>7.5 (10)</td>
<td>0.10</td>
</tr>
<tr>
<td>NIDDM</td>
<td>6.9 (116)</td>
<td>8.0 (21)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 2: Mean cardiovascular autonomic function score (CAFS) in subjects without and with (micro-)albuminuria. NGT = normal glucose tolerance, IGT = impaired glucose tolerance, NIDDM = diabetes mellitus. 'Actual' hypertension was defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg, with or without use of antihypertensive medication. All p-values by unpaired t-test.

(micro-)albuminuria. This relation did not vary greatly with glucose tolerance status or the presence of hypertension. Interestingly, (micro-)albuminuria was not seen in the group of subjects in the lowest quartile of the CAFS, even though patients with impaired glucose tolerance (n=29), diabetes (n=12) and hypertension (n=8) were present in this group. There was no evidence of a threshold effect in the relation between the CAFS and (micro-)albuminuria (data not shown).

None of the individual associations between the four separate measures of cardiovascular autonomic function and (micro-)albuminuria retained statistical significance after adjustment for potential confounders (data not shown). The CAFS, however, was significantly related to the presence of (micro-)albuminuria in the complete study group after adjustment for confounders (Table 3). Multiple logistic regression analysis was also performed in strata of glucose tolerance. In these multivariate analyses, the IGT and the NIDDM subjects behaved similarly with respect to the association between the CAFS and (micro-)albuminuria; the odds ratio (95% CI) (calculated as in model 2 of Table 3) for having (micro-)albuminuria was 1.26 (0.97 - 1.64) for IGT subjects, and 1.22 (0.98 - 1.52) for NIDDM subjects. Because of this similarity, and because of its contrast with the results obtained for NGT subjects, IGT and NIDDM subjects were analysed as a single group. The analyses indicated that the association between CAFS and (micro-)albuminuria was stronger in subjects with impaired glucose tolerance or NIDDM than in normal-glucose-tolerant subjects (Table 3). Additional adjustment for HbA1c or fasting glucose levels in the impaired glucose tolerance plus NIDDM group did not materially affect these results (data not shown).
Cardiovascular autonomic function and microalbuminuria

<table>
<thead>
<tr>
<th>All subjects:</th>
<th>crude</th>
<th>model 1</th>
<th>model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>1.22</td>
<td>1.15</td>
<td>1.14</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.08 - 1.37</td>
<td>1.01 - 1.30</td>
<td>1.00 - 1.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NGT:</th>
<th>crude</th>
<th>model 1</th>
<th>model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>1.14</td>
<td>1.03</td>
<td>1.05</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.91 - 1.44</td>
<td>0.81 - 1.32</td>
<td>0.81 - 1.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IGT and NIDDM:</th>
<th>crude</th>
<th>model 1</th>
<th>model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>1.20</td>
<td>1.20</td>
<td>1.19</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.04 - 1.39</td>
<td>1.04 - 1.39</td>
<td>1.02 - 1.39</td>
</tr>
</tbody>
</table>

Table 3: Multiple logistic regression analyses with (micro-)albuminuria as the dependent variable and the autonomic function score (CAFS) as the independent variable.

The odds ratio is expressed for each point increase in the autonomic cardiovascular function score. Separate results are given for the complete study group and for the substrata of normal glucose tolerance, and impaired glucose tolerance plus NIDDM.

All subjects: model 1: adjustment for age, sex, and glucose-tolerance-category; model 2: as model 1, plus adjustment for ‘adual’ hypertension, waist-to-hip-ratio, triglycerides, and high-density- lipoprotein cholesterol. In substrata of glucose tolerance: identical models 1 and 2, but without glucose tolerance as a covariate. Additional correction for total protein intake, homocysteine, and current or ever smoking provided results virtually identical to model 2 in both the whole group and each of the substratum analyses (data not shown).

Note that we performed two measurements reflecting mainly parasympathetic function, one that measures mainly sympathetic function, and one that combines parasympathetic and sympathetic function. Combining the four autonomic function measures in one score carries the risk of unbalanced weighting of parasympathetic and sympathetic autonomic (dys)function. In order to address this, we constructed an alternative autonomic function score by combining the EIHR-diff (mainly parasympathetic) and the L→SABPsys (mainly sympathetic) in a similar way as was done for the CAFS. The EIHR-diff was chosen as parasympathetic test because it showed an even lower correlation with the L→SABPsys than did the L→SAHRmax (Pearsons correlation coefficients: 0.07 versus 0.13, respectively), indicating minimal co-linearity. This alternative autonomic function score resulted in odds ratios that were virtually identical to those reported for the CAFS in Table 3 (data not shown).
No evidence of an interactive effect between any measure of blood pressure and the CAFS with regard to the occurrence of (micro-)albuminuria was found (p>0.34 for each product term). Likewise, we found no evidence of interaction between CAFS and age (p=0.39), waist-to-hip ratio (p=0.42), or protein intake (p=0.50). Re-analysis of the data with an albumin-to-creatinine ratio of 2.0 and 2.5 as a cut-off level for (micro-)albuminuria had trivial effects on the outcomes, as did exclusion of subjects with leukocyturia (n=121), exclusion of the duplicate urine samples in 176 subjects, or exclusion of subjects with macro-albuminuria (ratio >30 mg/mmol, n=3) (data not shown). If hypertension defined as ‘blood pressure ≥160 and/or ≥95 mmHg and/or use of antihypertensive medication’ was entered instead of ‘actual’ hypertension, the multivariate test results as presented in Table 3 were essentially identical (data not shown). A total of 192 subjects met the criteria for ‘cardiovascular disease and/or drugs’ (CVD&D). After additional adjustment for CVD&D in the IGT plus NIDDM subgroup, the odds ratio (95% CI) for the CAFS decreased slightly, to 1.16 (1.00 - 1.34) and 1.14 (0.98 - 1.34) in models 1 and 2, respectively (from 1.20 and 1.19, cf Table 3).

DISCUSSION

This study demonstrates that cardiovascular autonomic function is related to the presence of (micro-)albuminuria in an age-, sex-, and glucose-tolerance-stratified random sample of an elderly Caucasian population. This association was independent of other determinants of (micro-)albuminuria in the Hoorn study population (glucose tolerance, blood pressure, waist-hip ratio, protein intake and homocysteine) (18,19), except for the fact that it was observed more clearly in subjects with impaired glucose tolerance or diabetes than in normal-glucose-tolerant subjects.

The prevalence of autonomic dysfunction is about 7% in newly diagnosed NIDDM (20). There have been reports indicating that autonomic dysfunction in NIDDM is associated with age (21,22), sex (23), weight (24,25), blood pressure (22,24), fasting insulin level (23,24), level of glycaemic control (25), and duration of NIDDM (23,25). As for NIDDM-related microvascular complications, several reports have suggested that a relation between autonomic dysfunction and retinopathy exists (22,25,26).

Some studies have looked in detail at autonomic cardiovascular function in relation to albuminuria in NIDDM. An early study found higher urinary albumin excretion rates in patients with impaired heart rate variability, which is a feature of cardiovascular autonomic
Cardiovascular autonomic function and microalbuminuria failure (24). Another report also indicated that autonomic cardiovascular dysfunction, measured with only a single test (deep breathing), was related to albuminuria in a large (n=949) number of relatively young, strictly hypertensive patients (25). In this study, only an association with overt proteinuria was reported, with normo- and microalbuminuric subjects taken as a single control group. An abnormal day-night blood pressure pattern was related to abnormal autonomic function measures and proteinuria in a study involving 76 subjects (27). Two small studies showed conflicting results (22,28). Finally, a recent study by Wirta et al. found that albuminuria was related to Valsalva and breathing ratios only in patients with a duration of NIDDM of >1 year (29). Taken together, the majority of studies performed so far in NIDDM support the concept of a relation between autonomic cardiovascular function and (micro-)albuminuria.

Compared to these previous studies, our study has the advantage of being large, truly population based, and including patients with normal and impaired glucose tolerance, and with normal and increased blood pressure. The relatively large study group allowed for the use of substratum analyses and multivariate testing. Although interaction effects were not found, our study may have lacked sufficient power to exclude such effects. An final advantage was that we were able to evaluate four different measures of autonomic function. Previous studies employed less extensive autonomic function tests, except for one (22), which unfortunately included only 9 NIDDM patients with (micro-)albuminuria.

There are two plausible explanations for a causal relation between cardiovascular autonomic function and urinary albumin excretion. Firstly, a reduced nightly drop in blood pressure, which is a feature of autonomic dysfunction not only in IDDM (11,12) but also in NIDDM (30), may result in (micro-)albuminuria. Secondly, a disturbance in glomerular arteriolar autoregulation may result in an inability of the glomerular apparatus to counteract hyperglycaemia-associated glomerular hypertension and glomerular hyperfiltration (31). Glomerular hyperfiltration has been reported to occur in both IDDM and NIDDM, but has also been found in subjects with IGT (32). Our findings may indicate that IGT- and NIDDM-associated effects on glomerular haemodynamics may be required for autonomic cardiovascular dysfunction to reveal its effect on urinary albumin excretion.

We cannot fully exclude the possibility that we have merely studied an association between two diabetic complications, caused by largely the same set of risk factors. However, if this would have been the case, then introduction of these risk factors as additional independent variables on top of the crude model with only the CAFS would...
have introduced significant co-linearity among the independents. This would normally be reflected by a marked decrease in the odds ratio and/or in the partial $R^2$ for the CAFS, which was not seen (see Table 3, the partial $R^2$ for the CAFS in the ‘IGT and NIDDM’ stratum was 0.15 in the crude model, 0.14 in model 1, and 0.12 in model 2).

Another issue that needs to be addressed is the way in which we analysed the results of the autonomic function tests. We did not regard the results as dichotomous variables for ‘normal’ and ‘abnormal’ results, as has been done in many previous studies. We chose this approach because abnormal values for autonomic function tests have been defined on the basis of statistical abnormality in a healthy control population, rather than on the basis of pathophysiological alterations. There is no evidence whatsoever to indicate that these statistically abnormal results have a pathophysiological meaning in the context of a possible association with (micro-)albuminuria. Also, we avoided the use of age-corrected autonomic function measures. Albumin excretion rises with increasing age. It is unknown whether this effect is (partly) mediated by deterioration in autonomic function. However, if this would be the case, then ‘taking the age effect out’ of the autonomic function variable by using age-corrected values would inadvertently exclude autonomic function as a determinant of (micro-)albuminuria. Correction for age in the multivariate model by including it as a separate independent variable, as was done in our analyses, is in our view the best option.

A final possible concern is whether it is legitimate to combine several autonomic function measures in a single score. We constructed the CAFS with the purpose of enhancing power, since a battery of autonomic function measures will by definition show a higher reproducibility than any single measurement. Also, the four measures are thought to convey distinct information about cardiovascular autonomic function (16,17). This is supported by generally poor correlations we found between the four measures. Except for a correlation of 0.60 between the $L \rightarrow S\Delta HR_{max}$ and the $L \rightarrow S_{max/min}$-ratio, all correlations were below 0.40. Even the $E\Delta HR$-diff and the $L \rightarrow S\Delta HR_{max}$, which are both considered to reflect mainly parasympathetic function, correlated poorly (correlation coefficient 0.37), and were quite differently associated with (micro-)albuminuria in the bivariate tests (Table 1), suggesting that these measures of cardiovascular autonomic function do not convey identical information. Even so, giving equal weights to measures that overlap even partly could possibly result in an CAFS that does not give a balanced impression of overall autonomic function. In our view, the virtually identical results that were obtained using an alternative score that combined a
parasympathetic with an uncorrelated sympathetic measurement make it unlikely that
the CAFS was heavily unbalanced.

In conclusion, our study shows that autonomic cardiovascular function is associated
with the occurrence of (micro-)albuminuria in subjects with impaired glucose tolerance
or NIDDM, and that this association is independent of age, blood pressure, and other
previously identified determinants of (micro-)albuminuria in the same study population.

REFERENCES

2. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset
4. Damsgaard EM, Froland A, Jørgensen OD, Mogensen CE. Eight to nine year mortality in known non-
5. Stehouwer CDA, Lambert J, Donker AJ, Hinsbergh V van. Endothelial dysfunction and pathogenesis
7. Molgaard H, Christensen PD, Sorensen KE, Christensen CK, Mogensen CE. Association of 24-h cardiac
9. Torffvit O, Lindeqvist A, Agardh CD, Palm O. The association between diabetic nephropathy and
10. Poulsen PL, Ebbehoj E, Hansen KW, Mogensen CE. 24-h blood pressure and autonomic function is
related to albumin excretion within the normoalbuminuric range in IDDM patients. Diabetologia
11. Spallone V, Gambardella S, Maiello M, Barani A, Frontoni S, Menzinger G. Relationship between
autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients.
Diab Care 1994;17:578-584.
12. Ittersum MFJ van, Spek JJ, Praet IJA, et al. Ambulatory blood pressure and autonomic nervous function
Switzerland. 1985.
15. Grootenhuys PA, Westenbrink S, Sie CMTL, Neeling JN de, Kok FJ, Bouter LM. A semi-quantitative
food frequency questionnaire for use in epidemiological research among the elderly: validation by


