Table 1. Independent Predictors of Urinary Albumin Excretion in Type 2 Diabetic Patients

Parameter	Correlation Coefficient	*P*
Glycated hemoglobin	0.27	<.05
Urinary tumor necrosis factor-α	0.36	<.01
Time of diabetes	0.42	<.001
C-reactive protein	0.50	<.001

more, urinary TNF-α excretion increased as diabetic nephropathy progressed. Simple univariate analysis showed that serum TNF-α was significantly related to urinary albumin excretion, but multiple regression analysis demonstrated that CRP and urinary TNF-α were independent predictors of urinary albumin excretion (Table 1).

An interesting aspect of our study was that although both serum and urinary TNF-α levels were greater in patients with diabetes with increased urinary albumin excretion, there was no significant correlation between these parameters.[11] That urinary excretion of TNF-α did not correlate with serum levels suggests that this cytokine can be produced within the kidneys. It is known that in these organs, endothelial, mesangial, glomerular, and tubular epithelial cells are able to produce cytokines. Moreover, in vitro studies have demonstrated increased expression of TNF-α messenger RNA in glomeruli of diabetic rats.[12]

In conclusion, serum and urinary inflammatory parameters have been shown to be independent predictors of urinary albumin excretion in type 2 diabetic patients. Interestingly, our recent studies suggest the production of pro-inflammatory cytokines within the kidneys. Therefore, in addition to metabolic and hemodynamic factors, inflammation is introduced as a potential pathogenic mechanism of diabetic nephropathy, with locally released cytokines, such as TNF-α, in the development of renal lesion through several mechanisms, including direct cellular injury, alteration of the glomerular protein permeability barrier, and development of intrarenal inflammatory damage.[11]

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REPLY

To the Editor:

We would like to thank Drs Navarro and Mora for their calling to attention the possible involvement of IL-18 in diabetic nephropathy in our study. Although IL-18 may play a role in the pathophysiology of diabetic nephropathy, besides the roles of TNF-α and IL-6, there are several problems with such a conclusion. First, as pointed out, the patients had several confounding factors, such as hypertension, cigarette smoking, and treatment with statin or aspirin, which may have been partly responsible for the increased serum IL-18 concentration in our diabetics, and we did not exclude these factors completely. However, since an acute rise in blood glucose level increases serum IL-18,[1] it is certain that IL-18 is related to diabetes. Second, though serum IL-18 increased with the progression of albuminuria, a multiple regression analysis of independent predictors of urinary albumin excretion was not performed in our study. Since IL-18 is a pro-inflammatory cytokine, inflammation within the kidney may be an independent factor for albumin excretion. Third, we did not measure IL-18 concentration in urine, although the urinary excretion of IL-18 is known to correlate with disease activity in patients with a minimal change nephrotic syndrome.[2] Moreover, it has been reported that the urinary excretion of IL-6 does not reflect its serum concentration,[3] which was also observed for TNF-α in the study of Navarro et al. Therefore, the serum concentration of IL-18 does not necessarily reflect the urinary excretion of IL-18, which is considered to be derived from its concentration in the

kidney. Finally, the cause of increased IL-18 in serum has not been clarified. In situ hybridization of IL-6 has demonstrated that IL-6 mRNA is expressed by glomerular resident cells and interstitial cells in the kidneys of patients with diabetic nephropathy.[4] Therefore, IL-18 may also be expressed in these tissues. To localize the expression of IL-18 in patients with diabetic nephropathy, measurement of urinary IL-18 and elucidation of its relationship to its serum counterpart are required, in addition to immunohistochemical and in situ hybridization analyses of IL-18.

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