The five most cited NDT articles from 1999 to 2004

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In the last decade of the twentieth century, the nephrology community has become increasingly aware of the tremendous cardiovascular disease burden carried by chronic haemodialysis patients, leading to a high incidence of cardiovascular morbidity and mortality [1]. Initially, congestive cardiomyopathy related to the uraemic state [2,3] and coronary artery disease as a consequence of dyslipidaemia associated with chronic kidney disease (CKD) [4,5] were thought to be the main culprits. The latter viewpoint was supported by the report of accelerated atherosclerosis by Lindner et al. in 1974 [6]. Even in these early times, however, not all reports were in favour of the hypothesis that the incidence of ischaemic heart disease was greater in dialysis patients than in the general population [7], in line with the present notion of a much more complex pathogenesis of myocardial disease in patients with CKD [8], including the role of metabolic abnormalities, inflammation and malnutrition [9,10].

Studies of Gérard London’s group in Fleury-Mérogis in the greater Paris area showed at the end of the past century that functional and morphological changes of large arteries resulted in arteriosclerosis, which is characterized by increased stiffness and loss of the normal cushioning function of the vessel wall [11], and thereby greatly contributed to cardiovascular disease and events in patients with end-stage kidney disease (ESKD) [12–14], as it does in the general population [15]. Braun et al. showed at the same time that these patients had a surprisingly rapid progression of arterial calcification, compared to non-renal patients with coronary artery disease and to subjects without cardiovascular disease, using for the first time a computerized tomography (CT)-based quantification of coronary calcium deposits [16]. Among the first morphologic descriptions of extensive arterial calcification in chronic dialysis patients probably is the report by Ibels et al. in 1979 [17]. Its early occurrence in CKD and its rapid progression have been amply confirmed by several subsequent reports [18].

Arterial stiffening and calcification in patients with CKD

In their report of the year 2000, which is the most cited article published in Nephrology Dialysis Transplantation...
(NDT) from the time period of 1999–2004, the Fleury-Mérogis group [19] showed for the first time an association between arterial stiffening and calcification in their single-centre cohort of 120 haemodialysis patients (CKD stage 5D according to the present nomenclature). This observation was based on B-mode ultrasonography examinations of three distinct arterial sites, namely the common carotid artery, the aorta and the femoral artery, to determine the elastic properties of the vessel wall and screen for presence of vascular calcifications. In addition, the authors measured aortic pulse wave velocity using transcutaneous Doppler flow recordings. Finally, the authors complemented ultrasonography with abdominal and pelvic X-ray examination to measure vessel wall calcification of the abdominal aorta, the iliofemoral axis and the leg arteries, and established a vascular calcification scoring system. These techniques do not enable a clear-cut distinction between intima and media calcification. Moreover, they are at best semi-quantitative, in contrast to quantitative CT methods. However, even the latter do not provide information on the precise location of calcium phosphate, i.e. apatite crystal deposits in the arterial wall. Plain posteroanterior and lateral abdominal/pelvic radiography, albeit only suggestive, remains at present the best in vivo technique to distinguish intima and media calcification. Moreover, they are at best semi-quantitative, in contrast to quantitative CT methods. However, even the latter do not provide information on the precise location of calcium phosphate, i.e. apatite crystal deposits in the arterial wall. Plain posteroanterior and lateral abdominal/pelvic radiography, albeit only suggestive, remains at present the best in vivo technique to distinguish intima (patchy) from media (pipeline) calcification. Moreover, they are at best semi-quantitative, in contrast to quantitative CT methods.

Physiological and pathological vascular remodeling entails degradation and reorganization of extracellular matrix, involving in particular matrix metalloproteinases that are activated by reduced NO bioavailability [21], oxidative stress [22] and inflammation [23]. Elastinolysis induced by elastolytic cathepsins [24] and matrix metalloproteinases (MMP) [25] may be a primary event, impairing the mechanical properties of the arteries and favouring the occurrence of vascular stiffness [26]. The vessel wall changes associated with the uraemic state probably occur first, the deposition of calcium phosphate being a secondary event. This sequence of events is suggested by recent experiments in mice with experimental chronic renal failure [27]. Of note, the degradation of medial elastin promotes calcification through an increase in elastin polarity that in turn enhances elastin affinity for calcium [28,29] and through induction of myocyte transdifferentiation into an osteo-chondroblast-like phenotype [24]. MMP inhibition [28] and cathepsin S deficiency [24] attenuate aortic calcification. In contrast, MMP-2 activation is associated with elastic fibre disorganization and fragmentation, vasomotor dysfunction, stiffness and calcification of the arterial vasculature, as recently shown in patients with CKD undergoing long-term dialysis treatment [30]. Whether MMP-induced elastin fragmentation with subsequent passive [31] or active [24] calcium deposition is among the initial events triggering vascular calcification associated with CKD remains to be seen. Numerous other passive and active mechanisms have been identified in the last decade, including high calcium and phosphate concentrations in the extracellular fluid [32–34]. Guérin et al. found an association of arterial calcification with prescribed doses of calcium-based phosphate binders [19]. However, whether high oral calcium intake is an important contributor remains a matter of debate (see below) [35].

**Arterial calcification and outcomes in patients with CKD**

The most important question for the patient is whether blood vessels are calcified or not and what the underlying mechanisms are. The patient wants to know whether this matters in terms of morbidity and survival, and if...
so, what can be done to halt or reverse the process. An association between vascular calcification and the relative risk of mortality has probably been reported for the first time in a population of middle-aged patients with non-insulin-dependent diabetes mellitus in the year 1994 [36]. It has been subsequently suspected to exist in patients with CKD as well [37,38]. It is only in 2003 that two reports qualified cardiovascular calcification as an important predictor for mortality in patients with ESKD. One of them is the original report by Gérard London’s group in the year 2003 [20], which is the second most cited article published in NDT from the time period 1999–2004. It showed that not only calcification of the arterial intima but also that of the media is a strong predictor for cardiovascular and all-cause mortality in long-term haemodialysis patients. The other report is that by Wang et al. [39], showing an association of cardiac valve calcification with cardiovascular and all-cause mortality in long-term peritoneal dialysis patients.

In the report by London et al. [20], ESKD patients with no vascular calcification had the best prognosis, those with pure or predominant media calcification had a significantly higher mortality risk and those with predominant intima calcification had the highest risk (Figure 2). Note that the patients with intima calcification were older than those with media calcification, which is a possible confounder. Of interest, lower serum albumin and higher serum C-reactive protein (CRP) levels were associated with higher odds ratios for the presence of both intimal and medial calcification. This suggests that chronic low-grade inflammation and/or malnutrition favour the occurrence of both types of calcifications in patients with CKD stage 5D. In contrast, medial calcification, but not intimal calcification, was closely related with haemodialysis vintage and the daily oral dose of elemental calcium prescribed as phosphate binder.

Role of phosphate in arterial calcification and control of hyperphosphataemia in patients with CKD

As already mentioned, vascular calcification is an extremely complex process involving a variety of passive and active mechanisms [32,40,41]. Disturbances of calcium and phosphate metabolism in CKD play a major role [33,42,43]. Moreover, several observational studies have demonstrated
a close association between hyperphosphataemia and relative mortality risk [44,45]. As to calcium, the role of oral overload with calcium salts, given as phosphate binders, in the prevalence and incidence of arterial calcification has been incriminated in several reports, including those by G. London’s group in Paris [19,20,46–49]. Considering both calcium and phosphate as major culprits in the pathogenesis of cardiovascular morbidity and mortality, it appeared important to achieve hyperphosphataemia control in patients with advanced stages of CKD in the absence of massive calcium overload by calcium-containing phosphate binders. Aluminium salts, despite their excellent phosphate chelating capacity, were found to be potentially dangerous because of aluminium absorption and toxicity. Therefore, there was a need for new, calcium-free and aluminium-free phosphate binders. Sevelamer-HCl was the first such new class of binders, followed by lanthanum carbonate as yet another new class.

The original article by Chertow et al. [50], which is the fifth most cited article published in NDT from the time period 1999–2004, presents the first long-term evaluation of the effect of sevelamer-HCl on hyperphosphataemia and dyslipidaemia in patients with ESRD, accompanied by four short-term studies [51–53]. The authors showed that this phosphate binder was effective in lowering serum phosphorus (Figure 3). It also reduced the Ca × P product although serum calcium increased slightly. Moreover, sevelamer-HCl improved the serum lipid profile, as reflected by a decrease in LDL cholesterol and an increase in HDL cholesterol. As subsequently shown by these and other authors, the phosphorus- and LDL-cholesterol-lowering actions as well as other, pleiotropic actions of this non-absorbable phosphate binder probably account for its inhibitory effects on the progression of vascular calcification [47,48] and mortality [54] in chronic dialysis patients. However, not all studies have confirmed this beneficial effect of sevelamer [55,56]. The reasons for the apparently discrepant findings may be methodological in nature [35], including insufficient sample size of existing trials [57].

Prevalence and type of coronary atherosclerosis in patients with CKD

In the early 1970s, at least four studies showed that myocardial infarction and stroke occupied an important place in the mortality of patients with ESKD [6,58,59], with particularly poor outcome in those with diabetes [60]. These observations have been supported by several subsequent studies, both in CKD patients without diabetes and in those with diabetes, although the adverse impact of ischaemic heart disease appeared to be mediated more often through the development of heart failure than myocardial infarction [7,61,62]. However, several recent cardiac imaging studies found again a high prevalence of significant coronary artery stenosis in patients with advanced stages of CKD [63–67]. Therefore, whether accelerated atherosclerosis, as postulated by Lindner et al. [6], or other pathogenetic mechanisms play the most important role in the dramatic progression of cardiovascular disease of ESKD patients remains unclear at present.

To clarify this issue, several morphological studies have been performed that were aimed to assess the structural changes of the vessel wall and their progression with the advancement of CKD, as outlined below. The report from the year 2000 by Schwarz et al. [68] by the Nephrology group in Heidelberg, then directed by E. Ritz, represents one of the most informative studies among them. It is the third most cited original article published in NDT from the time period of 1999–2004. The main merit of this article is the systematic post-mortem examination of coronary arteries of 27 elderly subjects with ESKD, compared with 27 matched non-uraemic control individuals. The coronary arteries of the ESKD patients displayed significantly more calcified plaques of coronary arteries than the control arteries. Media thickness and area, but surprisingly not intima thickness or area, were significantly higher in the uraemic patients (Table 1). Plaque area was comparable. Lumen area, however, was significantly reduced. The authors concluded that, in contrast to common belief, the most marked difference between uraemic and non-uraemic arteries was not in the size but the composition of the plaque, in particular its high calcium content.

A similar conclusion as to the absence of a significant increase in the prevalence of coronary atherosclerosis had already been reached by Rostand et al. in an autopsy study of 1979, which, however, did not include non-uraemic controls [7]. They found coronary artery narrowing of ≥70% in only seven among 132 deceased patients. Other, more recent autopsy studies reported a variable prevalence of coronary atherosclerosis in patients with ESKD [69,70]. In a very recent study, Nakano et al. performed a cross-sectional analysis of the severity of coronary atherosclerosis as a function of CKD stage in 126 elderly Japanese individuals [71]. The frequencies of advanced atherosclerotic lesions increased gradually from 34 to 53%, with decreasing esti-
et al. in inflammatory comorbid disease. From Stenvinkel response to factors such as chronic heart failure and infectious/inflammatory cytokines play a central role. They are generated in disease (MIA syndrome) in patients with chronic renal failure. Pro-

Fig. 4. The vicious circle of malnutrition and atherosclerotic cardiovascular disease (MIA syndrome) in patients with chronic renal failure. Pro-inflammatory cytokines play a central role. They are generated in response to factors such as chronic heart failure and infectious/inflammatory comorbid disease. From Stenvinkel et al. [72], with permission.

mated glomerular filtration rate down to values <30 mL/min and 1.73 m².

In sum, the prevalence and incidence of coronary atherosclerosis in patients with CKD appears to be variable, depending on the number of classical risk factors such as age, diabetes, hypertension, dyslipidaemia and smoking, and probably also on a variety of uraemia-associated factors, as reflected by the duration and severity of CKD, and the treatments given to the patients.

Role of inflammation and malnutrition in the atherosclerosis of patients with CKD

The report by Stenvinkel et al. [72], which is the fourth most cited article published in NDT from the time period 1999–2004, is a review that addresses the complex interaction between inflammation, malnutrition and atherosclerosis in CKD. The authors first define malnutrition and present the different ways to assess it. They subsequently point out the contribution of pro-inflammatory cytokines to both malnutrition and cardiovascular disease. Their noxious effects encompass muscle wasting by stimulating protein catabolism, as reflected by low serum albumin; an increase in serum CRP, which may be both a marker of and an actor in cardiovascular morbidity and mortality; a rise in resting energy expenditure, which in face of anorexia represents another major cause of weight loss and wasting; and an increase in oxidative stress with endothelial dysfunction and monocyte activation. The resulting chronic heart failure of CKD could in turn contribute to inflammation, malnutrition and atherosclerosis via increases in serum levels of TNF-α and IL-6, which have been found to be related to cardiac cachexia [73,74]. Figure 4 shows the vicious circle of interaction between these factors. The interrelationship is summarized by the authors’ proposal of the existence of a syndrome consisting of malnutrition, inflammation and atherosclerosis (MIA syndrome) in patients with advanced stage of CKD.

Schematically, one could distinguish two types of malnutrition in ESKD [75]. Type 1 would be mainly associated with the uraemic syndrome itself or factors associated with it, such as physical inactivity, anorexia, low protein and energy intake, psychosocial factors and underdialysis. Protein catabolism would be decreased in this condition as a compensatory mechanism, and hypoalbuminaemia would be of modest degree. Type 2 malnutrition would be the result of inflammation, increased oxidative stress, high resting energy expenditure, high circulating levels of pro-inflammatory cytokines and more profound hypoalbuminaemia. In most instances, however, there is a continuous overlap of these two theoretically distinct conditions [72]. Recently, the International Society of Renal Nutrition and Metabolism has proposed to use the term ‘CKD-associated protein-energy wasting’ (PEW) for loss of body protein mass and fuel reserves [76]. It is based on the following three characteristics: (i) low serum levels of albumin, transthyretin or cholesterol; (ii) reduced body mass; and (iii) reduced muscle mass. Since the landmark paper by Stenvinkel et al. [72], other multiple pathophysiologic mechanisms have been suggested to explain the link between PEW and mortality in CKD, including derangements in adipose tissue and the gastrointestinal, haematopoietic and immune systems, micronutrient deficiencies, dietary overload with or excessive intestinal uptake of advanced glycation end-products and the potential role of novel factors such as circulating actin, gelsolin and pro-inflammatory HDL [77,78].

In terms of treatment and prevention, Stenvinkel et al. [72] outline that adequate nutritional support and dialysis are probably sufficient for type 1, but not for type 2, malnutrition. They suggest that prospective randomized trials be done to explore new strategies aimed at reducing inflammation and oxidative stress, such as treatment with ACE inhibitors, antioxidants, antiviral agents and antibiotics when appropriate, and anti-cytokine therapy.

Importance of the five most highly cited articles published in NDT 1999–2004

The five reports (four original articles and one review) from the early 1990s all deal with the importance of cardiovascular morbidity and mortality in patients with ESKD. They analyse the different mechanisms involved in the pathogenesis of cardiovascular disease and the various forms of clinical and morphological presentation. In addition to atherosclerosis, whether accelerated by CKD or not, they outline the importance of arteriosclerosis, as reflected by increased vascular stiffness, and massive arterial calcification as other, potentially major contributors to cardiovascular events and mortality. Since that time, a steadily growing number of experimental and clinical studies have been devoted to the association of cardiovascular disease with CKD, to a better understanding of its pathogenesis, and to therapeutic and prophylactic interventions aimed at halting its rapid progression. Concerning prophylaxis and treatment, a major focus has been on the best possible control of atherosclerosis and arteriosclerosis, of the disturbances of phosphate metabolism including vascular calcification and of protein-energy wasting, malnutri-
tion, and inflammation. The above highly cited NDT articles have already been instrumental in addressing these issues 20 years ago.

Potential conflict of interest declaration

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