studies are required to determine the value of renal biopsy in this setting.

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14. Scotland’s Census 2001; General Register Office for Scotland 2002

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Chronic kidney disease and cardiovascular risk in hypertensive type 2 diabetics: a primary care perspective

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Abstract

Background. Chronic kidney disease (CKD) is associated with poor renal and cardiovascular (CV) outcome, and early identification largely depends on the general practitioners’ (GPs) awareness of it. Only a few studies have evaluated the...
prevalence of CKD in type 2 diabetes in primary care, and no studies are available on hypertensive diabetics. Thus, the aim of this study was to assess the prevalence of CKD and its association with CV morbidity in such a population.

Methods. On the basis of an Italian national project involving GPs and nephrologists, we retrieved demographic, laboratory and clinical data regarding 7582 hypertensive type 2 diabetics (3564 men; age 25–89 years) who were selected using the diagnostic code Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for diabetes and hypertension. Blood pressure (BP) values, serum creatinine, ECG-diagnosed left ventricular hypertrophy (LVH) and the occurrence of previous major CV events were obtained for each patient from the GPs' Health Search Database. Estimated glomerular filtration rate (GFR) was calculated according to the four-variable MDRD equation. CKD was defined as an estimated GFR < 60 mL/min/1.73 m².

Results. CKD prevalence was 26%, although renal disease was diagnosed by GPs in only 5.4% of cases. The prevalence of both LVH and major CV events was 8%. Adequate BP control was only achieved in 10.4% of patients. Patients whose GFR was < 60 mL/min/1.73 m² were older, prevalently female, had increased pulse pressure and higher prevalence of dyslipidaemia. Moreover, the prevalence of both LVH and major CV events was higher in patients with CKD as compared to patients with normal GFR. Multivariate logistic regression analysis showed that patients with CKD had a higher risk of LVH and/or CV events adjusted for eight covariates, and this risk increased by 23% with each 21 mL/min/1.73 m² decrease in GFR.

Conclusions. This study shows that CKD is highly prevalent in hypertensive type 2 diabetic patients, where it is a strong predictor of CV adverse outcome. However, awareness of CKD by GPs is low. Equations for calculating estimated GFR should be included in the GPs' database in order to detect the presence of CKD and to improve CV outcome of such a high-risk population.

Keywords: cardiovascular morbidity; chronic kidney disease; hypertension; primary care; type 2 diabetes

Introduction

Chronic kidney disease (CKD) is increasingly recognized as a public health problem since it is associated with poor cardiovascular outcome as well as progression to end-stage renal disease (ESRD), both being conditions that require high health care expenditures. Early identification of patients with CKD may allow health care systems to implement interventions aimed at decreasing disease progression and reducing cardiovascular risk. Tests for the detection of CKD are simple, freely available and low cost. The guidelines of the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF-K/DOQI) recommend carrying out CKD screening among people who are at increased risk for kidney disease, including those with diabetes and hypertension [1]. Moreover, regular testing of renal function is encouraged by all the major guidelines dealing with the management of diabetes. The American Diabetes Association Guidelines recommend that serum creatinine be measured at least annually in all adults with diabetes, regardless of the degree of albuminuria [2]. Serum creatinine should be used to estimate glomerular filtration rate (GFR) and to stage the degree of CKD, when present. Although estimates suggest that renal impairment occurs in 25–40% of patients with diabetes [3], few studies have systematically assessed the prevalence of CKD defined as estimated GFR < 60 mL/min/1.73 m² in primary care diabetic patients [4–8].

This study is part of the larger GENOA (GENeral practitioners and Nephrologists for Outpatient Assistance) program, and it was carried out with the collaboration of nephrologists and with Italian general practitioners (GPs). The aim was to evaluate the prevalence of CKD observed in primary care, and its relationship with major cardiovascular risk factors in a population that is highly selected for unfavourable cardiovascular outcome, such as hypertensive type 2 diabetics.

Methods

This study was carried out on the basis of a national cooperative project set up by the Italian College of General Practitioners (Società Italiana di Medicina Generale, SIMG) and a group of nephrologists who are members of the Italian Society of Nephrology (Società Italiana di Nefrologia, SIN).

Data source

Data were extracted from the Health Search Database (HSD). The HSD was set up in 1998 and is managed by the Italian College of GPs. It includes a large and representative sample of the Italian population and its primary aim is to carry out observational studies on the incidence and prevalence of chronic diseases. At the time of this study, the HSD contained information provided by more than 650 Italian GPs and included a total of more than 900 000 individuals. After intensive training, all participating GPs had to use specially designed software to record data during their normal daily clinical practice (Millewin). The software system codes all the diagnostic records by using the Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Prescription records are also coded according to the anatomical therapeutic chemical (ATC) classification system. Data provided by the 400 physicians who met the standard quality criteria were included in this study. Altogether, they covered nearly 500 000 subjects.

Patients

Figure 1 shows the flow between the available starting sample and the group of patients who were actually analysed on the basis of the restriction criteria, i.e. having type 2 diabetes, arterial hypertension and recorded serum creatinine levels.

Between 1 January and 31 December 2005, we identified 11 114 patients with arterial hypertension and type 2 diabetes from among a population of nearly 500 000.
Methods

Demographic, clinical and laboratory data, namely age, sex, body weight, height, blood pressure (BP) values, lipid profile, serum creatinine, ECG-diagnosed left ventricular hypertrophy (LVH), smoking habits, and the occurrence of previous major cardiovascular events, such as stroke, angina and myocardial infarction, were extracted from the HSD for each patient. The number and the various classes of antihypertensive medications were also retrieved for each patient. Body mass index (BMI) was calculated as body weight (kg)/height (m)^2, and obesity was defined as BMI ≥ 30 kg/m^2. Pulse pressure (PP) was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). A target BP of 130/80 mmHg was considered adequate BP. Accordingly, a cut-off value of 50 mmHg was taken to identify patients with elevated (≥50 mmHg) or normal PP (<50 mmHg). LDL cholesterol was calculated by using Friedewald et al.’s formula [9]. Hypercholesterolaemia was defined as total cholesterol ≥200 mg/dL and/or LDL cholesterol ≥100 mg/dL. Hypertriglyceridaemia was defined as triglycerides ≥150 mg/dL. Low HDL cholesterol levels were <40 mg/dL in men and <46 mg/dL in women. GFR was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula, that is GFR = 186 × (creatinine in mg/dL)^(-1.154) × (age in years)^0.203 × (0.742 if female) × (1.21 if black). The NKF-K/DOQI classification was used to define the stage of CKD [1]. For the purpose of our study, clinically significant CKD was defined as K/DOQI CKD stages 3–5 (eGFR < 60 mL/min/1.73 m^2).

Statistics

Data are presented as mean ± SD. A one-way ANOVA model was used to compare continuous variables between groups, after checking for homosedasticity using the Levene test. Comparison of proportion between the two groups was performed by using the chi-square test. Correlations were assessed by the Spearman rank correlation coefficient. A multivariate logistic regression was used to assess variables independently associated with the probability of being affected by either CKD or both previous major cardiovascular events and LVH. Odds ratio and 95% confidence intervals were calculated by exponentiation of logistic regression coefficients. All statistical analyses were performed with the use of SPSS (version 13.0). A value of P < 0.05 was considered statistically significant.

Results

Between 1 January and 31 December 2005, we retrieved information concerning 11,114 subjects with a diagnostic code (ICD-9-CM) of type 2 diabetes and hypertension, which corresponds to a prevalence of 2.2%. Recorded serum creatinine levels were only available for 69% of patients. However, an analysis comparing patients with and respectively without reliable creatinine measurements showed no differences in either continuous variables or prevalence data, thus excluding the possibility of a selection bias. Table 1 shows the demographic and clinical data of

Table 1. Demographic and clinical data of patients in the study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7582</td>
</tr>
<tr>
<td>Age, years</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>53</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Obesity, % (BMI ≥ 30 kg/m^2)</td>
<td>43</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>14</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Estimated GFR, mL/min/1.73 m^2</td>
<td>73 ± 21</td>
</tr>
<tr>
<td>Total serum cholesterol, mg/dL</td>
<td>201 ± 42</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>153 ± 96</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51 ± 14</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>120 ± 37</td>
</tr>
<tr>
<td>Total cholesterol ≥ 200 mg/dL, %</td>
<td>50</td>
</tr>
<tr>
<td>LDL cholesterol ≥ 100 mg/dL, %</td>
<td>70</td>
</tr>
<tr>
<td>Triglycerides ≥ 150 mg/dL, %</td>
<td>39</td>
</tr>
<tr>
<td>LDL cholesterol &lt; 40 mg/dL in men and &lt;46mg/dL in women, %</td>
<td>M 24; F 28</td>
</tr>
<tr>
<td>ECG determined LVH, %</td>
<td>8</td>
</tr>
<tr>
<td>Major cardiovascular events, %</td>
<td>8</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>142 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>No antihypertensive therapy, %</td>
<td>8.3</td>
</tr>
<tr>
<td>One or two antihypertensive drugs, %</td>
<td>61.9</td>
</tr>
<tr>
<td>Three or more antihypertensive drugs, %</td>
<td>29.8</td>
</tr>
<tr>
<td>ACE-I/ARB treatment, %</td>
<td>77.4</td>
</tr>
<tr>
<td>Patients with achieved BP &lt; 130/80 mmHg, %</td>
<td>10.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; LVH, left ventricular hypertrophy; ECG, electrocardiogram; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
this population. The prevalence of CKD was 26%, of which stages 3, 4 and 5 made up 24%, 1.7% and 0.3%, respectively. Conversely, on the basis of the data provided by the GPs, we found that only 5.4% of the study cohort had a diagnosis of renal disease. The prevalence of ECG-determined LVH was 8%, as was that of major cardiovascular events. Despite the diagnosis of arterial hypertension, 8.3% of patients received no antihypertensive treatment. Optimal BP control, consistent with the recommendations issued by the international and national guidelines for diabetic patients (BP < 130/80 mmHg), was only achieved by 10.4% of patients. When patients were sub-divided into two groups according to the presence or absence of CKD, subjects whose GFR was <60 mL/min/1.73 m² were found to be older and prevalently female. They also had higher serum triglycerides and lower HDL cholesterol levels as compared with non-CKD subjects (Table 2). Interestingly, only 17% of patients whose GFR was <60 mL/min/1.73 m² had been diagnosed as having CKD, according to the data provided by GPs. A higher prevalence of both ECG-determined LVH (11% versus 7%, \( P < 0.001 \)) and major cardiovascular events (12% versus 7%, \( P < 0.0001 \)) was observed in CKD patients as compared with subjects whose GFR was ≥60 mL/min/1.73 m² (Figure 2). As regards BP behaviour, higher PP as an expression of lower diastolic BP values together with similar systolic BP values was observed in CKD patients. Patients with CKD were also more likely to receive antihypertensive therapy (93.4% versus 91.1%, \( P < 0.002 \)) and to achieve adequate BP targets (13.8% versus 9.3%, \( P < 0.001 \)), although BP control was poor in both groups (Table 3). Correlation analysis showed that GFR was inversely associated with age (\( r = −0.43; P < 0.001 \)), with PP (\( r = −0.1; P < 0.001 \)) and with triglyceride levels (\( r = −0.1; P < 0.001 \)). Moreover, the mean GFR was significantly lower in women (69 ± 20 versus 77 ± 21 mL/min/1.73 m², \( P < 0.001 \)), in patients with LVH (68 ± 22 versus 74 ± 21 mL/min/1.73 m², \( P < 0.001 \)) and in patients with major cardiovascular events (67 ± 23 versus 74 ± 21 mL/min/1.73 m²). Multivariate logistic regression analysis showed that an increased risk of CKD adjusted for systolic hypertension and hypercholesterolaemia was associated with the female gender (adjusted OR 1.91, 95% CI 1.66–2.20; \( P < 0.001 \), age ≥65 years (adjusted OR 4.44, 95% CI 3.68–5.36;
Table 4. Multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>1.68</td>
<td>1.41–2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.41</td>
<td>1.21–1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>1.57</td>
<td>1.31–1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure ≥ 50 mmHg</td>
<td>1.31</td>
<td>1.0–1.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglycerides ≥ 150 mg/dL</td>
<td>1.37</td>
<td>1.17–1.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Relationship between the presence of CKD and other variables and the prevalence of ECG-determined LVH and/or major cardiovascular events adjusted for systolic blood pressure, total cholesterol, smoking habit and obesity. CKD, chronic kidney disease; LVH, left ventricular hypertrophy; ECG, electrocardiogram.

P < 0.001, PP ≥ 50 mmHg (adjusted OR 1.59, 95% CI 1.22–2.07; P = 0.001), triglycerides ≥ 150 mg/dL (adjusted OR 1.49, 95% CI 1.29–1.72; P < 0.001), previous CV events (adjusted OR 1.62, 95% CI 1.30–2.03; P < 0.001) and the presence of LVH (adjusted OR 1.57, 95% CI 1.26–2.0; P < 0.001). In contrast, smoking habit and obesity were not significantly related to CKD.

Lastly, a higher prevalence of CKD was observed in patients with ECG-determined LVH (36% versus 25%, χ² analysis; P < 0.0001, OR 1.716, 95% CI 1.437–2.049) and in patients with major cardiovascular events (38% versus 24%, χ² analysis P < 0.0001, OR 1.889, 95% CI 1.603–2.251). Multivariate logistic regression analysis showed that patients with CKD had a higher risk of LVH and/or cardiovascular events adjusted for sex, age, SBP, PP, smoking habit, BMI, triglycerides and LDL-cholesterol (Table 4). Furthermore, this risk increased by 23% with each 21 mL/min/1.73 m² decrease in GFR.

Discussion

The prevalence of CKD we observed in hypertensive, type 2 diabetic patients attending the GPs’ office was 26%, with older subjects and women showing higher rates. Only a few studies have previously assessed the prevalence of CKD in diabetics in primary care, reporting values ranging from 15% to 36% [4–8]. Data from these studies, however, refer to diabetic subjects per se, regardless of the presence of arterial hypertension. To our knowledge, our study is the first to evaluate the prevalence of CKD in very high-risk patients such as hypertensive diabetics in primary care. Moreover, this is the first study conducted in a geographical area that is considered at lower CV risk compared to both the USA and the UK [10–12].

An interesting finding of our study is that the awareness of renal disease among GPs is low. In fact, CKD diagnosed by ICD-9-CM was 5.4% in our population at large, and only 17% in subjects with GFR < 60 mL/min/1.73 m². This discrepancy between reported and actual prevalence data is consistent with findings of the NEOERICA study [13] and a recently published Italian study [14], both of which evaluated the general population. This picture probably reflects the fact that GPs were adopting serum creatinine as the index of renal function. Indeed only 34% of our hypertensive diabetics whose GFR was < 60 mL/min/1.73 m² had serum creatinine values above the normal limits of 1.2 mg/dL for women and of 1.3 mg/dL for men, which correspond to the cut-off values for defining renal dysfunction according to the recommendations of the guidelines of the joined European Society of Hypertension (ESH) and Cardiology (ESC) [15].

By contrast, it is important to emphasize that a reliable and correct diagnosis of CKD is pivotal for global cardiovascular risk profile assessment in hypertensive diabetics. Patients with reduced GFR are in fact more prone to develop coronary heart disease and cardiovascular events than to reach ESRD [16–18], thus further confirming the role of the kidney as an integrated sensor of cardiovascular risk [19]. Consistent with these observations, a main finding of our study is that CKD is associated with both ECG-determined LVH and the occurrence of previous CV events. In our sample, hypertensive diabetic patients with CKD were older, had greater prevalence of dyslipidaemia and had increased PP, a well-known expression of increased stiffness of the large arteries, all factors that are implied in the occurrence of CV morbidity. More interestingly, and this is the most important and novel finding of our study, the strength of the association of CV morbidity with CKD proved to be even higher than that of cardiovascular disease with well-known risk factors, be they unmodifiable, such as age and male gender, or modifiable, such as hypertension or smoking habit. Furthermore, this association was found to be progressive in our patients, with the prevalence of LVH and cardiovascular events increasing as GFR decreased.

Another relevant finding of our study is that although arterial hypertension management was even more adequate in CKD patients than in subjects with normal GFR, only a few patients achieved target BP levels according to the recommendations of the international guidelines for diabetics. In fact, patients with CKD were more likely to receive three or more antihypertensive medications and to be prescribed ACE-I and/or ARB therapy. However, nearly 90% of these patients had BP levels above the target values of 130/80 mmHg. This further emphasizes the need for a substantial improvement in the BP management of diabetic patients, especially those with CKD.

The strength of our study is that it involves an evaluation of the largest ever sample of hypertensive type 2 diabetic patients to date, showing a reliable scenario of the current diagnostic approach to CKD in primary care in Italy. Evaluating the prevalence of CKD that is seen in the GPs’ offices, and assessing the GPs’ awareness of renal disease, is pivotal, since GPs are involved in the difficult task of providing first step renal and cardiovascular prevention and treatment strategies [1]. This is consistent with the recommendations issued by the Kidney Disease Improving Global Outcomes (KDIGO) panel that highlighted the need for a targeted screening program for CKD in all countries. High-risk groups should include patients with hypertension, patients with diabetes and those with overt CV disease, i.e. the same categories we evaluated in our study. Furthermore, additional criteria of this surveillance programme should include GPs’ awareness [20].

Of course, some limitations must be acknowledged in our study. First of all, proteinuria has not been included since
a standardized method for both sampling and measuring the urinary albumin excretion rate was not available, thus rendering the use of this data unreliable and even misleading, especially for identifying patients with stage 1 and 2 CKD. However, while screening for CKD based on estimated GFR alone cannot be recommended in the general population, it may be effective in high-risk populations, such as hypertensive diabetics [21]. Secondly, due to the retrospective nature of our study and the large dispersion of data collection from different geographical areas in Italy, serum creatinine was not calibrated in our sample, thus possibly leading to overestimation of the actual prevalence of CKD. However, we only analysed patients with stage 3–5 CKD whose estimated GFR was <60 mL/min/1.73 m². Values below this cut-off seem to have an acceptable degree of accuracy even without serum creatinine calibration [22].

Lastly, adopting GFR levels <60 mL/min/1.73 m² as the threshold for stage 3–5 CKD captures a large number of older subjects. However, this could be a true limitation among healthy subjects but not in a high-risk population such as hypertensive type 2 diabetics, since it is probably safer to label an otherwise non-CKD hypertensive diabetic as being affected by renal disease than to miss and consequently undertreat a true CKD patient.

Even taking these potential shortcomings into account, our survey addresses the largest cohort of hypertensive diabetic patients in Europe, where data comparable to the large US studies are not available, and provides a reliable picture of CKD in primary care.

Conclusions

Our study shows that CKD is highly prevalent in type 2 diabetic patients, in whom it is the strongest predictor of cardiovascular adverse outcome. However, the awareness of CKD by GPs is low. On the basis of our findings we feel that greater efforts must be adopted to increase the awareness of the physicians involved in the primary care of hypertensive diabetic patients with regard to CKD. This could be done by considering estimated GFR as a reliable tool for ascertaining renal disease and therefore by including equations for calculating GFR in their database in order to improve cardiovascular outcome of such a high-risk population.

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