



Increased Serum Macrophage Migration Inhibitory Factor (MIF) Concentrations as Potential Risk Factors in Steroid-Resistant Nephrotic Syndrome

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Abstract

Background: Patients with steroid-resistant nephrotic syndrome (SRNS) tend to progress to end-stage renal disease (ESRD). Although the risk of steroid resistance depends mainly on histopathology, other factors, such as cytokines, may contribute to this condition. Cytokine macrophage Migration Inhibitory Factor (MIF) acts to counter-regulate glucocorticoids, which have become the main drug therapy for NS. The aim of this study was to evaluate whether raised serum MIF levels represent a potential risk factor for SRNS patients.

Methods: A prospective study was conducted in a multi-centre hospital and school in Medan, Sumatera, Indonesia. A total of 99 subjects were included in the study consisting well child (n=31) and NS patients (n=68). Serum macrophage migration inhibitory factor (MIF) was collected and measured. Patient's data about demographics, blood pressure, threshold steroid dosage at inclusion, urinary albumin creatinine ratio, plasma angiotensin II and serum MIF were compared between groups.

Results: Majority of subjects showed MIF levels between 10.4 and 31.8 ng/ml. Group SRNS had significantly higher serum MIF (median 31.9 (14.3-117.2) ng/mL) compared to the levels in group SSNS (median 21.8 (10.4-31.8) ng/mL) and well child (median 24.1 (11.4-31.1) ng/mL). Half of SRNS subjects (n=20) showed higher levels of MIF. In logistic regression analysis, diastolic blood pressure and plasma angiotensin II levels were found to be independently associated with higher serum MIF. There was a weak positive linear correlation between concentration of MIF serum and angiotensin II plasma.

Conclusions: The serum MIF levels in group SRNS is higher than SSNS and well child. Diastolic blood pressure and plasma angiotensin II levels were found to be independently factors associated with higher MIF serum.

Keywords: Macrophage; Migration inhibitory factor; Hypertension; Steroid resistant; Nephrotic syndrome

Introduction

Idiopathic Nephrotic Syndrome (NS) represents a heterogeneous group of glomerular disorders occurring mainly in children. Generally, NS is divided into steroid sensitive (SSNS) and Steroid Resistant Nephrotic Syndrome (SRNS), depending on the response to steroid therapy. SRNS accounts for more than 10% of children who progress to chronic kidney disease [1]. This group of NS has in common permanent loss of selectivity of the glomerular barrier to protein filtration. It has been recognized that patients with persistent high grade proteinuria are more likely to develop chronic kidney disease than patients with low grade or no proteinuria [2].

The risk of steroid resistance among NS children is affected by many factors. While the risk of steroid resistance depends mainly on histopathology, other factors, such as cytokines, may contribute to this condition. The production of MIF cytokine represents a physiologic counter regulator to the anti-inflammatory and immunosuppressive effects of glucocorticoids [3]. This cytokine is induced by glucocorticoids, and then acts to counter-regulate the inflammatory action of glucocorticoids [4]. Higher MIF levels can inhibit the action of glucocorticoids [5]. While MIF is central to determining chronicity in steroid resistance [6], data regarding serum MIF levels in SRNS are scarce.

Renal macrophage infiltration may persist if there are persistent MIF cytokine, originally described as a T cell-derived cytokine.

Liao et al. demonstrated an increase renal macrophage infiltration in angiotensin II-induced hypertension [7]. It was shown that T lymphocyte is required for angiotensin II to induce vascular remodeling. Furthermore, angiotensin II increased the expression of macrophage infiltration in the vascular neointima [8].

The role of higher serum MIF levels and their correlation with level of plasma angiotensin II have not yet been elucidated especially as risk factor for steroid resistance in NS. One study reported elevated serum MIF concentrations in chronic kidney disease patients [9]. However, that study focused on adults with a wide range of glomerular filtration rates. Furthermore, since most mechanical aspects of serum MIF action have not yet been fully elucidated, the current study sought to determine whether higher serum MIF levels are a potential risk factor for SRNS patients.

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Received October 20, 2013; Accepted November 18, 2013; Published November 22, 2013

Citation: Ramayani OR, Sekarwana N, Trihono PP, Sadewa AH, Lelo A, et al. (2013) Increased Serum Macrophage Migration Inhibitory Factor (MIF) Concentrations as Potential Risk Factors in Steroid-Resistant Nephrotic Syndrome. J Nephrol Ther 3: 142. doi:10.4172/2161-0959.1000142

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