Impact of renal dysfunction as a cardiovascular risk factor

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Abstract

This review summarizes the available evidence concerning the relationship between renal dysfunction and cardiovascular risk in non-diabetic patients. Based on numerous studies, there remains no more doubt today, that even minor renal dysfunction, as reflected by microalbuminuria and/or decreased estimated glomerular filtration rate, causes a dramatic increase in cardiovascular risk. Renal dysfunction as a novel risk indicator should be incorporated into currently used algorithms to assess risk factor profile, not to the least because evaluation of renal function helps to select the most appropriate strategy to reduce the cardiovascular risk.

Key words: cardiovascular risk, microalbuminuria, reduced glomerular filtration rate.

Introduction

It has recently been recognized that both microalbuminuria and a reduced glomerular filtration rate impact heavily on the cardiovascular risk in non-diabetic patients. This had been well known for a long time in diabetic patients but the information in non-diabetic patients is novel [1].

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Epidemiological information

Following several early observations the best currently available information comes from the so-called PREVEND-Study covering 40,856 inhabitants of the Dutch city of Groningen [2]. A normal urinary albumin concentration in one spot urine sample was seen in 73%, a high normal concentration between 10-20 mg/l in 19% and frank microalbuminuria in 8%. Those patients had mostly no comorbidity but in approximately 25% of the patients hypertension, diabetes or a combination of both was noted. It is of interest to look at the correlates, which were associated with increased albumin excretion. In men a highly significant relation between fasting plasma glucose concentration and urinary albumin excretion rate was found; this was less pronounced in women. It is of particular note that this was true not only for plasma glucose concentrations in the hyperglycaemic range but was seen even in the high normal range of plasma glucose concentration. This finding is not without interest because impaired plasma glucose concentration is a feature of the metabolic syndrome, which is associated with a particularly high cardiovascular risk. Another facet of the metabolic syndrome, i.e. an increased body-mass-index (BMI), was also correlated to the urinary albumin excretion rate – again more pronounced in men compared to women. This was not only true for morbid obesity. The relation extended even into the range of low normal BMI values. This finding is of interest in view of the observation of Mykkanen [3]: in a large study covering 982 non-diabetic individuals he had noted that insulin sensitivity, when measured with the intravenous glucose tolerance test, was significantly reduced in patients who exhibited microalbuminuria. In those patients elevated concentrations of immune reactive insulin were also noted.

Fliser et al. [4] examined patients with primary renal disease using the intravenous glucose tolerance test. Even when the inulin clearance was only not below 80 ml/min. patients on average had significantly impaired insulin sensitivity. Conversely Chen et al. [5] found in the general population that insulin resistance (measured as the HOMA-index) increased the risk

of a future development of renal dysfunction. Finally in renal patients, similarly as in non-renal patients, insulin resistance is an independent predictor of total mortality and cardiovascular mortality [6]. So the two phenomena of insulin resistance and renal dysfunction are tightly related and may be linked by common pathomechanisms.

Microalbuminuria and reduced glomerular filtration rate (GFR) are two different aspects of renal dysfunction. The question arises whether the two are somehow interrelated. Unfortunately, there are no studies available where renal function had been measured with exact clearance techniques. Nevertheless, Pinto Sietsma [7] noted in the PREVEND-Study in Groningen that in individuals with a moderate increase in urinary albumin excretion the average creatinine clearance, was significantly higher. Only in the highest quantiles of albuminuria was a reduction of creatinine clearance found. This is reminiscent of the finding of Mogensen [8] in patients with type 2 diabetes in whom he found increased GFR in the early stage of microalbuminuria. It was only when proteinuria progressed markedly that the GFR decreased.

A further question is whether such minor albuminuria is relevant for all-cause mortality and cardiovascular mortality respectively? Again the Groningen study [9] noted a slight but significant increase of mortality which started in the range of high normal urinary albumin concentrations and rose progressively in the microalbuminuric range (20-200 mg/l). The HOPE study had also shown that the risk rises progressively with increasing albuminuria, similar to the relation between cardiovascular events and plasma cholesterol concentration [10]. This was true even in the range of normal urinary albumin concentrations. It follows that the definition of "microalbuminuria" is somewhat arbitrary and that urinary albumin excretion rate should be treated as a continuous value.

This continuous relationship corresponds to what Rachmani [11] had noted in patients with diabetes. Compared to the range of low normal albuminuria, albuminuria in the range 10-20 mg/day increased the risk to progress to frank microalbuminuria by a factor of 2.34 and the risk to experience a cardiovascular endpoint by factor of 1.9. In the range of frank microalbuminuria the risk was significantly higher by a factor of 12.4 and 9.8 respectively.

The high cardiovascular risk associated with reduced renal function

In parallel with the interest in microalbuminuria, the issue of the relation between moderately impaired renal function and cardiovascular risk has recently also attracted considerable interest.

The first observation in this direction was made in the Hypertension Detection and Follow up Programme. Shulman [12] reported on a 96-months follow up study in which he found a highly significant correlation between serum creatinine concentration and cumulative mortality. An increase was seen even between serum creatinine concentrations of 1.20 and 1.49 mg/dl. This finding has considerably epidemiological importance. *Tab. 1* summarizes the epidemiological analysis of Levey [13] based upon the data of NHANES (National Health and Nutrition Survey) in the USA. The number of patients with chronic kidney disease (CKD) stage 5 is very low, i.e. 300 000. In contrast in USA 5.3 million inhabitants have CKD stage 2 and 7.6 million inhabitants CKD stage 3.

Table 1. **Frequency of impaired renal function in the general population of the USA (NHANES data)**

Chronic kidney disease (CKD)	Estimated glomerular filtration (eGFR)	Percent population
stage	ml/min	%
5	<15	0.1
4	15-29	0.2
3	30-59	4.3
2	60-89	3.0
1	>90	3.3

A relation between impaired renal function and increased cardiovascular risk was found in several distinct cohorts, i.e. in the general population, in hypertensive patients, in patients at high cardiovascular risk and patients with impaired cardiac function. Furthermore, a similar relation has also been noted in patients with an acute ischemic cardiac event.

In the Dutch city of Hoorn Henry observed elderly patients for up to 10 years [14]. He noted that the risk to die from cardiovascular causes increased by 26% per 5 ml decrease in GFR. In other words, if the filtrate decreases by 20 ml/min the risk doubles.

In hypertensive individuals Luis Ruilope noted in the HOT (Hypertension Optimal Treatment) study that – independent of the diastolic target blood pressure to which the patient was randomised – the frequency of cardiovascular event was significantly higher by a factor of 2, if the estimated creatinine clearance was less than 60 ml/min compared to hypertensive patients with a higher GFR [15]. Similarly in the HOPE study Mann [16] noted that with increasing concentrations of serum creatinine the rate of cardiac events was significantly higher if patients had a serum creatinine concentration higher than 1.4 mg/dl. The risk was then increased by 40% compared to an increase of 60% when patients had microalbuminuria. The risk was increased by 108% when the patients had elevated serum creatinine plus microalbuminuria.

A particularly impressive increase in the risk of death in individuals with impaired renal function is seen in patients suffering from congestive heart failure. In a randomised prospective study Hillege [17] examined the relation between estimated GFR, severity of congestive heart failure (New York Heart Association category) and use of ACE inhibitors. In the highest compared to the lowest quartile the relative risk was increased by a factor of 2.85. An inverse relation was noted between GFR and atrial natriuretic peptid (ANP) plasma concentration. This finding may point to an important role of hypervolemia. The adverse effect of an elevated serum creatinine concentration was not completely explained by the severity of heart failure suggesting that there was an independent pathogenetic relation between renal dysfunction and cardiovascular risk.

Figure 1. **Cockroft-Gault formula for creatinine clearance (C_{crea}) estimation**

$$C_{crea} = \frac{(140 - age) \times body\ weight\ [kg]}{S\text{-}creatinine\ [mg/dl] \times 72} \quad (x0.85)_{woman}$$

C_{crea}[ml/min.]

It is also known that patients with impaired renal function, who have an ischemic cardiac event, have higher in-hospital mortality as well as postdischarge mortality than patients with normal renal function. In a national sample of elderly Medicare-patients who had an acute ischemic event Shlipak [18] found a clear relation between survival after discharge from the hospital and serum creatinine concentration. In a monocentric study assessing 3000 patients with an acute cardiac ischemic event, Wright noted that hospital mortality as well as postdischarge mortality was dramatically increased when the estimated GFR was decreased. Disappointingly the patients with impaired renal function, despite their extreme cardiovascular risk, had also received less aspirin, less betablockers, and less invasive procedures such as thrombolysis or percutaneous transluminal coronary angioplasty (PTCA). But this iatrogenic factor does not fully explain the extremely high cardiac risk. Even when individuals with a creatinine clearance of 100 ml/min were compared to patients with a creatinine clearance of 90 ml/min, the risk was almost double in the latter. Reinicke [19] examined the cumulative mortality of patients who had been discharged after PTCA. Even when comparing a serum creatinine of 1 mg/dl with a concentration of 1.2 mg/dl the mortality increased from 5 to 8.5%.

What practical conclusions can we draw from these observations?

It is unfortunate, that the cardiovascular risk increases in a concentration range of serum creatinine where this analyte is very insensitive to changes in the glomerular filtration rate. It is therefore recommended that the chemical laboratory reports not only the serum creatinine concentration, but estimates the GFR based on information concerning age, body weight and gender. Several formulas such as the Cockroft-Gault formula (see *Fig. 1*) or the MDRD formula are currently available. The risk in a patient with moderate impaired renal function is comparable in magnitude to that of a patient with diabetes mellitus. The National Institute of Health (NIH) emphasized that, in analogy to what is done in diabetes mellitus, cardiovascular prophylaxis in the patients with renal dysfunction should be considered secondary and no longer primary prophylaxis.

Underlying pathomechanisms

Although the exact pathomechanisms linking renal dysfunction to cardiac mortality have not been completely clarified some very interesting recent observations suggest that a whole array of factors is involved.

Kielstein [20] examined a cohort of patients with primary renal disease and found elevated concentrations of asymmetric dimethyl-L-arginin (ADMA), an inhibitor of endothelial nitric oxide synthase (eNOS). It is remarkable that this was true even in patients in whom normal clearance values had been measured. It is of course clear that normal whole kidney clearance is perfectly compatible with a major reduction in renal parenchymal mass, because the remaining glomeruli compensate to a large extent by increasing single nephron GFR. Why should increased ADMA be linked to cardiovascular risk. ADMA interferes with the production of the endogenous vasodilator and endothelial protective factor nitric oxide (NO) and inhibits several diverse endothelial cell functions.

ADMA is excreted via the kidney but this is not the only explanation. There are very good arguments that a catabolic enzyme in endothelial cells, dimethylarginine dimethylaminohydrolase, is diminished as well.

As another potential pathogenetic factor Kronenberg [21] found marked abnormalities of apolipoproteins, particularly an increase in apolipoprotein-A-IV (which of course is cardioprotective but the finding illustrates that the regulation of apo-lipoprotein metabolism is abnormal). Kronenberg also found very early in renal disease an increase of the concentration of the cardiovascular risk factor Lp(a) [22].

In hypertensive patients with autosomal dominal polycystic kidney disease Klein [23] measured increased sympathetic nerve activity even when the glomerular filtration rate was still normal.

Furthermore, Shlipak [24] found that patients having only a minor increase of serum creatinine had elevated serum concentrations of biomarkers indicating a state of microinflammation, e.g. increased CRP, fibrinogen, interleukin 6 as well as evidence of a prothrombotic state (elevated factor VIII, D-dimers).

Finally, even when inulin clearance was still normal, Stefański [25] found that the night-time decrease of blood pressure was attenuated and left ventricular wall thickness was increased as evidence of concentric remodelling.

All the above factors could interact to increase the cardiovascular risk.

Finally, since the early days of dialysis it had been postulated that atherogenesis is accelerated in uremia [26]. Recently there have been several studies in a genetic model of spontaneous atherogenesis the apo-e -/- mouse. In these animals resection of renal parenchyma increases the rate of growth of atherosclerotic plaques. Of note, this was even seen when only one kidney was removed [27].

Conclusion

It is obvious from the above that minor renal dysfunction, as reflected by microalbuminuria or decreased estimated GFR, has a major impact on cardiovascular risk. Renal dysfunction is thus a novel risk factor, which must be incorporated into currently used algorithms to assess risk factor profile. Evaluation

of renal function is important in order to select the appropriate strategy to reduce the cardiovascular risk (www.eshonline.org/documents/2003_guidelines and www.escardio.org/scinfo/guidelines.htm).

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