Cardiovascular risk factors, smoking and kidney function

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Introduction

It is well known that the kidney, like the other organs, is not spared from the biological effects of ageing. The kidneys of elderly people show anatomical and structural alterations, including focal and segmental glomerular sclerosis, a reduction in the number of functioning glomeruli and small vessel atherosclerotic disease [1,2]. These morphological changes are associated with a progressive decrease in renal function, particularly in renal haemodynamic parameters: glomerular filtration rate (GFR) begins a slow decline in people aged >40 at rates up to 1 ml/min/year; a greater reduction in renal plasma flow also occurs with advancing age; and the rate of decline appears to accelerate in the oldest age group, to be more rapid in males than in females, and not to be secondary to superimposed renal disease [3–5].

Cardiovascular risk factors and renal function

The axiom of physiological loss of renal function with senescence seems to be partially true. In fact, the effect of age is variable, and not all subjects are destined to suffer a decline in their renal function with advancing age. The first doubts emerged from the first and most important study in this field, the Baltimore Longitudinal Study of Aging. In this study, an average decrease in GFR was found in the total population followed for a long period, but a small group of patients showed an increase in creatinine clearance with age; further, approximately one-third of the normal subjects had no decrease in renal function over time and the loss of renal function with advancing age was more marked in people with co-existing or intervening nephropathies and hypertension [6,7].

Thus, these and other observations suggest that the age-dependent decline in renal function is not a constant and uniform phenomenon. The reasons for this variability are not yet clear. Researchers wonder how much of the loss in kidney function with senescence is due to age and how much to other factors, identified as renal risk factors, some of which are already known to be related to the cardiovascular system, such as hypertension, diabetes mellitus, hyperlipidaemia and smoking, and to the kidney, such as protein intake and previous renal diseases.

Recently, Flisher et al. [9] performed a comprehensive study to compare several aspects of renal function in a young healthy normotensive group and in three groups of elderly subjects, normotensives, treated and untreated hypertensives, and elderly patients with compensated mild to moderate heart failure. Compared with young subjects and normotensive elderly patients, the elderly patients with hypertension and heart failure showed lower values of GFR and renal plasma flow, and increased renovascular resistance. In the authors’ opinion, the results suggest that co-morbid conditions confound renal function in the elderly.

In 1992, the Italian Longitudinal Study on Aging started; a random sample of 5632 individuals, aged 65–84 years, stratified by age and gender using the equal allocation strategy, was identified on the demographic lists of the registry of eight centres. The main objective of the project was to evaluate and identify the incidence and eventual risk factors linked to chronic cardiovascular, neurological, endocrine and metabolic diseases. We have used the data of the study to evaluate renal function related to age and the most common cardiovascular risk factors, with the aim of identifying the underlying variables that impair renal function in the elderly. The subjects with previous or actual renal diseases and with serum creatinine values >136 μmol/l were excluded. In this way, the analysis was limited to 2506 individuals, of which 1478 were males, equally stratified by age ranges. Multiple logistic regression analysis was performed considering as dependent variable the creatinine clearance estimated by the Cockroft–Gould formula [10], with a cut-off value of 52 ml/min/1.73 m², corresponding to the value of the first quartile of the population examined. Clinical, demographic and biochemical independent variables
were analysed by a stepwise procedure. Age, smoking and pathological high density lipoprotein (HDL) cholesterol plasma values were the only statistically significant and independent variables predicting the pathological level of creatinine clearance.

Apart from the limits of the study linked to the approach method, for the present only cross-sectional, and to the estimation of creatinine clearance by the Cockroft formula, the preliminary results of the Italian Study on Aging again confirm that age-dependent loss of renal function might be strongly influenced by the co-presence of conditions and/or risk factors, even if, for the present, researchers and clinicians have not reached univocal conclusions on their individualization and on the estimation of their relative role and importance.

**Smoking and renal function**

In our opinion, the most interesting and surprising result which is emerging from the Italian Study on Aging is the identification of smoking as an important risk factor for the kidney. In truth, this result was not a great surprise for us, but seems to confirm the hypothesis advanced by our group in the light of the results obtained by a previous pilot study, carried out to evaluate the effect of cigarette smoking on renal function [11]. Thirty subjects over 55, who had no known vascular disease risk factor other than cigarette smoking, and 24 age- and sex-matched controls without any vascular risk factor including cigarette smoking were selected from patients who were referred to the angiology service of Padua University Hospital for symptoms of possible atherosclerotic origin. Renal function was evaluated by radionuclide studies of renal plasma flow and GFR; plasma endothelin-1 (ET-1) concentration was also determined. Compared with non-smokers, smokers showed a renal function impairment, characterized by a normal GFR and a significant reduction in renal plasma flow. The renal dysfunction was associated with an increase in plasma ET-1 levels. No significant difference in these parameters was observed between former and current smokers, suggesting that cigarette smoking has a significant, irreversible effect on renal function. The step down multiple regression analysis, performed to determine whether renal haemodynamic values were related to other clinical, demographic and biochemical variables besides smoking, showed that age, current smoking, previous smoking and plasma ET-1 levels were the only statistically significant and independent variables influencing the renal plasma flow values observed in all subjects.

As far as we know, this is the first report demonstrating a detrimental effect of chronic smoking on renal function in subjects without co-existing renal disease or known risk factors other than cigarette smoking. The renal risks of smoking recently have been the subject of a perspective study in a clinical nephrology publication [12]. Until now, clinicians and researchers focused their interest essentially on evaluating the role of active and passive smoking as a risk factor for the cardiovascular system, where its importance is comparable with the other well-known risk factors, hypertension and hypercholesterolaemia; in fact, smoking is strongly associated with coronary, cerebral and peripheral vascular disease [13]. At the renal level, few studies have addressed the acute effect of smoking on renal function [14]; adverse renal effects of smoking have been reported in dialysed insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients, where the smoking habits increased the relative risk of myocardial infarction [15,16]. Several studies report consistent evidence that in IDDM patients the risk of developing microalbuminuria or proteinuria is higher in smokers [17].

The haemodynamic renal profile of smokers is similar to that observed in hypertensive arteriolar nephrosclerosis. It is known that the renal blood flow is redistributed in patients with long-standing hypertension, and the earliest impairment in overall renal function in hypertension is a decrease in the tubular maximum for hippurate, which is commonly observed in association with a reduction in renal plasma flow and usually normal GFR; this results in an increased filtration fraction. The functional changes are largely accounted for by a reduction in cortical blood flow and an increased efferent arteriolar resistance that maintains the GFR despite a reduction in renal plasma flow [18]. Some circulating and local vasoactive factors involved in determining renal haemodynamic dysfunction in hypertensive patients have been reported to be altered in smoking subjects as well, and might explain the effect of smoking on renal blood flow we observed. Cigarette smoking is associated with a release of the sympathetic neurotransmitter norepinephrine, as well as the adrenomedullary hormone epinephrine [19]. Furthermore, several clinical and experimental studies suggest that smoking interferes with prostacyclin and thromboxane A2 metabolism in the endothelium [20,21], and with the vascular response to acetylcholine [22], nitric oxide and ET-1 [23,24]. The plasma concentration of the latter was found to be increased in smokers, in particular in current smokers, confirming a previous report [25]. It is known that ET-1 is an important mediator of pathophysiological alterations in renal haemodynamics, because of its influence on vascular and mesangial cell tone, mitogenesis of mesangial cells, and sodium and water excretion. In particular, ET-1 is a very potent vasopressor agent, five times more potent than angiotensin, and the renal vasculature is up to 10 times more sensitive to the vasoconstrictor effects of ET-1 compared with other vascular beds [26]. The renal microvascular effects of ET-1 are mediated by both afferent and efferent arterioles. In rats, ET-1 infusion constrains the efferent arteriole more than the afferent arteriole, with an attendant increase in glomerular capillary pressure and a decrease in ultrafiltration coefficient [26,27]. In dogs, ET-1 at physiopathological plasma concentrations produced by exogenous endothelin reduces renal blood
flow and increases renal vascular resistance, without producing any significant modification of glomerular filtration [28]. Furthermore, ET-1 has potent mitogenic and atherogenetic activities on vascular smooth muscle and mesangial cells [26]. Thus, ET-1 might explain the picture of renal changes observed in active and former smokers, i.e. either functional or morphological alterations (renal arteriolar thickening) reported by previous autopsy studies [29,30].

Among the potential mechanisms of smoking-induced renal damage, one should take into account the effects of smoke on lipoprotein metabolism; epidemiological studies have revealed that cigarette smoking is associated with a change in plasma lipoprotein and fatty acid and that the atherosclerotic risk related to smoking is due partially to its influence on lipoproteins. Smoking, through sympathetic system nicotine stimulation, induces an increased plasma concentration of low density lipoproteins (LDLs) and triglycerides, and a decrease in HDLs [31]. Moreover, smoking causes oxidative modifications of biological components in humans, including LDL. Oxidative modification of LDL is thought to be a key process in the development of atherosclerosis; it has been shown that oxidatively modified LDL is recognized by scavenger receptors and taken up by macrophages, a process considered pivotal in the development of foam cells in atherosclerotic lesions [32].

On the other hand, we cannot forget the potential effect of smoke on the glycosaminoglycans (GAGs), the main constituents of the arterial wall, where they are synthesized by endothelial and smooth muscle cells [33]. These substances are involved in a series of biological processes and seem to play an important role in the pathogenesis of atherosclerosis by their ability to interact with lipoproteins [34]; these complexes cause the accumulation of LDL in the arterial wall and the subsequent development of atherosclerosis. Moreover, GAGs may influence the adhesion, migration and proliferation of the endothelial and smooth muscle cells, which are all events known to be crucial in the pathogenesis of atherosclerosis [35]. As confirmation of this, it is noteworthy that heparin and related compounds protect the endothelium from free radical damage, blocking the development and progression of atheroma [36]. Ageing itself causes quantitative and qualitative alterations of GAGs whether at the renal level or at the vascular wall [36–40]. Consistent evidence demonstrates that smoke, by hypoxic stress induction, might have an effect on GAG metabolism [41,42], aggravating the structural and biochemical GAG modifications related to physiological processes of senescence, in particular altering the anion charge density, which is crucial for carrying out their functions, specifically the interaction with lipoproteins. Furthermore, it is interesting to note that GAGs have important modulatory effects on some enzyme activities; the GAGs inhibit phospholipase A_2, protein kinase C and tyrosine kinase, thus interfering greatly with the main cellular functions, acting at the genomic level and modulating the second messenger intracellular cascade [43,44].

Thus, taken together, these observations stress the key role of GAGs and their alterations associated with age and other co-factors in the complex pathogenetic mechanism of atherosclerosis, where endothelial factors, coagulative factors, growth factors and components of the arterial wall interact in a way which is not yet well defined [45]. On the other hand, it is noteworthy that investigations in animals and humans suggest a similar pathobiological mechanism in atherosclerosis and glomerulosclerosis [46]. Moreover, many of the factors involved in the pathogenesis of atherosclerosis actually play a role in the progression of glomerular damage and age-dependent glomerulosclerosis [47].

Conclusions

In conclusion, our results show that loss of renal function with age is not unavoidable, confirming previous cross-sectional and longitudinal studies. An age-associated decline in renal function is more marked in patients with co-existent cardiovascular risk factors. Among these, smoking seems to have an important role in the detrimental effect on renal function also in subjects without co-presence of other cardiovascular risk factors or renal diseases. The observation of the negative effect of smoking on renal function should be taken into account in clinical practice.

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References


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