

Cardiovascular, renal and other chronic diseases. Early intervention is necessary in chronic kidney disease.

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In a meeting at the Spanish National Cardiovascular Research Centre (CNIC) in Madrid to discuss the need for earlier diagnosis and initiation of treatment in cases of Chronic Kidney Disease (CKD) in Spain (a relatively unknown illness in its early stages, and one about which the only real data we have relates to its advanced stages, where either dialysis or transplantation are required) we agreed that it is a mistake to focus solely on the heart and forget that there are other organ systems which are also adversely affected by those same risk factors (hypertension, diabetes, hyperlipidemia, obesity and smoking), all of which can be modified. A delay in prevention and treatment will make it impossible to deal with the extremely high cost involved in the treatment of advanced-stage renal disease. This document summarizes parts of that meeting as well as some of the commentaries.

For cardiologists, as well as for other physicians, one of the most important aspects of cardiovascular disease is the ability to frame the illness within the appropriate context in which it develops. Co-morbid conditions such as diabetes or arterial hypertension are clear and significant factors which ultimately affect what physicians' will indicate or prescribe for their cardiovascular patients. Perhaps the same is not true for Chronic Kidney Disease (CKD). This could be because many cases present with what we termed occult kidney disease; that is, patients with normal plasma creatinine levels but with a reduced Glomerular Filtration Rate (GFR) below 60/ml/min, a combination which occurs frequently among women after the age of 65.

In the industrialized countries today, chronic illnesses constitute a real and very serious threat, of an epidemic nature, to the health of their populations. Health authorities predict that the prevalence of cardiovascular disease will reach epidemic levels worldwide within the next few years, especially due to

the widespread increase in obesity and diabetes which we have recently witnessed.

Until now, chronic renal disease had never been considered to be a significant health problem for the population in general, as were heart disease, cerebrovascular disease and cancer. However, chronic kidney disease represents one of the leading causes of death within the industrialized world. And not only is this the result of those patients who reach the stage where they require either dialysis or transplantation and whose disease course is in many cases worse than that of terminal cancer, but also because those patients who do not yet require dialysis and present with either proteinuria or an asymptomatic reduction in their GFR, but who nonetheless have a very high prevalence of cardiovascular complications.^{1,2}

STAGES OF CHRONIC KIDNEY DISEASE

Chronic kidney disease is a progressive illness, and patients can be categorized into five stages.³ The first two, with a GFR > 60ml/min, are defined by renal damage lasting at least 3 months, with structural or functional abnormalities of the kidney, with or without a decrease in the GFR, as evidenced by pathological changes or markers of renal damage (changes in the composition of blood and/or urine, or abnormalities detected in renal imaging studies.) These two initial stages are very significant, because they may present with normal creatinine levels, although they are at risk of developing renal failure. Damage to the kidneys during these initial stages can be ascertained by the presence of albuminuria (defined as albumin/creatinine > 30mg/g, obtained in two or three separate urine samples.) In the more advanced stages, where there is a loss of renal function with a decreased GFR: stage 3 (GFR 59-30ml/min), stage 4 (GFR 29-15ml/min) and stage 5 (GFR < 15ml/min or undergoing dialysis), the GFR can be estimated using a simple formula which makes use of a calibrated serum creatinine level, as well as the sex, ethnicity (MDRD-4),⁴ and weight of the patient (Cockcroft-Gault).⁵

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CARDIOVASCULAR DISEASE AND THE KIDNEY

Cardiovascular disease is the leading cause of death, even in developing countries, followed by cancer.⁶ Unfortunately, renal disease, although clearly linked to cardiovascular disease, has not, until very recently, been adequately recognized in the statistics. A quite recent example of this is the prevalence of renal failure among 4,102 hospitalized patients with cardiac failure: 57% of those patients also had renal insufficiency, and yet in almost half of them it had not been previously recognized, since their plasma creatinine levels were essentially normal, although subsequent measurements of albumin excretion, by means of the ratio of albuminuria/creatinine, demonstrate that these patients had already suffered kidney damage.⁷

The presence of renal disease has now been included as an independent risk factor for cardiovascular disease in the most recent issue of the *Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure* (JNC VII)⁸ and within the definitions published by the *American Heart Association*. In fact, the percentage of patients with CKD who die from cardiovascular complications is much greater than those who progress to the point of requiring dialysis or transplantation. The HOPE and HOT^{9,10} studies demonstrated that those patients with plasma creatinine levels of 1.3 to 1.4mg/dl, compared to those with normal kidney function, have a significantly elevated incidence of primary cardiovascular events, cardiovascular mortality and overall mortality, which allows moderate chronic renal failure to be categorized as a risk factor for cardiovascular disease.

The relationship between CKD and cardiovascular disease is well established and it increases as the deterioration in renal function advances, so that cardiovascular mortality among patients undergoing dialysis is 500 times greater than in those people with normal renal function.

The Framingham Study had already demonstrated how the existence of even mild renal failure (Scr 1.4-3.0mg/dl), was associated with an increased risk for cardiovascular disease.¹¹ Subsequently, Go et. al., using a large database from northern California which included more than 1.1 million adults, looked at the relationship between the GFR (calculated using the MDRD formula) and the risk of mortality, cardiovascular events, and hospitalizations.¹² After adjusting for age, sex, race, co-morbidity and socioeconomic status, the researchers found that there was still a clear and significant increase in the risk for all three of these outcomes associated with a decrease in the GFR. In this way, the risk of mortality or a cardiovascular event was 1.2 and 1.4 in the CKD Stage 3a; 1.8 and 2.0 in Stage 3b, 3.2 and 2.8 in Stage 4; and 5.9 and 3.4 in Stage 5, respectively.

EPIDEMIOLOGY OF CKD

Most of the available data comes from patients with Stage 5 CKD, who are undergoing treatment with dialysis or transplantation. In 2007, more than 45,000 people in Spain,¹³ that is, approximately

1,000 people per million, were already undergoing dialysis treatment for-CKD, a figure which is expected to double in the next 10 years as a result of the progressive aging of the population and the concomitant increase in the prevalence of other chronic conditions such as diabetes mellitus and obesity. The same holds true in the developing world where, although the precise incidence has yet to be determined, the number of patients who are undergoing dialysis treatment or who have received a kidney transplant continues to increase at a considerable rate, having already reached the level of 1,500-1,900/million people in year 2005 in Japan, Taiwan, and the USA.¹⁴ This increase in the prevalence of CKD is alarming since it could create future havoc within the health care systems in several countries around the world.

The prevalence of Stage 1 through 4 chronic renal failure is pretty much unknown, since routine testing of renal function using serum creatinine is not an adequate measure in many cases, and it underestimates the true prevalence. The NAHNES III Study, which was carried out in the United States between 1988 and 1994, examined 15,626 adults for the purpose of establishing the prevalence of the various stages of CKD¹⁵ In this study, the overall prevalence of CKD was 11% of population, distributed as follows: 3.3% (Stage 1), 3% (Stage 2), 4.3% (Stage 3), 0.2% (Stage 4), and 0.1% (Stage 5). A more recent variation of that study design, carried out between 1998 and 2004 among 13,233 adults, showed an increase in the prevalence of CKD Stages 1 through 4, up to 13%; an increase which can be partially explained by the increase in the prevalence of both diabetes and hypertension which occurred during that same period.¹⁶ The Australian study on diabetes, obesity, and lifestyle (Ausdiar) examined the prevalence of diabetes, obesity, cardiovascular risk factors, and markers of kidney disease among Australian patients. It was found that 11.2% of patients suffered from a significant alteration in renal function (GFR <60 ml/min), and 2.4% had proteinuria.¹⁷

In Spain, there have been a few estimates, beginning with Primary Care,¹⁸ and in particular, the Spanish Society of Nephrology is conducting various epidemiological studies which indicate a prevalence of CKD with GFR < 60ml/min (Stages 3 to 5 without dialysis treatment) of approximately 6.8% among the general population over the age of 18 (EPIRCE)^{19,21} and 21% among patients seeking Primary Care, a population which is logically going to have a higher prevalence of cardiovascular comorbidities (EROCAP).²² The DISEHTAE Study (Diagnosis and Follow-up of HBP in Spain), undertaken by the Spanish Society of Family and Community Medicine, was an external audit review of 6,113 clinical records taken from hypertensive patients in Primary Care. It was found that 25.7% of the patients suffered from CKD, and 14.1% of the patients with a normal creatinine level had a GFR below 60ml/min. Also in Spain, the prevalence of CKD Stages 3-5 in approximately 14,000 hospitalized patients was found to be 28% (ERPHOS Study, to be published) and 62% among patients with a functioning kidney transplant (GERTRA Study, in progress). These figures justify the adoption of an action plan between the bodies concerned to control a future increase in the prevalence of renal disease as well as the socioeconomic conse-

quences: the Spanish Ministry of Health and the Regional Ministries of Health from the different Spanish Autonomous Communities, the Spanish Society of Family and Community Medicine, the Spanish Nephrology Society, and other organizations for renal patients.

REASONS FOR IMPLEMENTING A RENAL HEALTH PROGRAM

The high prevalence of CKD coupled with its tendency to go undiagnosed during its early stages, and its progressive yet modifiable nature make it necessary to put together, at the national level, a program to facilitate the diagnosis of renal disease in its early stages, in the hope of avoiding the subsequent development of related cardiovascular complications, progression of the renal disease, the inappropriate prescribing of medications and, as a last resort, earlier referral to a Nephrology specialist. It will permit the patient to become better prepared for the eventual need to undergo renal function substitution treatments (haemodialysis or peritoneal dialysis), or to receive a kidney transplant prior to initiating dialysis treatments.

Hospitalizations are very common among renal patients due to high comorbidity. Nowadays, the hospital stay represents more than 50% of the health care expenditure. If the above-mentioned trend were to continue, it would become impossible to continue offering the health care services that are available today, to the public in general. The particular case of renal disease is very illustrative of this looming crisis. In the USA, the annual cost of renal-function substitution treatments increases yearly, and will reach 28 billion dollars in year 2010.²⁴ For this reason, political decisions need to be aimed at achieving a more adequate balance between the money spent for treating illnesses in the advanced stages and the money spent to support research into the causes and mechanisms of those illnesses, as well as for health promotion and earlier diagnosis.

In October 2006, the KDIGO Organization (Kidney Disease: Improving Global Outcomes), a non-profit institution which brings together CKD experts from all over the world, published a document containing a series of recommendations which should be adopted worldwide in order to confront the problem of CKD in a rational way. Here are some highlights from their recommendations²⁵:

- Governments must adopt a health policy in the face of CKD, working closely together with non-governmental organizations and private industries (at the regional, national, and international level.)
- CKD should be incorporated into Public Health programmes.
- Governments must support and fund programs for the early diagnosis and follow-up of CKD including prevalence, incidence, disease progression, treatments and education.

Therefore, a strategy for renal health must be implemented which will effectively make healthcare professionals, patients, and the general public acutely aware of the importance of being knowledgeable about renal function, given the potential therapeutic and prognostic implications resulting from the early detection of this illness.

POSSIBILITIES FOR EARLY INTERVENTION IN CKD

CKD is a cardiovascular risk factor which can be modified through the mechanisms underlying the progression of the renal disease, and an adequate control with strict therapeutic objectives especially concerning the primary cardiovascular risk factors (hypertension, proteinuria, hyperlipidemia, obesity and smoking.)

Lifestyle modifications aimed at establishing a healthier way of life are certainly the first steps to prevent renal disease.²⁶ Reducing proteinuria through the use of Renin-Angiotensin system inhibitors and, probably, reducing the amount of protein intake will decrease renal failure in diabetic and non-diabetic nephropathies alike, to the extent that there have been case reports, in both animals and humans, of illness remission and kidney injury regression as a result of implementing these measures.²⁷

Notwithstanding certain controversies surrounding the effects of statins in the prevention of cardiovascular events in patients with CKD,²⁸ a recent meta-analysis of the TNT Study (Treating to New Targets) examined the effects which a dramatic reduction in lipid levels using atorvastatin would have on patients with coronary artery disease, with and without CKD. Compared to 10mg of atorvastatin, an 80mg dose reduced the relative risk of major cardiovascular events by 32% in patients with CKD and by 15% in patients without renal disease. Consequently, there appears to be a safe and effective means for lowering the risk of cardiovascular complications in patients who present with both CKD and dyslipidemia.²⁹

The concept of a polypill³⁰ was developed based on controlled, randomized clinical trials and epidemiological studies. Although several possible medication combinations exist, the concept is fundamentally based on the issues of patient compliance and cost. In renal patients, for all the reasons mentioned above, a combination of ACE, aspirin and statins could have a significant impact in reducing cardiovascular events. There is already a project in Spain, currently being developed by the CNIC, to move away from the stages of intellectual debate and towards the implementation of effective action concerning the prevention of cardiovascular disease, which could potentially be applied to CKD patients in the near future.³¹

CONCLUSION

Just like we stated several years ago,³² the lack of investment into cardiovascular disease and into other chronic illnesses such as renal disease is a mistake. The chronic illness epidemic requires an approach aimed primarily at the early stages of the disease processes.

With respect to CKD, the development and implementation of a renal health program is extremely important for several reasons:

1. CKD is a very common and devastating illness.
2. Little is known about CKD, yet it is progressive and very expensive to treat.
3. CKD can be diagnosed in its early stages using two sim-

ple and inexpensive tests: by evaluating renal function using equations (MDRD) and through an analysis of albumin excretion in the urine.

4. All patients with, or at risk for developing, cardiovascular disease should be evaluated to determine the degree of renal function and integrity.
5. Primary and secondary prevention measures are available, which can prevent the occurrence, slow the progression, and even promote the regression of CKD, and which, at the same time, reduce the risk of developing cardiovascular complications.

The steps and actions promoted within this program of prevention logically revolve around the family physician. The various Scientific Societies and Organizations (e.g. Family Medicine, Nephrology, Spanish National Transplant Organization, Cardiology, Clinical Biochemistry, etc...), together with Spanish Patient Renal Associations and the corresponding politicians in the Spanish Ministry of Health and in each of the 17 Spanish Autonomous Communities, must work diligently and cooperatively in its development and implementation, and in the subsequent control of its results.

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