

# Serum Total LDH Activity and LDH-2 Isozyme in Nephrotic Syndrome

Márton Mohás<sup>a</sup> Nóra Szigeti<sup>a</sup> Lajos Markó<sup>a</sup> Gergő A. Molnár<sup>a</sup> Judit Cseh<sup>a</sup>  
Boglárka Laczy<sup>a</sup> Mónika Tamaskó<sup>a</sup> József Balla<sup>b</sup> János Kappelmayer<sup>c</sup>  
László Wagner<sup>a</sup> Zoltán Wagner<sup>a</sup> Botond Csiky<sup>a</sup> Judit Nagy<sup>a</sup>  
István Wittmann<sup>a</sup>

<sup>a</sup>2nd Department of Medicine and Nephrological Center, Faculty of Medicine, University of Pécs, Pécs, and

<sup>b</sup>1st Department of Medicine, and <sup>c</sup>Department of Clinical Biochemistry and Molecular Pathology, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary

## Key Words

Lactate dehydrogenase · Lactate dehydrogenase isozymes · Nephrotic syndrome · Renal damage

## Abstract

**Background/Aims:** Proteinuria, hypoproteinaemia, hypoalbuminaemia and oedema are major characteristics of nephrotic syndrome. Aims of this study were to detect serum total LDH activity and its isozymes in nephrotic syndrome.

**Methods:** In a cross-sectional study, clinical parameters were compared in three cohorts, namely kidney patients with or without nephrotic syndrome and hypoalbuminaemic controls (NEPHR, NON-NEPHR, CONTR, respectively). **Results:** Serum total LDH activity in the NEPHR group was increased compared with the NON-NEPHR and CONTR groups ( $p < 0.001$ ) and correlated with serum total protein ( $r = -0.549$ ,  $p < 0.001$ ), serum albumin ( $r = -0.596$ ,  $p < 0.001$ ), proteinuria ( $r = 0.456$ ,  $p < 0.001$ ) and serum total cholesterol ( $r = 0.523$ ,  $p < 0.001$ ). LDH isozyme pattern was analysed in three subgroups of the patients. Serum LDH-2 activity was higher in the NEPHR subgroup compared with the NON-NEPHR and CONTR subgroups ( $p < 0.001$ ). Serum LDH-2 activity correlated with serum total protein ( $r = -0.665$ ,  $p < 0.001$ ), serum

albumin ( $r = -0.615$ ,  $p < 0.001$ ), proteinuria ( $r = 0.694$ ,  $p < 0.001$ ), and serum total cholesterol ( $r = 0.723$ ,  $p < 0.001$ ). Linear regression analysis revealed that serum total protein proved to be an independent predictor of serum total LDH activity, while serum total protein and proteinuria were predictors of LDH-2. **Conclusions:** These findings suggest that serum total LDH activity might be a marker of the activity of the nephrotic syndrome.

Copyright © 2008 S. Karger AG, Basel

## Introduction

In nephrotic syndrome proteinuria over 3.5 g/day develops with subsequent hypoproteinaemia, hypoalbuminaemia, generalised oedema and usually with dyslipidaemia. Several clinicopathological courses are involved in the aetiology of nephrotic syndrome among which the most common cause is primary glomerulopathy. The degree of proteinuria, serum total protein (SProt), serum albumin (SAlb), and the presence of dyslipidaemia are routinely used clinical parameters to characterize the severity of the nephrotic syndrome [1, 2].



Lactate dehydrogenase (LDH) is expressed in almost all human tissues and is a tetramer composed of four polypeptide chains transforming pyruvate to lactate. There are two major types of the chains: H (heart) and M (muscle), as well as subtypes. Combinations of these chains form five isozymes: LDH-1 (H<sub>4</sub>), LDH-2 (H<sub>3</sub>M), LDH-3 (H<sub>2</sub>M<sub>2</sub>), LDH-4 (H M<sub>3</sub>), LDH-5 (M<sub>4</sub>), which can be separated by electrophoresis. Human tissues contain all five isozymes but in different proportions. LDH-1 and LDH-2 are found mainly in the heart, erythrocytes and kidneys, but mostly LDH-2 is expressed in the kidney in larger proportions. LDH-3 originates from the spleen, lungs, lymphatic glands and the platelets, while LDH-4 and LDH-5 can be found mainly in the skeletal muscles and liver [3, 4].

Serum total LDH activity is a commonly used laboratory parameter in the daily clinical routine. When cells are injured the enzyme is released into the bloodstream. Measuring the enzyme activity is highly informative in several conditions such as hepatological, cardiological, or haematological disease [5]. Proximal tubular cells are seriously damaged due to the heavy nephrotic proteinuria [6, 7, 12]. According to our hypothesis, this renal lesion increases the serum total LDH activity in nephrotic syndrome.

In our present study, we analysed the relationship between LDH activity, including LDH isozymes and the clinical and laboratory parameters of nephrotic syndrome.

## Patients and Methods

### Study Population

In a retrospective cross-sectional study clinical data of kidney patients with or without nephrotic syndrome and hypoalbuminaemic controls were analysed in the 2nd Department of Internal Medicine and Nephrological Center, University of Pécs. 118 participants were involved in the study and were divided into three groups: patients with nephrotic syndrome (NEPHR,  $n = 62$ ), patients without nephrotic syndrome but with proteinuria of different origin (NON-NEPHR,  $n = 30$ ), and hypoalbuminaemic subjects with different gastrointestinal diseases to serve as a positive control group (CONTR,  $n = 26$ ). Patients with nephrotic syndrome suffered from the following diseases: membranous glomerulonephritis ( $n = 26$ ), focal segmental glomerulosclerosis ( $n = 7$ ), SLE nephropathy ( $n = 5$ ), minimal change glomerulonephritis ( $n = 6$ ), membranoproliferative glomerulonephritis ( $n = 2$ ), diabetic nephropathy ( $n = 10$ ) and cases in smaller proportion with IgA nephropathy, Henoch-Schönlein nephropathy and pregnancy nephropathy ( $n = 6$ ). In the NON-NEPHR group diseases were as follows: IgA nephropathy ( $n = 17$ ), then diabetic nephropathy ( $n = 6$ ), membranoproliferative glomerulonephritis ( $n = 2$ ), membranous glomerulonephritis ( $n = 2$ ) and others like IgM ne-

phropathy, minimal change glomerulonephritis and focal segmental glomerulosclerosis ( $n = 1$ , each). CONTR group involved hypoalbuminaemic subjects with the following gastrointestinal diseases: Crohn's disease ( $n = 7$ ), malabsorption ( $n = 9$ ), gastric cancer ( $n = 4$ ), ulcerative colitis ( $n = 4$ ), and adenocarcinoma of the colon or rectum ( $n = 2$ ). All patients were excluded from the kidney disease groups who were suffering from any of the diseases that may cause an elevation of serum total LDH activity, such as malignant tumours, thrombosis, embolism, haemolysis, hepatitis, pancreatitis, and severe coronary artery disease (NYHA class II or worse). Subjects with gastrointestinal malignancies were not excluded from the CONTR group.

### Clinical Data and Determination of LDH Isozymes

Serum total LDH activity and other clinical parameters were determined by the time when renal biopsy was carried out and in the case of CONTR group, at time of hospitalisation. Clinical characteristics of the patients are summarized in table 1. NEPHR group patients were followed for 300 weeks and a decline in renal function was assessed by survival analysis in patients with LDH above and below the median LDH value. Primary endpoints were as follows: doubling of the baseline serum creatinine, the time when GFR values were halved, reaching the creatinine point of no return ( $265 \mu\text{mol/l}$ ) and entry to dialysis.

LDH isozyme patterns were determined (prior to renal biopsy) from frozen serum samples of the three subgroups randomly selected from all groups (NEPHR  $n = 34$ , NON-NEPHR  $n = 12$ , CONTR  $n = 21$ ). Clinical characteristics of these groups did not differ significantly from the original groups. LDH isozymes were separated by agarose gel electrophoresis and the proportions of the enzymes were determined by their activity with densitometry. SEBIA HYDRASYS system (SEBIA, Cedex, France) and the Hydragel ISO LDH test (No: 4136) were used for the analysis.

### Statistics

The significance of differences was assessed with ANOVA (normal distribution), Kruskal-Wallis followed by Mann-Whitney U test (non-normal distribution) and  $\chi^2$  test (categorical variables). General linear model (ANCOVA) was used to compare differences between groups adjusted for age, gender, SALb and SProt. To test for correlation of the normally distributed variables, we used the Pearson's correlation coefficient. In case of the non-normally distributed variables the Spearman rho test was performed. A stepwise linear regression was carried out to determine the independent predictors of serum LDH and isozymes. Survival curves were calculated using Kaplan-Meier method and the curves were compared by log-rank test.  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using the SPSS 13.0 (SPSS, Chicago, Ill., USA) software.

## Results

Body mass index (BMI), SProt, SALb, serum bilirubin, serum total cholesterol (Schol) and proteinuria were considerably different between NEPHR and NON-NEPHR and CONTR groups. NON-NEPHR group differed significantly in BMI, SProt, SALb, Schol and pro-



**Table 1.** Clinical characteristics of the participants

	NEPHR (n = 62)	NON-NEPHR (n = 30)	CONTR (n = 26)
Gender, male/female	38/24	18/12	7/19 <sup>d</sup>
Age, years	51 ± 2	47 ± 3	65 ± 4 <sup>e</sup>
Body mass index	28 ± 1	24 ± 1 <sup>a</sup>	25 ± 2
Serum potassium, mmol/l	4.2 ± 0.1	4.3 ± 0.1	4.1 ± 0.1
Serum creatinine, µmol/l	157.2 ± 17.0	121.5 ± 14.6	73.2 ± 4.2 <sup>c</sup>
GFR, ml/min	75.1 ± 5.6	79.3 ± 6.4	92.7 ± 15.2
Serum total protein, g/l	50.9 ± 1.0	70.1 ± 1.5 <sup>c</sup>	64.0 ± 1.6 <sup>c</sup>
Serum albumin, g/l	25.8 ± 0.7	40.7 ± 1.2 <sup>c</sup>	31.9 ± 0.8 <sup>c</sup>
AST, U/l	22 ± 1	22 ± 3	18 ± 1
ALT, U/l	19 ± 2	20 ± 3	15 ± 2
GGT, U/l	28 ± 2	28 ± 4	31 ± 4
ALP, U/l	175 ± 8	177 ± 17	231 ± 14 <sup>b</sup>
Serum bilirubin, µmol/l	5.0 ± 0.5	9.7 ± 1.4 <sup>c</sup>	8.4 ± 0.7 <sup>c</sup>
Serum triglyceride, mmol/l	2.8 ± 0.2	2.5 ± 0.4	1.37 ± 0.1 <sup>c</sup>
Serum cholesterol, mmol/l	8.4 ± 0.4	5.5 ± 0.3 <sup>c</sup>	3.83 ± 0.2 <sup>c</sup>
Proteinuria, g/day	3.96 ± 0.71	1.08 ± 0.22 <sup>c</sup>	0.13 ± 0.04 <sup>c</sup>
Systolic blood pressure, mm Hg	135 ± 3	134 ± 3	124 ± 3
Diastolic blood pressure, mm Hg	84 ± 1	84 ± 2	78 ± 2

GFR = Glomerular filtration rate; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase. Data are expressed as mean ± SEM.

<sup>a</sup>  $p = 0.049$ , <sup>b</sup>  $p = 0.003$ , <sup>c</sup>  $p < 0.001$ , <sup>d</sup>  $p = 0.009$ , <sup>e</sup>  $p = 0.001$  vs. NEPHR.

teinuria from the NEPHR group. Nephrotic oedema was responsible for the significant difference in BMI. CONTR group differed significantly in gender, age, serum creatinine, AST, ALP and serum triglycerides from the NEPHR group. All subjects in the CONTR group were hypoalbuminaemic. Clinical parameters of the cohorts are presented in table 1.

Serum total LDH activity of the NEPHR group was significantly higher compared with the NON-NEPHR and CONTR groups ( $p < 0.001$ ) (fig. 1a). Serum total LDH activity did not correlate with any parameters related to the liver function (data not shown).

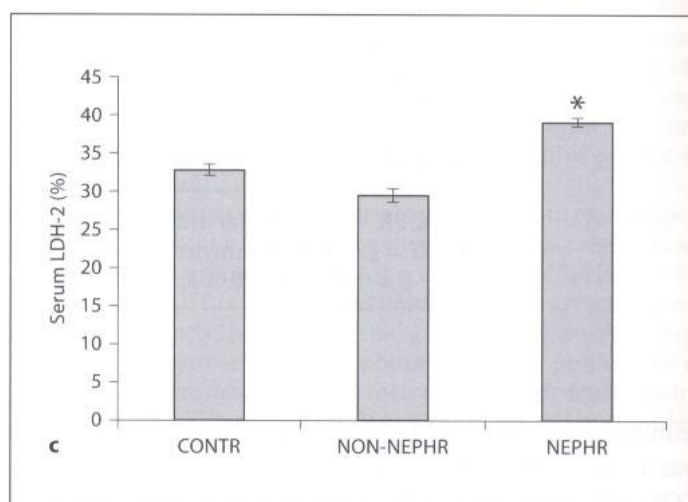
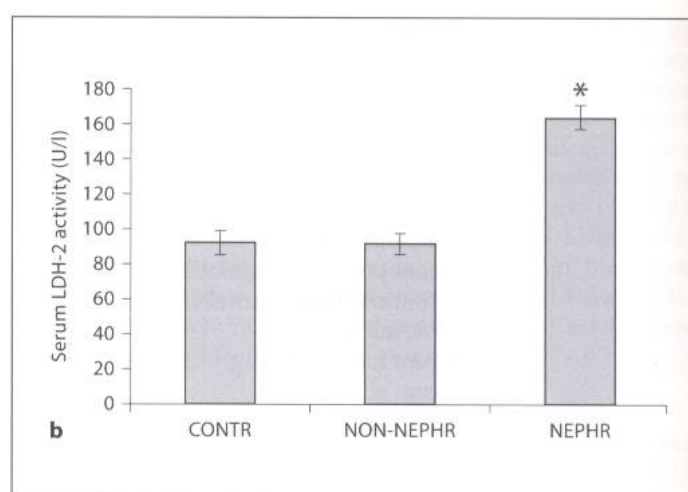
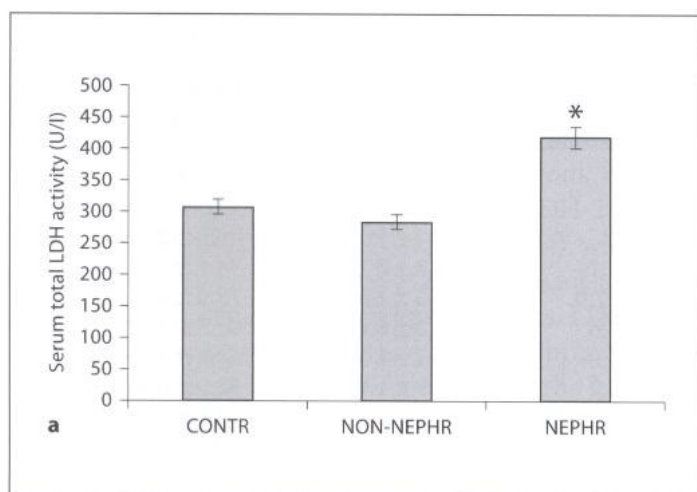
Serum total LDH activity correlated negatively with SProt and SALb ( $r = -0.549$ ,  $p < 0.001$ ;  $r = -0.596$ ,  $p < 0.001$ ) and positively with logarithmic form of proteinuria ( $\ln$ Proteinuria) and Schol ( $r = 0.456$ ,  $p < 0.001$ ;  $r = 0.523$ ,  $p < 0.001$ ) (fig. 2).

LDH isozymes were determined in subgroups randomly selected from all cohorts (NEPHR  $n = 34$ , NON-NEPHR  $n = 12$  and CONTR  $n = 21$ ). Both the activity and the ratio of LDH-2 were significantly higher in the nephrotic subgroup compared with the non-nephrotic and control subgroups ( $p < 0.001$ ) (fig. 1b, c).

Serum LDH-2 activity was found to correlate negatively with SProt, SALb and positively with proteinuria and Schol (fig. 3). We analyzed the correlations with the ratio of serum LDH-2 as well, and we found that it also correlated negatively with SProt and SALb ( $r = -0.607$ ,  $p < 0.001$ ;  $r = -0.482$ ,  $p < 0.001$ ), and positively with proteinuria and Schol ( $r = 0.658$ ,  $p < 0.001$ ;  $r = 0.648$ ,  $p < 0.001$ ). Serum total LDH activity correlated positively with the activity and ratio of LDH-2 isozyme ( $r = 0.943$ ,  $p < 0.001$ ,  $r = 0.655$ ,  $p < 0.001$ , respectively).

Serum total LDH activity, serum LDH-2 activity and the ratio of LDH-2 isozyme were all elevated in the NEPHR group compared with the NON-NEPHR and CONTR groups estimated with general linear model (ANCOVA) adjusted for age, gender, SALb and SProt (fig. 1).

As a result of the linear regression analysis, SProt proved to be the independent predictor of serum total LDH activity ( $B = -5.831$ ,  $\beta = -0.648$ ,  $p < 0.001$ ) while SProt and proteinuria were verified as predictors of LDH-2 ( $B = -0.273$ ,  $\beta = -0.457$ ,  $p = 0.007$ ;  $B = 1.121$ ,  $\beta = 0.428$ ,  $p = 0.011$ ). Linear regression model included age, gender, BMI, serum creatinine, glomerular filtration rate (GFR), SProt, SALb, proteinuria, serum aspartate aminotransfer-



**Fig. 1.** Serum total LDH activity (a), serum LDH-2 activity (b) and the ratio of LDH-2 isozyme (c) was significantly higher in the NEPHR group compared with the NON-NEPHR and CONTR groups (\*  $p < 0.001$ ). Adjusting the data for age, gender, SProt and SALb, the difference remained significant ( $p < 0.001$ ).

ase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), serum gamma-glutamyltransferase (GGT), serum bilirubin, systolic and diastolic blood pressure and serum total LDH activity.

During a 300-week follow-up period, renal survival curves of nephrotic syndrome patients did not differ significantly between patients with LDH above and below the median LDH value ( $p = 0.196$ ) (fig. 4).

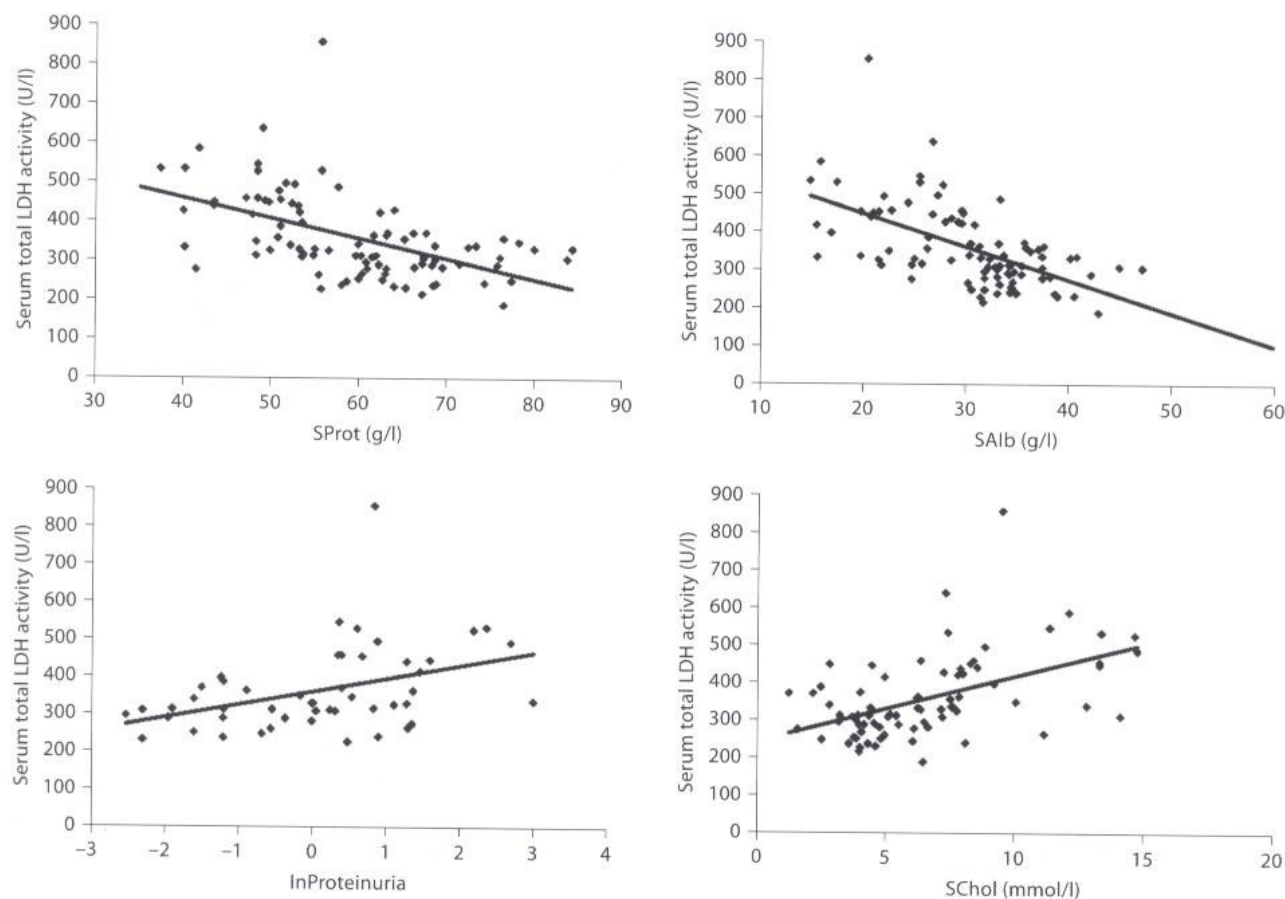
## Discussion

Measuring the serum total LDH activity is an important diagnostic parameter in different diseases with tissue damage because during cell lesioning this enzyme is released into the circulation [8]. Determination of the LDH isozyme pattern is a great assistance in elucidating

the origin of the enzyme. The role of serum total LDH activity in different kidney diseases has only been studied in a few studies so far.

In nephrotic syndrome the filtrated proteins overflow the proximal tubules where tubular cells reabsorb proteins by endocytosis. Since this is a high-energy-demanding procedure, tubular cells may get exhausted and damaged soon. Large quantities of proteins have a toxic effect on tubular cells by increasing cell proliferation and apoptosis thus the tubular cell turnover accelerates. The glomerular barrier normally protects serum proteins from filtration into the urine. Presumably, in nephritic syndrome some serum proteins (e.g. albumin and transferrin) get into the proximal tubules and induce inflammation resulting in damage of the apical and basolateral membranes of the epithelial cells, therefore LDH can freely flow out from the cytoplasm into the serum and





**Fig. 2.** SProt ( $n = 90$ ) and SALb ( $n = 90$ ) correlated negatively (Pearson:  $r = -0.549$ ,  $p < 0.001$ ; Pearson:  $r = -0.596$ ,  $p < 0.001$ ) while proteinuria ( $n = 60$ ) and SCHol ( $n = 77$ ) correlated positively with serum total LDH activity (Spearman rho:  $r = 0.456$ ,  $p < 0.001$ ; Pearson:  $r = 0.523$ ,  $p < 0.001$ ). Since proteinuria showed non-normal distribution, a logarithmic form (lnProteinuria) was used to graph the correlation.

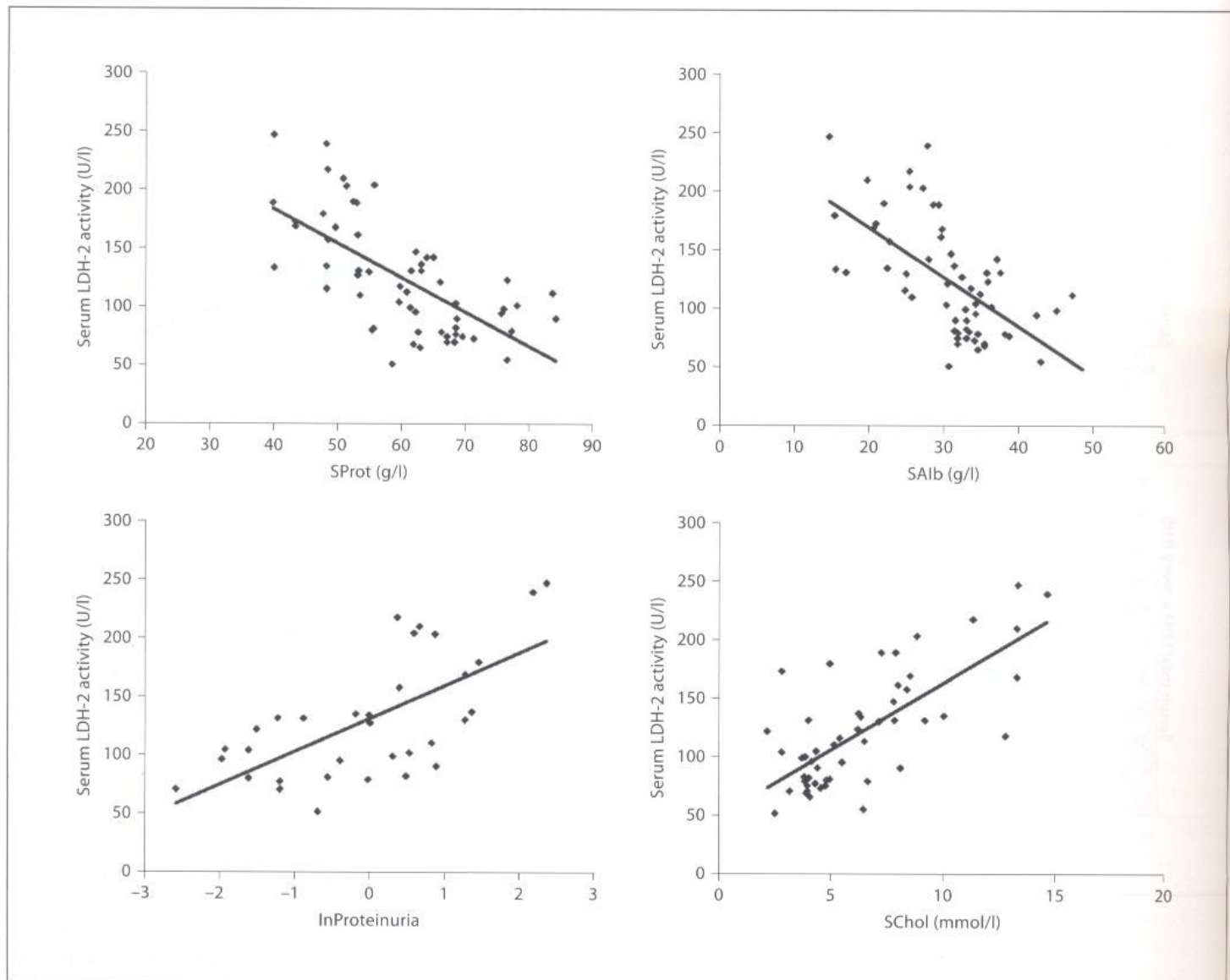
urine [6, 7]. The toxic effect of heavy proteinuria has been shown in a rat model, as well [7].

Mojžiš and Ninger [9] studied the urinary LDH activity in patients with nephrotic syndrome and in patients with non-nephrotic glomerulonephritides of different aetiology. They found a positive correlation between urinary LDH activity and the degree of proteinuria. Serban et al. [10] analysed the urinary LDH activity and isozyme pattern in patients with nephrotic syndrome and in healthy controls. Urinary LDH activity in nephrotic syndrome was significantly elevated compared with the controls and LDH-1 and LDH-2 isozymes were found in largest proportions in the urine. However, a relation between

proteinuria and urinary LDH activity cannot be found. They considered that tubular cell damage caused the elevated urinary LDH activity.

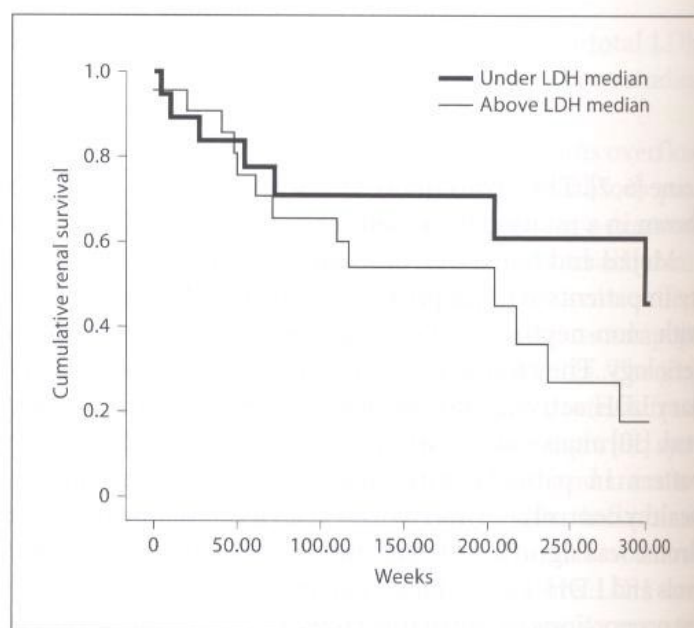
Murdock et al. [11] studied the serum LDH activity and LDH isozymes in different groups of paediatric subjects with nephrotic syndrome (patients in relapse and patients in remission with or without steroid treatment). Patients in relapse had significantly higher urinary and serum total LDH activity compared with the other groups. However, the authors did not draw an obvious conclusion about LDH isozymes in nephrotic syndrome.

In contrast to Murdock et al. [11], we determined the serum total LDH activity in adult kidney patients prior



**Fig. 3.** SProt ( $n = 58$ ) and SAlb ( $n = 58$ ) correlated negatively (Pearson:  $r = -0.665$ ,  $p < 0.001$ ; Pearson:  $r = -0.615$ ,  $p < 0.001$ ) while proteinuria ( $n = 33$ ) and SChol ( $n = 51$ ) correlated positively with serum LDH-2 activity (Pearson:  $r = 0.694$ ,  $p < 0.001$ ; Pearson:  $r = 0.723$ ,  $p < 0.001$ ). Since proteinuria showed non-normal distribution, a logarithmic form (lnProteinuria) was used to graph the correlation.

**Fig. 4.** Comparison of Kaplan-Meier renal survival curves in nephrotic syndrome patients ( $p = 0.196$ ).





to renal biopsy and in hypoalbuminaemic controls with different gastrointestinal diseases. We found higher serum total LDH activity and serum LDH-2 activity in the NEPHR group compared with the NON-NEPHR and CONTR groups. General linear model (ANCOVA) analysis adjusted for age, gender, SALb and SProt also confirmed the difference. Contrary to prior literature, we investigated all parameters of the nephrotic syndrome. We found a negative correlation between serum total LDH activity and SProt and SALb, while serum total LDH activity correlated positively with proteinuria and SChol. Serum LDH-2 activity correlated with the above-mentioned parameters in the same manner. Furthermore, a regression analysis confirmed that SProt and proteinuria are independent predictors of the serum LDH-2. Serum creatinine and GFR were followed and renal survival was calculated between patients with LDH above and below the median LDH value. During a 300-week follow-up period, a significant difference between renal survival curves could not be revealed. However, this result is not surprising because the applied treatment for nephrotic syndrome can slow down or stop the progression even in patients with higher LDH value. We conclude that LDH levels do not influence the therapeutic response in patients with nephrotic syndrome. This suggestion also deserves caution because patients with nephrotic syndrome of different aetiology received heterogeneous therapy.

Our results raise several questions. Could the impaired renal function cause elevated serum total LDH activity? We investigated 57 hemodialysis patients to clarify this and we found that the serum total LDH activity (prior to dialysis) was significantly lower compared with the NEPHR group and did not differ from the NON-NEPHR and CONTR groups (data not shown). So we conclude that elevation of serum total LDH activity in nephrotic patients is not a marker of retention.

In chronic renal diseases, particularly in diabetic nephropathy, neocytolysis should be taken into consideration as a possible cause of LDH elevation. In nephrotic syndrome, massive proteinuria damages the tubulointerstitial cells which can lead to a decrease in erythropoietin production. However, haemoglobin and haematocrit levels did not correlate either with the serum LDH/LDH-2 activity, or with proteinuria.

Thrombosis is considered as a common consequence of nephrotic syndrome because anti-thrombotic factors such as anti-thrombin-III, protein-C and protein-S are excreted in the urine and the increased fibrinogen synthesis causes a procoagulant state. Thrombosis can cause

elevation of serum LDH, but in pulmonary embolism the LDH-3 isozyme should be elevated. However, this isozyme did not differ significantly between the groups ( $p = 0.119$ ).

Conceivably, hypoalbuminaemia per se cannot be responsible for elevated serum LDH, because in hypoalbuminaemic control subjects the serum LDH was significantly lower and in the normal range compared with the NEPHR group. Neither serum total LDH activity nor serum LDH-2 activity correlated with SProt, SALb, SChol and proteinuria in the controls (data not shown).

As a conclusion, the kidney damage may be responsible for the elevated LDH activity in the nephrotic syndrome. Our observation further strengthens the hypothesis of Remuzzi [12], whereas the filtered excessive quantities of protein reach the proximal tubules and the protein over-reabsorption contributes to renal injury by activating inflammation.

We suggest considering elevated serum total LDH activity in nephrotic syndrome as a marker of the disease so its routine determination together with isozyme analysis might give important information about the activity and severity of the disease. However, it cannot replace the quantitative protein determination.

### Acknowledgements

This work was supported by the Hungarian national grants OTKA T-043788 of the Hungarian Scientific Research Fund of the Hungarian Academy of Sciences (István Wittmann) and the László Bolyai Fund of the Hungarian Academy of Sciences (László Wagner).

### References

- Quiros PL, Ceballos M, Remon C, Lozano A, del Castillo R, Aznar E, Perez Perez-Ruilopez MA, Rivero M, Fernandez RE: Study of the biopsied nephrotic syndrome for 20 years in the Cadiz Bay area: histological correspondence, renal prognosis and clinical prognostic factors. *Nefrologia* 2005;25:147–154.
- Togawa A, Yamamoto T, Hishida A: Nephrotic syndrome: pathophysiology, classification and diagnostic criteria. *Nippon Rinsho* 2004;62:1777–1783.
- Johnston ID, Jones NF, Scoble JE, Yuen CT, Price RG: The diagnostic value of urinary enzyme measurements in hypertension. *Clin Chim Acta* 1983;133:317–325.
- Kang KS, Ha YC, Cho HK, Park KS, Kim HU: Changes of lactate dehydrogenase and its isoenzyme activity in renal diseases. *Nephron* 1991;57:55–59.

- 5 Huijgen HJ, Sanders GT, Koster RW, Vreeken J, Bossuyt PM: The clinical value of lactate dehydrogenase in serum: a quantitative review. *Eur J Clin Chem Clin Biochem* 1997; 35:569-579.
- 6 Burton JC, Harper JS, Bailey E, Feehally J, Harris GPK, Walls J: Turnover of human tubular cells exposed to proteins in vivo and in vitro. *Kidney Int* 2001;59:507-514.
- 7 Scherberich JE: Immunological and ultrastructural analysis of loss of tubular membrane-bound enzymes in patients with renal damage. *Clin Chim Acta* 1989;185:271-282.
- 8 Javed MH, Jafri AH, Yousuf FA: Detection of lactate dehydrogenase isoenzyme-M in body fluids containing albumin. *Ann Clin Biochem* 1999;36:250-251.
- 9 Mojžiš A, Ninger E: Relation of the activity of urinary lactate dehydrogenase to the activity of glomerulonephritis. *Clin Chim Acta* 1970;27:145-148.
- 10 Serban M: Urinary LDH activity and its isoenzyme pattern in renal pathology. *Rev Roum Méd Int* 1973;10:43-47.
- 11 Murdock BC, Baker JP, DeLong E, Roe RC, Osofsky GS: Urine and serum lactic dehydrogenase, lactic dehydrogenase isoenzymes, and alkaline phosphatase in the nephrotic syndrome. *Kidney Int* 1981;19:710-715.
- 12 Remuzzi G: A unifying hypothesis for renal scarring linking protein trafficking to the different mediators of injury. *Nephrol Dial Transplant* 2000;15(suppl 6):58-60.