

Serum concentration and urinary excretion of β_2 -microglobulin and microalbuminuria in familial Mediterranean fever

Umit Saatci, Sila Ozdemir, Seza Ozen, Aysin Bakkaloglu

Abstract

Familial Mediterranean fever is characterised by recurrent and self limited attacks of fever and polyserositis and its devastating complication is the development of renal amyloidosis. In order to detect the presence of early glomerular and tubular damage in patients with familial Mediterranean fever and to assess the possible role of β_2 -microglobulin in the inflammatory attacks of this disease, serum and urine β_2 -microglobulin concentrations and microalbuminuria were evaluated in these patients. A total of 20 patients with familial Mediterranean fever were studied on and off colchicine treatment; seven of these patients developed a familial Mediterranean fever attack when they were off treatment. During the familial Mediterranean fever attacks serum β_2 -microglobulin concentrations decreased, whereas fractional excretion of β_2 -microglobulin, urine β_2 -microglobulin creatinine, and urine albumin/creatinine ratios increased. We conclude that glomerular and tubular functions deteriorate during the attacks. Further studies are needed to discover the effector(s) causing these transient glomerular and tubular disorders.

(Arch Dis Child 1994; 70: 27-29)

Familial Mediterranean fever is characterised by recurrent and self limited attacks of fever and polyserositis in the form of peritonitis, arthritis, or pleurisy.¹ Although the genetic defect has been identified in familial Mediterranean fever, the pathogenesis still remains unclear. A number of immunological parameters have been studied previously in these cases and it has been shown that CD8+ T lymphocytes are decreased in number.^{2,3}

β_2 -Microglobulin is distributed widely over the surface of many cells in the form of light chain molecules of major histocompatibility antigen class I HLA.^{4,5} Class I HLA interact with CD8+ cells during cytotoxic reactions. Thus, serum β_2 -microglobulin concentrations may be expected to correlate with suppressor T cell numbers.^{6,7} Serum β_2 -microglobulin is known to be increased during inflammatory disorders. β_2 -Microglobulin is subject to glomerular filtration and is reabsorbed almost completely in renal tubules.⁸ Therefore, increased urinary excretion of this protein is likely to be due to damage of tubular structures with decreased tubular reabsorption.⁹

An integral feature of familial Mediterranean fever is the development of renal amyloidosis.¹⁰ We and others have shown that prophylactic treatment with colchicine decreases the attacks and prevents the development of amyloidosis.^{11,12} The first clinical sign of renal amyloidosis is the detection of proteinuria. Thus, in familial Mediterranean fever patients, early renal glomerular and tubular damage may be expected to present with microalbuminuria and increased urinary β_2 -microglobulin excretion, respectively, before the detection of proteinuria by conventional techniques.^{13,14}

In this study, we have attempted to detect the presence of early glomerular and tubular damage in patients with familial Mediterranean fever by microalbuminuria and urine β_2 -microglobulin excretion, respectively, both during attacks and on and off colchicine treatment. We have also tried to assess whether β_2 -microglobulin played a part in the pathogenesis of the disease and whether colchicine was effective in this pathway.

Patients and methods

The study group consisted of 20 patients with familial Mediterranean fever (eight girls and 12 boys); the age range was 7-15 with a mean of 10.1 years. None of the patients had proteinuria on routine urinalysis. These patients were grouped as follows: the 'initial group' consisted of 20 patients who were on colchicine prophylaxis and had no attacks within the previous two months. After blood and urine sampling of these 20 patients, colchicine was discontinued for three weeks unless an acute attack developed during this period. The 'attack-free group' was defined by 13 of these 20 patients who did not have any attacks during this three week period. Samples were obtained at the end of three weeks, before restarting colchicine in this group. The remaining seven patients had an attack before the end of the three week period after the withdrawal of colchicine. These seven patients were defined as the 'attack group'. Blood and urine samples were obtained from these seven patients during the first 12 hours of the familial Mediterranean fever attack and then colchicine was started. Subsequent sampling from the subjects in this group was performed three weeks after the acute attack, while they were on colchicine treatment ('post-attack group').

The control group consisted of 10 healthy age and sex matched children with an age range of 7-15, mean 10.4 years (four girls and six boys).

Department of
Paediatric Nephrology,
Hacettepe University
Faculty of Medicine,
Sihhiye 06100, Ankara,
Turkey
Umit Saatci
Sila Ozdemir
Seza Ozen
Aysin Bakkaloglu

Correspondence to:
Professor Saatci.
Accepted 28 July 1993

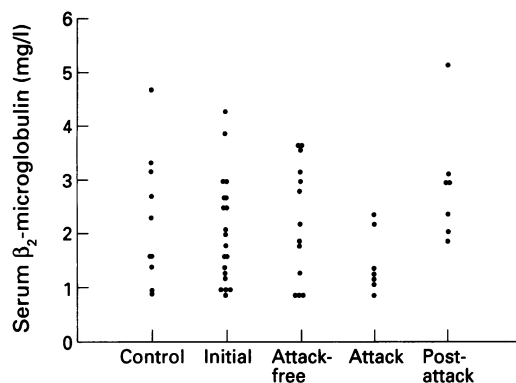


Figure 1 Serum β_2 -microglobulin concentrations in patients with familial Mediterranean fever and control group.

Routine urinalysis and biochemical analysis of blood samples were performed in all patients. Blood samples for β_2 -microglobulin were drawn from peripheral veins, centrifuged, and stored at -20°C until assayed. Urine samples were collected 2–3 hours after the first void and the pH of the samples was adjusted to between 6 and 8 with 1.0 N sodium hydroxide. Serum and urine β_2 -microglobulin concentrations were determined by a radioimmunoassay method (Euro-Diagnostics BV Netherlands). Microalbuminuria was determined by an enzyme linked immunosorbent assay (ELISA) using protein microdetermination (Sigma Diagnostics, USA).

Mann-Whitney U and Wilcoxon tests were performed for statistical analysis of the data.

Results

The overall results are displayed in the table.

SERUM β_2 -MICROGLOBULIN CONCENTRATIONS

There was no significant difference between the healthy subjects and patients with familial Mediterranean fever who were free of symptoms. Serum β_2 -microglobulin concentrations decreased in six of the seven patients during the acute familial Mediterranean fever attack when compared with their previous concentrations ($n=6$, $p<0.05$; fig 1). However, when the results from all seven patients were analysed, there was no significant difference in β_2 -microglobulin concentrations during the attack phase and after treatment with colchicine. Serum β_2 -microglobulin concentrations increased significantly three weeks after the attack. The patients had been started on colchicine once an attack was observed ($n=7$, $p<0.02$).

URINE β_2 -MICROGLOBULIN/CREATININE RATIO

This ratio significantly increased during a

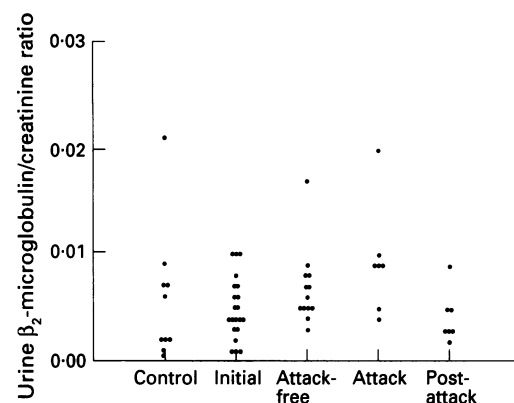


Figure 2 Urine β_2 -microglobulin/creatinine ratio in patients with familial Mediterranean fever and control group.

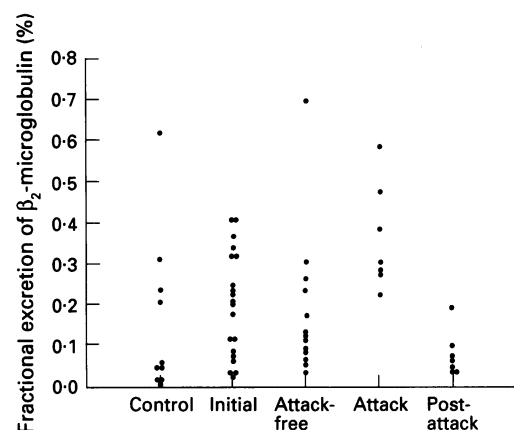


Figure 3 Fractional excretion of β_2 -microglobulin in patients with familial Mediterranean fever and control group.

familial Mediterranean fever attack compared with initial values ($p<0.05$). Three weeks after the attack the ratio decreased significantly ($p<0.05$; fig 2).

FRACTIONAL EXCRETION OF β_2 -MICROGLOBULIN

Excretion of β_2 -microglobulin significantly increased when the attack values were compared with both those previous to the attack ($p<0.05$) and to healthy controls ($p<0.05$). Excretion returned to normal three weeks after the termination of the attack ($p<0.02$; fig 3).

URINE ALBUMIN/CREATININE RATIO

This ratio was higher in the attack patients compared with the control group ($p<0.05$) and to their own previous values while on colchicine ($p<0.05$). Urine albumin/creatinine ratio decreased significantly and returned to the normal range three weeks after the attack ($p<0.05$).

Overall results of the patient and control groups

	Control (n=10)	Initial (n=20)	Attack-free (n=13)	Attack (n=7)	Post-attack (n=7)
Serum β_2 -microglobulin (mg/l)	2.3 (0.4)	2.1 (0.2)	2.3 (0.3)	1.5 (0.2)	3.0 (0.4)
Urine β_2 -microglobulin/creatinine ratio	0.006 (0.002)	0.005 (0.001)	0.007 (0.001)	0.009 (0.002)	0.004 (0.001)
Fractional excretion of β_2 -microglobulin (%)	0.16 (0.06)	0.20 (0.03)	0.19 (0.05)	0.37 (0.05)	0.09 (0.02)
Urine albumin/creatinine ratio	0.08 (0.02)	0.10 (0.01)	0.12 (0.02)	0.61 (0.41)	0.12 (0.03)

Discussion

The pathogenesis of the inflammatory attack and polyserositis in familial Mediterranean fever remains obscure. Immunological abnormalities that may accompany the acute inflammatory process in familial Mediterranean fever have been previously investigated; in untreated patients, an increase in the CD4+/CD8+ T lymphocytes has been reported.^{2,3}

β_2 -Microglobulin is a low molecular weight protein found on the cellular membranes of all nucleated cells, especially lymphocytes.⁵ Serum β_2 -microglobulin increases in malignancies and in autoimmune and rheumatic diseases.¹⁴ In cases of rejection there was a marked rise in serum β_2 -microglobulin whereas there was only a moderate increase in urine; this was attributed to the degradation of cell surface or to the functional properties related to T cell activation. On the other hand, urinary β_2 -microglobulin excretion increases in tubular diseases and renal tubular damage can be demonstrated by the increased urinary excretion of β_2 -microglobulin.⁹ Prischl *et al* have demonstrated an increase in urine β_2 -microglobulin whereas the serum values decreased in cyclosporin nephrotoxicity.¹⁵ The authors have suggested that this reflects renal tubular damage caused by cyclosporin.

Both the urinary β_2 -microglobulin/creatinine ratio and the fractional excretion of β_2 -microglobulin significantly increased during a familial Mediterranean fever attack when compared with the period when these patients were on colchicine treatment and free of symptoms. The increased concentrations returned to normal three weeks after colchicine treatment.

As serum concentrations of β_2 -microglobulin decreased during the attack, the increase of urinary concentrations cannot be explained by an acute immunological/inflammatory process alone. The marked increase in urine β_2 -microglobulin may be explained by a transient tubular dysfunction induced secondarily during a familial Mediterranean fever attack.

In this study, serum β_2 -microglobulin showed no significant difference between the healthy control subjects and our patient groups. However, concentrations decreased in six of the seven patients during a familial Mediterranean fever attack. The decrease in serum β_2 -microglobulin may be explained by increased filtration; it may not be due to decreased tubular reabsorption, as it makes no difference to the plasma component whether the filtered protein is reabsorbed and catabolised or excreted into the urine. Alternatively, the decrease in serum concentrations may be due to the decrease in CD8+ T lymphocytes as previously reported.

Renal amyloidosis is the most severe and mortal complication of familial Mediterranean fever.¹⁰ In cases of diabetic nephropathy, early renal glomerular damage can be detected by microalbuminuria before the development of proteinuria.¹³ In our patients with familial Mediterranean fever this increase in microalbuminuria may also be attributed to diminished tubular reabsorption. The urinary

albumin/creatinine ratio was higher during the familial Mediterranean fever attack and returned to normal after cessation of the attack. Administration of colchicine might also have been effective in reducing microalbuminuria, as all patients received the drug once an attack was observed. Colchicine is well known to alter the course of familial Mediterranean fever.

The mechanism of the markedly decreased incidence of amyloidosis in patients on colchicine treatment remains unknown.¹¹ In this study, in familial Mediterranean fever patients on and off colchicine treatment, we were unable to show any significant differences in the selected parameters regarding glomerular and tubular damage. However, longer periods off treatment may be required to allow accurate comment on this subject.

Our results demonstrate a transient deterioration in renal tubular and glomerular functions during an acute familial Mediterranean fever attack. Further studies may disclose whether microalbuminuria and β_2 -microglobulinuria are prognostic factors in the development of renal amyloidosis in patients with familial Mediterranean fever. The specific 'effector(s)' leading to this transient impairment of renal function in familial Mediterranean fever remain to be elucidated. Defining such factors may be crucial for understanding the mechanisms underlying the development of secondary amyloidosis in these patients.

This study has been supported by the Scientific and Technical Research Council of Turkey.

- Hayashi A, Suzuki T, Shimizu A, Yamamara Y. Periodic fever suppressed by reserpine. *Lancet* 1976; i: 592-5.
- Ilfeld DN, Weil S, Kuperman O. Suppressor T cell function in a family with familial Mediterranean fever. *Clin Exp Immunol* 1981; 43: 357-64.
- Melamed L, Shemer Y, Zakuth V, Tzehoval E, Pras M, Spirer Z. The immune system in familial Mediterranean fever. *Clin Exp Immunol* 1983; 53: 659-66.
- Bernier GM, Fanger MW. Synthesis of β_2 -microglobulin by stimulated lymphocytes. *J Immunol* 1972; 109: 407-9.
- Peterson PA, Rask L, Lindblom JB. Highly purified papain solubilized HL-A antigens contain β_2 -microglobulin. *Proc Natl Acad Sci USA* 1974; 71: 35-9.
- Bhalka RB, Safai B, Pahwa S, Schartz MK. β_2 -Microglobulin as a prognostic marker for development of AIDS. *Clin Chem* 1985; 31: 1411-2.
- Jacobson MA, Abrams DA, Volberding PA, *et al*. Serum β_2 -microglobulin decreases in patients with AIDS or ARC treated with azidothymidine. *J Infect Dis* 1989; 159: 1029-35.
- Gauthier C, Nguyen-Simonet H, Vincent C, Revillard JP, Pellet M. Renal tubular absorption of β_2 -microglobulin. *Kidney Int* 1984; 26: 170-5.
- Viberti GC, Keen H, Mackintosh D. β_2 -microglobulinaemia: a sensitive index of diminishing renal function in diabetics. *BMJ* 1981; 282: 95-8.
- Wolff SM. Familial Mediterranean fever. In: Wilson JD, ed. *Harrison's principles of internal medicine*. New York: McGraw Hill, 1991: 1469-70.
- Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long-term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum* 1991; 34: 973-7.
- Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986; 314: 1001-5.
- Berglund J, Lins P, Adamson U, Lins L. Microalbuminuria in long term insulin dependent diabetes mellitus. *Acta Medica Scandinavica* 1987; 222: 333-8.
- Nakao Y. β_2 -microglobulin. *Asian Medical Journal* 1990; 33: 630-40.
- Prischl F, Gremmel F, Schwabbe M, *et al*. Beta-2-microglobulin for differentiation between cyclosporin A Nephrotoxicity and graft rejection in renal transplant recipients. *Nephron* 1989; 51: 330-7.