Chapter 6

Relation between albumin in the urine and electrocardiographic markers of myocardial ischemia in patients without diabetes mellitus


Abstract

**Background**—The electrocardiogram (ECG) can be used to determine the presence of ischemic heart disease in a population at large. In addition, there is evidence that microalbuminuria increases cardiovascular risk in nondiabetic populations. Little is known about the precise relation between urinary albumin excretion (UAE) and cardiovascular disease. If UAE can be considered as a continuous variable this could have important implications for individual cardiovascular risk assessment. We evaluated the association between the level of UAE, including levels within the normal range, and ischemic electrocardiographic (ECG) abnormalities in a general nondiabetic population.

**Methods and results**—In a population-based study 7,579 subjects (mean age 48 years, 51% male) were eligible for analysis. UAE was measured as the mean of two 24-hour urine collections. Using computerized Minnesota coding, ischemic ECG abnormalities were divided into: infarct patterns, major ischemia, and minor ischemia. Furthermore, T axes deviations, as potentially more sensitive markers of cardiac disease, were categorized as normal, borderline, and abnormal. The presence of all ECG abnormalities increased with increasing levels of UAE, which was already seen at levels of UAE below 30 mg/24h. After adjustment for other cardiovascular risk factors UAE remained significantly associated with major ischemia (Odds Ratio, [95% CI] 1.13, [1.00-1.27]) and abnormal T-axis deviation (1.29, [1.10-1.51]).

**Conclusions**—In a large nondiabetic population a graded continuous relation was present between the level of UAE and ECG abnormalities, without an apparent threshold. In addition, UAE was associated with several ECG abnormalities, independent from conventional cardiovascular risk factors. These data suggest that the level of UAE can be used for establishing cardiovascular risk in the population at large.
Introduction

Microalbuminuria The electrocardiogram (ECG) can be used to determine the presence of ischemic heart disease in a population at large. Microalbuminuria is an independent predictor for cardiovascular disease in diabetes mellitus\(^1\). In addition, there is evidence that microalbuminuria increases cardiovascular risk in nondiabetic populations\(^2\). However, in almost all studies microalbuminuria was used as a dichotomous variable and little is known about the precise relation between urinary albumin excretion (UAE) and cardiovascular disease. If UAE can be considered as a continuous variable this could have important implications for individual cardiovascular risk assessment. We evaluated the association between the level of UAE, including levels within the normal range, and ischemic electrocardiographic (ECG) abnormalities in a general nondiabetic population. To establish the value of UAE as an independent risk factor, we also examined the relation between UAE and these ECG abnormalities, taking conventional cardiovascular risk factors into account.

Methods

Study design and patient population

The population analyzed in this study was part of the cohort from the PREVEND (Prevention of REnal and Vascular ENdstage Disease) study. The PREVEND study is designed to investigate the natural course of microalbuminuria and its relation with renal and cardiovascular disease in the general population. The study cohort is formed by male and female inhabitants, aged 28 to 75 years, of the city of Groningen, the Netherlands. These subjects were asked to send in a morning urine sample. A sample from the population, consisting of all subjects with an albumin concentration in the morning urine sample of > 10 mg/L, together with a randomly selected sample of the remaining population (morning urine albumin excretion < 10 mg/L) underwent 2 examinations at an outpatient clinic. Subjects using insulin or being pregnant were excluded.

Measurements

Measurements at the visits included anthropometry, blood pressure measurements for ten minutes with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical Inc, Tampa, Florida), collection of two 24-hour urine samples, ECG recording, and fasting blood samples. Furthermore, all participants completed a questionnaire on demographics and cardiovascular and renal history. A total of 8,592 subjects completed 2 visits to the outpatient clinic. For the pre-
sent study 18 subjects were excluded because of missing albuminuria data, 433 because of presence of erythrocyturia or leukocyturia, 91 because of macroalbuminuria and 63 because of missing ECG data. A total of 241 subjects met the criteria for non-insulin dependent diabetes mellitus and in 167 subjects presence or absence of non-insulin dependent diabetes mellitus could not be established because of missing data; these subjects were also excluded from analysis. Finally, 7,579 subjects were eligible for analysis. All participants gave written informed consent. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki.

Urinary volume and albumin were measured in each collection. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of less than 4.3% and 4.4%, respectively (Dade Behring Diagnostic, Marburg, Germany). Leukocyte and erythrocyte counts were determined by urine sticks (Nephur + leuco, Boehringer Mannheim, Mannheim, Germany). Plasma glucose and serum cholesterol were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA). The UAE was measured as the mean of two 24-hour urine collections. Albumin measurements were considered unreliable in the case of erythrocyturia or leukocyturia, according to dipstick analysis (erythrocytes > 50/µl or leukocytes > 75/µl, or leukocytes = 75/µl and erythrocytes > 5/µl)

Electrocardiogram

Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Rijswijk, the Netherlands), stored digitally, and classified using the computer program Modular ECG Analysis System (MEANS), which is also capable of performing a classification according to the Minnesota Code. Signal analysis and classification of MEANS have been extensively evaluated in both clinical and general population samples. Infarct patterns, suggestive for myocardial infarction, were defined by Minnesota codes 1.1 and 1.2. Major ischemic changes were defined by codes 4.1, 4.2, 5.1 or 5.2, after exclusion of codes 1.1 and 1.2. Finally, minor ischemic changes were defined by codes 1.3, 4.3 or 5.3, after exclusion of infarct patterns and major ischemia. T axes were computed from vectorcardiographic X, Y and Z leads which can be reconstructed from the standard ECG leads. The mean spatial axis is obtained by vectorially adding the instantaneous heart vectors during the T wave. The mean frontal axis is then taken to be the angle between the X-axis and the projection of the mean spatial axis on the frontal plane. T axes were classified into 3 groups: “normal” (15° to 75°), “borderline” (-15° to 15° and 75° to 105°), and “abnormal” (-180° to -15° and 105° to 180°).
Definitions

Mean blood pressure was defined as the mean of the last 2 measurements of both visits. Subjects were considered to be hypertensive when systolic blood pressure $\geq 160$ mmHg and/or diastolic blood pressure $\geq 95$ mmHg, or when using antihypertensive treatment. Non-insulin dependent diabetes mellitus was defined as fasting plasma glucose levels $\geq 7.8$ mmol/l or non-fasting glucose $\geq 11.1$ mmol/l, or the use of antidiabetic drugs. Hypercholesterolemia was defined as a total serum cholesterol $\geq 6.5$ mmol/l or the use of lipid lowering medication. Body mass index was calculated as the ratio between weight (kilograms) and height (square meters). Obesity was defined as a body mass index exceeding 27 kg/m$^2$. When first-grade relatives had established a cardiovascular event at $< 55$ years of age, subjects were considered having a positive family history for cardiovascular disease.

Statistical analysis

Continuous data are reported as mean with standard deviation. In case of a skewed distribution, the median was used. Patient characteristics were compared over various ranges of urinary albumin excretion and tested for a linear trend by means of 1-way analysis of variance or by chi-square statistics. Univariate and multiple logistic regression analysis was used to explore the effect of UAE and a group of known cardiovascular risk factors on the risk of ECG abnormalities. To evaluate the association between UAE and ECG abnormalities four alternative models were examined: linear, exponential, polynomial, and logarithmic. To compare the fit of the models, the statistical significance of the coefficients and the overall model, log-likelihood chi-square tests were assessed. The association between UAE and the ECG parameters appeared to be logarithmic. Coefficients of the logistic regression model were used to estimate prevalences of ECG abnormalities for each value of UAE. Interactions between UAE and the above-mentioned covariates were explored in logistic regression models that included UAE, the risk factor at issue, and the interaction term of these 2 factors. A two-sided $P$-value of $< 0.05$ was considered statistically significant. Analyses were performed using the statistical package SPSS 9.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics are listed in Table 1. Increasing levels of UAE were accompanied by an increase in almost all major cardiovascular risk factors. Both Figure 1 and Table 2 show that the presence of ischemic ECG abnormalities increased with the level of UAE, which is demonstrated at very low levels of UAE.
Table 1. Population characteristics stratified by various ranges of urinary albumin excretion

<table>
<thead>
<tr>
<th>Variable</th>
<th>0-15 (n = 5,563)</th>
<th>15-30 (n = 1,098)</th>
<th>30-150 (n = 833)</th>
<th>150-300 (n = 85)</th>
<th>Total (n = 7,979)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>47 ± 12</td>
<td>51 ± 13</td>
<td>55 ± 13</td>
<td>58 ± 11*</td>
<td>48 ± 12</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>47</td>
<td>60</td>
<td>65</td>
<td>71</td>
<td>51</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72 ± 9</td>
<td>77 ± 10</td>
<td>79 ± 11</td>
<td>81 ± 11*</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124 ± 17</td>
<td>135 ± 20</td>
<td>141 ± 23</td>
<td>148 ± 25*</td>
<td>128 ± 20</td>
</tr>
<tr>
<td>Systemic hypertension, %</td>
<td>11</td>
<td>26</td>
<td>36</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>5.6 ± 1.1</td>
<td>5.7 ± 1.1</td>
<td>5.8 ± 1.1</td>
<td>6.0 ± 1.1*</td>
<td>5.6 ± 1.1</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>22</td>
<td>27</td>
<td>33</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.4 ± 3.9</td>
<td>26.6 ± 4.2</td>
<td>27.6 ± 4.8</td>
<td>28.3 ± 4.4*</td>
<td>25.9 ± 4.1</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>30</td>
<td>43</td>
<td>51</td>
<td>57</td>
<td>34</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>44</td>
<td>46</td>
<td>47</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Cardiovascular family history, %</td>
<td>21</td>
<td>25</td>
<td>24</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

*P for trend < 0.001

Values are given as mean (standard deviation)

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Figure 1. Unadjusted predicted prevalences of ECG abnormalities by the level of urinary albumin excretion
Table 2. Prevalences of electrocardiographic abnormalities stratified by various ranges of urinary albumin excretion

<table>
<thead>
<tr>
<th>Variable</th>
<th>0-15 (n = 5,563)</th>
<th>15-30 (n = 1,098)</th>
<th>30-150 (n = 833)</th>
<th>150-300 (n = 85)</th>
<th>Total (n = 7,979)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct patterns</td>
<td>3.6</td>
<td>3.9</td>
<td>7.1</td>
<td>7.1*</td>
<td>4.1</td>
</tr>
<tr>
<td>Major ischemia</td>
<td>6.7</td>
<td>8.8</td>
<td>12.4</td>
<td>16.5*</td>
<td>7.7</td>
</tr>
<tr>
<td>Minor ischemia</td>
<td>14.1</td>
<td>16.8</td>
<td>21.6</td>
<td>24.7*</td>
<td>15.5</td>
</tr>
<tr>
<td>Borderline T-axis deviations</td>
<td>3.2</td>
<td>5.0</td>
<td>6.6</td>
<td>8.3*</td>
<td>3.9</td>
</tr>
<tr>
<td>Abnormal T-axis deviations</td>
<td>2.3</td>
<td>5.4</td>
<td>8.4</td>
<td>15.5*</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*P for trend < 0.001

Results of three different models examining the relation of UAE (logarithmically transformed) and ECG abnormalities are presented in Table 3.

Table 3. Results from univariate and multivariate logistic regression analysis, relating urinary albumin excretion with electrocardiographic abnormalities

<table>
<thead>
<tr>
<th>Log urinary albumin excretion (mg 24hour⁻¹)</th>
<th>Odds Ratio (95% Confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minor ischemic changes</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.25 (1.17-1.35)*</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.10 (1.02-1.18)‡</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.02 (0.93-1.11)§</td>
</tr>
</tbody>
</table>

* P <0.001 † P <0.01 ‡ P <0.05
Model 1 Unadjusted
Model 2 Adjusted for age and gender
Model 3 Adjusted for age, gender, diastolic and systolic blood pressure, cholesterol, body mass index, current smoking, and cardiovascular family history

The unadjusted model shows that log UAE was significantly associated with all categories of ECG parameters. When adjusted for age and gender log UAE remained significantly associated with minor and major ischemic changes, and borderline and abnormal T-axis deviations. Further adjustment for conventional risk indicators still disclosed a significant association between UAE, major ischemic abnormalities, and abnormal T-axis deviations. We performed secondary analyses evaluating several interaction terms. No interaction term was statistically significant in the multivariate analysis.
Discussion

By convention, microalbuminuria is defined as 30 to 300 mg UAE in 24-hour period. However, these criteria have been derived from studies in diabetic populations. We demonstrate that an increase of ECG abnormalities was seen in a large nondiabetic population with UAE levels < 30 mg in a 24-hour period; these abnormalities continued throughout the microalbuminuric range, without an apparent threshold. We confirmed the relation between UAE and other established cardiovascular risk indicators demonstrated in previous studies. After adjustment for these cardiovascular risk indicators, the association between UAE and cardiac abnormalities attenuated, but remained significantly associated with major ischemic changes and abnormal T-axis deviations. This suggests that UAE has an additional value to conventional cardiovascular risk indicators in predicting cardiovascular disease.

It has been postulated that UAE is a sensitive indicator of generalized vascular damage. An increased transcapillary albumin excretion rate, an increased plasma level of von Willebrand factor and an attenuated endothelium dependent response on vasodilator stimuli in subjects with microalbuminuria support this hypothesis. Thus, UAE might identify subjects at risk for vascular disease. The value of microalbuminuria as an independent predictor for cardiovascular disease has been demonstrated in diabetic as well as nondiabetic subjects. However, microalbuminuria is only currently used as a dichotomous variable. A relation has previously been demonstrated between UAE, expressed as a continuous variable, and a history of myocardial infarction. Our study supports this finding by demonstrating a continuous relation between UAE and cardiovascular risk in a general nondiabetic population. Moreover, this study shows that the urinary albumin level associated with increased cardiovascular risk might already be present at levels currently accepted to be normal, as reported before in smaller studies.

In conclusion, in a large nondiabetic population a graded continuous relation was present between the level of UAE and ECG abnormalities, without an apparent threshold. These data suggest that the level of UAE can be used for establishing cardiovascular risk in the population at large.
References


