The Effect of Antiproteinuric Treatment on Lipid Levels in Patients with Focal Segmental Glomerulosclerosis and Membranous Glomerulopathy

Fokal Segmental Glomerüloskleroz ve Membranöz Glomerülopatili Hastalarda Antiproteinürik Tedavinin Lipit Düzeylerine Etkisi

ABSTRACT

OBJECTIVE: The primary objective of our study was to investigate effects of antiproteinuric treatment on lipid levels of patients with idiopathic focal segmental glomerulosclerosis (FSGS) or membranous glomerulonephritis (MGN).

MATERIAL and METHODS: The clinical and laboratory data of the patients were recorded at three-month intervals during 18 months of follow-up. Patients with non-nephrotic proteinuria without hypoalbuminemia received conservative treatment while those with more severe disease received steroid therapy as well. Lipid parameters in the two groups and the factors effective on these parameters were investigated.

RESULTS: Sixty eight patients (36 with FSGS, 32 with MG) were included. The mean age of the patients and the follow-up period were 39.6±16.6 years and 16.4±8.9months, respectively. 36 (53%) patients received steroid therapy. The percentage of patients taking antilipemic treatment was statistically significantly higher in the group taking steroid therapy. LDL cholesterol levels were higher at the beginning in patients taking steroid therapy but the difference disappeared after the ninth month. Total and LDL cholesterol levels showed a negative correlation with albumin levels and a positive correlation with proteinuria level.

CONCLUSION: Treatment of hyperlipidemia in nephrotic syndrome should be directed towards increasing serum albumin levels, and therefore treatment of the glomerular disease. Antilipidemic therapies should be considered in patients who do not respond to other antiproteinuric treatment.

KEY WORDS: Hyperlipidemia, Primary glomerular disease, Proteinuria, Steroid, Statin

ÖZ

AMAÇ: Çalışmamızın amacı, idiopatik fokal segmental glomerüloskleroz (FSGS) ve membranöz glomerülopati (MGN) tanılı hastalarda antiproteinürik tedavinin lipit düzeylerine etkisini incelemektir.

GEREÇ ve YÖNTEMLER: Hastaların 18 aylık takibi boyunca üç ay aralarla klinik ve laboratuar bulguları kaydedildi. Hipoalbüminemisi olmayan ve non-nefrotik düzeyde proteinürisi olan hastalar konservatif tedavi alırken; daha ağır proteinürisi olan hastalar aynı zamanda steroid tedavisi aldı. Her iki grupta da lipit parametreleri ve bu parametreler üzerine etkili faktörler araştırıldı.

BULGULAR: 68 hasta (36 FSGS, 32 MGN) çalışmaya alındı. Ortalama yaşları ve takip süreleri sırası ile 39,6±16,6 yıl ve 16,4±8,9 ay olarak saptandı. 36 (%53) hasta steroid tedavisi aldı. Anti-lipemik ilaç kullanan hasta oranı steroid tedavisi gören hasta grubunda daha yüksekti. Başlangıç LDL kolesterol düzeyleri steroid tedavisi alan grupta daha yüksek olsa da bu fark dokuzuncu aydan sonra kayboldu. Total ve LDL kolesterol düzeyleri albümin ile negatif, proteinüri düzeyi ile pozitif korele bulundu.

SONUÇ: Nefrotik sendromda hiperlipideminin tedavisi serum albümin düzeyini yükseltmeye, dolayısıyla glomerüler hastalığın tedavisine yönelik olmalıdır. Anti-lipemik ajanlar diğer antiproteinürik tedaviye yanıt alınamayan hastalarda uygulanmalıdır.

ANAHTAR SÖZCÜKLER: Hiperlipidemi, Primer glomerüler hastalık, Proteinüri, Steroid, Statin

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Received : 21.03.2012
Accepted : 27.04.2012

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INTRODUCTION

Hyperlipidemia in nephrotic syndrome (NS) is thought to be due to increased synthesis by the liver to compensate the hypoalbuminemia and decreased metabolism of lipoproteins (1). Treatment strategies that target proteinuria also decrease the synthesis of lipoproteins by the liver (1). Serum cholesterol levels were correlated with serum albumin levels and with remission of nephrotic syndrome in a prior study involving non-diabetic subjects (2).

Hyperlipidemia, as a component of NS, may accelerate atherosclerosis. Increased incidence of cardiovascular diseases in patients with NS and hyperlipidemia has been reported in some studies; although they were not randomized prospective trials (3,4). Additionally; hypertension, predisposition to thrombosis and endothelial dysfunction may add to the atherosclerotic risk in NS patients.

There is also evidence that shows the contribution of hyperlipidemia to the progression of renal disease (5-7). It has been demonstrated in animal studies that hypercholesterolemia causes formation of lipid-loaded macrophages that in turn trigger focal glomerulosclerosis (8).

Statins treat hypercholesterolemia through inhibition of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase, and secondarily prevent atherosclerosis. They have been commonly used for the treatment of dyslipidemia in patients with NS, although their specific effect on the progression of coronary artery disease has not been clarified yet for this group of patients. There are conflicting results on the efficacy and safety of these agents in patients with renal disease. There is increased risk for rhabdomyolysis especially when combined with other medications like fibrates or cyclosporine (3,9). Statins may successfully reduce total and low density lipoprotein (LDL) cholesterol levels in patients with NS (10-12).

The primary objective of our study was to investigate the effects of antiproteinuric treatment on lipid levels of patients with idiopathic focal segmental glomerulosclerosis (FSGS) or membranous glomerulonephritis (MGN).

METHODS

Outpatient clinical charts of adult patients who were admitted to the three referral hospitals in our city between October 2000 and May 2007 were reviewed.

Patients with secondary glomerular diseases, malignancy, advanced cardiac, liver or lung disease, inconsistent and/or insufficient file data, previous history of hyperlipidemia and use of lipid lowering drugs, and those who discontinued their treatment for two or more weeks were excluded from the study.

The demographic data, physical examination findings (height, weight, blood pressure, edema, ascites, pleural effusion), biochemical values (serum glucose, urea, creatinine, albumin, total-, high density lipoprotein (HDL)- and LDL-cholesterol and triglyceride levels, creatinine clearance, daily proteinuria) and the medications that the patients were taking (statins, antihypertensives, steroids and other immunosuppressive drugs) were recorded at three-month intervals during the follow-up which was 18 months.

Biochemical examinations were performed by the Modular Automation System DPP (Roche-Japan). Daily proteinuria was measured by Esbach's method by collecting 24-hour urine or by the protein/creatinine ratio in spot urine. Creatinine clearance was calculated using the Cockcroft-Gault Formula and/or examination of the 24-hour urine sample. If the creatinine level in the 24-hour urine was lower than 10 mg/kg/day or higher than 30 mg/kg/day, the sample collection was discarded and not included in the final analysis.

Patients with non-nephrotic range proteinuria without significant hypoalbuminemia and symptoms and signs related with it were given conservative treatment including antiaggregant agents, renin angiotensin aldosterone system (RAAS) blockers and/or nondihydropyridine calcium channel blockers. Others were also given immunosuppressive medication, namely steroids.

The response of the patients to the treatment was classified as 'complete remission' (proteinuria less than 0.3 g/day on two consecutive measurements); 'partial remission' (proteinuria less than 3.5 g/day on two consecutive measurements or less than 50% of the baseline level) and 'resistance to treatment' (neither complete nor partial remission within 4-6 weeks of therapy). 'Relapse' was defined as proteinuria exceeding 0.3g/day for at least one week after a complete remission.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows ver. 13.0 (SPSS Inc, Chicago, IL, USA). Numerical values were given as mean±standard deviation (SD). The Student-t test and Mann-Whitney U test were used in the comparison of the groups when necessary. Chi-square test with Yates correction and Fisher's exact test were used for 2x2 contingency tables if applicable. The analysis of correlations between numerical parameters was performed by Spearman's rho Correlation Test. Tukey HSD was used in post-hoc comparison. P values less than 0.05 were accepted as significant.

RESULTS

Outpatient clinic charts of 200 patients were evaluated. A hundred and thirty two patients were excluded due to the presence of secondary glomerulonephritis, malignancy, advanced cardiac or liver or lung disease (n=48); insufficient and/or inconsistent file data (n=22), pre-existing hyperlipidemia and/or use of lipid-lowering drugs (n=20) and discontinuation of treatment for more than two weeks (n=42). The remaining 68 patients that were included consisted of 38 (56%) males and 30 (44%) females. The mean age was 39.6±16.6 years and the mean

Table I: The comparison of patient taking or not taking steroid treatment in regard of the medications they use.

	Steroid (+) group (n=36)	Steroid (-) group (n=32)	Total group (n=68)	p
Statin	33 (91%)	22 (68%)	55 (81%)	**0.016**
ACE inhibitor	23 (63%)	21 (66%)	44 (65%)	0.54
ARB	7 (19%)	7 (22%)	14 (20.6%)	0.50
Diuretic	8 (22%)	8 (25%)	16 (23.5%)	0.52
NDCCB	4 (11%)	4 (13%)	8 (11.7%)	0.57

NDCCB: Non-dihydropyridine calcium channel blocker
ACE: Angiotensin converting enzyme
ARB: Angiotensin receptor blocker

Table II: Laboratory values at presentation and 3 months intervals during the follow-up.

Laboratory Parameters	Time (months)						
	0	**3**	**6**	**9**	**12**	**15**	**18**
Glucose(mg/dl)	99.5±27.3	97.6±23.4	103.9±51.8	97.9±24.3	95.6±22.3	92.2±14.1	91.9±13.0
Urea(mg/dl)	34.9±27.0	35.7±22.0	31.0±16.8	29.0±20.2	31.2±18.9	31.0±19.2	30.2±18.1
Creatinine (mg/dl)	1.06±0.67	1.15±0.94	1.10±0.98	1.07±0.91	1.03±0.72	0.92±0.32	1.03±0.68
Albumin(g/dl)	2.74±0.87	3.16±0.79	3.4±0.86	3.64±0.78	3.60±0.99	3.78±0.90	3.71±0.88
Total cholesterol (mg/dl)	301±107	263±74	242±70	221±83	211±77	209±74	203±77
LDL-cholesterol (mg/dl)	165±83	145±70	149±69	138±78	132±67	111±60	107±40
Triglyceride (mg/dl)	252±150	204±104	196±100	193±92	211±140	174±92	164±72
Proteinuria (g/day)	4.19±3.85	3.43±2.95	2.73±2.47	2.55±3.18	2.33±3.12	1.95±5.63	1.49±2.56
Cr. Clearance (ml/min)	84±36	90±44	93±29	81±34	96±38	86±33	88±32

Table III: Comparison of the patients taking or not taking statin in regard of remission.

Response	Statin (+) group	Statin (-) group	Total
Complete remission	21 (38%)	8 (61.5%)	3
Partial remission	13 (24%)	2 (15.4%)	3
Resistant	21 (38%)	3 (23.1%)	62
Total	55	13	68

(p=0.30)

follow-up was 16.4±8.9 months. Thirty six patients (52.9%) had FSGS, whereas 32 (47.1%) had MGN. The basal mean systolic and diastolic blood pressures were 129±25 mmHg and 81±15 mmHg, respectively. The medications that the patients were given are presented in Table I.

Steroid therapy was administered to 36 (53%) patients (16 with FSGS and 20 with MGN). The criteria for giving steroid therapy were nephrotic range proteinuria together with hypoalbuminemia and the resulting overt clinical symptoms and signs. There was no statistically significant difference between patients taking or not taking steroid treatment regarding gender (p=0.357) and the type of the glomerular disease (p=0.137).

The medications that the patients were administered are presented in Table II. The percent of patients taking antilipemic treatment was statistically significantly higher in the group taking steroid therapy (91% vs. 68%; p=0.016). The number of patients using angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), diuretics and calcium

Table IV: Comparison of the groups in regard of remission.

Response	Steroid (+) group	Steroid (-) group	Total
Complete remission	19 (53%)	10 (31%)	29 (43%)
Partial remission	10 (28%)	5 (16%)	15 (22%)
Resistant	7 (19%)	17 (53%)	24 (35%)
Total	36	32	68

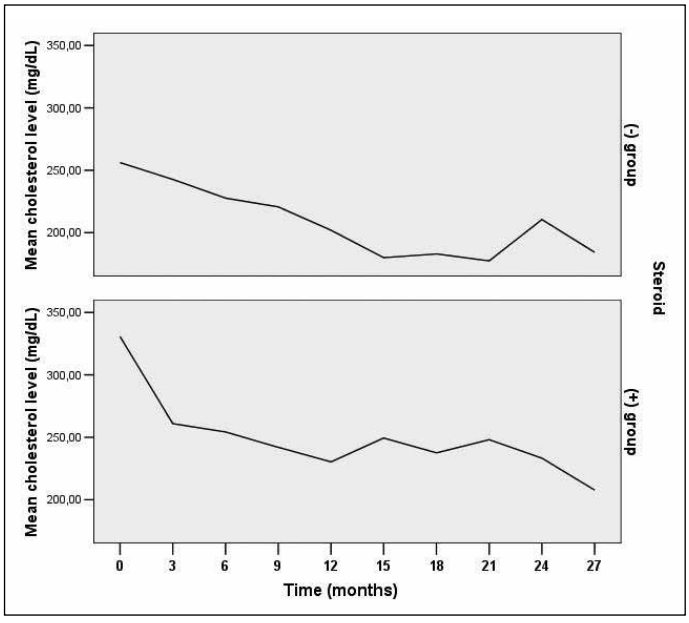

Figure 1: *Changes in mean cholesterol values.*

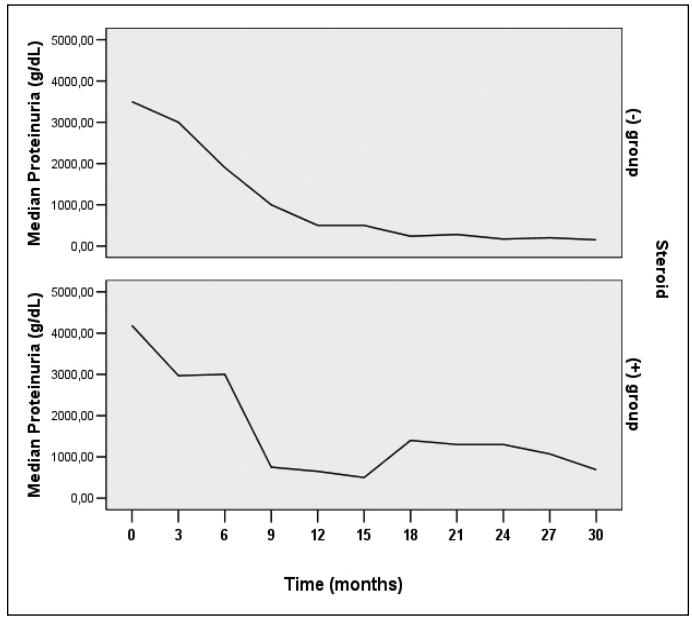

Figure 2: *Changes in median proteinuria.*

channel blockers were similar in both groups. Fifty-five (81%) patients were using statins as lipid-lowering drug (Table I).

Serum glucose, urea, creatinine levels and creatinine clearance did not change during follow-up. Serum albumin level increased progressively while daily proteinuria, total and LDL cholesterol, and triglyceride levels decreased progressively at measurements performed at three-month intervals (Table II).

No significant correlation was found between statin use and response to conservative antiproteinuric and immunosuppressive therapies (Table III).

Serum total cholesterol levels were higher in the group administered steroids (p=0.009). LDL cholesterol levels were higher at the beginning of follow-up in patients taking steroid therapy (193 mg/dl versus 135 mg/dl) but the difference disappeared after the 9th month (Figure 1). Similarly triglyceride levels were also higher in that group; and the decline throughout the follow-up was more pronounced than that of LDL cholesterol, especially in the 9th and 12th months of the follow-up.

Serum total and LDL cholesterol levels showed negative correlation with serum albumin levels and positive correlation with proteinuria level. Baseline serum albumin level was negatively correlated with serum total and LDL cholesterol levels (r=0.45, p=0.049). Age, sex, type of the glomerular disease, serum creatinine, proteinuria and total triglyceride levels, use of statins, steroid, ACEi or ARB were not correlated with LDL cholesterol levels.

Statin, steroid, ACEi or ARB use, age, sex, type of glomerular disease, serum creatinine, proteinuria and, total triglyceride levels were not found to change serum total and LDL cholesterol levels during the follow-up. Median proteinuria decreased from 4 gr/day to less than 0.5 g/day after the first year (Figure 2). Twenty-nine patients had complete remission while 15 had partial remission. Five patients relapsed after complete remission. In the group that was administered steroids, 29 (81%) had remission (partial or complete) and 7 (19%) were resistant to treatment. The numbers of responding and resistant patients were 15 (47%) and 17 (53%) in the group that was

not administered steroids (Table IV). The remission (complete or partial) rate was statistically significantly higher in patients taking steroid treatment (p=0.035).

DISCUSSION

Hepatic lipoprotein synthesis increases in response to hypoalbuminemia in NS (13). On the other hand, it is known that the conversion of very low density lipoprotein (VLDL) cholesterol to IDL (intermediate density lipoprotein) and then to LDL cholesterol is inhibited in this population of patients (14). These two mechanisms lead to increased levels of total and LDL cholesterol as well as triglyceride in proteinuric patients, particularly in NS, while serum HDL levels usually decrease (10). Thus, antiproteinuric treatment is expected to reduce indirectly the hepatic synthesis of lipoproteins by increasing serum albumin levels. We aimed to study the effect of antiproteinuric treatment on lipid parameters in patients with FSGS or MGN. The basic rationale to include patients with only MGN and FSGS in our study was that both diseases show no cellular infiltrations in their histopathological investigations and we can conclude the pathological diagnosis more precisely.

The serum total cholesterol levels of our patients (301±107 mg/dl) were very similar to the levels reported in the literature (15). These increased levels declined progressively throughout the study (Table I, Figure 1).

Only serum albumin level was found to have a negative correlation with serum total cholesterol level. Age, sex, type of the glomerular disease, serum creatinine, proteinuria and total triglyceride levels, use of statins, steroid, ACEi or ARB were not correlated with LDL cholesterol levels. This may be regarded as indicating that the treatment of hyperlipidemia in nephrotic syndrome should be directed towards increasing serum albumin levels which is possible with the treatment of the underlying glomerular disease. These may show that serum albumin level is a stronger indicator of serum lipid levels than urinary albumin loss in primary glomerular diseases. Furthermore, there may be no need for extra medication to treat hyperlipidemia in the initial period of treatment in those without established cardiovascular risk factors. We showed in the present study the decrease in serum total and LDL cholesterol levels in parallel to proteinuria indirectly due to increased serum albumin levels (Figure 1 and 2).

The use of statins in NS is controversial. There are some studies reporting an antiproteinuric effect of statins; while there are others indicating that high dose statins may provoke proteinuria (16-19). Proteinuria was shown to decrease in patients taking atorvastatin when compared to those not taking them in a study performed with 31 patients with chronic glomerulonephritis followed-up with conservative treatment without immunosuppressive medication (17). It has also been observed in our study that proteinuria decreased in parallel with serum cholesterol levels in 55 patients who were administered statins. Serum lipid level shows reverse correlation with serum albumin level and oncotic pressure in patients with nephrotic proteinuria (2), and albumin infusion returns serum lipid levels to normal ranges (20,21). In our study, serum total and LDL cholesterol levels showed a negative correlation with the serum albumin level, which is consistent with the current knowledge.

The role of steroids in the treatment of FSGS and MG was also investigated in our study. Patients with more severe proteinuria were given immunosuppressive therapies beside conservative therapies (36 patients), whereas patients with non-nephrotic proteinuria were given only conservative therapies. The complete or partial responses in patients who received steroids have been found to be statistically higher (p=0.035) (Table IV). Patients who were administered steroids had high cardiovascular risk with higher proteinuria, LDL cholesterol and lower albumin levels, all of which lead to a tendency to thrombosis and endothelial dysfunction. They were therefore given statins due to lack of evidence to wait for the effect of antiproteinuric treatment in these high risk patients. It is therefore difficult to comment on the effect of statins and antiproteinuric treatment on lipid levels separately.

CONCLUSION

The most crucial step in the treatment of hyperlipidemia in idiopathic NS is the treatment of the underlying glomerular disease. Thus, statins may not be necessary in patients whose proteinuria decreased with antiproteinuric therapies, either conservative or immunosuppressive. Antilipidemic therapies, primarily statins, must be considered only in patients who do not respond to antiproteinuric treatment.

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