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MYCOPHENOLATE MOFETIL IN THE TREATMENT OF GLOMERULAR DISEASES

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A b s t r a c t: *Aim:* Treatment of primary glomerular diseases may be unsuccessful or have potential toxicities. Mycophenolate mofetil (MMF) is a new, relatively non-toxic drug. It has been introduced as an immunosuppressive drug, but it also has effects on non-immune cells (vascular smooth muscle cells, fibrocytes). Therefore, we evaluated the use of MMF for the treatment of glomerular diseases at different stages of the disease.

Methods: The daily dosage of MMF was 2 for the first 6 months and 1.5 g for a further 18 months, combined with steroids. The follow-up period was two years.

Results: 18 patients with lupus nephritis were treated. Patients with a high histological activity index showed a significant decrease of serum creatinine ($p < 0.05$) and proteinuria ($p < 0.01$), while patients with a high chronicity index showed only a decrease of proteinuria ($p < 0.05$).

15 patients with membranous nephropathy were treated. They showed stable renal function and a significant decrease of proteinuria ($p < 0.05$). Complete remission was achieved only in patients with MMF as a first choice drug.

4 patients with focal segmental glomerulosclerosis did not show any significant decrease of proteinuria, while the nephrotic syndrome in minimal change nephropathy (3 patients) showed a complete recovery.

Partial improvement of the nephrotic syndrome was noted in 5 patients with membranoproliferative glomerulonephritis and in 4 patients with crescentic glomerulonephritis. Patients with crescentic glomerulonephritis also presented a significant decrease of serum creatinine ($p < 0,05$).

MMF in 3 patients with IgA nephropathy grade I showed a significant improvement of the nephrotic syndrome. In grade III (5 patients) the response was partial.

Conclusions: We can conclude that MMF in our patients showed both actions, as an immunosuppressive drug in the early stages of the disease, and as an anti-fibrotic agent in the chronic phase of the disease.

Key words: glomerulonephritis, immunosuppression, Mycophenolate mofetil, nephrotic syndrome, proteinuria, steroids.

Introduction

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase, which is involved in *de novo* purine synthesis. MMF is a suppressor of both T and B cell lymphocyte proliferation and has been used successfully for the prevention of acute and chronic rejection of renal allografts. MMF has a selective antiproliferative effect on lymphocytes, inhibits antibody production by B lymphocytes and suppresses the formation of specific antibodies when transplant patients received polyclonal antithymocyte globulins. All these actions of MMF were documented experimentally. MMF also induces deoxyguanosine nucleotide depletion, and the transfer of fucose and mannose to glycoproteins including glycoprotein adhesion molecules. Knowing the functions of adhesion molecules (facilitating the attachment of leucocytes to endothelial cells, their role in the initial interaction between leucocytes and endothelial cells, and involvement in the interaction between antigen presenting cells and lymphocytes as well as in the interaction between effector lymphocytes and target cells) it is clear that MMF can reduce the inflammatory process early on [1,2,3,4].

At higher concentrations, which may be reached in the clinical setting, MMF has effects on cells not related to the immune system. It has an antiproliferative effect on vascular smooth muscle cells, even when pro-proliferative stimuli (angiotensin II, β-FGF) are present. This effect is not shared by other immunosuppressive drugs (cyclosporine, tacrolimus). This antiproliferative effect on vascular smooth muscle cells may be of relevance concerning the effect of MMF on chronic allograft dysfunction. As some glomerulopathies are associated with vascular lesions and microthrombus formation, which resemble vascular rejection, MMF might be of use in advanced stages of chronic glomerulopathies. Other documented chronic actions of MMF are: reduction of glomerular hypertrophy and hyperfiltration, reduction of myofibroblast formation and collagen III deposition, and reduction of tubular cell proliferation and interstitial fibrosis.

MMF was a useful drug in the treatment of recurrent glomerulonephritis in allografts, all forms of primary glomerulonephritides, especially with nephrotic syndrome, lupus nephritis and vasculitides [2, 3, 4, 5].

The aim of our study was to analyse these principal actions of MMF:

– as an immunosuppressive agent in the early stages of glomerulopathies (rapidly progressive glomerulonephritis (GN), membranoproliferative GN, membranous nephropathy, minimal change nephrotic syndrome, IgA nephropathy grade I, lupus nephritis with high activity index (AI))

– as an anti-fibrotic agent in advanced stages of GN (membranous nephropathy stage III-IV, IgAN stage III and lupus nephritis with high chronicity index (CI)).

Patients and methods

Patients

The study population consisted of patients who attended outpatient nephrology treatment at our nephrology department and who had biopsy-proven primary glomerulonephritis complicated by nephrotic syndrome and/or renal insufficiency. Patients with lupus nephritis were also included in the study. Standard procedures were used for the processing of renal biopsy specimens and semiquantitative score for grading of histological changes in IgA nephropathy and lupus nephritis.

Histological activity and chronicity indices were estimated in patients with lupus nephritis. Active lesions consisted of: glomerular cellular proliferation, disruption of capillary walls, karyorrhexis, haematoxylin bodies, crescents, wire loops, hyaline thrombi, segmental fibrin deposition, necrotizing arteritis of intrarenal blood vessels, tubular degeneration and necrosis, and active interstitial infiltration. Sclerosing lesions consisted of segmental, mesangial or global sclerosis, fibrous crescents, tubular atrophy, interstitial fibrosis and vascular sclerosis. Patients were not selected according to the class of lupus nephritis.

Histological grading of IgA nephropathy was done according to H.S.Lee's glomerular grading system [6].

Staging of membranous nephropathy was done according to the degree of the glomerular basement membrane changes; only patients with stage III–IV were included in the study.

All patients with crescentic glomerulonephritis included in the study had > 80% crescents at biopsy of clinically non-oliguric form.

Treatment regimen

MMF was initiated 2 g/daily for the first 6 months, and the dose was decreased to 1.5 g/daily for a further 18 months. Steroids, prednisone or methyllprednisolone 0.4 mg/kg/daily was the concomitant therapy for the first 6

months, with a slow tapering off for a further 18 months. Other immunosuppressive drugs, or drugs which can reduce proteinuria (ACE inhibitors for example), were not used during the follow-up.

Follow-up

Clinical and laboratory parameters were monitored on a monthly basis for the initial 6 months, then at two-monthly periods. The whole follow-up period was two years. Laboratory parameters included a complete blood count, serum creatinine, blood urea nitrogen, plasma protein level, albumin, and protein excretion rate. The whole follow-up period was two years. For nephrotic syndrome, a complete remission was defined as proteinuria to < 0.3 g/d, partial for proteinuria 0.3–2 g/d.

Responses in excretory renal function in those patients with renal insufficiency were assessed based on changes in serum creatinine before and at the end of treatment. Renal insufficiency was defined as serum creatinine >109 μmol/l. Complete remission was defined as a decrease of serum creatinine to normal values, a favourable response included either a > 15% decrease in serum creatinine or stabilization of the serum creatinine in a patient with rapidly rising values prior to MMF treatment.

Results

Lupus nephritis

18 patients were treated, 16 female and two male, aged 28.6 ± 5.34. 8 of them had a high histological activity index (AI) (13.4 ± 2.34) and a low chronicity index (CI) (1.45 ± 0.85). The other 8 patients had a high CI (6 ± 0.7) and low AI (2.98 ± 0.86). Low AI and CI were found in two patients (AI 3.5, CI 0 and AI 0.5, CI 1.5) (Figure 1).

High AI patients

Serum creatinine levels showed a significant decrease during the follow-up, from 286 ± 112.95 to 131.2 ± 44.65 μmol/l, $p < 0.05$, as well as proteinuria, from 6.97 ± 1.81 to 0.9 ± 0.31g/daily, $p < 0.01$. Two patients with acute oligoanuria were withdrawn from dialysis treatment.

High CI patients

Serum creatinine levels decreased, but not significantly, from 178.5 ± 47.73 to 129.25 ± 22.88 μmol/l, $p > 0.05$. Partial improvement of the nephrotic syn-

drome was noted, with a decrease of proteinuria from 4.63 ± 1.57 to 1.14 ± 0.39g-/daily, $p < 0.05$.

Patients with low indices

The patients with higher AI showed a recovery of the renal function, serum creatinine from 196 to 72 μmol/l, and improvement of proteinuria, from 7.93 ± 3.4g/daily.

The patients with higher CI did not respond to therapy and presented slow worsening of the renal function (Figure 1).

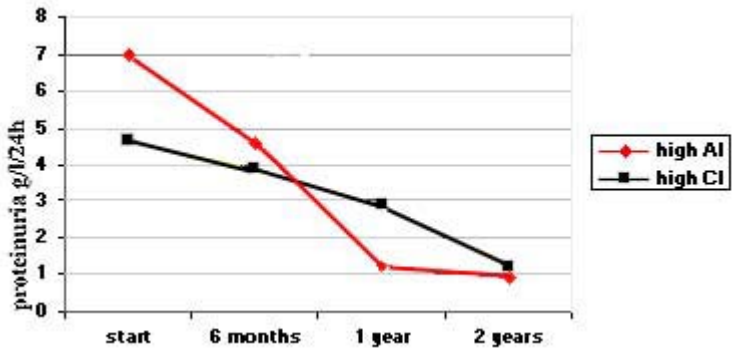

Figure 1 – Proteinuria in lupus patients with high AI and CI index
Слика 1 – Протеинурија кај пациенти со лупус со висок AI и CI индекс

Membranous nephropathy

15 patients, aged 50.57 ± 3.96, 8 of whom were treated with MMF after previous treatments had failed, and in the other 7 cases MMF was the first choice drug.

Renal function was normal at the start and did not worsen during the follow-up. Proteinuria decreased significantly, from 4.01 ± 0.8 to 1.86 ± 0.48g/-daily, $p < 0.05$. Complete remission of the nephrotic syndrome was noted in 2/15 patients, both first choice treatment, and in the other 13/15 it was partial (Figure 2).

Focal segmental glomerulosclerosis

4 patients aged 55.25 ± 4.7 were treated. Renal function was stable during the follow-up and a slight increase of serum creatinine was noted after two years, from 108±11.2 to 130 ± 8.3 μmol/l. Proteinuria decreased significantly, but not enough to correct the nephrotic syndrome, from 6.06 ± 1.28 to 3.18 ± 0.74 g/daily (Figure 2).

Minimal change nephrotic syndrome

3 patients, aged 34.5 ± 2.3 were included in the study. They presented a complete remission of the nephrotic syndrome, without a relapse during the follow-up period of two years. Proteinuria decreased significantly, from 4.7 ± 2.7 to 0.25 ± 0.15 g/daily, $p < 0.05$ and the plasmaprotein level increased from 53.67 ± 3.84 to 66.67 ± 0.88 g/l (Figure 2).

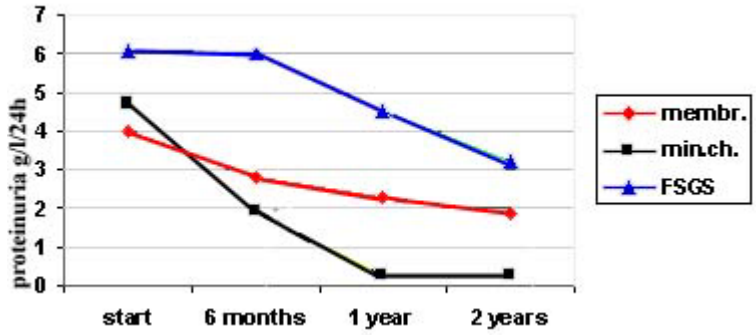

Figure 2 – Proteinuria in membranous nephropathy, minimal change nephrotic syndrome and focal segmental glomerulosclerosis
Слика 2 – Протеинурија кај мембранозна нефропатија, нефротски синдром со минимални промени и фокална сегментална гломерулосклероза

Membranoproliferative glomerulonephritis

5 patients aged 35.4 ± 6.7 were treated. A slight, not significant, increase of serum creatinine was noted at the end of the follow-up, from 97 ± 27.22 to 121.6 ± 41.59 μmol/l, but partial remission of the nephrotic syndrome was observed (proteinuria from 3.96 ± 0.74 to 1.4 ± 0.23 g/daily) (Figure 3).

Crescentic glomerulonephritis

4 patients were treated as previously described. They presented a significant improvement of serum creatinine, from 431.75 ± 148.53 to 136 ± 41.3 μmol/l, $p < 0.05$ and decrease of proteinuria, from 3.82 ± 0.98 to 1.5 ± 0.74 μmol/l (Figure 3).

IgA nephropathy

3 patients with grade I IgAN, aged 20.67 ± 0.88, proteinuric 2.89 ± 1.19 g/daily with normal serum creatinine 58.33 ± 7.31 μmol/l and normal blood pressure were included in the study. They presented a significant decrease of

proteinuria to 0.51 ± 0.2 g/daily, but the remission of the nephrotic syndrome was not complete.

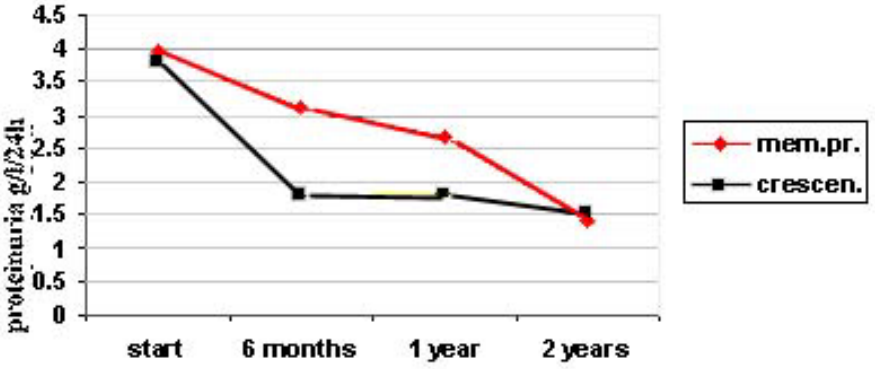

Figure 3 – Proteinuria in membranoproliferative and crescentic glomerulonephritis
Слика 3 – Протеинурија кај мембраноproлиферативен и гломерулонефритис со полумесечинасти дерозити

5 patients with grade III IgAN were also treated. They all were male, aged 31 ± 2.5, proteinuric 3.37 ± 0.73 g/daily, with a slight elevation of serum creatinine at the start 155.4 ± 25.89 μmol/l and regulated hypertension in 4/5. One of the patients showed a slow worsening of the renal function during the follow-up, serum creatinine from 160 to 286 μmol/l, without a significant change of proteinuria (from 5.48 to 4.46 g/daily). Another patient showed an improvement of the renal function, serum creatinine from 255 to 187 μmol/l and a decrease of proteinuria from 2.42 to 0.79 g/daily. The remaining three patients showed stable renal function and a slight decrease of proteinuria (Figure 4).

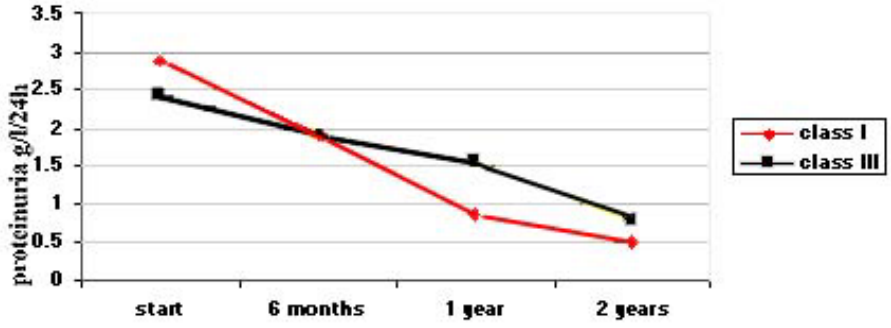

Figure 4 – Proteinuria in IgA nephropathy

Слика 4 – Протеинурија кај IgA нефропатија

Discussion

We noted a significant improvement of renal function and proteinuria in patients with lupus nephritis and high AI, and some improvement in patients with high CI. Other authors have also reported a remarkable improvement in serum creatinine and proteinuria and they also combined MMF with corticosteroid treatment in severe lupus nephritis [5, 7, 8, 9]. Comparative studies on MMF + steroids and cyclophosphamide + steroids presented similar results, the rates of remission and the rates of relapse were similar in the two groups, but more side-effects were seen with cyclophosphamide than with MMF. A significant improvement of clinical parameters in patients with high AI was not documented with a new biopsy in our patients. A histological study of other authors with severe lupus nephritis showed that treatment with MMF for 6 months led to a more pronounced reduction of glomerular immune deposits, glomerular necrosis, microthrombus formation and vascular changes, i.e. an improvement of the components of histological AI. Furthermore, this improvement was better than in patients who had received cyclophosphamide.

Membranous nephropathy is often complicated by nephrotic syndrome with moderate to severe oedema/anasarca, requiring intensive diuretic therapy. Treatment considerations are quite controversial because of the unpredictable outcome of the disease from spontaneous remissions, through relapsing disease to a slow progressive course towards end-stage renal failure. Reports on MMF effectiveness on membranous nephropathy are also controversial [11, 12, 13]. Some reports document complete remission in a high percent of the patients, others a suboptimal outcome. Our results were between these two extremes, we had only two patients with complete remission, but a high percent of partial.

Steroid-dependent minimal change nephrotic syndrome is problematic because of the need for repeated moderate-to-high dose steroid exposure. Adults with this disorder are more likely to be steroid-resistant or steroid-dependent. Historically, the treatment of relapsing or resistant patients has been with either cyclosporine or a cytotoxic drug. Taking into consideration their adverse effects, it is clear why MMF can be used in these patients [1, 2, 12]. This drug has a steroid-sparing effect without toxic effects. Our experience (only 3 patients) is not representative. Results of other authors suggest that a more prolonged course of treatment with MMF may lead to a sustained complete remission after stopping MMF.

Focal segmental glomerulosclerosis is especially significant because it has become the leading cause of nephrotic syndrome in adults and, more impor-

tantly, because of its propensity to progress to end-stage renal disease. Nephrotic proteinuria and decreased excretory renal function are independent risk factors for progression. Induction of complete and even partial remission of nephrotic proteinuria has been shown to favourably modify the renal prognosis in FSGS. High-dose and prolonged steroid treatment has been found to be effecttive for the induction of remissions in nephrotic proteinuria in substantial proportions of affected patients. Although generally satisfactorily tolerated, the downside of such treatment includes both the total cumulative steroid exposure and steroid intolerance in some patients. MMF treatment was reported effective in inducing substantial remissions of proteinuria in the majority of nephrotic FSGS patients, it also has major steroid-sparing effects. The majority of nephrotic patients with FSGS have concomitant renal insufficiency, so it is clear that there are no complete remissions in the reported data. A stabilization, and especially an improvement in excretory renal function, in several patients was noteworthy. We noted some improvement of nephrotic syndrome in our patients, and relative stable renal function, but the number of patients was too small to draw exact conclusions.

We noted a similar observation in our 5 patients with membranoproliferative glomerulonephritis, a stable renal function and slight improvement of the nephrotic syndrome. This is very important taking into consideration that MPGN has a poor long-term kidney survival, for which there is little evidence for a specific treatment to improve the outcome in adult patients. As has been mentioned, MMF has antiproliferative effects on endothelial and mesangial cells and is non-nephrotoxic, so it is an ideal agent for treating proliferative forms of glomerulonephitis, membranoproliferative and crescentic [14]. Our results in patients with crescentic glomerulonephritis were significantly better and very encouraging.

The last group of our patients consisted of 2 small subgroups of IgA patients. Stage I, nephrotic patients, presented recovery from the nephrotic syndrome but persistent slight proteinuria, and stage III patients, with proteinuria and renal insufficiency, with improvement in some of them. It is very difficult to make any conclusions in IgA nephropathy, especially because of the slow progressive course of this disease. Nevertheless, there are reports that MMF alleviates persistent proteinuria in IgAN, may have some effects in a moderately advanced form of the disease, etc. [15].

Summarising our results, we can conclude that MMF in glomerular disease expresses both actions: 1) as an antiproliferative drug it acts in severe forms of lupus nephritis with high AI, crescentic and membranoproliferative GN and 2) as an antifibrotic agent it acts in lupus nephritis with high CI, FSGS and advanced form of IgAN [1–19].

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Р е з и м е

МИКОФЕНОЛАТ МОФЕТИЛ ВО ТРЕТМАН НА ГЛОМЕРУЛАРНИТЕ БОЛЕСТИ

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Цел: Третманот на примарните гломеруларни болести може да е неуспешен или да е потенсијално токсичен. Микофенолат мофетил (ММФ) е нов, релативно нетоксичен лек. Воведен е како имуносупресивно средство, но има ефекти и врз неимуните клетки (мазната мускулатура, фиброцитите). Целта на истражувањето беше да ја евалуираме употребата на ММФ во терапија на гломеруларните болести во различни фази од болеста.

Методи: Дневната доза на ММФ беше 2 g во текот на првите 6 месеци и 1.5 g во текот на наредните 18 месеци, комбинирано со стероиди. Времето на следење беше две години.

Резултати: Беа третирани 18 пациенти со лупус нефритис. Пациентите со висок индекс на хистолошка активност покажаа статистички сигнификантно намалување на нивото на серум креатинин ($p < 0.05$) и протеинуријата ($p < 0.01$), додека пациентите со висок индекс на хроницитет покажаа намалување само на протеинуријата ($p < 0.05$).

Беа третирани 15 пациенти со мембранозна нефропатија. Тие покажаа стабилна бубрежна функција и сигнификантно намалување на протеинуријата ($p < 0.05$). Комплетна ремисија се постигна само кај пациентите кај кои ММФ беше лек од прв избор.

^етири пациенти со фокална сегментална гломерулосклероза не покажаа сигнификантно намалување на протеинуријата, додека пациентите со

нефротски синдром со минимални промени (тројца) покажаа комплетно оздравување.

Парцијално подобрување на нефротскиот синдром беше забележано кај 5 пациенти со мембранопролиферативен гломерулонефритис и кај 4 пациенти со krescenten гломерулонефритис со полумесечинасти депозити. Пациентите со krescenten гломерулонефритис исто така покажаа сигнификантно намалување на серум креатининот ($p < 0,05$).

ММФ кај 3 пациенти со IgA нефропатија градус 1, покажаа сигнификантно подобрување на нефротскиот синдром. Кај пациентите со IgA нефропатија, градус 3 (5 пациенти) одговорот беше парцијален.

Заклучоци: Може да се заклучи дека ММФ кај испитаните пациенти покажа ефекти и како имуносупресив во раната фаза на болеста и како антифибротичен агенс во хроничната фаза на болеста.

Клучни зборови: гломерулонефритис, имуносупресија, микофенолат мофетил, нефротичен синдром, протеинурија, стероиди.

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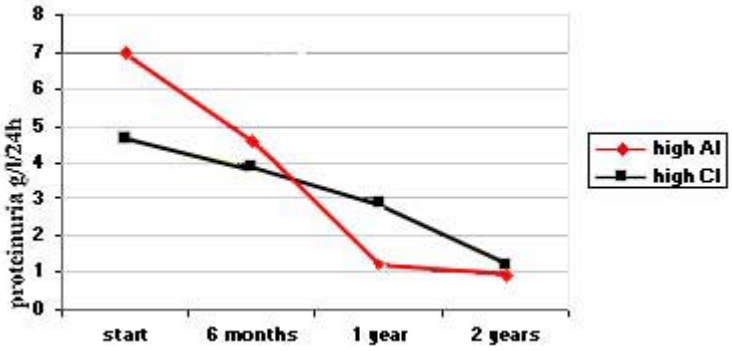

Figure 1: Proteinuria in lupus patients with high AI and CI index
Слика 1. Протеинурија кај пациенти со лупус со висок AI и CI индекс

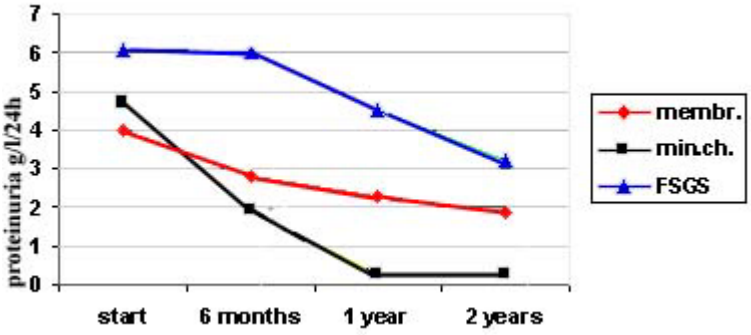

Figure 2: Proteinuria in membranous nephropathy, minimal change nephrotic syndrome and focal segmental glomerulosclerosis

Слика 2. Протеинурија кај мембранозна нефропатија, нефротски синдром со минимални промени и фокална сегментална гломерулосклероза

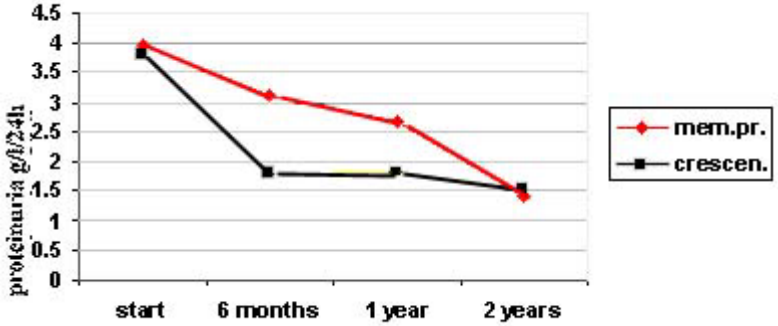

Figure 3: Proteinuria in membranoproliferative and crescentic glomerulonephritis

Слика 3. Протеинурија кај мембранопролиферативен и гломерулонефритис со полумесечинасти депозити

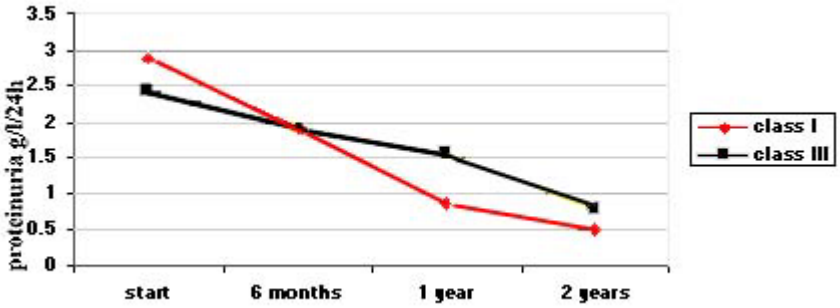

Figure 4: Proteinuria in IgA nephropathy
Слика 4. Протеинурија кај IgA нефропатија