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ORIGINAL ARTICLE

Effects of three months fluvastatin treatment on lipid metabolism and proteinuria in patients with nephrotic syndrom

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We evaluate the effect of HMG-Co A reductase inhibitor fluvasatin on lipid disorders and proteinuria in patients with nephrotic syndrome (NS).

Seven female (F) and 12 male (M) pts, average age 39 years, with glomerular filtration rate (GRF) over 90 ml/min and NS with proteinuria over 4.0g/24 h and severe hyperlipidemia were investigated. All pts were treated with corticosteroids alone or in combination with cytotoxic drugs, because of the illness activity. Fluvastatin was administered 40 mg/d for 3 months. Tchol, TG, LDL, HDL and 24 hour's proteinuria were examined before the start of the study and after 3 months.

Administration of fluvastatine led to a significant reduction of lipid fractions: Tchol mean value (MV) before the treatment 9.3±3.2mmol/l and after 5.9±1.32mmol/l ($p<0.001$). TG: MV before 5.9± 1.87mmol/l and after 2.74±1.04 mmol/l ($p<0,01$). LDL: MV before 6.35±1.34 mmol/l and after 3.57±0.81 mmol/l ($p<0.001$). HDL levels were normal in all pts. MV before 1.61± 0.53 mmol/l and after 1.04 ± 0.23mmol/l ($p=0.01$).

The changes of 24 hour proteinuria were not significant: MV before 4.21 ± 2.4 g/24h and after-3.03±1.68 g/24h ($p= 0.10$).

Significant reduction of hyperlipidemia was detected in pts. with NS receiving corticosteroid treatment regardless of the fact that the nephrotic proteinuria remains and is not affected by fluvasatin.
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Hyperlipidemia in NS can occur in several forms. Most common is combined hyperlipidemia with an increase in serum cholesterol, or more specifically low density lipoproteins (LDL), VLDL, IDL and also serum triglycerides. HDL cholesterol may be normal, high or low. Both increased hepatic synthesis and decreased catabolism of lipoproteins contributes to the hyperlipidemia. The reduction of the plasma oncotic pressure in NS stimulated lipoprotein synthesis by the liver. Enhanced synthesis of ApoB- containing lipoproteins may account for the rise in cholesterol levels. There are *in - vitro* studies supporting this hypothesis. They found that low oncotic pressure directly stimulates hepatic Apo B gene transcription and in this way increase liver lipoprotein production[1]. Impaired metabolism can be responsible for nephrotic hypertriglyceridaemia. The delipidetion cascade from VLDL to IDL and to LDL is impeded as a result of reduced plasma albumin or urine loss of the lipoprotein regulatory substance[2]. The reduction of the ApoB/E receptor activity is a third mechanism for hyperlipidemia in NS. Garber et al suggests that the reduction of the lipoprotein lipase activity was responsible for delayed lipolysis in rats with NS[3].

The atherogenous risk presented in NS hyperlipidemia is very controversial. It depends on the duration of the disease, the clinical course -especially if there is renal function impairment, hypertension, the response to corticoid and cytotoxic therapy, as well as patients age and gender. Long- term corticoid therapy induced lipid changes of the mixed type hyperlipidemia. Treatment of hyperlipidemia is highly controversial and was particularly disappointing before the introduction of hydroxylmethylglutaryl-CoA (HMG-CoA) reductase inhibitors. They reduced both levels of cholesterol and triglycerides. Many experimental models suggest that lipid disorders may modulate progressive renal injury[4]. HMG-CoA inhibitors have demonstrated beneficial effects in different models of progressive renal failure[5]. Recent data suggest that this drugs play role in the prevention of glomerulosclerosis and interstitial fibrosis effect which are independent from their lipid lowering properties[6]. We evaluate the effect of HMG-Co A reductase inhibitor fluvasatin on lipid disorders and proteinuria in patients with NS.

Patients and Methods

Seven F and 12 M, average age-39 with glomerular filtration rate (GRF) over 90 ml/min and NS with proteinuria over 4.0g/24 h and sever hyperlipidemia-Tchol>8.5 mmol/l were investigated. All patients were with biopsy proven glomerulonephritis. The types of glomerulonephritis are shown in table 1.

Four hour creatinin clearance was used to estimate GFR. All pts were treated with immunosuppressive agents because of the illness activity. Steroids (Urbason -3 days 1000 mg i.v and after that Dehydrocotrison 1 mg/kg/daily p.o with slow tapering after the first month of

Table 1. *Type of glomerular disease in patients with NS*

Type of glomerulo nephritis (GN)	Membranous GN	Focal segmental hyalinosis and sclerosis	Primary mesangiocapillaris GN	Lupus nephritis
Number of pts.	9	4	3	3

the treatment) were given alone or in combination with a cytotoxic drug- Cyclophosphmide. Cyclophosphamide was administered intravenously every month- 1000 mg or 2 mg/kg/daily p.o. for 3 months. Elevated blood pressure (RR more then 140/90 mmHg) was detected in 10 of all pts. In this cases hypertension was well controlled with ACE- inhibitors alone or in combination with non dihydropiridin Ca blocker and blood pressure was below 135/ 80 mmHg.

Fluvastatin was administered 40 mg/d for 3 months. Tchol, TG, LDL, HDL and 24 hours proteinuria were examined before the start of the study and after the 3 rd month as well as evaluation of GFR . Blood control was done at the beginning and in the end of the study. All pts were followed up about the side effects during the treatment.

All the data were expressed as a mean value (MV) ±SD (standard deviation). One way analysis of the variance followed by Levene test also was used to compare the values of the parameters mentioned above- values before and after the treatment with Fluvastatin. Differences with a P value less than 0.05 were considered to be statistically significant.

Results

There were significant reductions of the Tchol, TG and LDL levels after the 3rd month of treatment with 40 mg/ daily Fluvastatin. The mean value of Tchol before the treatment was 9.3± 3.2 mmol/l and after the 3rd month 5.9 ± 1.32 mmol/l ($p<0.001$). This change was shown in figure 1. Very good control of the levels of TG was detected: before the start- 5.95±1.87 mmol/l and in the end of the Fluvastatin administration- 2.74 ±1.04 mmol/l ($p<0,01$). The statistically significant reduction of TG levels was shown in figure 2. The figure 3 demonstrate the reduction o LDL: before 6.34 ±1.34 mmol/l and after 3.57±0.81 mmol/l ($p< 0,001$).

HDL levels were normal in all of the examined patients (1.61 ± 0.53 mmol/l) and remains normal without any significant changes in the course of the treatment with fluvastatin (1.04 ± 0.23 mmol/l, p= 0.1).

All patients entered the study were with severe nephrotic syndrom and because of this they were treated with high doses of steroids alone or in combination with cytotoxic drugs parallel with Fluvastatin administration. After the third month we detect reduction of the 24 hours proteinuria but it still remains in nephrotic range.

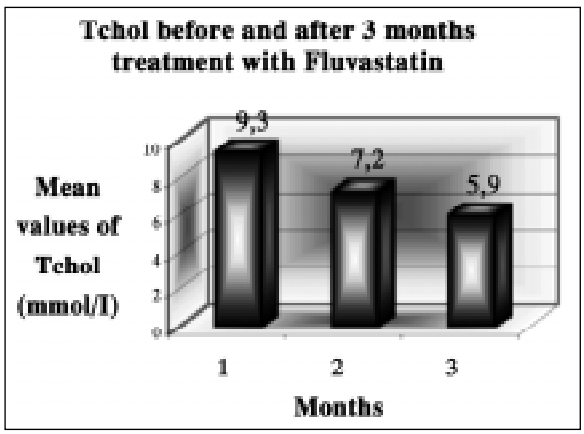

Fig. 1. *Tchol changes during the treatment with Fluvastatin*

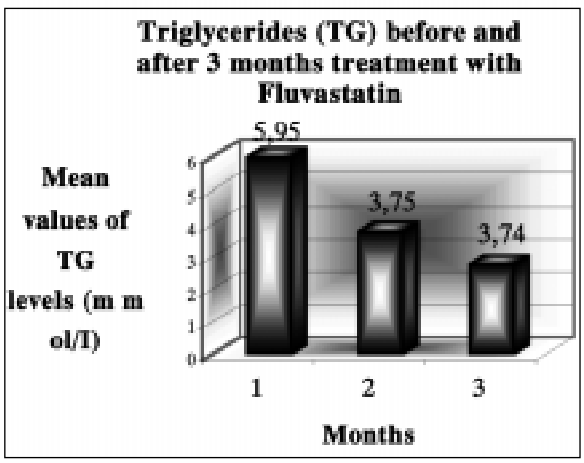

Fig. 2. *TG before and after the fluvastatin administration*

Including criteria for the study were:

GFR ml/min	24 h proteinuria	Immuno-suppressive treatment	Hyperlipidemia		
			Total cholesterol Tchol in mmol/l	Triglycerides - TG in mmol/l	LDL in mmol/l
>90 ml/min	>4.0 g/24h	Steroids and/or Cyclophosphamide	> 7.0	> 3.0	LDL > 5.0

Table 2. *Summery of the changes of the all followed parameters*

Time	Tchol (mmol/l)	TG (mmol/l)	LDL (mmol/l)	HDL (mmol/l)	Proteinuria (g/24 h)
Range before the treatment	15.0-7.3	8.05-1.2	8.5-3.5	2.9-0.78	9.2-2.97
MV*±SD**	9.3±3.20	5.9±1.87	6.35±1.34	1.619±0.53	4.21±2.4
Range after the treatment	7.0-5.0	7.0-1.1	4.72-2.5	1.9-1.01	6.8-1.9
MV*±SD**	5.9±1.32	2.74±1.04	3.57±0.81	1.04±0.237	3.03±1.68
p	p<0.001	p<0.01	p<0.001	p=0.1	p=0.10

*MV: mean value, ** SD: standart deviation

This change was shown in figure 4. The values of proteinuria before the start of the treatment were 4.9 ± 2.2 g/24h and after the 3rd month 2.91 ±1.68 g/24h (p= 0,1). In contrast regardless of the fact that nephrotic syndrom persist in some of the patients hyperlipidemia was well corrected in all of examined one.

The summary of the changes of the all followed parameters were given in table 2.

Discussion

Statins impair cholesterol synthesis by inhibiting 3 hydroxy-3 methyl-glutaryl coenzyme A reductase activity.

Now we have sure evidence from clinical trials in general population that HMG-CoA reductase inhibitors lead to a significant correction of dyslipidemia decreasing TChol, LDL and TG levels. Beneficial effect of statins based on normalization of the lipid metabolism is a reduction of cardiovascular risk[7]. But there is another theory challenging the well-known concept that lipid lowering therapy leads to plaque regression. This is the non lipid-lowering action of statins: improvement of endothelial function, reduction of lipoprotein oxidation, platelet aggregability as well as levels of procoagulating factors and inhibition of smooth muscle cell proliferation[8].

In our study the administration of 40 mg fluvastatin daily in patients with nephrotic syndrom leads to sufficient reduction of the levels of Tchol, TG and LDL. We do not reach the " gold standard" for the levels of the above mentioned parameters, but the mechanism of dyslipidemia in patients with nephrotic syndrom is different compared to the lipid disturbances in general population. During the follow up period our pts. were treated with high does of steroids alone or in combination with cytotoxic drugs. This therapeutic regime influenced lipid metabolism. After the 3rd month of immunosuppressive treatment many of the patients were with nephrotic proteinuria but there was a marked tendency of correction of dislipidemia due to the Fluvastatine therapy. In our study the values of Tchol, Tg, LDL, HDL after the 3rd month of Fluvastatine administration are similar to those published trails about the lipid lowering effect of statins in general population and closed to the recommended values by National Cholesterol Educational program[9].

There are many studies about antiproteinuric effects

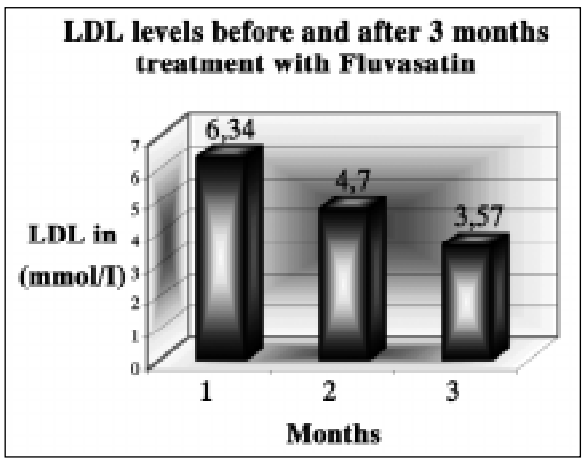

Fig. 3. *LDL changes in the course of the fluvastatin treatment*

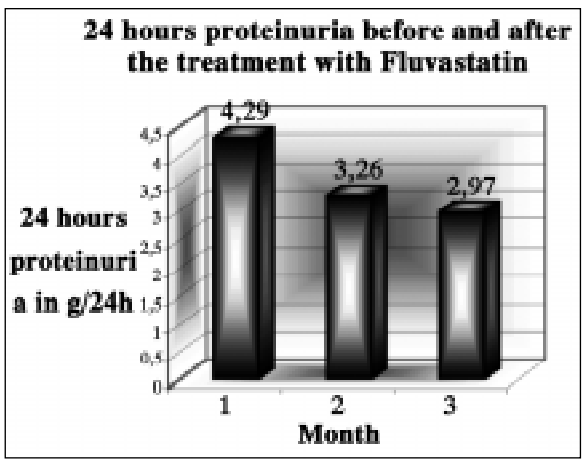

Fig. 4. *Changes in 24 hours proteinuria during the treatment with 40mg/d fluvastatin*

of statins and the results are very controversial, and many of the authors make the conclusion that these drugs do not influenced proteinuria. In our study the 24 hours proteinuria reduction is not significant (mean values were still in nephrotic range). We can explain the changes in proteinuria as the effect of aggressive immunosuppressive treatment. HMG-CoA reductase inhibitors may play a secondary role in the process of the reduction of protein loss through the kidney. To evaluate the antiproteinuric effect of the statins a long-term study with carefully selected patients without immunosuppressive treatment is needed. It is now apparent that statins can modify the inflammatory process, inhibit the mesangial, smooth muscle cells and tubular epithelial cells proliferation by inhibition of many growth factors: platelet derived growth factor, insulin like growth factor, transforming growth factor B1[10-12]. The motives of using the HMG-CoA reductase inhibitors in patients with nephrotic syndrom are:

- Correction of hyperlipidemia
- Decreasing Tchol, TG, LDL statins reduced cardiovascular risk especially in pts not responding to immunosuppressive treatment
- Although there is no significant reduction of 24 hours proteinuria recent data suggest that HMG-CoA reductase inhibitors have vascular and renal protective properties based on:

– Reduction of mesangiocellular and matrix proliferation
– Decreasing of interstitial fibrosis
– Modifying inflammatory response
– Modifying endothelial dysfunction

HMG-CoA reductase inhibitor Fluvastatin have an important role in complex treatment of nephrotic syndrom and proved to be effective and saved in correction of hyperlipidemia which is one of the important cardiovascular risk factors.

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