The role of collagen metabolism in CKD-associated arterial senescence: underestimated and underappreciated

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Keywords: arterial stiffness; collagen; kidney disease; ventricular hypertrophy

The excessive cardiovascular risk in patients with chronic kidney disease (CKD) is well established and includes atheromatous lesions as well as medial disease (arteriosclerosis or Mönckeberg’s sclerosis) with a marked propensity for calcification of these lesions. The changes in geometry and viscoelastic properties of the arterial wall in uraemia are very similar to those seen with ageing and include arterial dilatation, aortic stiffness and medial wall calcification. Despite some ongoing controversy as to whether intimal and medial calcification really represent different pathophysiological processes [1–3], it seems reasonable to consider CKD as a metabolic abnormality associated with accelerated vascular ageing, comparable to diabetes. This is supported not only by epidemiologic studies [4–6] showing that traditional risk factors are insufficient to explain the increased cardiovascular risk in CKD but also by data from mechanistic, biochemical and molecular biology studies: in uraemia, like with increasing age, free amino groups on proteins such as collagen, become more vulnerable to non-enzymatic glycation and oxidation resulting in the formation of advanced glycation end-products (AGEs) and advanced oxidation protein products (AOPPs), even in normoglycemic conditions [7–9]. AGE cross-linking renders collagen fibers stiffer and resistant to normal hydrolytic turnover, leading to a less distensible arterial wall matrix [7, 8, 10, 11]. Glycation of collagen I induces premature senescence-like phenotypic changes in endothelial cells without affecting telomere length [12]. Thus, the underlying cellular and molecular mechanisms of arterial changes in uraemia are markedly similar to those observed with ageing.

Much research has been focused on cellular, subcellular, genetic and biochemical factors in this evolution, with little attention for structural non-cellular factors, i.e. the matrix. This seems unjustified, as many arguments support the view that ageing is primarily the consequence of a degeneration of non-living body components rather than a cellular process. Just as the cells in leaves of old and young trees are similar, also in man, the structure of most cells is identical in youth and old age, apart from the telomere length. Passage of nutrients and water to the cells, however, is dependent on the surrounding non-cellular structures, as is the ability to withstand mechanical forces such as the effect of gravity on bones or blood pressure (fluctuations) on the arterial wall. The study by Dellegrottaglie et al. [13] tries to overcome this lack of information and is one of the first to evaluate this aspect in the context of uraemia. The authors measured serum levels of collagen type III and type I turnover, the N-terminal procollagen type III propeptide (PIIINP) and the C-terminal telopeptide of type I collagen (C1TP) and explored their relationship with aortic pulse-wave velocity (PWV) and echocardiographically measured left ventricular mass index (LVMI), markers of arterial stiffness and left ventricular hypertrophy, respectively. This is quite an endeavour since not only two types of collagen are studied but also two markers of target organ damage, one pertaining to the heart and one to the large (elastic-type) arteries. Additionally, it should be noted that PIIINP is a marker of collagen synthesis, while C1TP reflects collagen degradation.

The population of the study published in this issue consisted of 242 patients with CKD Stages 3–5, a subset of the larger Renal Research Institute observational cohort (n = 834). The general characteristics were comparable to most European CKD populations with 30% diabetics and 53% males; 80% of patients were Caucasian. Levels of PIIINP and C1TP increased with advancing stage of CKD, and this association remained significant in multivariate analysis.
Whether this is due to enhanced collagen turnover or reduced renal clearance remains to be explored, but this relationship with kidney function by itself is important to take into account in future studies. Not surprisingly, both markers of collagen turnover and both surrogate measures of cardiovascular damage also positively correlated with each other. PIIINP and C1TP were positively (univariately) correlated with LVMI, while for PWV, only the correlation with PIIINP was significant. In multivariate analysis, only the relationship between PIIINP and PWV remained significant. The schematic representation of the key findings in Figure 5 is very helpful for an overall appreciation of these complex data.

Markers of collagen turnover (mostly PIIINP) have mainly been studied in myocardial disease and remodelling. PIIINP was measured in a sub-study of the Randomized Aldactone Evaluation Study (RALES), a placebo-controlled randomized trial that demonstrated an improved survival of add-on treatment with spironolactone in severe congestive heart failure [14].

In contrast, no independent relationship could be detected with PWV or LVMI. The negative results regarding C1TP are in line with a recent study in patients with hypertrophic cardiomyopathy, where biomarkers of collagen degradation alone, including C1TP, were not informative [16].

When also taking into account in the latter study, the corresponding marker of collagen I synthesis, the C-terminal propeptide of type I procollagen (PICP), it appeared that the PICP:C1TP ratio correlated best with the presence of overt hypertrophic cardiomyopathy. Unfortunately, Dellelagrottaglie et al. did not measure markers of collagen I synthesis, which may be one of the reasons for the observed differences between PIIINP and C1TP. Since type I collagen is also a major component of bone, CKD-related disturbances in bone metabolism may have influenced the results in the CKD population under study as well. One simple way to explore this potential confounding effect would be to measure serum markers of bone turnover such as bone-specific alkaline phosphatase. Finally, collagen markers measured in serum may not truly reflect tissue levels, although this limitation is difficult to overcome in a clinical study.

An additional point that complicates the interpretation of the present study is the attempt to evaluate at the same time surrogate markers pertaining to the myocardium as well as the central arterial system. As the authors acknowledge, the link between collagen turnover and left ventricular hypertrophy may be indirect through an effect on aortic stiffness. In dialysis patients, a high PWV is associated with an increased LVMI, partly due to an earlier arrival of peripherally reflected pressure waves [17]. The resulting increase (augmentation) of the central systolic pressure thereby entails a higher cardiac workload. Interestingly, in the present study, PWV indeed was independently related with LVMI and after adjustment for age, diabetes and blood pressure, only PWV remained independently related to PIIINP, which may support the view that PWV and LVMI are part of a common causal pathway.

Over the past decade, an increasing number of studies have been published on the independent prognostic value of PWV [18]. The risk appears to be independent of the population characteristics and has been reported in both renal and non-renal populations. Even more, the relative risk per increment in PWV is very similar in dialysis patients and non-renal populations [19], supporting a direct mechanistic link between wave velocity and arterial wall stiffening as a measure of vascular ageing. The underlying non-cellular processes pertaining to medial wall matrix degradation have remained underexplored so far, the present study being one of the few welcome exceptions. Many questions remain to be addressed and it is clear that only the surface of this complex matter has been scratched.

Conflict of interest statement. None declared.

References


Received for publication: 9.6.11; Accepted in revised form: 20.6.11