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Referral to sub-specialists: who have the most to gain from early specialist intervention among patients with markers of renal disease?

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ABSTRACT

Chronic kidney disease (CKD) is associated with various consequences to the cardiovascular system and metabolic profile. The classification into stages should be useful for the physician to anticipate and treat early the manifestations of this disease. We have reviewed the current evidence of the potential benefits from screening, monitoring and treating adult patients for CKD stages 1-3 to counter the progression of kidney damage towards end-stage renal disease. In particular, we advocate an integrated vision of kidney and cardiovascular diseases in clinical practice. A Medline/PubMed, Embase and Cochrane Library search from 2001 to 2013 was performed. All articles related to this topic were reviewed. The search strategy was limited to papers on adult patients in English and Italian. The resulting data was organized on the basis of the current guidelines (evidence-based medicine levels of evidence).

Current understanding of chronic kidney disease

Chronic kidney disease (CKD) is defined as decreased kidney function and/or kidney damage which persist for at least 3 months. Renal impairment may be expressed by a reduction of glomerular filtration rate (GFR) below 60 mL/min per 1.73 m^2, whereas the so-called kidney damage most frequently appears with an increased urinary albumin excretion.[1]

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On the basis of these findings, CKD has been categorized into 5 stages, as shown in Table 1.[2]

Several analyses of prospective cohort studies have clarified the association of each level of estimated GFR and increased urinary albumin excretion with end-stage renal disease (ESRD) and total or cardiovascular mortality.[3] On the basis of this data, the Italian Department of Health, the National Institute of Health and the Italian Society of Nephrology have updated the official guidelines in keeping with international consensus, subdividing the stage 3 into stages 3a (GFR 45-59 mL/min per 1.73 m^2) and 3b (GFR 30-44 mL/min per 1.73 m^2). In addition, the suffix *p* was introduced to indicate the presence of urinary loss of proteins in the staging of CKD, defined as urine albumin-creatinine ratio (UACR).[4]

CKD is a major public health problem in all developed or developing countries. International institutions, such as the United States Center for Disease Control and Prevention, identify CKD as a priority in an era of epidemiological transition.[5] A systematic review of the prevalence of CKD in Europe has shown that its proportion is similar to that of the United States.[6] In the United Kingdom, many plans have been launched to identify subjects with renal dysfunction or lesser degrees of renal impairment.[7] The prevalence of CKD varies with the average age of the population and socio-economic conditions. Although the percentage is lower than in the United States, where the prevalence of CKD is nearly 20%,[5] it is estimated that in the Italian adult population about 1 out of 7 indi-

viduals (13%) have a so-called moderate renal impairment, *i.e.* a GFR at least half of the standard level.[4] However, in Italy the problem is still unknown to the general population and underestimated by physicians and institutions in charge of public health.

The epidemiology of CKD has changed significantly. Today CKD is rarely caused by primary, glomerular or tubulo-interstitial kidney disease. In the majority of cases, it is associated with other common clinical conditions, such as diabetes mellitus or metabolic syndrome, hypertension and cardiovascular diseases.[8] For this reason, some authors have speculated that cardio-nephrology will become a new branch of medicine, which may gradually replace traditional nephrology.[9]

Methods of research

In recent years, while the effectiveness, efficiency and sustainability of healthcare systems are being discussed worldwide, the planning of economic resources has become an emerging issue. This review examines the current evidence of potential benefits from screening, monitoring and treating adult patients for CKD stages 1-3, in order to counter the progression of kidney disease into ESRD. For obvious epidemiological reasons, patients with CKD at stages 1-3 are usually observed and evaluated by general practitioners or primary care physicians, internal medicine hospitalists or specialists from disciplines other than nephrology.

A Medline/PubMed, Embase and Cochrane Library search for 2001 to 2013 was performed. All articles on this topic were reviewed. The search strategy was limited to papers on adult patients in English and Italian. This data was organized on the basis of the current guidelines [evidence-based medicine levels of evidence (LE)] (Table 2).[10]

Slowing the progression of chronic kidney disease: is it really possible?

An in-depth analysis of the literature shows that the trials are too heterogeneous to be compared. The problem already emerges in the inclusion criteria and definition of kidney damage or impaired renal function, which are not always in line with the classical definition of CKD stages 1-3 according to the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).[11] Since studies rarely report outcomes stratified by CKD stages or kidney damage markers, it is often difficult to determine whether the benefits of a clinical trial are applicable to the individual stages of CKD, or different values of GFR or degrees of albuminuria.

Table 1. Chronic kidney disease stages.

Stage no.	GFR	Disease
1	GFR≥90 mL/min per 1.73 m^2	Evidence of kidney damage
2	GFR 60-89 mL/min per 1.73 m^2	Evidence of kidney damage
3a	GFR 45-59 mL/min per 1.73 m^2	*with* Normal or high-normal urine albumin excretion (UACR<20 M, 30 F mg/g)
3b	GFR 30-44 mL/min per 1.73 m^2	
4	GFR 15-29 mL/min per 1.73 m^2	*or* Microalbuminuria (UACR 20-200 M, 30-300 F mg/g)
5	GFR<15 mL/min per 1.73 m^2 or kidney failure treated with RRT	*or* Macroalbuminuria (UACR>200 M, 300 F mg/g)

GFR, glomerular filtration rate; UACR, urine albumin-creatinine ratio; RRT, renal replacement treatment (dialysis or transplantation); M, male; F, female.

Table 2. Levels of evidence.

Level of evidence	Scientific substrate
Ia	Systematic revision or meta-analyses of randomized clinical studies
Ib	At least one controlled, randomized clinical study
IIa	At least one controlled clinical study, but non randomized
IIb	Other well-conducted controlled studies
III	Well-conducted, non-controlled studies (case reports, correlation studies, descriptive and retrospective studies)
IV	Opinion of experts

Assuming that randomized controlled trials of patients with CKD stages 1-3 are well conducted, the investigated therapies actually the risk of clinical outcomes, but the benefits appear to be limited to specific CKD subgroups, some of which have already a clinical indication for the treatment studied (LE Ib). In fact, in most patients with CKD stages 1-3, treatment is not directed to CKD, but to associated comorbidities or cardio- and nephro-vascular risk factors, such as arterial hypertension and/or diabetes mellitus. Conversely, in an effort to reduce the risk of complications from these conditions, therapeutic goals in these settings are sometimes determined more strictly for CKD than non-CKD subjects. These considerations make it even more difficult to apply theoretical models to individual patients (LE Ia).[12]

It has been suggested that common medications, such as angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), may specifically treat CKD. However, it has not been fully elucidated whether their impact on CKD outcomes (*e.g.*, incident ESRD, need for renal replacement therapies) or markers (*e.g.*, urine albumin excretion) is independent of their effect to lower blood pressure.[13] Indeed, patients with urinary protein excretion, diabetes mellitus or arterial hypertension may benefit from the blockade of the renin-angiotensin system, at least within the limits of the explanations below.

According to the literature, normoalbuminuric patients with CKD stages 1-3 treated with ACEIs show no reduced risk of mortality *versus* placebo or no treatment (LE Ia, Ib).[14-16] On the contrary, ACEIs could significantly reduce the risk of mortality in subjects known to have microalbuminuria, who have either cardiovascular disease or a combination of diabetes mellitus and other cardiovascular risk factors (LE Ia, Ib).[17-19] Even if it has been shown that ACEIs significantly reduce the risk of ESRD in patients with macroalbuminuria, diabetes and hypertension, ESRD cannot not clearly or effectively prevented in patients with CKD stages 1-3 with no abnormal urine protein excretion.[20] Lastly, although subjects treated with ACEIs at CKD stages 1-3 have no statistically significant reduction in the risk of myocardial infarction or stroke, current trials in this setting have found a reduced risk for composite, vascular and renal outcome (LE Ia, Ib).[21]

In randomized, controlled studies comparing ARBs with placebo or no treatment, patients with CKD stages 1-3 receiving the therapy have no reduced risk of mortality. Results seem to be similar in subgroups with or without urinary albumin excretion. ARBs reduce risk for ESRD in these patients: however, because ESRD occurs in macroalbuminuric, diabetic and hypertensive subjects, it is not possible to determine whether ARBs reduce the risk of ESRD in microalbuminuric patients with impaired GFR only. Moreover, the risk of cardiovascular comorbidities has not differed significantly between treatment and placebo (LE Ia, Ib).[22-26]

It has been shown that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) significantly reduce the risk of death, stroke or coronary disease in hyperlipidemic patients with impaired GFR, but no large trials have reported outcome data for albuminuric subjects.[27-30] β blockers reduce the risk of mortality, myocardial infarction and heart failure (chronic heart failure) in patients with CKD.[31-34] A low-protein diet has not reduced the risk of mortality or ESRD compared with a usual protein diet, at least in the course of CKD stages 1-3.[35-39]

Screening for patients with chronic kidney disease stage 1-3: facts and fallacies

The theoretical rationale for the screening of CKD stages 1-3 is based on clinical and epidemiological considerations, which are summarized in Table 3. Scientific societies, study groups and prevention programs have long provided guidance on the correct use of this approach in this setting (Table 4). Indeed a screening program for CKD can be truly effective only if it is aimed at improving significantly clinical outcomes in screened subjects and can lead to a remarkable difference in terms of prognosis between CKD patients identified at an early stage and patients who start any specific treatment at later stages.

Table 3. Rationale for the screening for chronic kidney disease stages 1-3.

Chronic kidney disease
High and rising prevalence
Known risk factors or predisposing conditions
Known adverse clinical consequences
Prolonged asymptomatic phase or with few symptoms
Potential availability of screening tests on a large scale
Medical treatments that can alter the progression of the disease, reduce the complications and control the comorbidities

However, as seen above, there is no specific therapy to slowdown the progression of CKD, in fact drugs can only attempt to correct metabolic or cardiovascular coexisting morbidities.[12] For this reason it is difficult to separate the clinical history of CKD from that of concomitant diseases, as well as the direct or indirect effects of any treatment. Virtually, a benefit of early screening in the CKD population can be demonstrated only when in the subpopulation of patients with an indication for a specific treatment of comorbidities, CKD patients *vs* non CKD subjects receive this treatment and have greater overall benefits in terms of outcome and reduced pharmacological doses or different therapeutic targets. Therefore the benefit of systematic screening for CKD stages 1-3 is currently unclear (LE Ia, Ib).[12] However, the screening of individual patients for the detection of urinary albumin loss in the diabetic and hypertensive population may allow for an earlier administration of drugs blocking the renin-angiotensin system and thereby reduce the risk of mortality and ESRD in this patients (LE Ib). Similarly, screening these subjects for impaired GFR in the hyperlipidemic population could lead to initiate earlier a statin treatment and reduce the risk of mortality, myocardial infarction or stroke (LE Ib).

Actually, most patients with CKD stages 1-3 are unrecognized. Since even subjects with a high CKD prevalence (*e.g.* patients with arterial hypertension or diabetes mellitus) are not routinely tested for CKD, the introduction of a systematic screening might lead to a large increase in CKD diagnoses. Urine albumin excretion and estimated GFR with the modification of diet in renal disease equation (Table 5) are actually used for screening CKD stages 1-3, but false positive rates are significant, and their sensitivity and specificity for CKD in terms of renal impairment lasting at least 3 months are unclear.

Table 4. Main recommended screenings in selected populations.

Society/Association	Guideline
Kidney Disease: Improving Global Outcomes (KDIGO)	Screening for CKD (GFR, urine albumin excretion) of all patients with arterial hypertension, diabetes mellitus or cardiovascular disease
American Diabetes Association (ADA)	Annual screening (GFR, urinary albumin excretion) of all adults with diabetes, based on *expert consensus or clinical experience*
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)	Annual screening (GFR, urinary albumin excretion) of all patients with arterial hypertension and diabetes mellitus
European Society of Cardiology - European Society of Hypertension (ESC-ESH) Guidelines for the Management of Arterial Hypertension	*Microalbuminuria has now been considered an essential component in the assessment of organ damage, because its detection is easy and relatively inexpensive*

CKD, chronic kidney disease; GFR, glomerular filtration rate.

Table 5. Estimated renal function in clinical practice.

Name	Equation
Creatinine clearance	$cl=\frac{[cr]u \times Vu}{[cr]s}$ cl=creatinine clearance (mL/min) [cr]u=24 h urine creatinine concentration (mg/dL) Vu=daily urinary volume/min [cr]s=serum creatinine (mg/dL)
Cockcroft-Gault formula	$cl=\frac{(140-a) \times bw}{72 \times [cr]s}$ cl=creatinine clearance (mL/min) a=age (years) bw=body weight (kg) [cr]s=serum creatinine (mg/dL) 0.85 correction factor if female
Modification of diet in renal disease equation	$eGFR = 186 \times [cr]s^{-1.154} \times a^{-0.203}$ eGFR=estimated glomerular filtration rate (mL/min per 1.73 m^2) [cr]s=serum creayinine (mg/dL) A=age (years) 0.74 correction factor if female, 1.21 correction factor if African-American

The progression of chronic renal disease over time

The rate of asymptomatic, continuous GFR decline in patients with CKD stages 1-3 varies among individuals, considering that various factors seem to impact progression. The protocols to monitor kidney damage over time have been already drawn up by the major scientific societies (Table 6). The benefits from monitoring subjects with known CKD stages 1-3 over time to identify any variation in renal function and/or albuminuria can be confirmed on the basis of the same evidence required to confirm the usefulness of CKD screening in the general population. The changes to any treatment, as suggested by the results of the monitoring process, would need to improve significantly clinical outcomes, but there is no conclusive evidence that this can occur (LE Ia, Ib).[12]

As to potential indirect observations, monitoring the onset of albuminuria in the CKD stages 1-3 population in order to start earlier a pharmacological blockade of the renin-angiotensin system might reduce the risk of mortality and ESRD at least in hypertensive and diabetic patients. Likewise, monitoring the CKD stages 1-3 population to identify a worsening of GFR could lead to initiate earlier a statin treatment and reduce the risk of mortality, myocardial infarction or stroke in subjects with relevant hyperlipidemia. In clinical practice, serum creatinine is measured regularly in almost all patients who are in CKD stages 1-3. Hence, the implementation of systematic GFR monitoring may have only a limited impact. Conversely, only a minority of subjects with CKD stages 1-3 are annually tested for urine albumin excretion. Therefore a systematic monitoring of albuminuria might be likely to identify a greater number of patients with a clinical worsening of CKD. However, it should be remembered that the real sensitivity and specificity of GFR and urine albumin detection to identify the CKD progression have not yet been fully clarified on a routine basis.

Conclusions

A few years ago, some literature argued that a delayed cooperation with the nephrologist (*i.e.* in the 4 months prior to the start of renal replacement therapy) would result in a worse outcome in terms of complications and survival, as well as in a significant increase in the costs involved in the management of patients with CKD.[40-45]

In the past, various guidelines recommended that the nephrologist was to be consulted by general practitioners or hospitalists in internal medicine, when creatinine clearance would fall below 60 mL/min.[40-45] This approach would enable the nephrologist to take effective measures to slow the progression of renal damage. However, if we consider the percentage of patients with this indication in the current general population, we understand that the systematic application of this recommendation would have a dramatic impact on the territorial networks of renal care.

Consequently, the large population of subjects with mild renal damage or at risk of CKD, or in general in CKD stages 1-3, requires the definition of strategies for screening and monitoring of CKD progression that are based on clear epidemiologic evidence in terms of outcomes. Because of the clinical and epidemiological importance of the problem, it is therefore necessary to implement adequate clinical governance to establish a proper management approach to CKD in all its phases by correctly allocating resources and defining adequate indicators for a periodic review of results.

The data emerging from our analysis of the scientific literature does not seem encouraging as to the real effectiveness of screening and monitoring patients to identify early stages of CKD. Indeed, the results of any modification of treatment on relevant outcomes (ESRD, mortality) are convincing exclusively in patients with comorbidities, such as diabetes mellitus and hypertension, but not in those suffering only from kidney disease.

However this data may lead to some critical considerations, which may be useful in clinical practice. Although the decline of GFR and urinary albumin excretion are simply placed side by side in the tables of progression of renal disease for classification purposes, albuminuria and low estimated GFR have been considered co-factors in cardiovascular mortality risk in various studies. Also the use of both UACR and estimated GFR have shown to improve cardiovascular risk strat-

Table 6. Monitoring the progression of chronic kidney disease.

Society/Association	Guideline
Kidney disease outcomes quality initiative (KDOQI)	At least annual eGFR measurement in adults with known CKD in order to predict onset of ESRD and evaluate the effect of CKD treatments More frequent monitoring of CKD patients with worsening kidney function
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)	Annual quantitative measurement of urine albumin Excretion in all patients with known kidney disease

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ESRD, end-stage renal disease.

ification at all ages, in particular in over 70s and older.[46] The importance of these findings is explicitly reaffirmed in Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.[47] Therefore, the problem of interpretation may lie upstream, emphasizing the need to develop a CKD classification system which is more integrated and also includes the overall cardiovascular risk. In this way, the theoretical screening approach under consideration would be disappointing only if based on the traditional classification in 5 stages, because the simultaneous measurement of UACR and GFR instead appears to be effective in predicting cardiovascular events and progression towards final stages of the disease.[48,49] The first stages of CKD should be classified on the basis of a more general, cardio-nephrovascular and metabolic prevention approach, that necessarily involves general practitioners and hospitalist in internal medicine rather than nephrologists.

It is also true that only a sub-group of CKD patients will evolve towards the final stages of kidney disease, but it is also known that all renal patients are burdened with a risk of cardiovascular morbidity and mortality greater than the normal population.[50] This is also confirmed by the significant therapeutic options (statins, angiotensin antagonists) available for these patients. It has been shown, for example, that the reduction in the absolute risk is clear even in patient subgroups defined by low levels of GFR. In addition, the number needed to treat to prevent one adverse event is about half that of the general population in the case of cholesterol-lowering treatment.

Lastly, early identification of CKD would have a general prophylactic implication in terms of safety, forcing doctors and patients to pay particular attention to the effects of potentially nephrotoxic drugs or instrumental procedures. It is becoming increasingly clear, in fact, that even acute kidney injury is a crucial factor in the progression of CKD.[51,52]

On the basis of our observations, after reading carefully and reviewing critically the literature, which is at times contradictory, it seems reasonable to conclude that the relationship between CKD and its frequently associated comorbidities (diabetes, hypertension, dyslipidemia) is indivisible and should only be seen in its entirety. In this perspective, CKD patients should be considered at high cardiovascular risk and monitored and managed accordingly.

Hence, within the framework of this nephro-cardiovascular disease, the nephrologist can find a new and more effective role in the treatment of subjects with rapid progression to ESRD. This is also the approach implemented to codify the renal risk scores for the general population and the predictive models of CKD progression towards the terminal stages.[53,54]

Consequently, a great deal of attention should be paid to an adequate cultural education of physicians, who currently have only a superficial knowledge of the clinical history of renal disease and the epidemiological and clinical issues related to it. In the future, new and appropriate plans based on the cooperation of nephrologists, internists, cardiologists, diabetologists and general practitioners may be the most effective solution to this problem. Even the CanPREVENT (Canadian prevention of renal and cardiovascular endpoints) trial, a physician/nurse-based multifaceted approach, has shown to reduce costs without affecting the quality of life of CKD patients.[55]

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