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Original article

Value of urinary levels of interleukin-6, epidermal growth factor, monocyte chemoattractant protein type 1 and transforming growth factor β1 in predicting the extent of fibrosis lesions in kidney biopsies of patients with IgA nephropathy☆

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ABSTRACT

Objective: To analyse the associations between urinary levels of IL-6 EGF, MCP-1 and TGFβ1 and clinical, biochemical and histopathological characteristics in patients with primary IgA nephropathy and their ability to predict the extent of lesions of glomerular and/or interstitial sclerosis.

Patients and methods: A total of 58 patients with IgA nephropathy were studied. We determined the urine levels of IL-6, EGF, MCP-1, and TGFβ1 at the time of diagnosis. The extent of glomerular and interstitial fibrosis was analysed by quantitative morphometry and kidney biopsies were classified according to the Oxford criteria. We analysed the ability of these molecules to predict the extent of glomerular and interstitial fibrosis lesions.

Results: IL-6, TGFβ1 and MCP-1 were associated with focal glomerulosclerosis and interstitial fibrosis extension but not with the presence of mesangial, extracapillary or endocapillary proliferation. EGF showed a negative association with interstitial fibrosis. By categorising patients according to the Oxford classification, patients with T1 and T2 scores had significantly higher levels of IL-6, MCP-1, TGF-β1 and significantly lower levels of EGF than patients with T0 scores. By multiple regression and logistic regression analyses, the levels of MCP-1,

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IL-6 and EGF were independent predictors of the fibrosis surface, after adjusting for age and eGFR.

Conclusion: The urinary concentration of IL-6, EGF and MCP-1 provides additional information that significantly improves the estimation of the surface of interstitial fibrosis in patients with IgA nephropathy.

Valor de los niveles urinarios de interleucina 6, factor de crecimiento epidérmico, proteína quimioatractante de monocitos de tipo 1 y factor de crecimiento transformante β1 para la predicción de la extensión de las lesiones de fibrosis en biopsias de enfermos con nefropatía IgA

Palabras clave:
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Factor de crecimiento transformante β1
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RESUMEN

Objetivo: Analizar las asociaciones entre el nivel urinario de IL-6, EGF, MCP-1 y TGFβ1 y las características clínicas, bioquímicas y anatomopatológicas en enfermos con nefropatía IgA primaria y determinar su capacidad para realizar una estimación de la extensión de las lesiones de esclerosis glomerular e intersticial.

Pacientes y métodos: Se estudió a 58 enfermos con nefropatía IgA. Se determinaron los niveles urinarios de IL-6, EGF, MCP-1 y TGFβ1 en el momento del diagnóstico. Tras realizar un análisis de la extensión de las lesiones renales mediante morfometría cuantitativa y mediante los criterios de Oxford, se analizó la capacidad de dichas moléculas para estimar la extensión de las lesiones glomerulares e intersticiales de fibrosis.

Resultados: La IL-6, MCP-1 y TGF-β1 se asociaron a glomeruloesclerosis focal y a la extensión de la fibrosis intersticial, pero no a la presencia de proliferación mesangial, intracapilar o extracapilar. EGF presentó una asociación negativa con la fibrosis intersticial. Al categorizar a los enfermos según la clasificación de Oxford, los enfermos con *scores* T1 y T2 presentaron niveles significativamente superiores de IL-6, MCP-1 y TGFβ1, y niveles de EGF significativamente inferiores que los enfermos con T0. Tanto mediante regresión múltiple como mediante regresión logística, los niveles de MCP-1, IL-6 y EGF fueron predictores independientes de la superficie de fibrosis, tras ajustar por edad y FGe.

Conclusión: La determinación de la concentración urinaria de IL-6, EGF y MCP-1 proporciona una información adicional que mejora de forma significativa la estimación de la superficie de fibrosis intersticial.

Introduction

Mesangial IgA nephropathy is one of the most common primary nephropathies and has a very variable clinical course that ranges from indolent forms to those with rapidly progressive kidney failure.[1–4] Approximately 20–25% of patients go on to develop long-term chronic kidney failure. Poor prognosis factors identified to date include the presence of kidney failure, proteinuria that persistently remains above 1 g/day, arterial hypertension and mesangial C4d deposits.[5] The extent of the glomerular and interstitial lesions has prognostic value in untreated patients, but not in those who have undergone treatment with glucocorticoids or other immunomodulators.[6] At present, it is accepted that, after the mesangial deposition of IgA, the kidney lesion results from the activation of the complement through either the alternative pathway, the lectin pathway or both.[7] This process results in the generation of various cytokines and growth factors that act as mediators of kidney damage, stimulating cell proliferation and an increase in the production of the mesangial matrix.[7,8] There are also data that indicate that the cytokines produced by the mesangial cell may lead to alterations in the structure and function of the podocytes and proximal tubule cells, which are related to the appearance of glomerulosclerosis and interstitial fibrosis lesions.[9–11] Of the different molecules that may be involved, interleukin-6 (IL-6),[12–15] epidermal growth factor (EGF),[16–18] monocyte chemoattractant protein type 1 (MCP-1)[19–23] and transforming growth factor β1 (TGFβ1)[24] have been the subject to detailed studies. The available data demonstrate a significant correlation between the urinary excretion and the renal expression of IL-6[15] and EGF,[15] as well as a significant correlation between urinary levels of IL-6,[15,16] EGF,[15,17,18] MCP-1[22,23] and TGFβ1[24] and the extent of the interstitial fibrosis lesions and tubular atrophy. These data indicate that the urinary levels of these cytokines and growth factors could