To our knowledge, overt renal failure due to interstitial nephritis (unrelated to nephrotoxic administration) has not been previously reported among UC patients. In a study of 43 UC patients, 23% of cases had pathologic enzymuria (a marker of early renal tubular injury) that almost normalized with anti-inflammatory therapies [2]. Furthermore, a strong correlation between disease activity and tubular proteinuria has also been found in IBD patients [3]. These findings may support the hypothesis that a tubulointerstitial disorder may be a natural part of IBD. We recommend that clinicians consider tubulointerstitial disease and renal failure as possible extraintestinal manifestations of UC.

Conflict of interest statement. None declared.


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The search for a link between inflammation and hypertension—contribution from Bartter’s/Gitelman’s syndromes

Sir,

The involvement of inflammation and its mediators in cardiovascular pathophysiology and atherogenesis is increasingly recognized [1]. Plasma level of inflammatory molecules such as C-reactive protein (CRP); cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6); chemokines, such as monocyte chemoattractant protein (MCP-1) and adhesion molecules, such as P-selectin and leucocyte adhesion molecules, intercellular adhesion molecules (ICAM-1), are


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increased CRP level has also been reported to be a predictor of future cardiovascular disease [5,6]. In addition, further emphasising the involvement of inflammation and its mediators in cardiovascular pathophysiology is the importance of the search for a possible pathophysiological link between inflammation and hypertension; however, this awaits definitive clarification. Recent epidemiological observation of a systemic low inflammatory status preceding the onset of essential hypertension [7] strengthens this possibility, and thus stimulates the search for evidence that inflammation can promote hypertension. This issue was recently reviewed and discussed by Pauletto and Rattazzi [7] in their editorial comment published in NDT, which we read with great interest. These authors reviewed data from the literature and from their laboratory, supporting the possibility of a pathophysiological link between inflammation, hypertension and long-term complication such as atherogenesis [7]. The expression and plasma level of CRP, TNF-α, IL-6, MCP-1, P-selectin and ICAM-1 have been reported to be increased in these conditions and linked with nuclear transcription factor kappa B (NFκB) system activation [7]. Suggested mechanisms for the increase of these molecules and the activation of NFκB include the pro-inflammatory effect of angiotensin II (Ang II) via induction of NFκB, stimulation of NADPH oxidase activity with increased production of reactive oxygen species and oxidative stress followed by reduction of NO bioavailability, endothelial dysfunction and impairment of endothelial-dependent vasodilation [8].

Recent results from our ongoing studies in patients with Bartter’s/Gitelman’s syndromes (BS/GS) provide additional support and evidence for the existence and importance of a relationship between inflammation and hypertension. Of direct relevance is our recent demonstration in BS/GS patients of unchanged CRP plasma level, as well as acute phase reactants such as serum amyloid A, vascular cell adhesion molecules (VCAM) and ICAM, and inflammatory process-related cytokines such as IL-6 and TNF-α compared with healthy subjects [9]. BS/GS, caused by gene defects in specific kidney transporters and ion channels, present a puzzling clinical picture characterized by hypokalaemia, sodium depletion, activation of the renin-angiotensin–aldosterone system (RAAS), with increased plasma levels of Ang II and aldosterone, yet normo/hypotension, reduced peripheral resistance and hyporesponsiveness to pressor agents [10]. BS/GS have been considered a good human model to explore the mechanisms responsible for maintenance/controlling vascular tone and vascular remodelling [10,11]. In fact, understanding why patients with BS/GS do not develop hypertension and its complications such as cardiovascular remodelling and atherogenesis in spite of high Ang II and activation of RAAS, sheds considerable light on the cellular basis of hypertension. In BS/GS specifically, the short-term Ang II signalling pathway is blunted as documented by the increased regulator of G-protein signalling-2 [12] reduced Gαq gene and protein expression [13,14], and reduced related downstream cellular events such as intracellular Ca2+ and IP3 release, and PKC activity [10]. The long-term signalling pathway of Ang II, which modulates the cell redox state to promote cardiovascular remodelling and atherosclerosis, is also altered in BS/GS (reduced gene expression and response to Ang II of p22phox, TGF-β and reduced low density lipoproteins oxidative susceptibility and increased antioxidant power) [10,15,16]. We have also reported that RhoA/Rho kinase pathway is blunted, as shown by the reduced gene and protein expression and response to Ang II challenge of Rho kinase and plasminogen activator inhibitor-1 (PAI-1) [17], and by the reduced gene and protein expression of the upstream regulator of RhoA, p115RhoGEF [18]. The down-regulation of Rho/Rho kinase pathway occurred in a context of the increased level of the endothelial subunit of NO synthase (eNOS) mRNA alongside elevated urinary NO metabolites and cGMP levels [19,20]. Therefore, the reduced peripheral resistance, vascular hyporeactivity and normohypotension typical of BS/GS patients and their collection of biochemical characteristics present a mirror image of those found in hypertension. In addition, the BS/GS patients’ unchanged level of CRP and other inflammatory mediators included VCAM, ICAM, IL-6 and TNF-α [9], whose expression is known to be dependent of NFκB activity, also provide, in a human model of altered vascular tone regulation, confirmatory data in support of a relationship between inflammation and hypertension. In fact, evidence has been recently provided for the involvement of Rho/Rho-kinase signalling in CRP-induced atherothrombogenesis. CRP has been shown to activate Rho/Rho-kinase signalling, which through activation of NFκB activity results in PAI-1 expression, a known atherothrombogenic factor [21]. One possible mechanism for the CRP-mediated activation of NFκB is through the RhoA-induced phosphorylation of the inhibitory subunit of NFκB (IκB) [22] and the activation of IκB kinase by Rho kinase [23]. Relevant to this mechanism, we have preliminary data that show, in BS/GS patients compared with normotensive healthy subjects, an increased expression of IκB, while NFκB is unchanged; this is in keeping with a reduced activity of NFκB (L.A. Caló and E. Pagnin, personal observation).

Conflict of interest statement. None declared.

5. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA 2003; 290: 2945–2951
Sir,

Chronic kidney disease (CKD) influences the development and progression of cardiovascular disease. It has been demonstrated that the number of cardiovascular events, global mortality and the rate of hospitalization increase while glomerular filtration rate (GFR) decreases, independently of other cardiovascular risk factors [1]. Also, in accordance with National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines, it is known that the prevalence of cardiovascular risk factors, such as arterial hypertension and anemia, increase in every stage of CKD [2]. Obesity is likewise associated with an increased risk of cardiovascular disease and mortality. Data from the Framingham Heart Study show that overweight and obesity account for 23% of the cases of coronary heart disease in men and 15% in women [3]. Due to the high number of patients with CKD and cardiovascular disease in western populations, our aim was to learn the prevalence of obesity and other risk factors in patients attending general practices in two localities. Stages of CKD were defined by abbreviated-Modification of diet in Renal Disease Study (MDRD) or body surface-adjusted Cockcroft-Gault (CG) equations, following the recommendations of NKF-DQOJ guidelines, although MDRD and CG equations were originally developed to estimate GFR and creatinine clearance, respectively [2].

A total of 1000 patients were studied over a period of 1 year. Serum creatinine was determined by means of a kinetic Jaffé method with sample blank on a Hitachi 917 analyzer (Hitachi, Tokyo, Japan) with reagents from Roche (Roche Diagnostics, Mannheim, Germany). In order to avoid the bias secondary to the lack of a common calibration of the serum creatinine assay across different laboratories, GFR was estimated by equations before and after recalibrating serum creatinine (‘new’ serum creatinine = 1.08 × serum creatinine − 0.215) [4].

We found that the relationships between body mass index (BMI) and GFR were different, depending on the equation used. While CG-estimated GFR was directly related with BMI ($R = 0.077$, $P = 0.016$), MDRD-GFR was inversely correlated ($R = -0.140$, $P < 0.001$) (Figure 1). Similar results were found after recalibrating creatinine (CG-CGF = 0.070, $P = 0.027$; MDRD-GFR = -0.110, $P = 0.001$). The relationships between GFR and BMI were different in males and females. In 367 male patients, CG-GFR was directly related with BMI ($R = 0.233$, $P < 0.001$), while MDRD-GFR was not significantly related ($R = -0.026$, $P = 0.627$). On the other hand, in 633 female patients, although CG-GFR was not significantly related with BMI ($R = 0.010$, $P = 0.811$), MDRD-GFR remained inversely correlated ($R = -0.199$, $P < 0.001$).

BMI means were significantly different in stages 2 and 3 (26.8 ± 4.4 vs 28.1 ± 4.6 kg/m², $P = 0.001$) using the MDRD equation, but not with CG-GFR (26.8 ± 4.2 vs 27.0 ± 4.2 kg/m², $P = 0.605$). After recalibrating creatinine, BMI means remained significantly different in stages 2 and 3 (27.1 ± 3.9 vs 28.4 ± 4.0 kg/m², $P = 0.020$) using the MDRD equation, but not with CG-GFR (27.4 ± 4.0 vs 26.6 ± 4.4 kg/m², $P = 0.064$). The percentage of overweight patients was significantly lower in stage 2 with respect to stage 3 (64.0 vs 75.8%, $P = 0.007$) defined by MDRD, but differences were not significant with CG (65.5 vs 67.0%, $P = 0.712$). Similarly, the percentage of obese patients was significantly lower in stage 2 than in stage 3.