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The metabolic syndrome and chronic kidney disease epidemics: severing the link?

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INTRODUCTION

Life span in western countries has increased by as much as 50% in just one century, from 50 years in 1900 to 75 in 2007. The trade-off of a longer life span and affluence is the ascendancy of the new epidemics of overweight and obesity, the main causes of type 2 diabetes which have long been regarded as health risks in western countries. Profound changes in life style, the quality and quantity of food consumed and the decrease in levels of physical activity over the last decade have led to an increase of diabetes and its complications.

The recent World Health Organization (WHO) report "Preventing Chronic Diseases: a Vital Investment" highlights the need for global action to address the major risks linked to chronic diseases worldwide[1]. Of these, the dangers posed by smoking have received the most attention so far, but in recent years the additional risks of overweight, obesity and the resulting impact on diabetes and cardiovascular (CV) disease have become the main priorities. About 1 billion people worldwide are overweight or obese, compared to 850 million who are underweight. It is often stated that "overweight and obesity have become to diabetes what tobacco is to lung cancer." Roughly 60% of all cases of diabetes can be directly attributed to excess weight[2]. Only two decades ago, type 2 diabetes was diagnosed in only 1-2% of diabetes cases in children. It was considered primarily a disease of adulthood and labelled adult-onset diabetes. With the rising incidence of obesity, type 2 diabetes has begun to appear in children at alarming rates and in some countries represents up to 80% of all cases of diabetes reported in the paediatric population[3,4].

All these considerations strongly support the concept that famine and infections, the exact opposite of obesity and CV complications, are diseases of the past. Even though the share of wealth is unbalanced, at least in western countries, the emerging problem is the opposite of famine: it is the unlimited access to food. The most worrying consequence of that is obesity and its related morbidities of hypertension, dyslipidemia and diabetes; in short, the metabolic syndrome.

HISTORICAL BACKGROUNDS, DEFINITION AND PATHOGENESIS

The syndrome has been known since the last century, when several distinguished scientists made clinical observations in patients with metabolic abnormalities and described the very common coexistence of various cardiovascular risk factors, giving several names to it. The first description of the clustering of various components of the metabolic syndrome goes back to the period when insulin was discovered[5] but the modern era of what we now call the metabolic syndrome or the "insulin resistance syndrome" began with the description of the X syndrome

by Reaven in the late 1980s[6]. Reaven reported that this disorder was present not only in the majority of subjects with type 2 diabetes mellitus or impaired glucose tolerance (IGT), but also in almost 25% of the individuals with normal glucose tolerance. He was therefore able to formulate the hypothesis that insulin resistance is the common aetiological factor for a group of disorders consisting of IGT, hyperinsulinemia, dyslipidemia and hypertension. It was called syndrome X to stress its unknown features and Reaven also highlighted the increased risk of atherosclerosis in individuals with this syndrome, emphasising the effect of both genetic and environmental factors (physical exercise and obesity) on the severity of insulin resistance[7]. The better-accepted current definition is included in the recommendations for dyslipidemia testing and management of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) in the USA[8]. The panel also mentioned the high prevalence of the syndrome and the absence of well-accepted criteria for its diagnosis. It proposed five criteria, three of which are declared to be sufficient for the clinical identification of the syndrome. These are abdominal obesity, elevated triglycerides, low HDL cholesterol, blood pressure (BP) higher than 130/85 mmHg and fasting glucose above 110 mg/dl. The NCEP/ATP III proposed[8] the term "metabolic syndrome" to facilitate a careful scrutiny of the overweight and obese population with evidence of medical complications. That said, the metabolic syndrome concept has been strongly criticised[9,10]. The criteria have been found to be ambiguous and incomplete. Doubts have also been cast on the widely-held belief that the pathogenesis of the metabolic syndrome is insulin resistance, and even on the actual existence of the syndrome, with some scientists claiming that CV disease risk associated with this syndrome is not greater than the sum of its parts. This criticism notwithstanding, others firmly believe the definition is of great value[11,12]. In a paper published in the British Medical Journal, Sundstrom *et al* showed that the metabolic syndrome increases cardiovascular risk by 40-60% and this effect is stated to be independent from other risk factors such as smoking, diabetes, hypertension or dyslipidemia[13].

On the other hand, insulin resistance plays a key role in the development of metabolic syndrome, as a number of observations linking insulin resistance with each of the syndrome's components suggest[14]. More recently, Cirillo P *et al* [15] published a review highlighting the role of uric acid in the pathogenesis of metabolic syndrome. Uric acid was also suggested as a pathogenetic agent in the metabolic syndrome that was induced experimentally by fructose[16]. The rise in uric acid after fructose ingestion could induce insulin resistance by reducing nitric oxide. In turn, the intake of fructose, which constitutes 50% of table sugar and is a major component of several sweeteners, correlates with the recent rise in metabolic syndrome epidemics[17].

CLINICAL CONSEQUENCES OF THE METABOLIC SYNDROME

Whether the deadly cluster of traditional risk factors should be called a syndrome or not, this combination of risk factors has greatly worried the international scientific community because of the strong links to complications related to obesity, diabetes and coronary heart disease.

On a global scale, it is estimated that there are 1.6 billion overweight or obese individuals and this number is expected to increase to 2.5 million over the next 30 years. A survey published some years ago documented that there were 120 million diabetics worldwide, a figure that is expected to double by 2010[18].

The estimated number of hypertensive patients is currently 1.6 billion and this will have reached 2.5 billion by 2030. A number of studies coherently show that patients with metabolic syndrome are at high risk of developing cardiovascular events and death[19,20], meaning the probability of coronary artery disease in these patients ranges from 30 to 400%. This wide range most likely depends on the type of population studied as well as differences in the definition of metabolic syndrome and follow-up duration.

The INTERHEART study[21] reported that five of the nine risk factors (cigarette smoking, abnormal ratio of blood lipids, high blood pressure, diabetes, abdominal obesity, stress, lack of daily consumption of fruits and vegetables, lack of daily exercise and of regular consumption of small amounts of alcohol)

which collectively predict more than 90 per cent of the risk of myocardial infarction worldwide belonged to the metabolic syndrome risk factors cluster. Recently, Sundstrom *et al* [13] showed that the metabolic syndrome (as defined in the NCEP-III) accounted for 40% and 60% of the variation observed in total and cardiovascular mortality respectively. This effect was independent of other traditional risk factors such as smoking, diabetes, hypertension and cholesterol[13]. A recent paper by Mancia *et al* [22] showed that the best predictors of early death were hypertension and hyperglycemia and this association was no stronger if the components of metabolic syndrome were concomitantly present.

Moreover, metabolic syndrome adversely affects not only the CV system but also the kidneys. The prevalence rate of chronic kidney disease (CKD) is as low as 0.9% in patients without risk factors but it rises to 9% in those with five risk factors (Fig. 1). In fact recent studies have emphasised that metabolic syndrome was strongly correlated with CKD (defined as GFR less than 60 ml/min) and microalbuminuria and that the risk increased in tandem with the presence of more of the syndrome's criteria[23]. In another study, of Native Americans without diabetes, a positive relationship was identified between microalbuminuria and features of metabolic syndrome[24].

From a public health perspective, CKD is perhaps the most worrying aspect of metabolic syndrome. The main reason for concern in these patients is not just the risk of end-stage renal disease (ESRD) but the high probability of CV complications and death.

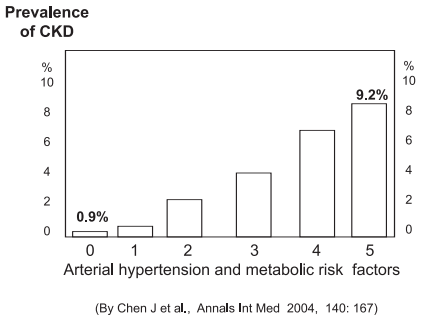

Figure 1

Association between the presence of hypertension and metabolic risk factors and the prevalence of CKD.

In a recent study by the Kaiser Permanent Center of the Oregon Clinical Database of 29000 CKD patients, only 1% of patients with mild renal failure and an equal proportion of patients with moderate renal failure developed ESRD over a 5-yr follow-up[25]. In 19% of patients with mild and 25% of those with moderate CKD, death was largely due to CV causes and it was a far more common outcome than ESRD in this population. Metabolic syndrome and classical (Framingham) risk factors apart, a variety of factors, i.e. risk factors peculiar to CKD and a series of new risk factors collectively defined as emerging risk factors, increasingly contribute to both renal disease progression and CV complications as renal function declines. These factors are reviewed in detail elsewhere[24-27]. The NHANES III, a survey based on a random sample of the US population, has produced reliable estimates of CKD epidemics[28]. The figures are extremely worrying because as many as 55 million individuals presented a mild degree of renal impairment (glomerular filtration rate (GFR) ‹90 ml/min and ›60 ml/min) and 7.5 million presented moderate renal insufficiency (GFR ‹60 ml/min ›30 ml/min). CKD at community levels has been little investigated in Europe. Some observations have been made in the Netherlands, where De Jong *et al* [29] found a prevalence rate of mild and moderate CKD even higher than that of the NHANES III survey; a phenomenon that in part might depend on the fact that the population involved is elderly. Thus, although the available data are scanty, the renal disease epidemics situation in Europe seems essentially similar to the USA picture.

We can therefore conclude that the metabolic syndrome is a perverse combination: a CV events trigger and a factor strongly associated with CKD which is in itself an event trigger. To gain an insight into this double link of metabolic syndrome with events and CKD we can start from the kidney side and nephrosclerosis, the most frequent anatomical alteration in patients with CKD. Nephrosclerosis is a disease affecting the medium and small renal arteries and its characteristic lesion is an intimal hyperplasia. This lesion is widespread from renal arterioles to aorta in renal patients as an expression of endothelial dysfunction.

Thus the whole story of metabolic syndrome and the link between heart and kidney may start in the

endothelial cell, where the L-Arginine is the fundamental aminoacid. This aminoacid is the substrate of the enzyme NOs which transforms L-arginine into a vasodilating, anti-atherogenic substance such as nitric oxide. This is a fundamental reaction which under physiological conditions can be modulated, amplified or reduced by some substances. One of the most important of these substances is the parasympathetic neuromediator acetyl choline (ACh) which enhances the activity of the enzyme NO syntethase and increases the production of NO. Conversely, this reaction can be affected by endogenous inhibitors of eNOS such as asymmetric dimethyl arginine (ADMA). ADMA competes for the active sites of the enzyme with L-Arginine, reduces the synthesis rate of NO and thereby triggers a pro-atherogenic situation characterised by vasoconstriction, platelet and leucocyte adhesion to the endothelium, smooth muscle cells proliferation. The regional endothelial function within the kidney can be studied by testing the effect on renal blood flow of substances that stimulate or inhibit eNOS or by administering high doses of L-Arginine. These studies have a poor reproducibility and are time consuming and extremely laborious to perform, however.

To overcome this problem and to obtain information on the renal endothelial function, the most common area for testing endothelial function is the forearm. The information from this test performed in the forearm is transferable to other districts, including the kidney. During these studies eNOs is stimulated by administration of acetylcholine and the resulting changes in forearm blood flow are recorded by strain gauge plethysmography.

In brief, endothelial function is studied as the response of forearm blood flow (FBF) to progressively increasing doses of acetylcholine (Fig. 2). The response differs depending on clinical situations. Indeed, normotensive subjects have a dose response relationship meaning the higher the dose, the higher the response. Conversely, this response is markedly blunted in essential hypertensives and this finding indicates the presence of endothelial dysfunction.

Other than in hypertensive subjects, the response to acetylcholine is lessened in those with other traditional risk factors such as hypercholesterolemia, age, smoking, overweight and obesity; two situations in which there is insulin resistance.

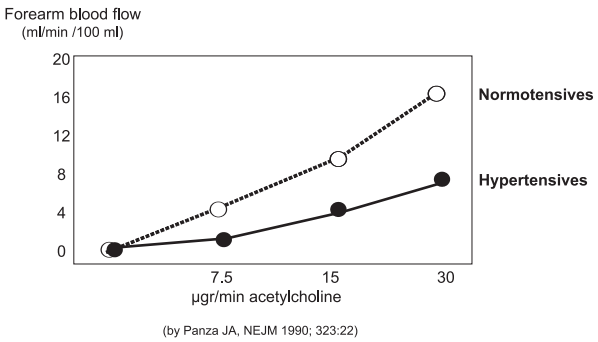

Figure 2

Vasodilatory response to acetylcholine in normotensive and hypertensive individuals.

As stated earlier, the results of tests on endothelial function in the forearm may be transferable to other districts such as the heart and the kidney.

The response of coronary blood flow to acetylcholine appears quite parallel to that in the forearm. This finding was reported about 10 years ago by Anderson[30] who demonstrated that the increase in the coronary artery diameter in response to acetylcholine was strongly related to that in the brachial artery diameter. But what of the endothelial function in the kidney?

Endothelial function in the kidney is very difficult to assess. Given the difficulties in measuring the endothelial function in the kidney, Perticone *et al* [31] thought of testing the relationship between the FBF response to ACh and a marker of renal function, such as serum creatinine. He then tested this relationship in 500 never-before treated patients with uncomplicated essential hypertension. In this study, a strong inverse relationship between the maximal forearm blood flow response to Ach and serum creatinine was found: the higher the serum creatinine, the lower the FBF. This relationship occurred in the so-called normal range of renal function, with serum creatinine between 0.6 and 1.5 mg/dl. Conversely, FBF was directly related to renal function as estimated by the MDRD formula.

These results indicate that endothelial function is strongly linked to renal function and when serum creatinine is high, that is, when renal insufficiency is present, the endothelial function is compromised. Another important question to be addressed is whe-

ther endothelial function tested in the forearm is helpful in predicting CV events or not. Indeed, the answer is that it is. In fact, in hypertensive patients the response to acetylcholine predicts CV events: patients with a compromised endothelial function have more CV events and death than those with a good endothelial function[32]. This relationship between endothelial function and CV events suggests that heart and kidney have a common pathogenetic pathway. One hypothesis explaining this link between heart and kidney is that ADMA accumulates in renal failure, reducing the production of nitric oxide which has antiatherogenic properties. Moreover, ADMA is a substance which might be of some relevance in metabolic syndrome. Indeed, Stuhlinger *et al* [33] showed that ADMA is related to insulin resistance and it could go towards explaining the association between metabolic syndrome and renal insufficiency. In patients with CKD, ADMA is largely dependent on renal function: the lower the GFR, the higher the ADMA. This relationship is important because accumulation of ADMA in patients with CKD may have implications both for renal disease progression and for the risk of death.

In a survival plot analysing the risk of progression to ESRD and the risk of death, the stratification of patients on the basis of median plasma ADMA concentration showed that both risks were relatively smaller in CKD patients with ADMA below the median value while they were much higher in those with ADMA greater than the median value and the hazard ratio for such events was 2.2. Thus in patients with CKD, ADMA is a risk factor both for renal disease progression and death[34].

So far we have discussed the link between the metabolic syndrome and chronic kidney disease, but not dialysis. At this stage the final item to take into consideration is the relationship between metabolic syndrome and patients on dialysis. This is a peculiar population of patients which deserves special attention. It is well known that overweight and obesity, two of the principal components of metabolic syndrome, are directly associated with CV events and mortality in the general population and they precede diabetes, hypertension and dyslipidemia in a high proportion of subjects. In recent years the relationship between obesity and onset and progression of renal diseases has become an important field of clinical research. There is no doubt that obesity triggers renal diseases and this is particularly true in the relatives of renal patients. On the other hand, obesity has been found to be inversely related to CV events and death in dialysis patients: the higher the body weight, the lower the mortality and morbidity[35]. Therefore in ESRD patients on dialysis, obesity as well as hypertension and other components of the metabolic syndrome have a different impact on clinical outcomes in comparison to the general population. These findings belong to the well known effect of "reverse epidemiology". Inverse or reverse epidemiology is a frequent problem in studies of patients with renal failure in which some variables such as blood pressure, cholesterol level, body weight and homocysteine level that are consistently associated in a direct fashion with adverse clinical outcome in the general population show an apparently paradoxical inverse link with the same outcome in patients with end-stage renal disease (ESRD). In recent years the concept of Mendelian randomisation has been increasingly used to infer causality in epidemiological studies of the general population and in patients with various clinical diseases[36]. Gene-disease associations may offer important clues to the study of intriguing questions raised by many apparently paradoxical associations described in patients with ESRD. The existence of an obesity paradox suggests that implications of the metabolic syndrome in patients on dialysis are of no value at all. Conversely, returning to the negative effect of obesity in the initial steps of renal insufficiency, it is clear that making greater efforts to manage patients at risk of developing these diseases is becoming more and more vital. It is important to note that obesity, as the main cause of diabetes and hypertension, could be the clue to the renal disease epidemics rather than diabetes and hypertension *per se*. It seems clear that obesity mainly among adolescents and young adults is the first risk factor to be targeted because failure to solve the growing problem of obesity worldwide will certainly result in an even higher proportion of patients with renal disease.

The crucial question is what nephrologists can do to try to halt metabolic syndrome epidemics and their sequelae. Strict guideline applications and patient education could be of some help, especially in the first stages of renal dysfunction, although contact with patients at early stages of disease is somewhat of a major problem in CKD patients in that the late referral situation remains extremely worrying.

Effective involvement of all health care professionals and patients' organisations should be sought with patience and perseverance, trying to maximise efforts to control obesity and obesity-related diseases with the same eagerness and commitment that have been invested in anti-smoking campaigns.

Conflict of interest statement. None declared.

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