

## Selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome

**Beata Bieniaś, Małgorzata Zajązkowska, Halina Borzęcka, Przemysław Sikora, Marek Majewski, Ewelina Książek, Anna Wiczorkiewicz-Plaza, Grzegorz Borzęcki**

Received: 15 June 2011 / Received in revised form: 03 August 2011, Accepted: 13 August 2011, Published online: 25 February 2012  
© Sevas Educational Society 2008-2012

### Abstract

The purpose of our study was to evaluate selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome (INS) at three stages of the disease (I – in acute phase before steroid therapy, II – during steroid therapy after resolution of proteinuria and III – in remission after completion of steroid therapy). In all children, serum total homocysteine, lipoprotein (a), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides levels were measured at three stages of the disease. Plasma antithrombin III, fibrinogen and D-dimer levels were also determined. At all stages of INS, the serum t-HCY levels were similar and significantly higher than in controls. Serum lipoprotein (a) level, plasma antithrombin III, fibrinogen and D-dimer levels were significantly higher at stage I than at stages II, III and controls. In conclusion, children with INS are at high risk of thrombosis and atherosclerosis.

**Keywords:** Homocysteine, Lipoprotein (a), Antithrombin III, Fibrinogen, D-dimer, Nephrotic syndrome

### Introduction

The idiopathic nephrotic syndrome is associated with complex disturbances in coagulation system and numerous abnormalities of lipid and homocysteine metabolism which may increase the risk of thromboembolic complications and atherosclerosis. Homocysteine is a sulfur amino acid derived from methionine during transmethylation. Remethylation to methionine in a folate- and

cobalamine - dependent reaction is also possible (Welch & Loscalzo 1998; Dudman et al. 1996). Homocysteine directly injures endothelium, induces platelets aggregation and decreases coagulation inhibitors activity (Welch & Loscalzo 1998; Dudman et al. 1996; Harker et al. 1974; Boushey et al. 1995; D'Angelo et al. 1997; Woo et al. 1997; van Guldner & Stehouwer 2000). It also generates oxidation stress and oxidation of low-density lipoprotein, increases fibrinogen level, stimulates angiogenesis and proliferation of smooth muscle cells and fibroblasts (van Guldner et al. 2000; Tsai et al. 1994; Joseph et al. 2009; Lentz et al. 2005; Harpel et al. 1992; Kronenberg 1998).

According to published data homocysteine can partially dissociate apolipoprotein (a) from lipoprotein (a) and can induce its binding to fibrin intensifying prothrombotic effect (Harpel et al. 1992; Leerink et al. 1994). Lipoprotein (a) is also recognized as a prothrombotic and atherogenic agent. The atherogenic effects of lipoprotein (a) is probably similar to those of low-density lipoprotein cholesterol (Naruszewicz et al. 1992). Its prothrombotic effects is combined with impaired fibrinolysis (Hajjar et al. 1989). Hyperhomocysteinemia in combination with decreased serum antithrombin III and increased serum lipoprotein (a), cholesterol and fibrinogen levels may contribute to high incidence of vascular diseases (Bostom et al. 1996; Berenson et al. 1998) and may also accelerate the progression of renal disease (Muntner et al. 2000).

Recently, numerous studies have demonstrated increased homocysteine levels in a variety of diseases (Bostom et al. 1996; Guven et al. 2005; Hwang et al. 2011; Sagheb et al. 2010; Ferechide & Radulescu 2009; van Guldener & Robinson 2000). The data on serum homocysteine level in patients with idiopathic nephrotic syndrome are scarce and conflicting. These data most often concern adult patients.

The purpose of our study was to evaluate selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome at different stages of the disease.

---

**Beata Bieniaś\*, Małgorzata Zajązkowska, Halina Borzęcka, Przemysław Sikora, Marek Majewski, Ewelina Książek, Anna Wiczorkiewicz-Plaza,**

Department of Pediatric Nephrology, Medical University of Lublin, Chodźki 2, 20-093 Lublin, Poland

**Grzegorz Borzęcki**

Department of Hygiene, Medical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland

\* Tel: 0048 503029541, Fax: 0048 817430117  
Email: beata.bienias@umlub.pl

Table 1. Concentrations of assessed parameters in patients at three stages of nephrotic syndrome and in control group

		N	Median	Range	statistical analysis		N	Median	Range	statistical analysis	
albumin (g/dl)	stage I	36	2.5	1.2-3.6	I-II p=0.0008	HDL-CH (mg/dl)	stage I	36	62.2	47.0-82.0	I-II p=0.84
	stage II	36	3.3	2.3-4.4	I-III p=0.0000001 II-III p=0.00002		stage II	36	63.1	48.0-83.4	I-III p=0.22 II-III p=0.23
	stage III	36	4.5	3.6-5.0	I-K p=0.0000001 II-K p=0.00001		stage III	36	57.3	39.9-71.5	I-K p=0.06 II-K p=0.06
	controls	33	4.3	4.1-5.5	III-K p=0.35		controls	33	44.5	31.0-63.0	III-K p=0.09
t-HCY (umol/l)	stage I	36	12.6	9.4-20.8	I-II p=0.29	TG (mg/dl)	stage I	36	157.0	57.0-732.0	I-II p=0.49
	stage II	36	12.1	9.0-18.9	I-III p=0.57 II-III p=0.1		stage II	36	130.0	60.0-599.0	I-III p=0.0001 II-III p=0.01
	stage III	36	12.6	9.1-16.5	I-K p=0.002 II-K p=0.04		stage III	36	53.0	41.0-121.0	I-K p=0.000002 II-K p=0.0002
	controls	33	11.3	7.8-12.8	III-K p=0.04		controls	33	71.0	46.0-104.0	III-K p=0.13
Lp (a) (mg/dl)	stage I	36	11.3	3.1-80.2	I-II p=0.04	AT III (%)	stage I	36	66.6	35.0-97.2	I-II p=0.0000001
	stage II	36	7.5	2.4-61.2	I-III p=0.0001 II-III p=0.08		stage II	36	108.8	84.8-157.6	I-III p=0.0002 II-III p=0.30
	stage III	36	6.3	1.9-10.6	I-K p=0.00008 II-K p=0.04		stage III	36	109.0	80.0-130.0	I-K p=0.0000001 II-K p=0.06
	controls	33	5.2	1.7-9.0	III-K p=0.06		controls	33	117.0	98.2-150.1	III-K p=0.18
T-CH (mg/dl)	stage I	36	276.0	157.0-702.0	I-II p=0.14	fibrinogen (mg/dl)	stage I	36	499.0	261.0-1434.0	I-II p=0.0000001
	stage II	36	259.0	142.0-424.0	I-III p=0.00003 II-III p=0.01		stage II	36	273.0	190.0-443.0	I-III p=0.0001 II-III p=0.86
	stage III	36	162.0	124.0-238.0	I-K p=0.000001 II-K p=0.0000001		stage III	36	255.0	209.0-380.0	I-K p=0.0000001 II-K p=0.01
	controls	33	160.0	98.0-185.0	III-K p=0.46		controls	33	228.5	165.0-312.0	III-K p=0.29
LDL-CH (mg/dl)	stage I	36	175.9	86.8-613.0	I-II p=0.99	D-dimers (ng/ml)	stage I	36	505.0	243.0-1118	I-II p=0.000001
	stage II	36	166.5	63.0-305.0	I-III p=0.0009 II-III p=0.01		stage II	36	207.0	90.0-341.0	I-III p=0.0003 II-III p=0.29
	stage III	36	102.9	57.3-166.0	I-K p=0.0005 II-K p=0.0005		stage III	36	151.5	115.0-243.0	I-K p=0.0000001 II-K p=0.04
	controls	33	103.0	79.0-129.8	III-K p=1.0		controls	33	161.5	112.0-221.0	III-K p=0.85

## Patients and methods

The study comprised 36 children (32 boys and 4 girls) aged 1-17 years with idiopathic nephrotic syndrome (INS) and 33 gender- and age-matched healthy controls.

In all children, serum total homocysteine (t-HCY), lipoprotein (a) (Lp (a)), total cholesterol (T-CH), low-density lipoprotein cholesterol (LDL-CH), high-density lipoprotein cholesterol (HDL-CH) and triglycerides (TG) levels were measured. Plasma antithrombin III (ATIII), fibrinogen and D-dimer levels were also determined.

The measurements were performed at three stages of the disease: I – in acute phase before steroid therapy, II - during steroid therapy after resolution of proteinuria (2-4 weeks after diagnosis of INS), III - in remission after completion of steroid therapy (6-8 months after diagnosis of INS).

Serum t-HCY levels were assessed with enzyme-linked immunosorbent assay (ELISA). Serum Lp (a) levels were measured with turbidimetric method. Serum T-CH, LDL-CH, HDL-CH and TG levels were determined using biochemical analyzer - Architekt c 8000. Plasma ATIII and fibrinogen levels were measured using Thrombolyzer Compact X whereas Mini Vidas analyzer was used to determine D-dimer level.

The statistical analysis was performed using STATISTICA 7.1. Differences between groups were assessed using Mann-Whitney test and correlation coefficients were calculated using Spearman test. A  $p \leq 0.05$  was regarded as statistically significant.

## Results

The results of our study are presented in Table 1. In children at stage I of INS, the median of proteinuria per 24 hours, the median of serum albumin level and the median of GFR were  $173.9 \pm 99$  mg/kg,  $2.5 \pm 0.82$  g/dl and  $110.3 \pm 27$  ml/min/1.73 m<sup>2</sup>, respectively. There were no significant differences in GFR between patients at particular stages of the disease.

At all stages of INS, the serum t-HCY levels (I – 12.6 umol/l, II – 12.1 umol/l, III – 12.6 umol/l) were similar and significantly higher than in controls (11.3 umol/l) ( $p < 0.05$ ). Serum Lp (a) levels were significantly higher at stage I (11.3 mg/dl) than at stages II and III and in controls (7.5 mg/dl, 6.3 mg/dl, 5.2 mg/dl, respectively,  $p < 0.05$ ). The differences in serum Lp (a) levels between stages I and II and between stage II and controls were also statistically significant.

The serum T-CH, LDL-CH and TG levels were significantly higher at stage I (276.0, 175.9 and 157.0 mg/dl, respectively) and at stage II (259.0, 166.5, 130.0 mg/dl, respectively) than at stage III (162.0, 102.9, 53.0 mg/dl, respectively) and in controls (160.0, 103.0, 71.0 mg/dl, respectively) ( $p < 0.05$ ). The serum HDL-CH levels were

similar at all three stages of INS (I - 62.2 mg/dl, II - 63.1 mg/dl, III - 57.3 mg/dl) and in controls (44.5 mg/dl).

Plasma ATIII levels were significantly lower at stage I (66.6 % than at stages II and III and in controls (108.8%,  $p=0.0000001$ ; 109.0%,  $p=0.0002$ ; 117.0%,  $p=0.0000001$ , respectively). Plasma fibrinogen levels were significantly higher at stage I (499.0 mg/dl) than at stages II and III and in controls (273.0 mg/dl,  $p=0.0000001$ ; 255.0 mg/dl,  $p=0.0001$ ; 228.5 mg/dl,  $p=0.0000001$ , respectively). Plasma fibrinogen levels were also significantly higher at stage II than in controls ( $p=0.01$ ). Similar differences were observed in plasma D-dimer levels. At stage I plasma D-dimer levels (505.0 ng/ml) were significantly higher than at stages II and III and in controls (207.0 ng/ml,  $p=0.0000001$ ; 151.5 ng/ml,  $p=0.0003$ ; 161.5 ng/ml,  $p=0.0000001$ , respectively). Plasma D-dimer levels were also significantly higher at stage II than in controls ( $p=0.04$ ).

Significant positive correlation between serum albumin and plasma ATIII levels was observed ( $r = +0.54$ ,  $p<0.05$ ) whereas correlations between levels of serum albumin and plasma fibrinogen ( $r = -0.49$ ,  $p<0.05$ ), plasma D-dimer ( $r = -0.49$ ,  $p<0.05$ ) and serum T-CH ( $r = -0.64$ ,  $p<0.05$ ) were significantly negative. Serum t-HCY levels showed significant positive correlation with serum Lp (a) levels ( $r = +0.5$ ,  $p<0.05$ ). No correlations between serum t-HCY levels and serum albumin, T-CH, LDL-H, TG levels were observed. Similarly, serum t-HCY level did not correlate with plasma antithrombin III, fibrinogen and D-dimer levels.

## Discussion

The disturbances in coagulation system and lipid metabolism observed in patients with INS have been well established (Joseph et al. 2009; Wheeler & Bernard 1994; Citak et al. 2000; Singhal & Brimble 2006; Schlegel 1997; Fujita et al. 1992; 2006; Louis et al. 2003). They are due to well-known factors such as loss of albumin and anticoagulant factors (ATIII, protein C, protein S) with urine, increased number and activity of platelets, increased plasma fibrinogen and serum lipids levels, plasma volume contraction and use of diuretics and corticosteroids (Citak et al. 2000; Thabet et al. 1993; Radhakrishnan et al 1993). These disturbances give rise to higher risk of thrombosis and early atherosclerosis. In INS patients, the prevalence of thromboembolic complications vary between 1.8% to 5.3% (Fujita et al. 1992).

The development of cardiovascular diseases due to atherosclerosis in patients formerly treated for INS was also demonstrated (Kniażewska et al. 2009).

Recently, hyperhomocysteinemia is reported to be another independent risk factor for thromboembolic complications and early development of atherosclerosis. Numerous studies showed a positive correlation between hyperhomocysteinemia and risk of coronary and cerebrovascular events, peripheral vascular disease and thromboembolic complications (Boushey et al. 1995; Quere et al. 2005; Huang et al. 2000; Nygard et al. 1999; Marouf et al. 2006). An increased serum t-HCY level in adult patients with acute phase of INS was demonstrated. (Podda et al. 2007; Joven et al. 2000; Herrmann et al. 2000; Dwivedi & Sarkar 2009). Kniażewska et al. (2009) showed increased serum t-HCY levels in young patients (9 - 22 years of age) 4 to 15 years after completion of treatment for INS. In our study, we found elevated serum levels of t-HCY at all stages of INS. Our results confirm that increased serum t-HCY levels occurs not only at stage I of INS but also a lot of months after resolution of proteinuria. Similar results concerning serum t-HCY level in adult patients with nephrotic syndrome were reported by Dawivedi and Sarkar (2009). In children with INS, persistent

elevated serum t-HCY levels may increase the risk of thromboembolic complications and may accelerate development of atherosclerosis. Proven causes of hyperhomocysteinemia are low serum levels of folic acid, B 6 and B12 vitamins and their administration significantly decreases serum t-HCY level (Ferechide & Radulescu 2009; Van Guldener & Robinson 2000; Podda et al. 2007; Thambyrajah et al. 2001; Rimm et al. 1998). Supplementation with these vitamins could probably be an additional therapy in patients with INS.

Previous studies demonstrated increased serum levels of Lp (a) in patients with kidney diseases and its association with the development of atherosclerosis and cardiovascular complications (Kronenberg 1998; Bostom et al. 1996; Querfeld et al. 1993; Gasevoort et al. 1994; Greiber & Wanner 1997; Kronenberg et al. 2004; Kwan et al. 2007). Other studies disclosed elevated serum Lp (a) levels in nephrotic children (Herrmann et al. 2000; Hu et al. 2009). Our studies confirmed increased serum Lp (a) levels at stage I of INS. We also observed positive correlation between serum Lp (a) and t-HCY levels. This coexistence of two thrombogenic and atherogenic factors may significantly increase the risk of acute and chronic cardiovascular diseases in children with INS.

It has been well established that in almost all patients with INS, elevated serum T-CH, LDL-CH and TG levels occur (Citak et al. 2000; Fujita et al. 2006; Thabet et al. 1993; Radhakrishnan et al. 1993; Hu et al. 2009). Serum HDL-CH level may be normal, low or high (Thabet et al. 1993; Radhakrishnan et al. 1993). Our study demonstrated increased serum T-CH, LDL-CH and TG levels at stages I and II of INS. At these stages, serum T-CH, LDL-CH and TG levels correlated negatively with serum albumin level. Children at stage III of INS had serum T-CH, LDL-CH and TG levels similar to controls. Dissimilar results were obtained by Kniażewska et al. (2009) who reported higher levels of T-CH and LDL-CH in patients 4 - 15 years after completed steroid therapy for INS. Mérouani et al. (2003) observed hyperlipidemic profile in nearly half of their nephrotic patients in remission and recommended regular monitoring of serum lipids levels, especially in those with frequent relapses. This indicates that other factors may contribute to hyperlipidemia including number of relapses of INS and perhaps genetic predisposition. However, the study by Książek et al. (2009) did not confirm the significant impact of polymorphisms of specific genes coding proteins involved in lipoprotein metabolism on persistent dyslipidemia in patients with remission of INS.

Decreased plasma level of ATIII was commonly observed in patients with INS (Lentz 2005; Citak et al. 2000). Occurrence of thromboembolic events in patients with nephrotic syndrome was demonstrated in numerous case reports (Louis et al. 2003; Kniażewska et al. 2009; Quere et al 2005; Huang et al. 2000; Balci et al 2007; Zaffanello et al. 2009). Previous studies suggested that the risk of thrombosis was significantly increased when serum albumin levels were below 2.0 g/dl and plasma ATIII levels were lower than 75% (Bernard 1988; Llach 1985). Our data confirmed significantly lower plasma ATIII levels at stage I of INS and its significant positive correlation with serum albumin levels. Hyperfibrinogenemia is often associated with INS and it is thought to be a risk factor for thromboembolic complications (Woo et al. 1997; Louis et al. 2003; Zaffanello & Franchini 2007). In our patients, increased plasma fibrinogen levels were found not only at stage I of INS but also at stage II of the disease whereas a few months after diagnosis of INS (stage III) plasma levels of fibrinogen were similar to that in healthy controls. Significant negative correlation between plasma fibrinogen and serum albumin levels was also observed.

D-dimer is a well-known molecular marker of coagulation activation. In nephrotic patients with thromboembolic complications, elevated plasma D-dimer levels were reported (Oikawa et al. 1997; Citak et al. 2000; Zaffanello et al. 2009; Morikawa et al. 2009). An increased plasma levels of D-dimer were often revealed in patients with pulmonary embolism (Huang et al. 2000). In our studies, increased plasma D-dimer levels were found at stages I and II of INS. This might confirm hypercoagulation state at these stages of the disease.

In conclusion, children with INS are at high risk of thrombosis and atherosclerosis. In children with severe hypoalbuminemia, their coagulation state should be monitored especially thoroughly and in those with thromboembolic risk factors, prophylactic treatment with anticoagulant should be initiated. An elevated serum t-HCY level persisting despite resolution of proteinuria additionally increases the risk of thromboembolic complications and early development of atherosclerosis. Therefore, in patients with INS and hyperhomocysteinemia, supplementation with folic acid, vitamin B6 and B12 in order to decrease serum homocysteine level and reduce the risk of atherosclerosis should be considered.

## References

- Balci YI, Tavil B, Fidan G et al (2007) Cerebral sinovenous thrombosis in a child with steroid sensitive nephrotic syndrome. *Eur J Pediatr* 166(7):757-758
- Berenson GS, Srinivasan SR, Bao W et al (1998) Association between multiple cardiovascular risk factor and atherosclerosis in children and young adults: The Bogalusa Heart Study. *N Engl J Med* 338:1650-1656
- Bernard DB (1988) Extrarenal complications of the nephrotic syndrome. *Kidney Int* 33(6):1184-202
- Bostom AG, Shemin D, Lapane KL et al (1996) Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein (a) excess in maintenance dialysis patients: a matched case-control study. *Atherosclerosis* 23:125(1):91-101
- Boushey CJ, Beresford SAA, Omenn GS et al (1995) A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes *JAMA* 274:1049-1057
- Citak A, Emre S, Sâirin A et al (2000) Hemostatic problems and thromboembolic complications in nephrotic children. *Pediatr Nephrol* 14(2):123-142
- D'Angelo A, Selhub J (1997) Homocysteine and thrombotic disease. *Blood* 90:1-11
- Dudman NPB, Guo XW, Gordon RB et al (1996) Human homocysteine catabolism: Three major pathways and their relevance to development of arterial occlusive disease. *J Nutr* 126:1295S-1300S
- Dwivedi J, Sarkar PD (2009) Study of oxidative stress, homocysteine, copper & zinc in nephrotic syndrome: therapy with antioxidants, minerals and B-complex vitamins. *J Biochem Tech* 1(4):104-107
- Ferechide D, Radulescu D (2009) Hyperhomocysteinemia in renal diseases. *J Med Life* 2(1):53-59. Review
- Fujita T, Nakamura N, Kumasaka R et al (2006) Comparison of lipid and fatty acid metabolism between minimal change nephrotic syndrome and membranous nephropathy. *In Vivo* 20(6B):891-893
- Fujita T, Saito E, Ohi H et al. (1992) Lipoprotein(a) predicts the risk of thrombotic complications in nephrotic syndrome. *Nephron* 1992;61:122-122
- Gansevoort RT, Heeg JE, Dikkeschei FD et al (1994) Symptomatic anti-proteinuric treatment decreases serum lipoprotein (a) concentration in patients with glomerular proteinuria. *Nephrol Dial Transplant* 9(3):244-250
- Greiber S, Wanner C (1997) Lipoprotein(a) in nephrotic syndrome and end-stage renal disease. *Miner Electrolyte Metab* 23(3-6):161-165
- Güven A, İnanc F, Kilinc M et al (2005) Plasma homocysteine and lipoprotein (a) levels in Turkish patients with metabolic syndrome. *Heart Vessels* 20:290-295
- van Guldener C, Robinson K (2000) Homocysteine and renal disease. *Semin Thromb Hemost* 26(3):313-324. Review
- van Guldener C, Stehouwer CD (2000) Hyperhomocysteinemia, vascular pathology, and endothelial dysfunction. *Semin Thromb Hemost* 26(3):281-289. Review
- Hajjar KA, Gavish D, Breslow JL et al (1989) Lipoprotein (a) modulation of endothelial cell surface fibrinolysis and its potential role of atherosclerosis. *Nature* 339:303-305
- Harker LA, Slichter SJ, Scott CR, Ross R (1974) Homocysteinemia: vascular injury and arterial thrombosis. *N Engl J Med* 291:537-543
- Harpel P C, Chang V T and Borth W (1992) Homocysteine and other sulfhydryl compounds enhance the binding of lipoprotein(a) to fibrin: a potential biochemical link between thrombosis, atherogenesis, and sulfhydryl compound metabolism. *Proc Natl Acad Sci U S A* 89(21): 10193-10197
- Herrmann W, Quast S, Ellgass A et al (2000) An increased serum level of free Apo(a) in renal patients is more striking than that of Lp(a) and is influenced by homocysteine. *Nephron* 85(1):41-49
- Hu P, Lu L, Hu B et al (2009) Characteristics of lipid metabolism under different urinary protein excretion in children with primary nephrotic syndrome. *Scand J Clin Lab Invest* 69(6):680-686
- Huang J, Yang J, Ding J (2000) Pulmonary embolism associated with nephrotic syndrome in children: a preliminary report of 8 cases. *Chinese Medical Journal* 113(3):251-253
- Hwang SY, Siow YL, Au-Yeung KK et al (2011) Folic acid supplementation inhibits NADPH oxidase-mediated superoxide anion production in the kidney. *Am J Physiol Renal Physiol* 300(1):F189-198
- Joseph J, Pencina MJ, Wang TJ et al (2009) Cross-sectional relations of multiple biomarkers representing distinct biological pathways to plasma markers of collagen metabolism in the community. *J Hypertens* 27(6):1317-24
- Joven J, Arcelús R, Camps J et al (2000) Determinants of plasma homocyst(e)ine in patients with nephrotic syndrome. *J Mol Med* 78(3):147-154
- Kniażewska MH, Obuchowicz AK, Wielkoszyński T et al (2009) Atherosclerosis risk factors In young patients formerly treated for idiopathic nephrotic syndrome. *Pediatr Nephrol* 24:549-554
- Kronenberg F (1998) Homocysteine, lipoprotein(a) and fibrinogen: metabolic risk factors for cardiovascular complications of chronic renal disease. *Curr Opin Nephrol Hypertens* 7(3):271-278
- Kronenberg F, Lingenhel A, Lhotta K (2004) Lipoprotein(a)- and low-density lipoprotein-derived cholesterol in nephrotic syndrome: Impact on lipid-lowering therapy? *Kidney Int* 66:348-354
- Książek J, Ciechanowicz A, Wierzbicka A et al (2009) Is dyslipidemia sustained during remission of nephrotic syndrome genetically determined? *Pol Arch Med Wewn* 119(1-2):11-16
- Kwan BC, Kronenberg F, Beddhu S et al (2007) Lipoprotein metabolism and lipid management in chronic kidney disease. *J Am Soc Nephrol* 18:1246-1261
- Leerink CB, van Ham AD, Heeres A et al (1994) Sulfhydryl compounds influence immunoreactivity, structure and

- functional aspects of lipoprotein(a). *Thromb Res* 1;74(3):219-232
- Lentz SR (2005) Mechanisms of homocysteine-induced atherothrombosis. *J Thromb Haemost* 3:1646-1654
- Llach F (1985) Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. *Kidney Int* 28(3):429-439
- Louis CU, Morgenstern BZ, Butani L (2003) Thrombotic complications in childhood-onset idiopathic membranous nephropathy. *Pediatr Nephrol* 18(12):1298-300
- Marouf R, Zubaid M, Mojiminiyi OA et al (2006) Determinants of plasma homocysteine in relation to hematological and biochemical variables in patients with acute myocardial infarction. *South Med J* 99(8):811-816
- Mérouani A, Lévy E, Mongeau JG et al (2003) Hyperlipidemic profiles during remission in childhood idiopathic nephrotic syndrome. *Clin Biochem* 36 (7): 571-574
- Morikawa T, Yamashiro Y, Okano K (2009) Soluble fibrin is not excreted in urine and its plasma level is elevated in nephrotic syndrome. *Rinsho Byori* 57(4):319-323
- Muntner P, Coresh J, Smith JC et al (2000) Plasma lipids and risk of developing renal dysfunction: The Atherosclerosis Risk In Communities Study. *Kidney Int* 58:293-301
- Naruszewicz M, Selinger E, Davignon J (1992) Oxidative modification of lipoprotein (a) and the effect of beta-carotene. *Metabolism* 41:1215-1224
- Nygård O, Vollset SE, Refsum H et al (1999) Total homocysteine and cardiovascular disease. *J Int Med* 246(5):425-454
- Oikawa T, Muramatsu Y, Akashi S et al (1997) A coagulation of fibrinolytic study in children with nephrotic syndrome: evaluation of hypercoagulability by measuring with plasmin-alpha 2 plasmin inhibitor complex and FDP D-dimer. *Nippon Jinzo Gakkai Shi* 39(2):144-149
- Podda GM, Lussana F, Moroni G et al (2007) Abnormalities of homocysteine and B vitamins in the nephrotic syndrome. *Thromb Res* 120(5):647-652
- Quere I, Gris JC, Dauzat M (2005) Homocysteine and venous thrombosis. *Semin Vasc Med* 5(2):183-189
- Querfeld U, Lang M, Friedrich JB et al (1993) Lipoprotein(a) serum levels and apolipoprotein(a) phenotypes in children with chronic renal disease. *Pediatr Res* 34:772-776
- Radhakrishnan J, Appel AS, Valeri A et al (1993) The nephrotic syndrome, lipids, and risk factors for cardiovascular disease. *Am J Kidney Dis* 22:135
- Rimm EB, Willett WC, Hu FB et al (1998) Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 279(5):359-364
- Sagheb MM, Ostovan MA, Sohrabi ZJ et al (2010) Hyperhomocysteinemia and cardiovascular risks in hemodialysis patients. *Saudi J Kidney Dis Transpl* 21(5):863-866
- Schlegel N (1997) Thromboembolic risks and complications in nephrotic children. *Semin Thromb Hemost* 23(3):271-280
- Singhal R, Brimble KS (2006) Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. *Thromb Res* 118(3):397-407
- Thabet MA, Salcedo JR, Chan JC (1993) Hyperlipidemia in childhood nephrotic syndrome. *Pediatr Nephrol* 7:559-566
- Thambyrajah J, Landray MJ, Jones HJ et al (2001) A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. *J Am Coll Cardiol* 37:1858-1863
- Tsai JC, Perrrella MA, Yoshizumi M et al (1994) Promotion of vascular smooth muscle cell growth by homocysteine: A link to atherosclerosis. *Proc Natl Acad Sci USA* 91:6369-6373
- Welch GN, Loscalzo J (1998) Homocysteine and atherothrombosis. *N Engl J Med* 338:1042-1050
- Wheeler DC, Bernard DB (1994) Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. *Am J Kidney Dis* 23:331-346
- Woo KS, Chook P, Lolin YI et al (1997) Hyperhomocysteinemia is a risk factor for arterial endothelial dysfunction in humans. *Circulation* 96:2542-2544
- Zaffanello M, Brugnara M, Fanos V et al (2009) Prophylaxis with AT III for thromboembolism in nephrotic syndrome: why should it be done? *Int Urol Nephrol* 41(3):713-716
- Zaffanello M, Franchini M (2007) Thromboembolism in childhood nephrotic syndrome: a rare but serious complication. *Hematology* 12(1):69-73