

Review Article

The Emerging Role of Subclinical Inflammation in Hypertension-Associated Early Renal Dysfunction: Focus on Microalbuminuria

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Microalbuminuria (MA), the presence of low but abnormal levels of albumin in the urine, is the earliest clinical sign of diabetic nephropathy¹⁻³ and for hypertensive patients it is also a marker for greatly increased cardiovascular risk, regardless of the presence of diabetes.³⁻⁷ The association of MA with elevated blood pressure (BP) is consistent and independent, and increased urinary albumin excretion (UAE) has also been linked to lipid abnormalities, reduced insulin sensitivity, impaired endothelial function, peripheral vascular disease, diffuse inflammatory processes and prothrombotic state.⁵⁻¹⁶ All the above define MA as a marker of generalised vascular dysfunction beyond the renal glomerulus.

Cumulative evidence suggests that hypertension is an inflammatory disease and that diverse inflammatory and pro-atherogenic mechanisms may be involved in both the pathogenesis of hypertension and the progression of target organ damage.¹⁶⁻²¹ The observed interrelationships of MA with inflammatory mediators provide further support to the notion that in the vicious circle connecting essential hypertension, microalbuminuric state and atherosclerotic cardiovascular events, subclinical inflammation participates in all stages of this deleterious process.^{5,7,9-11,18-21}

The purpose of this article is to review the available data regarding the role of proinflammatory processes in the context of hypertensive cardiovascular disease and to focus on their relation with MA, a promising marker of subclinical atherosclerosis. A better understanding of MA could clarify the link between increased UAE and unfavourable outcome and underscore the value of screening for MA in the setting of non-diabetic essential hypertension.

Essential hypertension and “the fire that burns within”: A unifying hypothesis

The notion that essential hypertension may be in part an inflammatory disorder¹⁸⁻²¹ seems quite intriguing, in view of the central role of low-grade inflammation in all phases of atherosclerosis, which suggests a pathophysiological link between the hypertensive state and increased cardiovascular risk.²¹⁻²⁶ A significant number of cross-sectional and prospective studies showed a positive relationship between BP levels and C-reactive protein (CRP), while hypertensive subjects, when compared to normotensives, exhibited higher concentrations of inflammatory mediators.¹⁷⁻¹⁹ There is also recent evidence regarding the increased risk of hypertension in normotensives with augmented CRP values.¹⁷

Pioneering studies have shown that the pulsatile flow triggers the inflammatory cascade by stimulating vascular adhesion molecule expression and leukocyte adhesive properties.^{17-20,24,27-29} Accordingly, higher levels of CRP augment BP by reducing nitric oxide production of endothelial cells, increasing endothelin-1, up-regulating angiotensin I receptor expression, thus affecting the renin-angiotensin system and contributing to the pathogenesis of essential hypertension.¹⁷⁻²⁶ These relationships are supported by cross-sectional associations not only of CRP but also interleukin-6, intercellular adhesion molecule-1, and tumour necrosis factor- α , with either BP or hypertension.¹⁸⁻²⁶

New definition of microalbuminuria: Breaking the cut-off points for cardiovascular risk

The prevalence of MA increases with age and the duration of hypertension and varies from 20% to 30% in untreated patients and up to 25% in treated patients.^{2-3,8,30} Nowadays, MA is recognised as a predictor of atherosclerotic cardiovascular disease in non-diabetic individuals.^{1-8,30} In a 10-year prospective study of more than 2000 patients with essential hypertension, an albumin to creatinine ratio (ACR) >1.07 mg/mmol strongly and independently predicted ischaemic heart disease, more than doubling the risk.³¹ The relative risk of all cause mortality associated with MA was about 5 times higher among hypertensive than normotensive subjects in the Hoorn Study.⁵ It should be mentioned that in subjects with untreated or borderline essential hypertension, MA was the strongest predictor of ischaemic heart disease when adjusted for all other atherosclerotic risk factors, including age and gender.³¹

However, even minimal increases of UAE could be clinically significant in hypertensives.^{2,8,28} More specifically, in the Heart Outcomes Prevention Evaluation study (HOPE), with a median of 4.5 years of follow-up, any degree of albuminuria was proven to be a risk factor for cardiovascular events. The risk increases with the ACR, starting well below the MA cut-off,⁴ even as low as 0.5 mg/mmol. For every 0.4 mg/mmol increase in ACR, the adjusted hazard of major cardiovascular events was augmented by 5.9%.^{4,8}

Very recent evidence seems to alter our perspective towards MA assessment in essential hypertension.³⁰ More specifically, in a study that included 16,000 hypertensive subjects with no history of heart disease, after 17,216 person-years of follow-up, incident cardiovascular disease occurred among 11% of microalbuminurics compared with 5% of normoalbuminurics, and death occurred in 28% versus 13%. The age-adjusted relative risks of cardiovascular events were significantly increased from the level of UAE >5 μ g/min. According to these results, MA is the strongest predictor for adverse cardiovascular outcome in hypertensive subjects, after adjustment for the conventional atherosclerotic risk factors (i.e. age, sex, BP, use of antihypertensive drugs, diabetes, lipoproteins, renal creatinine, smoking and body mass index). The investigators found that hypertensive subjects with MA, defined as UAE \geq 5 μ g/min or ACR \geq 0.7 mg/mmol, have a 100% higher risk of incident cardiovascular disease than those with lower UAE values.³⁰ These data suggest that there should be a new definition of MA in the setting of essential hypertension and that future risk assessment of hypertensives should include MA measurement.

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Microalbuminuria and blood pressure levels: Is there any role for inflammation?

BP has been shown to be the mainstay determinant of MA in diabetes and hypertension.^{20,32} Data regarding the correlation of CRP with increased UAE are rather scarce at the level of the hypertensive population. However, in a recent cross-sectional study of 8592 patients, the relation of BP level to MA was more pronounced in subjects with an elevated CRP plasma concentration, while elevated CRP enhanced the relationship between BP and MA independently of other covariates.²⁰ This could be because low-grade inflammation apparently increases the likelihood of augmented glomerular leakage of albumin in response to BP. This leakage of albumin may involve either increased transmission of systemic BP or decreased barrier function of the glomerulus due to inflammatory involvement.^{8,17-20,32,33} This observed interaction is fundamental for the comprehension of the pathophysiology of MA in this setting.

Microalbuminuria and inflammation: A detrimental cardiovascular duo

Acute inflammatory reaction and increased UAE

MA could possibly be a marker of an acute inflammatory reaction, since a relation between UAE and increased CRP and other inflammatory markers has been previously reported in hypertensives and patients with coronary heart disease.^{7,34-37} Towards this direction, a marked increase in UAE was found in subjects admitted to hospital for acute myocardial infarction.^{7,8,35-37} This

increased UAE was proved to be a strong predictor of in-hospital mortality, better than the Killip class or the echocardiographic left ventricular ejection fraction. The elevation of UAE was attributed to a systemic increase in vascular permeability as part of the acute inflammatory process that accompanies the myocardial infarction. It is likely that, in hypertensive subjects, the inflammatory injury in the kidney structures consequent to that of myocardial infarction causes a greater albumin leak from the glomerulus.^{7,35} Of note is that augmented UAE, detected in the presence of an acute ischaemic event or peripheral vascular disease, is proportional to the severity of the infarct or the claudication.^{8,35} Thus, measurement of UAE could be a rather sensitive tool for the assessment of acute inflammatory processes related to cardiovascular disease and its complications.

Chronic inflammatory processes and augmented UAE: Promising data

Chronic low-grade inflammation is closely associated with unfavourable cardiovascular outcome, mediating all stages of the atherosclerotic disease from initiation through progression and ultimately thrombotic complications. Increased levels of vascular cell adhesion molecule-1, CRP and fibrinogen are related to augmented UAE in diabetic and non-diabetic subjects.³⁶⁻³⁹ Of note is that higher amounts of vascular cell adhesion molecule-1 and CRP are more strongly related to MA in non-diabetics than in diabetics.³⁶ Accordingly, there was a positive association between UAE, diastolic BP and CRP plasma levels in a study from which patients with diabetes mellitus were excluded.³⁷

The underlying pathophysiological mechanisms for the observed relation between UAE and inflammatory processes in the setting of essential hypertension have not been well defined. One could only hypothesise about the plausible different links between inflammatory involvement and subclinical renal injury. Firstly, the interplay between low-grade inflammation and the renin-angiotensin system may contribute to this relationship. In this context, through proinflammatory mechanisms (i.e. stimulation of adhesion molecules and interleukin-6) the latter system could promote diffuse damage to the renal glomerulus. Moreover, angiotensin II-induced direct generation of superoxide anions in the vasculature and adhesion molecule stimulation may also contribute to the progression of the hypertensive renal impairment.^{33,42,43} In animal models, interleukin-6 upregulates angiotensin II type I receptors and angiotensin-II mediated production of reactive oxygen species, provid-

ing an additional link between inflammation and activation of the renin-angiotensin-aldosterone system.²⁵⁻³⁰ Cytokines stimulate renin secretion and tubulointerstitial inflammation and may have an unfavourable effect on the adaptive responses of glomerular haemodynamics to impaired renal function, leading to augmented inflammatory reaction and finally to the development of MA.^{23,24,33,42-44} The above are further supported by the observation that angiotensin converting enzyme inhibitors and angiotensin II receptor blockers suppress free radical generation, nuclear factor-kB activity and CRP concentrations in healthy and hypertensive subjects.^{33,46} Such effects again raise the possibility that the suppression of proinflammatory reactions by these categories of antihypertensive drugs could be partially responsible for their beneficial effects in the prevention of microalbuminuria and further renal injury, along with the arrest of atherosclerosis progression.⁴²⁻⁴⁶

Secondly, adipose tissue-derived proinflammatory cytokines may play a key role in the combined insulin resistance syndrome and endothelial dysfunction state, of which MA seems to be an integrated marker.^{8,41,47,48} Adiponectin, an adipocyte-derived plasma protein, apart from regulating insulin sensitivity, acts as an endogenous antiatherogenic factor and is also associated with subclinical inflammation.^{41,47,48} In a recent study, we found an inverse relationship between ACR and adiponectin in newly diagnosed essential hypertensive subjects.⁴⁸ Moreover, MA was accompanied by attenuated levels of adiponectin in this setting. This suggests that the presence of MA identifies a subgroup of hypertensives who exhibit more stimulated adipocyte-associated proinflammatory reaction and may be at greater cardiovascular risk due to their augmented atherosclerotic burden. Since circulating adiponectin modulates vascular endothelium functions and inflammatory reaction, it is plausible that decreased levels of adiponectin could be partially responsible for the inflammatory processes observed in microalbuminuric hypertensives.^{39-41,47-49} In this sense, hypoadiponectinaemia, via its proinflammatory effects, may trigger the development of MA. Adiponectin and ACR may also be correlated because of their common underpinning with the hyperinsulinaemic state and due to the fact that MA could be considered as a component of the metabolic syndrome.^{8,10,14,48} Additionally, common genetic background may predispose certain hypertensives to both decreased adiponectin concentrations and augmented ACR.

Thirdly, the observed correlation of inflammatory markers with MA could be attributed to the fact that subclinical inflammation may cause injury to the renal

glomerulus directly, by pathways not related to the renin-angiotensin-aldosterone system as described above.^{8,36-39,49,50} Alternatively, MA and increased levels of low-grade inflammatory markers may simply be two facets of the same underlying biological mechanism associated with diffuse atherosclerotic disease.^{2,8,16,36,39,50-52}

All the abovementioned hypotheses must be further investigated in properly designed studies. Thus, in a further attempt to shed more light on the interrelationships between early renal dysfunction and alternative cascades of proinflammatory activation in essential hypertensives, we reported for the first time that microalbuminurics as compared to normoalbuminurics exhibited no difference in soluble CD 40 ligand and interleukin-18 values.⁵³ It could be maintained that the potential sources for soluble CD 40 ligand (i.e. T-lymphocytes, mononuclear phagocytes and endothelial cells) are perhaps not stimulated to a sufficient degree in the microalbuminuric state of non-diabetic essential hypertension, while both soluble CD 40 ligand and interleukin-18 exhibit no correlation with CRP-associated inflammatory pathway, as others have previously suggested.⁵³⁻⁵⁵ Consequently, both soluble CD 40 ligand and interleukin-18 could mirror more advanced inflammatory and atherosclerotic involvement than CRP and MA in this clinical setting.

Recently, a pioneering study provided a promising insight into the pathophysiological link between MA and inflammation. Only non-diabetic hypertensives were included in the protocol and subjects with MA, when compared to normoalbuminurics, exhibited significantly greater concentrations of CRP and fibrinogen.⁵⁰ In this sense, a novel pattern in the setting of essential hypertension emerged, the so-called "inflammatory MA" that characterises a subset of patients with a highly adverse risk profile. It seems that augmented UAE without evidence of subclinical inflammation is a result of isolated abnormalities of glomerular permeability or genetic predisposition, whereas MA combined with inflammation is associated with diverse mechanisms of vascular damage.^{8,49-51}

To conclude, MA is related to diverse inflammatory processes in the setting of essential hypertension, reflecting diffuse vascular dysfunction beyond the renal glomerulus. The recently reported data on the interrelationships of UAE with subclinical inflammation add a new facet to the progression of hypertensive cardiovascular atherosclerotic disease. Thus, whether or not we are ushering in an era in which lowering the cut-off value for diagnosing MA may facilitate prediction and improve overall cardiovascular risk stratification in this setting remains to be further elucidated in future studies.

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