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Review article

Stroke and renal dysfunction

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ABSTRACT

Stroke is the most frequent neurological disease and represents a continuously evolving medical and social problem. Chronic kidney disease (CKD) is also an important worldwide public health problem. Renal dysfunction carries a substantial risk of cardiovascular morbidity and mortality and an independent, graded association between renal function and cardiovascular events was found. In the last 15 years the link between CKD and cerebrovascular disease has become more apparent. Patients with end stage renal disease treated with maintenance hemodialysis have a much higher incidence of stroke than the general population and stroke is one of the major causes of death in these patients. Nowadays ischemic subtype of stroke is present in approximately 70% of dialysis patients. In population based studies conflicting results have been reported about the association between stroke and CKD before replacement therapy. However, in high risk patients, defined by the presence of either cardiovascular disease or cardiovascular risk factors, different stages of CKD are clearly associated with subsequent stroke.

In patients with stroke the exact prevalence of renal dysfunction is not known. Reported prevalence from a few published studies is up to 38% and it is higher than that in age-matched control groups. Furthermore, in patients suffering from stroke renal dysfunction is associated with short and long term mortality.

The most effective treatment of stroke in patients with CKD is not known and further studies are needed.

1. Introduction

Coronary heart disease (CHD) and stroke are the main forms of the cardiovascular disease (CVD) which is the leading cause of death worldwide [1]. Chronic kidney disease (CKD) is also an important public health problem and the prevalence is estimated to be 8 to 16% worldwide [2]. CKD is defined as kidney damage (generally ascertained from albuminuria, but also including abnormalities in urine sediment, pathology or imaging studies, acid–base and electrolyte disorders due to tubular disorders, or history of kidney transplantation) or estimated glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause and classified into stages according to the level of GFR [3,4]. The stages of CKD are presented in Table 1 [3].

Renal dysfunction carries a substantial risk for cardiovascular morbidity and mortality and this was first shown in patients with end stage renal disease. Nowadays it is known that the prevalence of coronary artery disease in patients with end stage renal disease is approximately 40% and mortality due to CVD in these patients is up to 20 times higher than in the general population [5]. The high prevalence of CVD found in patients starting dialysis treatment suggests that CVD begins in the early stages of CKD [6]. The risk for CVD increases with a decline in kidney function [7,8]. An independent, graded association was observed between renal dysfunction estimated with GFR and the risk of death, cardiovascular events, and hospitalization in a large, community-based population [8]. Studies have also demonstrated that albuminuria is associated with the increased CVD risk [4,9]. The hazard ratio for incident CVD was elevated for both markers of renal dysfunction (GFR and albuminuria), independently of each other [9]. Furthermore, the patients with CKD are more likely to die of CVD than to start with replacement therapy because of end stage renal disease. In the study by Keith et al. [10] the rate of renal replacement therapy over the 5-year observation period was 1.1%, 1.3%, and 19.9%, respectively, for the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) stages 2, 3, and 4, but that the mortality rate was 19.5%, 24.3%, and 45.7%.

The main reason for the high prevalence of CVD in patients with renal dysfunction is accelerated atherosclerosis. Studies, using B-mode ultrasonography of carotid arteries (intima media thickness and plaques), showed advanced asymptomatic atherosclerosis in end stage renal disease patients [11,12]. Atherosclerosis was not associated with the duration of dialysis treatment, suggesting that atherosclerosis may be accelerated by renal dysfunction in earlier stages of CKD rather than by dialysis treatment (hemo- and/or peritoneal dialysis) [11,12]. Later in patients with CKD advanced asymptomatic atherosclerosis in the carotid arteries compared with healthy control subjects was

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Table 1
Stages of chronic kidney disease [3].

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR — glomerular filtration rate.

confirmed [13,14]. Intima media thickness increased directly with the level of renal dysfunction [13,14]. Independently from atherosclerotic process characterized by intima calcifications within atherosclerotic plaque media calcifications occur frequently in patients with CKD. Media calcification is concentric, not extending into arterial lumen and is associated with abnormal cushioning function of blood vessels (arteriosclerosis) by promoting arterial stiffness [15,16]. The consequences are an abnormal arterial pressure wave resulting in high pulse pressure and increased aortic characteristic impedance [16]. Intima calcifications might be mainly associated with ischemic stroke events while media calcification with high pulse pressure might be associated with hemorrhagic stroke events.

Despite atherosclerosis being a systemic disease, attention has centered mainly on cardiac aspects and/or manifestations. Less is known about the association of renal dysfunction and stroke. In 1998, the National Kidney Foundation convened a Task Force on Cardiovascular Disease in Chronic Renal Disease, members reviewed evidence linking CKD and CVD. They were unable to draw any conclusions about cerebrovascular disease because the literature was scant [17,18].

2. Stroke and chronic kidney disease

Cardiovascular morbidity and mortality are associated with proteinuria/albuminuria (kidney damage) and decreased GFR. The association between stroke and dialysis is presented separately (dialysis patients are CKD stage 5 patients) because dialysis procedure itself is associated with higher cardiovascular morbidity and mortality (chronic inflammation, hypotension during dialysis, etc.). Transplant patients have additional risk factors (chronic inflammation, graft rejection, immunosuppressive therapy, etc.) compared to CKD patients with similar stage of CKD and are at higher risk for cardiovascular morbidity and mortality.

2.1. Stroke and proteinuria/albuminuria

Already in 1984 Mogensen described the importance of microalbuminuria not only as a renal risk factor but also as a cardiovascular risk factor in patients with diabetes [19]. In 1994 Kannel et al. in the Framingham study also established that proteinuria is an important risk marker of cardiovascular mortality in the general population [20]. It took 20 years before the topic attained proper attention again and several important studies were published [21]. They all showed that microalbuminuria is predictive for cardiovascular events [21]. One of the first reports about the association between proteinuria and stroke was published in 1990 by Nakano et al. [22]. In this study 1611 participants underwent baseline health examinations and were followed up for 20 years [22]. The most frequent cause of death was malignant neoplasms, followed by stroke and heart disease [22]. Albuminuria had significant positive relationships to stroke mortality [22]. Interestingly, in the study by Nakayama et al., where patients were followed up for 15.5 years, albuminuria was the risk factor for stroke only in men and not in women [23]. The sample size was rather small in this study and sole dependence on clinical information for half of the stroke subtypes was a major limitation. In Finish study non-diabetic and non-insulin-dependent diabetic (NIDDM) patients were included and were followed up for 7 years [24]. The incidence of stroke was 1.6% in non-diabetic subjects without proteinuria (<150 mg/l), 3.2% in subjects with borderline proteinuria (150 to 300 mg/l), and 8.5% in subjects with clinical proteinuria (>300 mg/l); in NIDDM patients, the corresponding rates were 7.2%, 11.1%, and 23.0%, respectively [24]. The association between clinical proteinuria and the incidence of stroke remained significant both in non-diabetic and in NIDDM subjects after adjustment for other cardiovascular risk factors [24]. Beamer et al. showed that microalbuminuria was 3 times more prevalent in patients with recent stroke than in those with clinical risk factors for stroke; after controlling for major clinical risk factors, microalbuminuria remained an independent significant predictor of future stroke [25]. In the last 10 years some important studies have been published and 12 studies with 48,596 participants and 1263 stroke events were included in a meta-analysis published by Lee et al. [26]. Microalbuminuria was strongly and independently associated with incident stroke across various population subtypes after adjustment of established cardiovascular risk factors [26]. Meta-analysis is based on observational studies and cannot prove causality. It is not clear whether microalbuminuria is just a risk marker or a potentially modifiable risk factor for stroke. The limitation is that the meta-analysis was conducted on epidemiological studies rather than randomized controlled trials and included studies varied with respect to the characteristics of participants, definition of stroke, follow-up duration, etc.

2.2. Stroke and mild to severe glomerular filtration rate impairment

Association between CKD and stroke is less conclusive than in end stage renal disease patients; most studies suggest an independent association between the presence of CKD and cardiovascular disease. In most studies authors had included stroke as part of an aggregate cardiovascular event. One of the most important studies was published by Go et al.; the strength is that over 1 million adults were included in this investigation [8]. An independent, graded association between renal function and cardiovascular events was found; a cardiovascular event was defined as hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease [8]. The limitation was that only subjects who used medical services were included and some important information is missing (tobacco use, physical activity, etc.). Secondary evaluation of four community based studies (the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study and the Framingham Offspring Study) showed that CKD was an independent risk factor for the primary composite study outcome [27]. The primary study outcome was a composite of myocardial infarction, fatal coronary heart disease, all-cause mortality, and fatal and nonfatal strokes [27]. In a separate analysis no increased risk of stroke was found in patients with CKD compared with patients without CKD [27]. The strength of the study is its large sample and that serum creatinine results across all studies were calibrated to the central laboratory where GFR was estimated. The limitation of this study is that some risk factors for CVD that are especially prominent in CKD patients, including albuminuria and C-reactive protein, were missing and were not analyzed. Authors were also unable to adjust for changes in medication use during follow-up or to assess the impact of newer therapies, such as statins and RAS blockade, on outcomes [27]. In the NOMAS (Northern Manhattan) study, a prospective population based study designed to document the incidence of stroke, 3298 stroke-free subjects were included and were followed up for an average of 6.5 years [28]. In the observation period there were 177 ischemic strokes and 24 intracerebral hemorrhages; in a multivariate analysis estimated GFR between 15 and 59 ml/min was associated with a significant 43% increased stroke risk in the overall cohort [28]. Interestingly, in a separate analysis renal dysfunction was a significant predictor of incident stroke only in Blacks and not in Whites and Hispanics [28]. Renal function was estimated using the Cockcroft–Gault formula in this study, which is less accurate than the MDRD formula in estimating GFR [28]. In an analysis