**Identifying patients with type 2 diabetes at high risk of microalbuminuria: results of the DEMAND (Developing Education on Microalbuminuria for Awareness of reNal and cardiovascular risk in Diabetes) Study**

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**Abstract**

**Background.** We evaluated to what extent the presence of risk factors and their interactions increased the likelihood of microalbuminuria (MAU) among individuals with type 2 diabetes.

**Methods.** Fifty-five Italian diabetes outpatient clinics enrolled a sample of patients with type 2 diabetes, without urinary infections and overt diabetic nephropathy. A morning spot urine sample was collected to centrally determine the urinary albumin/creatinine ratio (ACR). A tree-based regression technique (RECPAM) and multivariate analyses were performed to investigate interaction between correlates of MAU.

**Results.** Of the 1841 patients recruited, 228 (12.4%) were excluded due to the presence of urinary infections and 56 (3.5%) for the presence of macroalbuminuria. Overall, the prevalence of MAU (ACR = 30–299 mg/g) was of 19.1%. The RECPAM algorithm led to the identification of seven classes showing a marked difference in the likelihood of MAU. Non-smoker patients with HbA1c <7% and waist circumference ≤102 cm showed the lowest prevalence of MAU (ACR = 3.5%) for the presence of macroalbuminuria. Overall, the risk of MAU (ACR = 30–299 mg/g) was of 19.1%, and represented the reference class. Patients with retinopathy, waist circumference >98 cm and HbA1c >8% showed the highest likelihood of MAU (odds ratio = 13.7; 95% confidence intervals 6.8–27.6). In the other classes identified, the risk of MAU ranged between 3 and 8. Age, systolic blood pressure, HDL cholesterol levels and diabetes treatment represented additional, global correlates of MAU.

**Conclusions.** The likelihood of MAU is strongly related to the interaction between diabetes severity, smoking habits and several components of the metabolic syndrome. In particular, abdominal obesity, elevated blood pressure levels and low HDL cholesterol levels substantially increase the risk of MAU. It is of primary importance to monitor MAU in high-risk individuals and aggressively intervene on modifiable risk factors.
Introduction

The prevalence of type 2 diabetes (T2DM) is rapidly growing worldwide and so its complications. Cardiovascular events occur from 2 to 4 times more frequently, while cardiovascular mortality is 1.5–4.5 times higher in diabetes than in individuals without diabetes [1]. This risk is further increased in the presence of diabetic nephropathy. A great percentage of patients can develop diabetic nephropathy within some years from diabetes onset in the absence of specific interventions [2].

Microalbuminuria (MAU) represents the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease [3]. At the same time, it is associated with increased cardiovascular morbidity and mortality risk in both type 1 and type 2 diabetes. In particular, the risk of cardiovascular events and mortality in the presence of MAU is estimated to be 2–8 times higher in patients with diabetes and hypertension [4]. However, it is not clear whether MAU represents an independent predictor or rather a marker of organ damage, since mechanisms linking MAU with end-organ damage have not been fully explained. However, generalized endothelial dysfunction might play an important role since loss of albumin in the urine is believed to reflect endothelial dysfunction expressed in the glomerulus that, in turn, reflects the status of the circulation at large [5]. For the same reason, MAU is associated with other cardiovascular risk factors, especially hypertension and dyslipidaemia [6], and it was chosen as a clinical criterion for metabolic syndrome by the WHO classification [7] and as an additional metabolic measurement for research in the IDF definition [8].

While epidemiological studies have evaluated factors associated with the presence of MAU in individuals with T2DM [6,9], the extent to which the interaction between these factors affects the likelihood of MAU has not been explored.

The aim of the DEMAND (Developing Education on Microalbuminuria for Awareness of reNal and cardiovascular risk in Diabetes) study was to evaluate the interaction among the different variables and identify distinct and homogeneous subgroups of patients with different risks of MAU.

Subjects and methods

The DEMAND study is a multicentre study involving 55 Italian diabetes outpatient clinics. The protocol was approved by local ethical committees. Every centre was asked to enrol 36 eligible consecutive patients among those with a scheduled visit. Six days during 2 weeks were chosen for sampling, more specifically Monday, Tuesday and Wednesday in the first week, and Wednesday, Thursday and Friday in the second week, so that up to six patients a day had to be selected. Patients were enrolled between December 2004 and May 2005.

The eligibility criteria were T2DM according to WHO criteria [10], age between 18 and 80 years and both genders. The exclusion criteria were type 1 or gestational diabetes, urinary infections, fever, menstrual cycle and overt diabetic nephropathy. All the patients signed an informed consent at study entry.

Every patient underwent a medical examination, and clinical data were collected on diabetes duration, cardiovascular risk factors, comorbidities and pharmacologic treatments, height, weight, waist circumference and blood pressure (two measurements rounded to the nearest 2 mmHg in the sitting position after at least 5 min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V). A morning spot urine sample was collected, stored at −20 °C and then sent on dry ice to the core laboratory (Department of Laboratory Medicine, University Milano-Bicocca, Hospital of Desio, Desio-Milano, Italy). Urinary albumin and creatinine concentrations were determined by the immune turbidimetric method (albumin tina-quant, Roche Diagnostics,Rotkreuz, Switzerland) and the kinetic Jaffé method performed with the autoanalyzer Modular (Hitachi-Roche Diagnostics, Manneheim, Germany), respectively. The urinary ACR (albumin creatinine ratio) was then calculated; ACR values falling between 30 and 299 mg/g creatinine identified the MAU range, while ACR ≥ 300 mg/g defined macroalbuminuria [11]. Urinary infections were defined as the presence of nitrites or leucocytes ≥ 250 leucocytes/ml in the urine sample. Patients with urinary infections were not included in the statistical analysis.

Because normal ranges for glycated haemoglobin varied among the different centres, the percentage change with respect to the upper normal value (actual value/upper normal limit) was estimated and multiplied by 6.0.

Statistical analysis

Correlates of MAU were initially examined by univariate analyses. Baseline characteristics are expressed as mean and standard deviation for continuous variables, and frequencies and percentages for categorical ones. Patient characteristics according to the presence of MAU were compared using the Mann–Whitney U-test or Kruskall–Wallis one-way ANOVA for continuous variables and the Pearson or Mantel–Haenszel χ² test for categorical ones. The following covariates were tested: age, sex, HbA1c, presence of ATP-III metabolic syndrome [7], BMI, waist circumference, smoking, hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), dyslipidaemia [12], total cholesterol, HDL cholesterol, LDL-cholesterol, triglycerides, treatments with specific pharmacological agents (oral antihyperglycemic agents, insulin, ACE-inhibitors and/or angiotensin II receptor blockers, statins) and comorbidities (retinopathy, diabetic foot, cardiovascular complications, cerebrovascular complications and peripheral vascular complications). A multivariate logistic regression was performed to evaluate factors associated with an increased likelihood of MAU. Results are
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expressed in terms of odds ratios (ORs) with their 95% confidence intervals (95% CI).

Furthermore, to evaluate the interaction among the different variables and identify distinct and homogeneous subgroups of patients with different risks of MAU, the RECURSive Partitioning and AMalgaMation (RECPAM) method was used [13, 14]. This method attempts to integrate the advantages of the main effects of logistic regression and tree-growing techniques [13]. At each partitioning step, the software automatically chooses the covariate and its best binary split to maximize the difference in the outcome of interest (i.e. presence of MAU). The algorithm stops when user-defined conditions (stopping rules) are met. The set of variables tested in the RECPAM analysis were the same as tested in the multiple logistic regression analysis, without categorizing continuous variables so as to allow the algorithm to choose the natural cut-off points. Patient age and systolic blood pressure were set as global predictors. The figure legend reports major details that can be helpful for interpreting the analysis. Patient characteristics according to RECPAM classes were compared using Kruskall–Wallis \( \chi^2 \) test for linear trend for categorical variables.

Finally, to detect additional global correlates (i.e. variables playing their role in the whole sample, irrespective of RECPAM classes), we run a final logistic analysis with the classes identified by RECPAM forced in the model, testing all other characteristics not entering the tree.

All analyses were performed using SAS® Language (Release 9.1. Cary, NC, USA: 2002–2003). For the RECPAM analyses we used an SAS macro routine written by F. Pellegrini.

Results

Overall, 1841 patients were enrolled. A urinary infection was detected in 228 patients (12.4%); therefore, the prevalence of MAU and macroalbuminuria, estimated on 1613 patients, was 19.1% (\( N = 308 \)) and 3.5% (\( N = 56 \)), respectively. Patients with macroalbuminuria were excluded from the analysis, leaving 1557 evaluable patients.

Patient characteristics for the whole sample and according to the presence of MAU are shown in Table 1. Patients with MAU were significantly older than those without MAU (65.0 ± 9.1 versus 62.9 ± 9.1 years; \( P < 0.0001 \)), had longer diabetes duration (11.7 ± 9.9 versus 9.4 ± 6.0 years; \( P < 0.0001 \)), higher levels of HbA1c (7.9 ± 1.6 versus 7.3 ± 1.5%; \( P < 0.0001 \)), blood pressure (SBP: 142.3 ± 16.5 versus 137.5 ± 16.5 mmHg; \( P < 0.0001 \). DBP: 81.8 ± 9.1 versus 80.1 ± 6.6 mmHg; \( P < 0.0001 \)) and BMI (29.8 versus 29.2 kg/m²; \( P = 0.02 \)), lower levels of HDL cholesterol (47.6 ± 11.9 versus 49.4 ± 12.8 mg/dl; \( P = 0.052 \)) and larger waist circumference (males: 104.4 ± 11.6 versus 101.7 ± 12.4 cm; \( P = 0.002 \); females: 101.9 ± 13.4 versus 98.5 ± 12.8 cm; \( P = 0.02 \)). As expected, they also had more often a diagnosis of hypertension (73.8 versus 61.6%; \( P < 0.0001 \)), ATP-III metabolic syndrome (85.3 versus 74.3%; \( P = 0.003 \)) and three or more of its components (48.3 versus 36.1%; \( P = 0.006 \)). Furthermore, patients with MAU were more frequently treated with insulin and ACE inhibitors or ARBs (63.7 versus 49.2%; \( P < 0.0001 \)). Finally patients with MAU showed a higher prevalence of microvascular and macrovascular complications as compared with individuals without MAU (retinopathy: 28.8% versus 15.2%, \( P < 0.0001 \); cardiovascular complications: 24.9% versus 18.6%, \( P = 0.01 \) for patients with and without MAU, respectively).

The multiple logistic regression showed that several variables were related to the presence of MAU. In particular, poor metabolic control (HbA1c < 7% = reference category (RC); HbA1c 7–8%: \( \text{OR} = 1.48, 95\% \text{CI 1.02–2.17} \); HbA1c > 8%: \( \text{OR} = 2.20, 95\% \text{CI 1.49–3.23} \)) and insulin treatment (diet = RC; oral agents: \( \text{OR} = 2.17, 95\% \text{CI 1.12–4.19} \); oral agents + insulin: \( \text{OR} = 2.78, 95\% \text{CI 1.27–6.06} \); insulin: \( \text{OR} = 3.12, 95\% \text{CI 1.45–6.69} \)) were the strongest correlates of MAU. In addition, male gender (OR = 1.49, 95% CI 1.09–2.08), older age (OR = 1.03, 95% CI 1.01–1.05 by year), higher values of systolic blood pressure (OR = 1.06, 95% CI 1.02–1.11 by 5 mmHg) and waist circumference (OR = 1.07, 95% CI 1.01–1.13 by 5 cm), current smoking (OR = 1.71, 95% CI 1.12–2.64), presence of retinopathy (OR = 1.57, 95% CI 1.10–2.24) and lower levels of HDL cholesterol (HDL > 60 mg/dl = RC; HDL 50–60 mg/dl: \( \text{OR} = 1.47, 95\% \text{CI 0.94–2.31} \); HDL < 50 mg/dl: \( \text{OR} = 1.67, 95\% \text{CI 1.00–2.81} \)) were associated with a higher likelihood of MAU. The use of ACE inhibitors and/or ARBs (OR = 1.47, 95% CI 1.09–1.98) was also associated with a higher likelihood of MAU; this finding is easily attributable to an indication bias as well as to the higher prevalence of hypertension among individuals with MAU.

RECPAM analysis identified seven patient subgroups at different risk for having MAU. The tree-growing algorithm modelled ORs for MAU as an outcome following a multivariate logistic regression model in which age and systolic blood pressure were global variables. Splitting variables—that were automatically selected by the RECPAM routine among all the covariates used in the multivariate analysis—are shown between branches, while the respective cuts-off—also automatically identified by the macro-routine—sending patients to the left or right sibling, are reported on the relative branch (Figure 1). The most important variable in differentiating the risk of MAU was represented by metabolic control; in particular, patients with HbA1c < 7, associated with a waist circumference ≥ 102 cm and no smoking, showed the lowest prevalence of MAU and were considered as the reference class (class 7); the prevalence of MAU progressively increased from class 7 (7.5%) to class 1 (53.8%). ORs for all classes were estimated with respect to the reference class. The likelihood of MAU was 13 times higher in patients with retinopathy, waist circumference > 98 cm and HbA1c > 8% (OR = 13.7; 95% CI 6.8–27.6), and 5 times higher in patients with the same characteristics but HbA1c levels between 7% and 8% (OR = 5.4; 95% CI 2.6–11.3). Individuals with HbA1c levels between 7% and 8%, retinopathy, but a waist circumference ≤ 98 cm, showed a more than four-fold risk of MAU (OR = 4.8; 95% CI 2.5–9.3), while those without retinopathy and with HbA1c levels between 7% and 8% showed a more than three-fold risk of MAU (OR = 3.4; 95% CI 2.1–5.5). Finally, among individuals with HbA1c...
Table 1. Patient characteristics according to the presence/absence of MAU

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>Total (n = 1557)</th>
<th>Normoalbuminuria (n = 1249)</th>
<th>Microalbuminuria (n = 308)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.9 ± 9.2</td>
<td>62.9 ± 9.1</td>
<td>65.0 ± 9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>9.8 ± 8.2</td>
<td>9.4 ± 6.0</td>
<td>11.7 ± 9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.5</td>
<td>7.3 ± 1.5</td>
<td>7.9 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 ± 4.9</td>
<td>29.2 ± 4.9</td>
<td>29.8 ± 4.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>102.3 ± 12.3</td>
<td>101.7 ± 12.4</td>
<td>104.4 ± 11.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Females</td>
<td>99.1 ± 13.0</td>
<td>98.5 ± 12.8</td>
<td>101.9 ± 13.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension duration (years)</td>
<td>9.8 ± 7.6</td>
<td>9.5 ± 7.6</td>
<td>10.9 ± 7.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138.4 ± 16.6</td>
<td>137.5 ± 16.5</td>
<td>142.3 ± 16.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4 ± 8.7</td>
<td>80.1 ± 6.6</td>
<td>81.8 ± 9.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>202.8 ± 40.9</td>
<td>203.0 ± 41.1</td>
<td>202.1 ± 40.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>166.3 ± 106.5</td>
<td>163.8 ± 106.2</td>
<td>176.2 ± 107.4</td>
<td>0.1</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49.0 ± 12.6</td>
<td>49.4 ± 12.8</td>
<td>47.6 ± 11.9</td>
<td>0.052</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>122.7 ± 36.2</td>
<td>123.4 ± 36.3</td>
<td>119.8 ± 35.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Total cardiovascular complications</td>
<td>19.8%</td>
<td>18.6%</td>
<td>24.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Other renal disease</td>
<td>2.2%</td>
<td>1.9%</td>
<td>3.6%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Categorical variables

- Males: 59.5% 58.5% 63.6% 0.1
- Hypertension: 64.0% 61.6% 73.8% <0.0001
- Smoker: No 59.5% 60.1% 73.8% 0.1
- Yes 26.0% 26.1% 25.8% 17.0% 0.2
- Dyslipidaemia: 54.2% 54.0% 54.7% 0.8
- Metabolic syndrome (ATP-III): 76.5% 74.3% 85.3% 0.003
- Components of metabolic syndrome:
  - 1 7.0% 7.0% 7.4% 0.006
  - 2 21.8% 23.9% 13.6% 30.7%
  - 3 32.6% 33.0% 30.7%
  - >3 38.6% 36.1% 48.3%
- Antidiabetic treatments:
  - Diet 12.9% 15.0% 4.0%
  - Oral agents 65.0% 65.6% 62.2%
  - Insulin + oral agents 10.6% 9.1% 16.9%
  - Insulin 11.5% 10.2% 16.9% <0.0001
  - ACE inhibitors and/or ARBs 52.1% 49.2% 63.7% <0.0001
  - Statins 33.2% 32.8% 35.3% 0.4
  - Retinopathy 17.9% 15.2% 28.8% <0.0001
  - Diabetic foot 3.7% 3.3% 5.0% 0.18
- Total cardiovascular complications 19.8% 18.6% 24.9% 0.01
- Other renal disease 2.2% 1.9% 3.6% 0.07

Normoalbuminuria = ACR <30 mg/g and microalbuminuria = 30–299 mg/g; data are means ± SD for continuous variables and percentage for categorical ones.
*χ² test for categorical variables and Kruskal–Wallis test for continuous variables.

<7.0%, waist circumference >102 cm (OR = 3.0; 95% CI 1.7–5.3) or smoking (OR = 3.3; 95% CI 1.4–7.4) were also associated with a higher risk of MAU. The table under the RECPAM tree summarizes patient characteristics according to RECPAM classes.

A final stepwise logistic regression with the RECPAM classes forced in was performed to highlight the role of additional variables as global correlates (Table 2). This analysis showed that age (OR = 1.03; 95% CI 1.01–1.04), systolic blood pressure (OR = 1.05; 95% CI 1.01–1.10), antidiabetic treatment (diet = RC; oral agents: OR = 2.29, 95% CI 1.45–6.56; oral agents + insulin: OR = 3.08, 95% CI 1.48–6.58; insulin: OR = 3.12, 95% CI 1.08–1.92), use of ACE-I and/or ARBs (OR = 1.44; 95% CI 1.08–1.92) and HDL cholesterol levels (HDL >60 mg/dl = RC; HDL 50–60 mg/dl: OR = 1.5, 95% CI 0.98–1.17; HDL <50 mg/dl: OR = 1.89, 95% CI 1.17–3.08) were retained in the final model as globally predictive variables.

Discussion

Key findings

We found that about one-fifth of T2DM patients routinely cared for by outpatient diabetes clinics had MAU, and a non-trivial proportion (3.5%) of the same patients had macroalbuminuria.

RECPAM analysis added important and original information regarding the interactions between the several variables investigated and allowed us to identify subgroups of patients characterized by marked differences in the prevalence of MAU. In particular, patients with HbA1c >8, retinopathy and waist circumference >98 cm (class 1) had a risk of presenting MAU 13 times higher than the reference class; these patients also had an older age, a longer diabetes duration and were more frequently treated with insulin, suggesting a greater diabetes severity. In addition,
Prevalence and likelihood of microalbuminuria in type 2 diabetes

Fig. 1. RECPAM analysis identified patient subgroups at different likelihood of MAU. Tree-growing algorithm modelled ORs for MAU as an outcome following a logistic regression with age and SBP as global variables. Splitting variables (bold) are shown between branches, while the condition sending patients to the left or right sibling is on the relative branch. Class 7 with lowest prevalence of MAU was set as reference category (OR = 1). Circles indicate subgroups of patients. Squares indicate patient subgroup RECPAM classes. Numbers inside circles and squares represent number of patients with (italics) and without MAU, respectively. One-hundred twenty-three observations were excluded from this analysis due to the lack of the information relative to age or SBP.

these patients had higher levels of blood pressure, BMI and triglycerides; they were also more often treated with ACE inhibitors or ARBs, and had more often micro- and macrovascular complications.

In the intermediate RECPAM classes, the likelihood of presenting MAU was from three to five times higher than in the reference class. Classes 2 and 3 showed a risk of MAU about five times higher than the reference class. Nevertheless, these two classes showed marked differences: in fact, individuals in class 3 had substantially lower levels of BMI and waist circumference but worse metabolic control, while those in class 2 showed an elevated degree of obesity and a higher prevalence of hypertension and smoking, despite better metabolic control.

Among patients with HbA1c < 7%, the risk of MAU was three times higher in classes 5 and 6 than in class 7. Even in this case, despite a similar risk, the two classes showed important differences. In fact, patients in class 5
were characterized by the highest values of waist circumference and triglycerides, suggesting that the ‘hypertrigliceridemic waist’ can represent a correlate of MAU. On the other hand, individuals in class 6 had a higher risk of MAU as compared with the reference category despite being younger, with a lower prevalence of hypertension and with very good metabolic control. The only feature characterizing this class was the presence of smoking, confirming its fundamental role as a risk factor.

The final logistic model with RECPAM classes forced in further confirmed that patient age, systolic blood pressure and HDL cholesterol, represent independent and significant correlates of MAU, playing a role in all the RECPAM classes identified.

Comparisons with existing knowledge

The prevalence of MAU of 19.1% is similar to that reported by Barnett AH [15] among a sample of Caucasian patients with T2DM from the United Kingdom. Such a prevalence might underestimate the real frequency of MAU among these patients, because of the ongoing antihypertensive treatment, particularly the wide use of renin–angiotensin system blockers which significantly affect albuminuria [16]. In a recent report, Parving et al. [17] have shown in a very large multiethnic, population-based survey including more than 30,000 patients, a prevalence of MAU of 33% among Caucasian type 2 diabetic patients (n = 9441). The discrepancy with our results could be due, at least in part, to the different methods utilized in measuring ACR in the two studies. In addition, the prevalence of smokers was substantially higher (29% versus 14.3%) in Parving’s study.

Our study confirmed the association of MAU with well-established risk factors such as age, poor metabolic control, hypertension, smoking and microvascular complications. Furthermore, it highlights the role of central obesity in differentiating the risk of MAU either in individuals with an elevated risk profile (i.e., those with poor metabolic control and retinopathy) or with low risk (patients with good metabolic control and very low prevalence of retinopathy). These findings suggest the role of central obesity as a potential additional risk factor for MAU, in line with the results of recent studies conducted in patients with type 1 diabetes, type 2 diabetes or without diabetes [6,18,19].

Our findings also confirm the association of MAU with a less obvious risk factor such as low levels of HDL cholesterol, playing a global role in our sample; in other words, low levels of HDL cholesterol are associated with a higher likelihood of MAU in all RECPAM classes, irrespective of the overall risk profile of the patients. These data confirm previous findings of two longitudinal studies documenting the association between HDL cholesterol levels and MAU [20,21]. Whether this is due to the HDL cholesterol levels or whether they serve as a marker for some other mechanism remains to be determined.

Implications for clinical practice and clinical research

A recent update of the Steno-2 study clearly shows that of 10 MAU patients with type 2 diabetes and an average age of 55 years, two will die, two will suffer a stroke, two will suffer a myocardial infarction and one will suffer an amputation over a 13-year period, if intensified and target-driven treatment is not initiated early and continuously adjusted according to guidelines [22]. Despite its devastating consequences, MAU is still a largely unrecognized risk factor, and a large proportion of individuals with diabetes are not regularly screened.

Our study can help identify those patients more likely to present an initial renal function impairment, and more likely to benefit from intensive, multifactorial interventions. In addition, a more accurate knowledge of the complex relationship between MAU and organ disease (e.g. retinopathy) could suggest the use of this parameter as a trigger for an early evaluation of other end-organ disease, if not previously performed.

The study also offers interesting hints about the possible independent role of abdominal obesity and low HDL cholesterol levels as independent correlates of MAU. Whether they represent simple markers or true risk factors remains to be established in future longitudinal studies. The patho-physiologic mechanisms linking MAU to these factors also need to be further elucidated.

Strengths and limitations

There are several limitations of this study that need to be discussed. First, this was a cross-sectional study and, for this reason, it is not possible to establish a firm cause–effect relationship between risk factors identified, their interactions and MAU; second, although the measurements of urinary albumin and creatinine were centralized, we obtained only one measurement of the urinary albumin/creatinine ratio. However, the large number of patients studied and the good reproducibility of different measurements of ACR previously described [23] should minimize the effect of day-to-day variability of urinary albumin excretion. Finally, it should be considered that our study was conducted on

Table 2. Results of the final multiple logistic regression

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.01–1.04</td>
</tr>
<tr>
<td>Systolic blood pressure (by 5 mmHg)</td>
<td>1.05</td>
<td>1.01–1.10</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and lifestyle</td>
<td>1.0</td>
<td>1.19–4.40</td>
</tr>
<tr>
<td>Oral agents</td>
<td>2.29</td>
<td>1.45–6.56</td>
</tr>
<tr>
<td>Oral agents + insulin</td>
<td>3.08</td>
<td>1.48–6.58</td>
</tr>
<tr>
<td>Insulin</td>
<td>3.12</td>
<td>1.08–1.92</td>
</tr>
<tr>
<td>ACE inhibitors and/or ARBs</td>
<td>1.44</td>
<td>1.08–1.92</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
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<tr>
<td>&gt; 60</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>50–60</td>
<td>1.5</td>
<td>0.98–2.31</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1.89</td>
<td>1.17–3.08</td>
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<td>RECPAM Class</td>
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<tr>
<td>7</td>
<td>1.0</td>
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<tr>
<td>6</td>
<td>3.37</td>
<td>1.47–7.74</td>
</tr>
<tr>
<td>5</td>
<td>2.71</td>
<td>1.53–4.79</td>
</tr>
<tr>
<td>4</td>
<td>2.88</td>
<td>1.78–4.67</td>
</tr>
<tr>
<td>3</td>
<td>3.49</td>
<td>1.76–6.91</td>
</tr>
<tr>
<td>2</td>
<td>3.74</td>
<td>1.74–8.05</td>
</tr>
<tr>
<td>1</td>
<td>9.61</td>
<td>4.60–20.09</td>
</tr>
</tbody>
</table>
patients attending outpatient diabetes clinics; therefore, results obtained cannot be applied to the whole population of individuals with T2DM.

In conclusion, MAU is a common cardio-renal risk factor, affecting one in five patients with T2DM in Italy. The risk of MAU in the study population was not homogeneous and varied substantially according to the presence of other cardiovascular risk factors. In addition to the well-established risk factors, such as poor metabolic control, presence of other microvascular complications, smoking and hypertension, two additional typical features of the metabolic syndrome, such as abdominal obesity and low HDL cholesterol levels, contribute to substantially increase the likelihood of MAU.

Despite its role as an independent predictor of cardiovascular and renal outcomes, the importance of monitoring MAU and to act on modifiable risk factors is still underestimated. Our study calls for a strong educational monitoring MAU and to act on modifiable risk factors is important for the prevention of cardio-renal risk factors. In addition to the well-established risk factors, such as poor metabolic control, presence of other microvascular complications, smoking and hypertension, two additional typical features of the metabolic syndrome, such as abdominal obesity and low HDL cholesterol levels, contribute to substantially increase the likelihood of MAU.

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