Child–Adult Interface

Is atherosclerosis accelerated in young patients with end-stage renal disease? The contribution of paediatric nephrology

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Keywords: atherosclerosis; children; risk factors; renal osteodystrophy

Introduction

The concept of an acceleration of atherosclerosis due to end-stage renal disease (ESRD) was first proposed by Lindner et al. [1] who observed a very high incidence of myocardial infarction in the Seattle haemodialysis population in 1974. Subsequent studies have confirmed a high prevalence of atherosclerotic lesions in dialysis patients by autopsy [2], by in vivo examination of iliac artery specimens [3] and by coronary angiography [3,4]. Approximately 50% of mortality in the dialysis population is due to cardiovascular disease (CVD) and the risk of death from CVD is elevated 30-fold for patients with ESRD compared with the general population [5]. Similarly, the incidence of CVD is much increased after renal transplantation [6]. The epidemic of CVD in ESRD may be explained by a unique accumulation of risk factors for atherosclerosis [7]. However, it has been widely debated whether the high mortality is due to an acceleration of atherosclerosis promoted by ESRD per se or to pre-existing co-morbidity from other causes. For both of these conflicting views there is evidence from retrospective as well as prospective studies [8–11]. Apart from these data, two lines of reasoning argue against the concept of accelerated classical atherosclerosis in ESRD.

Firstly, many studies have not found any, or only a weak, correlation of cardiac death with hyperlipidaemia [12], even though the lipoprotein profile is clearly atherogenic in chronic renal failure, on dialysis and after transplantation [13,14]. This may be due to a number of reasons, including confounding factors (malnutrition associated with low cholesterol levels), strong effects of other non-traditional risk factors [Lp(a), inflammatory state] and oxidative modification of lipoproteins (not necessarily associated with an increase in lipoprotein particles) [15]. Nevertheless, this is in strong contrast to the fact that hyperlipidaemia has been shown to be a cardinal risk factor for atherosclerosis in the general population, characterized by a continuous and graded relationship with death from cardiac causes as well as total mortality [16–18]. Similarly, treatment of hyperlipidaemia is associated with a reduction in mortality from cardiac causes and overall mortality, but this has yet not been demonstrated in patients with ESRD.

Secondly, mortality from cardiac causes in patients with ESRD in the US and in Europe is only partly due to ischaemic heart disease and myocardial infarction [19]. Although significant regional differences in contributing factors exist within Europe [20], the majority of deaths are associated with several other cardiac causes, such as arrhythmia, cardiomyopathy, cardiac arrest, pulmonary oedema and cardiac failure from other causes such as valvular heart disease. Therefore, although it is common to group these diagnoses as ‘cardiac causes’, this may actually confuse the issue; in the absence of carefully conducted mortality studies (including autopsy data), a diagnosis of arrhythmia could reflect coronary artery disease, but also other causes such as hyperkalaemia (diet errors, uncompliance, acidosis). Thus, only a fraction of ‘cardiac deaths’ may actually result from atherosclerosis.

Therefore, it is obviously of interest to study this question in a young population without pre-existing multiple co-morbidities, i.e. young patients with ESRD occurring in childhood, who are now progressing into adulthood due to the accessibility of dialysis and transplantation at young age in Western countries [21].

Cardiac death in young patients

The current concept of atherosclerosis implies that risk factors drive a slow process of changes in the arterial wall over several decades. The process starts with the
formation of fatty streaks during childhood and adolescence, developing into complicated lesions most often around 40–50 years of age, and resulting in complications such as angina pectoris, myocardial infarction, stroke, peripheral arterial disease, and aneurysms later on. If this process were truly accelerated, we would experience the whole spectrum of atherosclerotic complications at a younger age, possibly at 30–35 years of age, with symptoms in many cases evolving even earlier, possibly in adolescence. Moreover, we would see ischaemic heart disease on a large scale in young patients. The clinical course might resemble homozygous familial hypercholesterolaemia, where a lack of LDL-receptors is associated with myocardial infarction in childhood. Clearly, this scenario is not supported by clinical experience in young ESRD patients.

Children and adolescents with ESRD usually have no clinical symptoms suggestive of heart disease or CVD. However, similarly to elderly patients, young adults with ESRD die primarily of cardiac causes. The relative mortality risk from cardiac causes is in fact excessively elevated in young patients (aged 25–34 years) compared with the general population, and is approximately equal to the risk in 75–80-year-old subjects without ESRD [5]. Similarly, cardiac death is the single largest contributor to mortality in young patients after renal transplantation. In transplanted US children aged 0–19 years, death from cardiac causes combined was approximately 35%, whereas death from other causes was less frequent (infection 24%, malignancy 7%) [22]. However, only 4% of the total mortality was due to myocardial infarction, and another 6% due to CVD [22]. In a German paediatric single-centre study of 150 transplanted patients (mean age 25.4 years, with a mean follow-up of 13.2 years), the mortality from CVD was 23% [21]. In a more detailed analysis of death from cardiac causes over a 5-year period among European children aged less than 15 years treated with dialysis or transplantation, only two of 55 patients died of myocardial infarction, whereas cardiac death in the majority was associated with hyperkalaemia, fluid overload, hypertensive cardiac failure or ‘other causes’ [23]. Taken together, the paediatric experiences show that patients are usually asymptomatic and die suddenly of cardiac arrest. Again, this is not the scenario one would expect if classical atherosclerosis was truly accelerated.

**Risk factors in the young**

It has been questioned whether atherosclerotic risk factors are already operative in young patients. As for the traditional risk factors, the studies by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) research group have provided a clearly positive answer [24]. Autopsies of young subjects who died of external causes (aged 15–34) have demonstrated that the surface area of the aorta and right coronary artery covered with atherosclerotic lesions was strongly correlated with the presence of traditional risk factors. Similarly, autopsy findings in 204 persons aged 2–39 years showed a strong correlation of coronary and aortic atherosclerosis with the risk factor load prospectively evaluated in the Bogalusa heart study [25]. In addition, non-traditional risk factors and cardiomyopathy risk factors are present (and probably just as frequent) in paediatric subjects as they are in adults with ESRD [26]. We have no reason to doubt, however, that they are less deleterious in young subjects. Recent data also suggest that among the non-traditional (‘uraemic’) risk factors, disturbances in calcium-phosphate metabolism and their treatment may play an exceptional role in promoting vascular changes in children and adolescents.

**Treatment of renal osteodystrophy in childhood: an iatrogenic risk factor?**

Recent studies in children and young adults have demonstrated severe calcifications in the coronary arteries by EBCT and spiral CT, respectively [27–29]. In two studies, the amount of calcification was associated with elevations in the serum calcium-phosphate product and with treatment by calcium-containing phosphate binders [28,29]. These drugs have been the mainstay of treatment for renal osteodystrophy in childhood, since aluminium-containing phosphate binders have been found to be associated with severe side effects, particularly encephalopathy in infants, and are therefore banned from use in children [30]. In addition, the growing skeleton of children has a high demand for vitamin D, which must be administered in virtually every growing patient with chronic renal failure. Since the physiologic levels of phosphorus are higher at young age, and high protein requirements necessitating milk-based formula feeding are associated with a high phosphorus load, the situation is indeed challenging for the paediatric nephrologist. We need to treat young patients with high doses of calcium-containing phosphate binders, and sometimes very large doses of vitamin D, in order to prevent secondary or even tertiary hyperparathyroidism, which can be associated with myopathy and immobilization at this young age. On the other hand, this therapy carries a risk for adynamic bone disease, growth suppression [31] and ectopic calcifications, including coronary calcifications.

The landmark report by Milliner et al. [32], based on autopsy data of children with ESRD, treated during 1960–1983, demonstrated soft tissue calcifications in 72 out of 120 patients (60%) and systemic calcinosis in 43 patients (36%). Twelve patients had coronary artery calcifications, 30 had non-myocardial vascular calcifications and 19 had myocardial calcifications, with extensive involvement of the conductance system in one patient. It is of note that, of all variables considered in this study, the use of vitamin D derivates,
and especially calcitriol, had the strongest correlation with calcinosi. In a small series of 12 adolescents aged 11–17 years undergoing renal transplantation after haemodialysis, intimal thickening, microcalcifications and atheromatous plaques were described in iliac artery specimens in six patients; these patients had higher serum phosphorus levels and higher serum calcium-phosphate product levels than the patients without arterial changes [33]. Therefore, data from imaging studies and histological findings indicate that the amount and extent of vascular calcifications can be severe and are dependent upon the patient’s age and duration of dialysis [28]. Further studies are now under way to evaluate the question of whether these calcifications are the result of the cumulative prescription of calcium-containing phosphate binders, vitamin D or both.

It is possible that the use of vitamin D or its derivatives poses a unique risk to children and adolescents with ESRD. Large doses of vitamin D are known to produce media calcifications as shown already in the experience of the 1970s [34,35]. Recent data has shown that calcification is a regulated process [36], and that smooth muscle cells in the media possess the capability to undergo transformation to osteoblast-like cells [37]. In fact, ectopic bone formation driven by growth and differentiation factors has been demonstrated in the media in Monckeberg’s sclerosis, and it is possible that a similar ossification process contributes to the dramatic stiffening of arteries found in uraemic subjects [38]. Moreover, this process may be distinctly different from atherosclerosis, both histologically and functionally, having no effect on lumen patency (as opposed to atheromatous protruding intimal lesions). That such a process may occur in the arteries of uraemic subjects is also suggested by recent in vitro experiments, which demonstrated that even small elevations of phosphate concentrations resulted in calcifications in human aortic smooth muscle cells, mediated by a sodium-dependent phosphate co-transporter [39]. It is therefore possible that an elevated calcium-phosphate product in uraemic patients could directly result in vascular calcifications. The role of vitamin D in this process is less clear. It was recently shown that arterial smooth muscle cells are able to express 1α-hydroxylase, leading to the conversion of inactive to biologically active vitamin D3 [40]. Figuratively speaking, this would suggest that a sleeping bone formation machinery in the arterial wall [41,42] could be awakened and respond to the vitamin D signal in the same way as bone tissue. On the other hand, circulating 1,25-(OH)2D3 has been found to be inversely associated with the amount of calcification in vivo in normal subjects [43]. However, it must be kept in mind that these data were not obtained in uraemic patients, for whom the presence of calcifying tissue in the media may have a different response to circulating vitamin D compared with that of normal arteries. Moreover, normal individuals with relatively low calcitriol levels may have low bone turnover osteomalacia or osteoporosis and may be unable to use extracellular calcium for bone formation, thus increasing calcium availability for soft tissues.

**Uraemic ateriopathy vs atheroma**

The accumulation of traditional and non-traditional risk factors as well as a specific uraemic cardiomyopathy seems responsible for the high mortality from cardiac causes in ESRD. While the risk factor load (which may well be without comparison) is likely to promote classical atherosclerosis, the combination with uraemic cardiomyopathy and vasculopathy, characterized by vascular stiffening, might best explain the occurrence of CVD at a much younger age than in the general population. The clinical scenario in young patients with ESRD, as well as recent molecular data, suggests that the process of sclerosis and stiffening is the leading phenomenon of the arterial changes in uraemia at this age and is clinically more apparent and possibly more important than the process of atheroma formation. Although risk factors are most likely to act in concert, producing both atheroma and sclerosis, this also implies that the driving force in this process is composed of a variety of factors leading to arterial stiffening, including hypertension, calcification and a decreased activity of endothelial relaxing factors. In more general terms, sclerosis develops faster than atheroma in young patients without significant co-morbidity.

Taken together, the current paediatric experience indicates that it is the ‘sclerosis’ part of atherosclerosis which is accelerated by ESRD, producing vascular changes for which the term ‘uraemic ateriopathy’ might be more appropriate. We do not believe that this distinction is only of academic interest. It implies that basic research as well as clinical studies will have to focus on the elimination of risk factors producing calcification and sclerosis, especially in young patients. Studies are under way to implement surrogate end-points for non-invasive measurements of arterial structure and function. This will allow us to better understand the process of vascular stiffening and hopefully monitor treatment studies in the near future.

**References**