Abstract

Background and objectives. Epidemiological studies have shown that the burden of chronic kidney disease (CKD) is huge. CKD is a non-specific diagnosis, however, and it is hard to say which renal disorders comprise the body of CKD diagnosed on the strength of the combination of albuminuria and estimated GFR.
of albuminuria and estimated glomerular filtration rate (eGFR) in epidemiological studies, or just how efficient such studies are in detecting chronic nephropathies.

**Methods.** The INCIPE study identified 524 CKD cases (using the K/DOQI definition based on albuminuria and eGFR) in a random sample of 4000 Italians >40 years old, 262 of whom were randomly chosen to be investigated in order to confirm their CKD and complete a diagnostic workup. We a priori defined diagnostic algorithms for 14 renal conditions based on personal family history, medical records, urine tests, kidney ultrasound with colour-Doppler and other tests.

**Results.** Among the subjects whose CKD was confirmed, a diagnosis of chronic nephropathy was reached in 68% of cases recognized as having either a specific (38%) or an undetermined (30%) kidney disease. Almost 50% of subjects with a specific chronic nephropathy had a diabetic or vascular renal disease. Abnormalities consistent with a chronic nephropathy were found in 50, 68, 70 and 100% of subjects with CKD Stages 1, 2, 3 and 4, respectively. Lone low eGFR and lone microalbuminuria were observed in 20 and 12%, respectively.

**Conclusions.** In Caucasians >40 years old with a confirmed CKD condition, (i) an impressive 68% of subjects have an underlying chronic nephropathy, so eGFR and albuminuria are very efficient in detecting renal diseases; (ii) in 32%, the only disclosed renal abnormalities were a glomerular filtration rate <60 mL/min/1.73m² or microalbuminuria; follow-up studies are needed to clarify whether these abnormalities do really identify a chronic nephropathy or just a cardiovascular risk condition.

**Keywords:** albuminuria; chronic nephropathy; CKD; diagnosis; eGFR

### Introduction

After the introduction of the seminal National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD (hereinafter, the term CKD is applied only as specified by the NKF-KDOQI classification, based on the association of albuminuria and eGFR) [1], analyses in large public health databases drew attention to the high burden of chronic kidney disease (CKD) in both developed and underdeveloped countries (see ref. [2] for a review). To gain a better insight into the causes of this phenomenon, typical epidemiological methods were used, i.e. databases were analysed to seek associations between CKD and related conditions (insulin resistance, metabolic syndrome, body mass index, diabetes, hypertension, age) [3–5]. Exactly what made up the bulk of CKD identified by epidemiological studies was never investigated, however.

As defined by the KDOQI, CKD is a ‘non-specific diagnosis’ [6] covering a very heterogeneous array of renal conditions. ‘Diagnosing chronic kidney conditions requires a description of ill health of the kidneys through elicitation of symptoms, observation of abnormal physical signs and investigations’ [6]. In other words, a diagnosis of chronic nephropathy requires a more extensive range of findings than those needed to diagnose CKD.

Knowing the different renal disorders and their prevalence in people with CKD should improve our understanding of the reasons for the large burden of CKD.

Furthermore, when CKD is determined by the combination of albuminuria and/or estimated glomerular filtration rate (eGFR) thresholds as in epidemiological surveys, it is hard to say how efficient such a combination can be in identifying chronic nephropathies.

We investigated these issues in the CKD subjects recognized by the ‘INCIPE’ study, which assessed the prevalence of CKD in north-eastern Italy [7]. CKD cases underwent a nephrological diagnostic workup to elucidate the disorders responsible for their CKD. The results are reported in this paper.

### Materials and methods

The INCIPE population, its recruitment and laboratory methods have recently been described in detail [7]. Briefly, 6200 randomly chosen individuals, all Caucasians and at least 40 years of age as of 1 January 2006, received a letter inviting them to participate in the study. A total of 3870 subjects (62%) accepted and were enrolled. CKD was defined using the Modification of Diet in Renal Disease formula for estimating the glomerular filtration rate (GFR), combined with serum creatinine measurements (kinetic rates using the Jaffe method, recalibrated to standardized creatinine determinations obtained at the Cleveland Clinic Research Laboratory) and the albumin-to-creatinine ratio (ACR) in a first morning void urine sample [7,8]. For the urine albumin assay, we chose to pre-screen samples with a strip test (Clinitek Microalbumin; Siemens Medical Solutions Diagnostics, Mishawaka, IN) and then confirm the positive results (≥3.4 mg/mmol creatinine) by measuring albumin immunochemically using a specific antibody and a nephelometer (Immage 800; Beckman Coulter, Inc., Fullerton, CA). Microalbuminuria was thus defined as an ACR of 3.4–30 mg/mmol creatinine (30 mg/g) up to 33.9 (299 mg/g) and macroalbuminuria (proteinuria) as a value >34 (300 mg/g). The prevalence of all CKD stages envisaged by the KDOQI classification [1] was 14.4% (524 cases). From these 524 CKD cases, a random sample of 262 was selected (1:2) and these subjects were invited back for further investigations. The study protocol complied with the principles of the Helsinki Declaration. All participants signed an informed consent form. The general practitioners provided their clinical records. These cases were re-examined for CKD (eGFR and ACR) a mean 4–6 months after their initial assessment.

We did not use the CKD Epidemiology Collaboration equation for GFR [9] because patients were recalled for investigation before its publication.

Diagnostic algorithms were discussed and developed, and 14 conditions were defined (Table 1) before recalling people for the diagnostic workup; a full description is given in Supplementary Appendix 1. Eleven conditions (numbered from 1 to 11) correspond to well-known kidney diseases, referred to here as ‘specific chronic nephropathy’ (SCN). CKD subjects not matching any of the SCN, but with an abnormal kidney US/Doppler (KUSD) nonetheless, were described as having an ‘undetermined chronic nephropathy’ (UCN). The KUSD abnormalities considered for such a condition were parenchymal hyperechogenicity, reduced cortical thickness, resistive index (RI) ≥0.75. Other abnormalities, such as multiple bilateral renal cysts, cortical scars, calycopelvic and ureteral dilations, etc., were considered as possible evidence of SCN. In subjects with diabetes or hypertension with no other clues suggesting a diagnosis of diabetic nephropathy or hypertensive nephrosclerosis (see Supplementary Appendix 1), the renal disease was classified as UCN provided the patients had an abnormal KUSD.

The categories of lone microalbuminuria (numbered 13) and lone low eGFR (numbered 14) had to have normal KUSD findings. In the lone microalbuminuria category, cases with obesity, metabolic syndrome or hyperfiltration were included and so were those associated with hypertension not complying with the algorithm for hypertensive nephrosclerosis (see Supplementary Appendix 1).

The primary aim of the diagnostic algorithms was to identify the most likely, or possible diagnosis in the least invasive way, based on personal and family history, previous medical records, comprehensive physical
examination, urinalysis, KUSD findings, biochemical tests (serum uric acid, protein profile, serum electrolytes, etc.) immunological analyses (complement, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, search for urine M component) and urine cytology in subjects with microhaematuria. Drug use was recorded (particularly for antihypertensive agents). It was not mandatory to confirm the diagnosis (e.g. by renal biopsy or renal angiogram); this decision was left to the nephrologist responsible for the patient.

The criteria chosen to define specific conditions (i.e. hypertensive nephrosclerosis) were possibly somewhat arbitrary and categorical, but this was to avoid overusing the diagnosis of hypertensive nephrosclerosis and overlaps with other conditions.

Three nephrologists (A.C., G.A. and G.G.) were involved in the diagnostic workup; they had discussed the diagnostic algorithms together and their application to particular, paradigmatic clinical cases before starting the diagnostic workup in CKD subjects. Two radiologists (S.M., G.D.C.) performed all the KUSDs; they had previously discussed and produced a common investigation protocol and data collection form (Supplementary Appendix 2). All KUSDs were performed before the nephrologists’ workup.

All the final diagnoses were reviewed and discussed jointly to reach shared conclusions. Further investigations were performed, as appropriate, to confirm the diagnosis.

Descriptive data are reported.

Results

Forty-four of the randomly selected sample of 262 CKD subjects identified in the INCIPE study refused to take part or could not be contacted, and four had died (Figure 1). The ages, gender composition and clinical characteristics (including CKD stages) of the 48 subjects not involved in the diagnostic workup were comparable with those of the subjects who took part. When ACR and eGFR evaluation were repeated for the remaining 214 subjects (126 females; mean age 67 years, range 47–81), including 6 who had initially been classified as CKD 1, 28 as CKD 2 and 22 as CKD 3. The diagnosis was not confirmed because (i) the second ACR was normal in 34 subjects (16%); (ii) the second eGFR was >60 mL/min in 22 subjects (10%)—all normoalbuminuric and provisionally allocated in the CKD 3 stage. On the other hand, KUSD disclosed abnormalities (cortical hyperechogenicity and/or reduced cortical thickness) in four subjects provisionally classified as having CKD (Stages 2 and 3), whose CKD diagnosis was consequently confirmed (all cases in Stage 2).

The reported data thus refer to 162 subjects (80 females) with confirmed CKD, whose mean age was 69 years (range 45–90); 54 of them (33%) were under 65 years of age and 32 (20%) were >80 years. None had diabetes mellitus Type 1 and 30 were normotensive (≤140/80 mmHg). In this group, the relative proportions of the various stages of CKD were similar to those in the original INCIPE population (Table 2).

Sixteen subjects were classed as CKD 1, and notably only two and four had ‘primary chronic glomerulonephritis’ and ‘interstitial nephropathy/chronic pyelonephritis/ureterovesical reflux nephropathy’, respectively. Two could not be classified in any SCN, although they had KUSD signs of chronic nephropathy (thus they were considered as having UCN). The other eight had microalbuminuria with no evidence of any SCN or UCN.

Among the 38 CKD 2 subjects, 12 had microalbuminuria with no evidence of any of the SCN or UCN.

In subjects with CKD 3—the most prevalent stage (106 cases)—only 38 had one of the SCN; the two most common categories were lone low eGFR (32 subjects) and UCN (36 cases). Among those with lone low eGFR, 12 were hypertensive and only 5 were treated with submaximal doses of renin–angiotensin system (RAS) inhibitors.

Very few cases of CKD 4 were identified in the general Caucasian population ≥40 years of age in the INCIPE study (0.22%) [7] and no SCN diagnosis could be established for the two subjects with CKD 4 investigated in the present study.

The clinical characteristics of patients with UCN belonging to CKD Stages 1–3 in comparison with other conditions are shown in Table 3: hypertension in UCN was more common and it had lasted more than a decade and two decades in 18 and 12 cases, respectively. These UCN patients’ personal and family histories were otherwise unremarkable.

Twenty subjects in stages CKD 1 and 2 had lone microalbuminuria (Table 3). Since six patients in CKD stages 1 and 2 were proteinuric, while the remainder (48 subjects) were microalbuminuric, a chronic nephropathy—either SCN or UCN—was confirmed in 28 subjects, 58% cases with microalbuminuria.

Table 1. Renal conditions identified by diagnostic algorithms

<table>
<thead>
<tr>
<th>Specific renal disease</th>
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<tr>
<td>1. Diabetic nephropathy</td>
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<td>2. Primary chronic glomerulonephritis</td>
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<td>3. Secondary chronic glomerulonephritis</td>
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<td>4. Cystic inherited nephropathy</td>
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<td>5. Non-cystic inherited nephropathy</td>
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<td>6. Inherited malformative nephropathy</td>
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<td>7. Sporadic malformative nephropathy</td>
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<td>8. Single kidney (acquired or congenital)</td>
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<td>9. Ischaemic nephropathy</td>
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<tr>
<td>10. Interstitial nephropathy/chronic pyelonephritis/ureterovesical reflux nephropathy</td>
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<tr>
<td>11. Hypertensive nephrosclerosis</td>
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<tr>
<td>12. Undetermined chronic nephropathy</td>
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<tr>
<td>13. Lone microalbuminuria</td>
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<td>14. Lone low eGFR</td>
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Fig. 1. Subjects flow chart.
The diagnosis was confirmed by renal biopsy in three and four patients with suspected primary and secondary glomerulonephritis, respectively. Renal angiography confirmed the diagnosis in six patients with suspected ischaemic nephropathy (asymmetric kidneys and/or abnormal waveforms and/or a decreased RI at KUSD). No other patients underwent renal biopsy or angiography, either because nephrologists judged the diagnosis to be sufficiently clear already, or because the patients' general or renal clinical conditions did not justify the investigation.

Only 25% of the subjects with a confirmed CKD were aware of having (or having had) a renal disease. Half of them had been referred to a nephrologist in the previous 12 months. A current or previous nephropathy was reported by 37 and 33% of the subjects with SCN and UCN, respectively, and also by 13% of those with lone microalbuminuria or a lone low eGFR.

### Discussion

The present study is the first to explore the CKD diagnosis by a nosological approach, and to test, how effectively the KDOQI definition of CKD identifies chronic nephropathies.

Although the detection rate for a specific diagnosis in subjects in the INCIFE population confirmed as having a CKD proved to be only 38%, adding people with UCN meant that a large number of patients (68%) had abnormalities consistent with a chronic nephropathy in their further workup, i.e. 50, 68, 70 and 100% of cases in CKD Stages 1, 2, 3 and 4, respectively. This is an impressively large number of patients whose underlying disease could easily be detected by combining two very simple tests serum creatinine (and eGFR) and ACR in a morning urine sample.
Microalbuminuria alone is also an important marker of chronic nephropathy and should not be disregarded even if it is minimal nor should it be considered merely as a ‘biomarker’ of systemic vascular disease [6]. In actual fact, when cases with CKD Stages 1 and 2 who were recognized essentially because of their microalbuminuria were investigated more carefully, other features of renal disease came to light in 60% of cases (thus enabling the diagnosis of a chronic nephropathy). Microalbuminuria thus served as a valid marker of a process occurring in the kidney in a sizable proportion of microalbuminuric subjects.

The tools for detecting CKD in large epidemiological surveys are therefore very efficient (particularly for CKD Stage 2 and the more severe stages) in detecting an underlying chronic nephropathy. Almost 50% of the subjects with SCN had a diabetic or vascular renal disease, as was to be expected in relatively old, western populations. The true prevalence of chronic nephropathy related to degenerative disorders is probably higher, however, given that all subjects with UCN were >60 and 80% of them were >70; most of them also had concurrent systemic atherosclerosis and hypertension. This clinical picture is similar to the one seen in patients developing end-stage renal disease (ESRD) after stroke and acute myocardial infarction [10]. A tentative explanation might be that the underlying renal disorder in UCN is the same as the one observed by Kasiske in an autopsy study, i.e. a severe age-related increase in the number of sclerotic glomeruli in subjects with concomitant systemic atherosclerosis [11].

Whether these subjects, with lone microalbuminuria conditions or lone low eGFR, really have a chronic nephropathy is debatable [12]. Recent observations in the general population suggesting that a reduced eGFR and/or microalbuminuria increase(s) the risk of developing not only cardiovascular (CV) complications [13] but also ESRD support the conviction that they reflect a chronic nephropathy [14, 15]. In general terms, however, nobody knows whether the unfavourable prognosis for people in the general population with microalbuminuria and/or a low GFR is basically due to subjects who have an underlying renal disease or to the existence of the microalbuminuria or reduced GFR per se. Since a renal biopsy is unethical in such conditions, only follow-up studies in more extensively investigated subjects such as ours will clarify this issue.

Only 25% of the subjects with a chronic nephropathy were aware of having (or having had) a renal disease, however, and an even smaller number of subjects were receiving nephrological treatment for their current condition. Almost all of those who were aware of their kidney problem had an SCN or UCN. For CKD subjects to be aware that they have a history of renal disease is thus very helpful in confirming the existence of an underlying chronic nephropathy. Indeed, information on prior nephropathies is only provided by 13% of subjects with lone microalbuminuria or lone low eGFR, suggesting that these are particular types of CKD.

Our study has a number of limitations. We did not address the possible existence of false-negative CKD subjects by means of a second test, so the prevalence of CKD and SCN may not be as we estimated, and the performance of the CKD definition cannot be formally calculated.

In addition, adult polycystic kidney disease, malformation nephropathies and single kidneys could be more prevalent in the general population than they might seem from the figures recorded in this study. This is due to the criteria adopted to intercept cases of CKD.

In most cases, our diagnoses were not supported by biopsic or arteriographic investigations. The diagnostic algorithms we used were nonetheless based generally on reasonable evidence of the corresponding renal disease, and our diagnoses were confirmed in cases that did undergo renal biopsy or angiography.

Only two subjects were suspected of having hypertensive nephrosclerosis. Since the criteria for diagnosing this condition are somewhat arbitrary, and the majority of subjects with UCN had a very long history of hypertension, it may be that some of the latter actually have hypertensive nephrosclerosis. A diagnosis of hypertensive nephrosclerosis would need to be confirmed by renal biopsy, however [16].

KUSD is strongly operator dependent. To minimize its variability, only two experienced radiologists were involved in this study, and they had previously discussed and shared the examination protocol. They were not blinded to the patients’ CKD conditions, but they were asked to recognize specific, previously defined renal imaging abnormalities, which were listed on an approved test sheet. Since small differences in the RI could be influenced by operator variability, we did not consider absolute values but only broad RI categories (taking 0.75 units as the threshold) [17]: this method has its weaknesses in terms of sensitivity and sampling problems, however, so scarcely perceptible and/or focal renal lesions cannot be completely ruled out in cases with apparently normal test results.

Albuminuria was not adjusted for gender, though a higher cut-off should probably be used in females [6]. Our threshold (≥3.4 mg/mmol creatinine, 30 mg/g) is higher than is generally suggested (17 mg/g in males and 25 mg/g in females) [6], so we may have underdiagnosed the condition in both genders: this could be a relevant caveat given the finding that the risk of CV disease and ESRD increases at a much lower ACR [13,15].

It may be that subjects with lone low eGFR who were taking RAS inhibitors also had a masked microalbuminuria. This would not have changed our conclusions, however, since they would neither meet the criteria for any SCN nor have KUSD abnormalities.

Finally, our data most likely apply only to western Caucasian countries since the incidence of glomerulonephritis and toxic nephropathies could be much higher elsewhere.

Conclusions

In conclusion, among Caucasians >40 years old with a confirmed CKD condition, an impressively large proportion of subjects (68%) has an underlying renal disease. The tools used in large epidemiological surveys, i.e. serum creatinine (and eGFR) and ACR, to detect CKD are very effective, particularly for CKD Stage 2 and higher.
In 32% of our sample, the only renal dysfunction was a GFR < 60 mL/min/1.73 m² or microalbuminuria. Only follow-up studies will be able to clarify whether these individuals really have a chronic nephropathy or merely a CV risk condition.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Conflict of interest statement. None declared.

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