Fractional Excretion Magnesium (FE Mg) in Systemic Lupus Erythematosus

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Background: *Tubulointerstitial fibrosis is an index of clinical severity. FE Mg has been delineated to correlate directly with the magnitude of tubulointerstitial fibrosis in clinical setting of glomerulonephropathy. A correlation between FE Mg tubulointerstitial fibrosis has never been assessed in nephritis associated with systemic lupus erythematosus.*

Material and Method: *Thirty-six patients diagnosed of having lupus nephritis were included for the determination of renal functions namely creatinine clearance, FE Mg, urinary protein. Of these 36 patients, 18 patients were associated with intact tubulointerstitial structure (group I) and 18 age matched patients were associated with tubulointerstitial fibrosis (group II)*

Results: *The mean FE Mg observed in group I was 1.5 $\pm$ 0.3 which differed significantly from that observed in group II; 2.6 $\pm$ 1; p = 0.006. CCr, total urinary protein, systolic and diastolic pressure were not significantly different between the two groups.*

Conclusion: *FE Mg is a sensitive marker for the detection of tubulointerstitial disease in lupus nephritis. It is useful in early screening of disease severity in systemic lupus erythematosus.*

Keywords: *Lupus nephritis, FE Mg, Tubulointerstitial fibrosis, Tubular function, Clinical severity*

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Tubulointerstitial disease is presently considered a final common pathway of progressive renal disease eventually leading to end-stage renal failure[1-3]. A search for functional study that would correlate with the structural change of tubulointerstitial compartment is mandatory. In this regard, the presence or absence of tubulointerstitial disease does not correlate with the change in glomerular function namely creatinine clearance or glomerular filtration rate since the state of hyperfiltration secondary to hemodynamic maladjustment characterized by preferential constriction of the efferent arteriole, has been commonly encountered in a severe form of glomerulonephropathies associated with tubulointerstitial fibrosis or chronic renal failure[4]. However, a tubular function test by mean of fractional excretion of magnesium has recently been reported to correlate directly with the magnitude of tubulointerstitial fibrosis in a clinical setting of nephrosis and can differentiate the minimal change nephrosis or mesangial proliferative disease with intact tubulointerstitial structure from focal segmental glomerulosclerosis which is commonly associated with tubulointerstitial fibrosis[5]. Therefore, it was the purpose of the present study to assess FE Mg in correlation with the status of tubulointerstitial fibrosis in 36 patients with lupus nephritis.

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Material and Method

Thirty-eight patients who had clinically fulfilled the criteria of systemic lupus erythematosus with renal involvement were subject to the following studies. Two patients were excluded due to poor compliance and incomplete investigation.

I. Renal Functions

(A) Glomerular function

Glomerular function was determined by measuring the 10-hour endogenous creatinine clearance (CCr) and the value was converted to the body surface area of 1.73m^2 by the method of calculation below:

$$\text{Body surface area} = \sqrt{\frac{\text{body weight (kg) x height (cm)}}{3600}}$$

(B) Tubular function

Tubular transport was assessed by a 10-hour urine collection as previously described[5]. Diuretics were not administered during or within 24 hours before the test. Briefly, after a regular supper, no additional food except drinking water ad lib was allowed. The patients were instructed to void at 7 pm, and then urine was collected from 7 pm to 5 am. Clotted blood from venipuncture was drawn at the end of the test for the analysis of creatinine and magnesium levels. Urine samples were analyzed the same as blood samples by the Renal Metabolic Laboratory Unit. Analysis of (i) creatinine was determined by the method described by Faulkner and King and (ii) magnesium was determined by Atomic Absorption Spectophotometer (model 1100 B; Perkin Elmer, Norwalk, CT). A reflection of indirect tubular transport was derived from the determination of FE Mg which was calculated through the formula.

$$\text{FE Mg} = \frac{\text{U/P magnesium}}{\text{U/P creatinine}} \times 100$$

II. Renal Histopathologic Study

Kidney tissue was fixed in 4% buffered formation and embedded in paraffin. Sections (3 μm) were prepared and stained with hematoxylin and eosin, periodic acid-Schiff reagent, silver methenamine and Masson trichrome. At least eight renal sections were prepared from each case and examined. The number of glomeruli ranged from 7 to 37. Tubulointerstitial fibrosis was quantitated in a single-blind fashion by a pathologist who had no information regarding the tubular functional value of each individual case. Tubulointerstitial fibrosis was scored semiquantatively in biopsy specimens stained with periodic acid-Schiff, Masson trichrome, and silver stain by means of the following scoring system: O, normal interstitium and tubules; +, mild fibrosis (1% to 25%) with minimal thickening between the tubules; ++, moderate interstitial thickening between the tubules (26% to 50%); and +++, severe fibrosis with severe interstitial thickening between the tubules (> 50%).

Statistical analysis

Comparison of the sample mean of two quantitative variables was determined by the nonparametric method using the Mann-Whitney u test. The difference between groups was performed by the Student's unpaired t-test. A p less than 0.05 was considered significant.

Results

Of the remaining 36 patients with lupus nephritis, 18 patients showed intact tubulointerstitial structure (group I). 18 patients were associated with various degrees of tubulointerstitial fibrosis (group II). Table 1 shows that there were no significant differences in age, systolic and diastolic blood pressure, creatinine clearance and total urinary protein between the two groups. The mean value of FE Mg observed in group I was significantly less than that of group II.

Discussion

The result of the present study indicates that creatinine clearance cannot differentiate whether there is presence or absence of tubulointerstitial fibrosis. However, a normal value of FE Mg is associated with an intact tubulointerstitial structure and that an enhanced FE Mg reflects tubulointerstitial fibrosis. Such correlation between the FE Mg and tubulointerstitial structure needs further clarification. FE Mg is dependent upon 2 crucial functions that relate to the tubular cells. First, it depends upon the ability of tubular cell to reabsorb the filtered magnesium from the glomerular filtrate. Second, magnesium is the most abundant intracellular cation (next to potassium), a normal tubular function would preserve this portion of intracellular magnesium as well as maximally reabsorb the filtered magnesium from the glomerular filtrate, therefore, it yields a low value of FE Mg. In contrast, any disturbance to the intracellular structure and function of the tubular epithelium would affect tubular magnesium wastage as well as its reabsorption capacity and thereby increase in value of FE Mg above the normal range. The finding of FE Mg in the present study correlates with the study of Futrakul[5] reported in a clinical setting of nephrosis. FE Mg

Table 1. Clinical and laboratory profiles in lupus nephritis

	Group I* n = 18 with no TIF	p value	Group II* n = 18 with no TIF
Age, years	11±2	NS	12±2
Systolic blood pressure (mm Hg)	118±14	NS	117±13
Diastolic blood pressure (mm Hg)	72±10	NS	75±10
FE Mg, %	1.5±0.3	0.006	2.6±1
CCr, ml/min/1.73m^2	70±22	NS	69±17
Protein, g/24 h	1.4±0.9	NS	1.4±0.7

TIF = tubulointerstitial fibrosis

* Presented as Mean ± Standard deviation

appears to be sensitive since it has been proved to correlate directly with the magnitude of tubulointerstitial fibrosis by multiple regression analysis. In addition, FE Mg is noted to correlate inversely with the peritubular capillary flow which supplies the tubulointerstitial compartment[7]. Since renal perfusion deficit[8] or chronic ischemia and chronic hypoxia[9-11] have been believed to be the determinant of renal disease progression, a direct or indirect information relevant to the renal perfusion status would be beneficial to the therapeutic and preventive strategies of renal disease progression; therefore, FE Mg would easily provide an indirect information regarding the peritubular capillary flow in particular in a situation where the facility to perform intrarenal hemodynamic study is not available. From the practical point of view, FE Mg has been useful in assisting to titrate the therapeutic doses of vasodilators. In case of good therapeutic response, FE Mg would be lower than the pre-treatment value and on the contrary, FE Mg would progressively enhance in case of therapeutic unresponsiveness[12].

References

1. Nath KA. Tubulointerstitial changes as a major determinant in pregression of renal damage. Am J Kidney Dis 1992; 1: 1-17.
2. Eddy AA. Molecular insights into renal interstitial fibrosis. J Am Soc Nephrol 1996; 7: 2495-508.
3. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med 1998; 339: 1448-56.
4. Futrakul N, Futrakul P. Microvascular disease and renal disease progression. J Med Assoc Thai 2004; 87: 854-9.
5. Futrakul P, Yenrudi S, Futrakul N, Sensirivatana R, Kingwatanakul P, Jungthirapanich J, et al. Tubular function and tubulointerstitial disease. Am J Kidney Dis 1999; 33: 886-91.
6. Wacker WEC, Parisi AF. Magnesium metabolism. N Engl J Med 1968; 278: 658-63.
7. Futrakul N, Yenrudi S, Futrakul P, Cherdkiatkul T, Laohaphaibul A. Peritubular capillary flow and tubular function in idiopathic nephrotic syndrome. Nephron 2000; 85: 181-2.
8. Futrakul P, Sitprija V, Yenrudi S, Poshyachinda M, Sensirivatana R, Watana D, et al. Glomerular endothelial dysfunction determines disease progression: a hypothesis. Am J Nephrol 1997; 17: 533-40.
9. Manotham K, Tanaka T, Matsumoto M, Ohse T, Inagi R, Miyata T, et al. Transdifferentiation of cultured tubular cells induced by hypoxia. Kidney Int 2004; 65: 1-10.
10. Ohashi R, Kitamura H, Yamanaka N. Peritubular capillary injury during the progression of experimental glomerulonephritis in rats. J Am Soc Nephrol 2000; 11: 47-56.
11. Norman JT, Stidwill R, Suiger M, Fine LG. Angiotensin II blockade augments renal cortical microvascular pO_2 indicating a novel, potentially renoprotective action. Nephron Physiol 2003; 94: 39-46.
12. Futrakul N, Tohsukhowong P, Patumraj S, Siriviriyakul P, Tipprukmas N, Futrakul P. Treatments of hemodynamic maladjustment and oxidative stress prevent renal disease progression in chronically severe glomerulonephritides. Ren Fail 2003; 25: 839-44.

ค่า Fractional excretion magnesium (FE Mg) และการตายชนิดเพิ่มพังผืดของเนื้อไตในโรคลูปัส

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เพื่อศึกษาความสัมพันธ์ระหว่างค่า FE Mg และการตายชนิดเพิ่มพังผืดของเนื้อไตในผู้ป่วยโรคลูปัส (systemic lupus erythematosus) โดยศึกษาในผู้ป่วยเด็กโรคลูปัส (SLE) จำนวน 36 ราย ที่มีความผิดปกติที่ไต (lupus nephritis) และได้รับการตรวจพยาธิสภาพของเนื้อไต (renal biopsy) แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มที่ 1 ไม่มีการตายชนิดเพิ่มพังผืดของเนื้อไต (tubulointerstitial fibrosis) และกลุ่มที่ 2 มีการตายชนิดเพิ่มพังผืดของเนื้อไต ใช้วิธีการเก็บปัสสาวะ 10 ชั่วโมงเพื่อตรวจการทำงานของไต ได้แก่ creatinine clearance, FE Mg และปริมาณโปรตีนในปัสสาวะ ผลการศึกษาพบว่าค่าเฉลี่ยของ FE Mg ในกลุ่มที่ 1 (ไม่มีการตายชนิดเพิ่มพังผืดของเนื้อไต) เท่ากับ 1.5 $\pm$ 0.3 มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p = 0.006$) จากกลุ่มที่ 2 ที่มีการตายชนิดเพิ่มพังผืดของเนื้อไต (ค่าเฉลี่ย FE Mg เท่ากับ 2.6 $\pm$ 1) สรุปผลการศึกษาพบว่าค่า FE Mg มีประโยชน์ในการคัดกรองผู้ป่วยโรคลูปัส (SLE) ที่มีพยาธิสภาพของเนื้อไตแบบการตายชนิดเพิ่มพังผืด (tubulointerstitial fibrosis)