LECTURE 7

PATHOPHYSIOLOGY OF THE RENAL SYSTEM (I)

Outline:
Pathophysiology of glomerular nephropathies
  I. Definition, classification
  II. Pathogenesis
  III. Glomerular syndromes

I. PATHOPHYSIOLOGY OF GLOMERULAR NEPHROPATHIES – Definition, classification

- Definition:
  Glomerular nephropathies are bilateral, acute or chronic, renal disorders, induced by the exclusive or predominant damage of renal glomeruli

- Classification:
  – primary → the kidney is the only impaired organ
  – secondary → renal involvement is an integrant part of a systemic disease

The structure and function of the GLOMERULAR FILTRATING MEMBRANE

The glomerular filtrating membrane consists of 3 layers:

1. The ENDOTHELIAL membrane (lamina fenestrata)
   - highly fenestrated (70-100 nm)
   - effective barrier for blood cells
   - covered by the glycocalyx which contains negatively charged proteoglycans and glycosaminoglycans that reject plasma albumins (which dissociate as anions)

2. BASAL membrane (BM)
   - consists of 3 layers (lamina rara interna, lamina densa and lamina rara externa)
   - contains 4 major components: laminin, type IV collagen, nidogen and heparan sulfate-type proteoglycans (the latter gives the negative charge of the BM)
   - achieves an effective barrier for negatively charged large-molecular-weight proteins (> 69 kDa, > 8 nm diameter) and for albumins (GM = 67 kDa, diameter approx. 3.6 nm)

3. EPITHELIAL membrane
   - consists of podocytes with cytoplasmic footlike radiating processes (pedicels) which serve to attach to the BM
     – between the pedicels, there are tunnel-like spaces called filtration slits (20-30 nm)
     – filtration slits are covered by a thin diaphragm, mainly consisting in a transmembrane glycoprotein called nephrin which is the main filtration barrier against protein loss
     – the surface of pedicels is covered with acid glycoproteins (sialoglycoproteins) which give them a high negative charge

Important!
The mechanical and electrostatic barrier function of the glomerular filter prevents the urinary loss of proteins and blood cells. Consequently, the alteration of this function such as in incipient glomerular
nephropathies triggers the occurrence of isolated urinary alterations characterised by proteinuria and asymptomatic haematuria.

II. PATHOGENESIS OF GLOMERULAR NEPHROPATHIES

The pathogenesis of glomerular damage is COMMON for all the types of glomerular nephropathies or glomerulonephrites (GN). This damage is caused by:

- **primary** mechanisms → trigger glomerular damage
- **secondary** mechanisms → induce the progression of glomerular damage

A. TRIGGERING mechanisms of glomerular damage

Glomerular damage is triggered by immune mechanisms, both in primary glomerular nephropathies and in most of the secondary ones, with the involvement of both humoral and cellular immunity:

- **humoral immune response** — is controlled by Th2 lymphocytes and leads to the formation of Ag deposits and glomerular complement activation
- **cellular immune response** — is controlled by Th1 lymphocytes and leads to mononuclear cell glomerular infiltration (lymphocytes and macrophages)

a) IMMUNE mechanisms activated at GLOMERULAR level:

I. **UMORAL** mechanisms

According to their size and electrical charge, antigens (Ag) and immune complexes (Ag/Ab) can form deposits on three levels:

- **subendothelial**: between the endothelial cells and BM → in the case of anionic Ag
- **subepithelial**: between BM and podocytes → in the case of cationic Ag which can cross polyanionic BM
- **mesangial**: in the case of neutral Ag

1. Ac formation against glomerular Ag (type II hypersensitivity - HS) and *in situ* immune complex deposits

   - **FIXED intrinsic Ag**:
     - in glomerular BM (collagen IV) in Goodpasture syndrome defined by:
       - GN with glomerular anti-BM Ac
       - Pulmonary vasculitis with pulmonary capillary anti-BM Ac
     - at podocyte level (A2 phospholipase receptor, PLA2R) in membranous GN

   - **Extrinsic „PLANTED” Ag**:
     - endogenous: DNA and nuclear proteins, Ac, immune complexes, protein aggregates
     - exogenous: bacterial, viral, parasitic products, medicines, cow-milk proteins

2. Cytotoxic Ab formation with subsequent direct glomerular damage (type II HS):

   - mesangial anti-Ag Ab → mesangial cell lysis
   - endothelial anti-Ag Ab → endothelial damage and capillary thrombosis
   - epithelial anti-Ag Ab → epithelial damage, podocyte process fusion, podocyte retraction and detachment from the BM

3. Circulating immune complex deposits (type III HS) containing Ag of any of the origins below:

   - **Endogenous**:
     - DNA and nuclear proteins (SLE)
     - Tumoral cells (pulmonary, colon neoplasia)
   - **Exogenous**:
     - bacterial (streptococcal infection)
- viral (B and C hepatitis)
- parasitic (malaria)
- spirochete (syphilis)

II. CELLULAR immune mechanism

T lymphocyte and NK cell activation are involved in the progression of GN by perpetuating chronic inflammatory reaction.

b) Consequences of IMMUNE MECHANISM activation at GLOMERULAR level

Local formation/immune complex deposits at glomerular level and the attraction of sensitised T lymphocytes induce glomerular damage by releasing cellular and plasmatic regulators shown in Table 1, and triggering an extensive inflammatory reaction with variable consequences, as follows:

- in the NEPHRITIC syndrome — immune complex deposits at subendothelial, mesangial or BM level are associated with an important inflammatory reaction which may act as a „double-edged sword“:
  - if it is controlled → accelerates the healing process
  - if it is exacerbated or persistent → aggravates glomerular damage

- in the NEPHROTIC syndrome
  - immune complex deposits form at subepithelial level
  - glomerular damage is less severe, but in the absence of an important inflammatory response (which favours healing), proteinuria will persist for months even years

Table 1. Consequences of GLOMERULAR IMMUNE MECHANISM activation.

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<thead>
<tr>
<th>1. COMPLEMENT system activation</th>
<th>— generating:</th>
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<tr>
<td>Chemotactic mediators (C5a) → attracting leucocytes to glomerular level and forming local inflammatory infiltration</td>
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<tr>
<td>Anaphylatoxins (C3c &amp; C5a) → hyperpermeability of capillary endothelium with proteinuria and haematuria</td>
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<tr>
<td>Membrane attack complex (C5b-9) → cellular lysis and proteinuria</td>
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<th>2. PHAGOCYTE activation</th>
<th>— releasing:</th>
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<tr>
<td>Arachidonic acid mediators (Tx, PG, LT) → haemodynamic disorders</td>
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<td>Lysosomal enzymes (collagenase, elastase) → damage to the BM</td>
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<td>Cytokines (IL-1 and TNF) → increased leucocyte adhesion</td>
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<td>Free oxygen radicals (anion superoxide) → aggravation of cellular damage</td>
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<th>3. RESIDENT CELL activation (mainly mesangial cells)</th>
<th>— releasing:</th>
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<tr>
<td>Cytokines → amplified inflammatory reaction</td>
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<td>Growth factors responsible for:</td>
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<td>— thickened BM (membranous GN)</td>
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<td>— proliferation of cellular component (proliferative GN)</td>
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<td>— extracellular matrix synthesis (sclerosing GN)</td>
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<td>— collagen deposits (fibrosing GN)</td>
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<th>4. Activation of PLATELET AGGREGATION and of COAGULATION with fibrin deposits</th>
<th>— responsible for:</th>
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<td>Glomerular capillary thrombosis</td>
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<td>Fibrin deposits in Bowman’s capsule → stimulates epithelial proliferation and crescent-cell formation</td>
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B. Mechanisms of glomerular damage PROGRESSION

Immune mechanisms and pro-inflammatory mediators are responsible for triggering glomerular damage which, if persistent, leads to the onset of chronic glomerular nephropathies. Consequently, identifying the factors predisposing to glomerular damage progression has a major therapeutic importance.
1. Development of the process of focal and segmental GLOMERULOSCLEROSIS

- **Cause:** compensating hypertrophy of remaining glomeruli to counterbalance nephron loss
- **Consequences:**
  - **haemodynamic alterations** → intraglomerular hypertension ± systemic HT
  - **increased protein permeability** → hyperfiltration and protein accumulation in the mesangial layer responsible for glomerular proliferative alterations:
    - hyperplasia of mesangial cells
    - extracellular matrix deposits
    - focal sclerosis (affects only some of the glomeruli) and segmental sclerosis (affects only certain parts of the glomerulus)
  - damage of epithelial and mesangial cells → proteinuria

2. TUBULO-INTERSTITIAL fibrosis

- **Causes:**
  - ischaemia of the tubular system distal to sclerosed glomeruli
  - inflammation of adjacent interstitium
  - tubular reabsorption by pinocytosis of proteins responsible for the stimulation of cytokine and growth factor stimulation in the tubular cells
- **Consequences:** tubulointerstitial fibrosis

**Important!**
Paradoxically, the degree of impairment of the renal function (decreased GFR) is better correlated with the severity of interstitial fibrosis and not with the extent of glomerular damage (glomerulosclerosis).

III. GLOMERULAR SYNDROMES

A. NEPHRITIC SYNDROME

a) **Definition:** set of signs/symptoms with **RAPID** onset, characterised by acute inflammation involving mesangial, endothelial and epithelial cells (glomerulonephritis)

b) **CLINICAL forms** – the commonest glomerular nephropathies associated with nephritic syndrome are:
   1. Acute poststreptococcal GN
   2. Rapidly progressive GN
   3. IgA nephropathy (Berger’s disease)

1. Acute POSTSTREPTOCOCCAL GN

- **Characteristics:**
  - The commonest form of nephritic syndrome in children and young people
  - It is the prototype of acute GN with a 2-4 weeks onset (the latency period is necessary for Ac synthesis and immune complex formation) from a cutaneous or respiratory infection with a **group A β-haemolytic streptococcus** (e.g., impetigo, pharyngitis)
- **PATHOGENIC mechanism:** immune complexes containing bacterial Ag are deposited in the glomerulus and locally activate the complement (decrease of serum C3) → glomeruli become larger, hypercellular, with leucocyte infiltration and granular IgG, IgM and C3 deposits at subepithelial level, in the BM, and mesangial level
- **Prognosis:** spontaneous remission in 6-8 weeks in 95 per cent of the cases in children and young people, and only 60 per cent of the adult cases
2. Rapidly-PROGRESSING GN (with crescent cells)

- **Characteristics:** the most severe form of glomerular impairment
- **PATHOGENIC mechanism:** according to the underlying immune mechanism, there are 3 types:
  - **type I:** induced by anti-MB glomerular Ac (type II HS) $\rightarrow$ *linear IgG and C3 deposits* in the BM
    - the damage can be confined to the kidney or can be associated with pulmonary haemorrhage (Goodpasture syndrome)
  - **type II:** induced by *circulating immune complex deposits in the glomeruli* (type III HS) with granular aspect associated with:
    - endothelial and mesangial cellular proliferation
    - BM rupture
    - monocyte-macrophage cellular infiltration
    - formation of crescent cells which obturate Bowman’s space
  - **type III:** (pauci-immune) characterised by the presence of *antineutrophil cytoplasmic antibody* (ANCA), associated with *systemic vasculitis*
- **Prognosis:**
  - Cases diagnosed at later ages have a *reserved* prognosis (require dialysis/transplant)
  - In the absence of treatment (type I plasmapheresis, corticosteroids and type II and III cytotoxic agents) progression *accelerates* (weeks, months) to renal failure and death

3. IgA nephropathy (Berger’s disease)

- **Characteristics:** the commonest form of GN in the world and major cause of recurrent haematuria
- **PATHOGENIC mechanism:** high serum level of IgA1 immune circulating complexes leads to deposit formation in the mesangium and alternate complement activation (mesangial IgA and C3 deposits)
- **Prognosis:** good, but in 15-20 per cent of the cases it progresses *slowly* (20 years) towards renal failure

c) **POSITIVE diagnosis of the NEPHRITIC syndrome** — consists in:

1. Haematuria (micro- or macroscopic)
2. Proteinuria < 3 g/day
3. Oliguria (< 400 ml/day)
4. Azotemia (increased serum urea and creatinine)
5. HT (mainly diastolic)
6. Oedema (peri-orbital)

1. Haematuria

- **Characteristics:**
  - The presence of *more than 3 red blood cells/microscope field*
  - **Erythrocyte dysmorphism:** more than 30% of the erythrocytes are dysmorphic (pale and small cells, acanthocytes) due to osmotic or chemical stress caused by erythrocyte passage through the nephron
  - **Association with haematic cylinders** (by incorporating erythrocytes into the Tamm-Horsfall protein matrix, a urinary glycoprotein normally secreted by the cells of Henle’s ascending branch and the distal tubes)
  - **Specific urine coloration** (“tea or cola”) caused by erythrocyte degradation while stagnating in the urine
  - **Association with polymorphonuclear neutrophils in the urine**

2. Proteinuria

- **Characteristics:** glomerular type, though *moderate* (1-3 g/day)
- **Cause:** hyperpermeability of glomerular capillaries due to the inflammatory process
- **Consequences:** albumin serum concentration (plasma oncotic pressure) remains approximately normal
3. Oliguria

- **Cause:** decrease of filtration surface and of glomerular filtration rate (GFR)
- **Consequences:**
  - Increased blood urea nitrogen (azotemia)
  - Triggering of hydrosaline retention mechanisms with hypertension and oedema

**Important!**
Most cases of glomerular impairment may develop towards a mixed syndrome, nephritic and nephrotic, kidney needle biopsy being mandatory for diagnosis.

B. NEPHROTIC SYNDROME (NS)

a) **Definition:** set of signs/symptoms, with PROGRESSIVE onset and SLOW remission, induced by the alteration of the glomerular membrane’s barrier function, though in the absence of an inflammatory process (glomerulopathy or glomerulosclerosis)

b) **ETIOPATHOGENIC classification**

   I. **Primary** nephrotic syndrome (idiopathic, primary glomerular impairment)
   II. **Secondary** nephrotic syndrome (secondary glomerular impairment within a systemic disorder)

I. PRIMARY NEPHROTIC syndrome

- **Characteristics:** represents 95% of the cases in children and 60% of the cases in adults
- **Clinical forms:** the commonest clinical forms are:
  1. Minimal change glomerulonephritis (lipoid nephrosis)
  2. Focal and segmental glomerulosclerosis
  3. Membranous glomerulonephritis
  4. Membranoproliferative glomerulonephritis

1. **MINIMAL CHANGE** glomerulonephritis (lipoid nephrosis)

- **Characteristics:** the commonest cause of NS in children (boys < 10 years, 65% of the cases), triggered by an infection or vaccination, in atopic background
- **PATHOGENIC mechanism:**
  - Pathological cellular immune response with the hypersecretion of a circulating factor by a T-lymphocyte subset (lymphokine?) which primarily alters epithelial cells with negative charge loss and subsequent albuminuria
  - Recent causes include genetic defects of the proteins nephrin and podocin contained in the diaphragm of filtration slits
  - The damage consists in podocyte process fusion, the development of microvilli and vacuoles in podocytes, and fatty deposits in proximal tubule cells
- **Prognosis:** good response to corticotherapy and favourable prognosis (< 5% of the cases develop chronic kidney disease after 25 years)

2. **FOCAL and SEGMENTAL** glomerulosclerosis

- **Characteristics:** the commonest cause of nephrotic syndrome in young, black males
- **PATHOGENIC mechanism:**
  - **Causes:**
    - Damage of epithelial cells caused by circulating cytokines
    - Genetic defects in the synthesis of nephrin and podocin leading to constant unselective proteinuria (possibly, haematuria and hypertension in 1/3 of the cases)
Consequences:

- Non-uniform sclerosis of only some of the glomeruli, and of parts within each glomerulus
- Fusion of podocyte processes, detachment of epithelial cells with denudation of BM, IgM and C3 deposits in the mesangium

- Prognosis: poor response to corticotherapy and reserved prognosis (> 50% develop chronic kidney disease in 10 years).

3. MEMBRANOUS glomerulonephritis

- Characteristics: the commonest cause of nephrotic syndrome in males aged between 40-50
- PATHOGENIC mechanism:
  - in situ immune complex deposits at subepithelial level (unknown kidney auto-Ab) with complement activation (C5b-C9) and unselective proteinuria
  - even thickening of glomerular capillary walls, podocyte process fusion and granular Ab deposits
- Prognosis: poor response to corticotherapy and slow progression to chronic kidney failure (40% of the cases)

4. MEMBRANO-PROLIFERATIVE glomerulonephritis (MP- GN)

- Characteristics:
  - 10-20% of NS cases occur in children and young adults
  - There are 2 forms: type I and type II
- PATHOGENIC mechanism:
  - Type I MP GN is the consequence of immune circulating deposits with complement activation via classical and alternate pathways
  - Type II MP GN is induced by complement activation only via an alternate pathway (by a circulating Ab called the nephritic factor which stabilizes and chronically activates alternate pathway C3 convertase)
  - Damage consists of: thickened BM, proliferation of mesangial and endothelial cells, immune complex subendothelial deposits, IgG and C3 granular deposits
- Prognosis: slow progression towards chronic kidney failure (50% of the cases)

II. SECONDARY nephrotic syndrome

- CLINICAL forms: it is induced by glomerular impairment in:
  1. Metabolic disorders: diabetes mellitus, amyloidosis
  2. Systemic disorders: SLE, Henoch-Schonlein purpura
  3. Infections: bacterial (infectious endocarditis)
  4. Drug-induced: gold salts, NSAIDs
  5. Neoplasms: solid tumours (carcinomas, sarcomas), leukemia, lymphomas

1. DIABETIC nephropathy

- Characteristics:
  - The commonest cause of secondary NS in adults
  - The main cause of chronic kidney disease (CKD)
- PATHOGENIC mechanism:
  - The glomerular damage in diabetic nephropathy, depending on its severity, induces 3 glomerular syndromes:
    - non-nephrotic proteinuria
    - nephrotic syndrome
    - chronic kidney failure
  - glomerular nephropathy is correlated with diabetic microangiopathy and has 2 major underlying mechanisms:
代谢缺陷 — 高血糖是导致最终高级糖化产物产生的原因，这些产物通过非酶糖化导致血红蛋白交联，进而导致基底膜变厚和系膜基质的生长。

- 血液动力学变化 — 初始阶段的特点是肾小球肥大，GFR 增加和高滤过导致蛋白尿和渐进性足细胞丢失。
- 肾小球损伤在糖尿病肾病中的后果：基底膜变厚，血管（？），弥漫系膜硬化，新月体硬化

d) 正确诊断的NEPHROTIC综合症 — 包括：

1. 蛋白尿 > 3.5 g/day
2. 低蛋白血症 (< 3 g/dl)
3. 水肿（也包括一般化肥大 — 皮下水肿）
4. 高脂血症 + 脂尿
5. 高凝血倾向

1. 蛋白尿

- 特征：
  - 包括高分子质量蛋白质的消除 > 3.5 g/day（甚至高达 15 g/day）
  - 可以是：
    - 选择性（纯，功能性 NS）— 由轻微的肾小球损伤引起，以独家白蛋白尿（蛋白尿）为主
    - 非选择性（混合，有机 NS）— 与高血压力、显微血尿相关，由严重的肾小球损伤引起，伴有白蛋白和红血细胞丢失

- 后果：尿中丢失的某些功能性蛋白可以有几种后果，如表 2 所示

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<thead>
<tr>
<th>蛋白质丢失</th>
<th>后果</th>
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| 甲状腺素结合球蛋白 | 减少 T4 血清水平 → 甲低，在一些患者中 

| IgG 和分解放凝血补体成分 | 增加对感染的敏感性，与包膜细菌（金黄色葡萄球菌，肺炎双球菌）相关，以及对（不凝）血栓形成的风险 

| 血红蛋白 | 贫血性小细胞贫血对铁治疗抵抗 

| 血红蛋白 | 与抗纤溶酶抑制物（抗-纤溶酶）

| 胆钙化醇运输蛋白（锌，铜） | 增加对感染的敏感性，由于细胞免疫力受损 

| 25-羟基胆钙化醇运输蛋白 | 降低血清 1.25 di- 胆钙化醇水平（活性 D 维生素）和低钙血症 

| 胆钙化醇 | 尽管上述所有这些，NS 患者并不出现继发性甲亢和骨软化症，这些是慢性肾病的特征性改变 

| 促皮质素（皮质类固醇结合球蛋白） | 胆钙化醇的分布异常可能导致药物的毒性表现，即使是在治疗性剂量下
Important!
The severity at onset and the persistence of proteinuria are used as predictors for the development/progress of chronic kidney disease. An increased protein quantity in the glomerular filtration stimulates their endocytosis in the tubular cells and triggers an inflammatory-fibrotic process which leads to nephron loss. Consequently, reduction of proteinuria using angiotensin converting enzyme inhibitors has a renoprotective role.

2. Hypoalbuminemia

- **Mechanisms:** has 3 underlying mechanisms (combined in various degrees):
  1. Massive renal protein loss (proteinuria > 3.5 g/day)
  2. Inadequate hepatic albumin synthesis which, though increased, cannot compensate for the decreased plasma protein level
  3. Increased renal protein catabolism: the increased GFR puts maximum strain on tubular albumin reabsorption which is accompanied by an increased protein catabolism in the tubular cells

- **Consequences:** decreased plasma oncotic pressure leads to a compensatory increase of globulin synthesis, resulting in *nephrotic syndrome dysproteinemia*, characterised by:
  - hypoalbuminemia
  - α2- and β-globulin increase
  - γ-globulin (IgG, with IgM, IgA) decrease and normal or lower IgE

3. Oedema

- **Characteristics:** is specific symptom of nephrotic syndrome patients, being commonly located in the face or generalised (anasarcia) in severe forms

**PATHOGENIC mechanism:**

1. **The classical underfill theory** according to which oedema is mainly induced by hypoalbuminemia with low plasma oncotic pressure → 2 consequences:
   - Passage of water from the vessels in the interstitium (oedema)
   - Decreased effective arterial volume (hypovolemia) which triggers an increased renal natrium and water reabsorption by:
     - RAA system activation by which ALDO stimulates natrium distal tubular reabsorption
     - increased sympathoadrenergic stimulation, with renal vasoconstriction (also favoured by angiotensin II) leading to decreased GFR and increased water and natrium proximal tubular reabsorption
     - increased ADH release with increased water reabsorption in the distal and collector tube
     - decreased serum level of natriuretic factors

2. **The overfill theory** according to which the main underlying factor of oedema is represented by an intrinsic renal defect of natrium excretion responsible for the primary natrium retention in the distal nephron with hypervolemia and hypertension inducing:
   - increased hydrostatic pressure in the systemic capillaries → fluid extravasation in the interstitium (oedema)
   - inhibition of RAA system activation

*Important!*
The two theories are not mutually exclusive, the patient’s volemic status depending on the stage of the disease. Thus, in the acute stage, massive proteinuria leads to hypoalbuminemia with significantly lower plasma oncotic pressure, water „migration“ from vessels into interstitium, and underfill of the vascular bed, while in the chronic stage chronic natrium retention occurs due to persistent moderate proteinuria and overfill of the vascular bed, respectively. The latter patients usually associate hypertension and severe tubulointerstitial inflammatory reaction.

4. Hyperlipemia and lipiduria

- **Characteristics:**
  - common in patients with nephrotic syndrome
  - hyperlipemia is the consequence of both the increased production and of the decreased
catabolism of serum lipoproteins

- Manifestations:
  1. Alterations of LDL metabolism and cholesterol:
     - increased LDL formation, including small and dense LDL particles, with the highest atherogenic risk
     - increased cholesterol synthesis due to increased HMG-CoA reductase activity
     - LDL catabolism deficiency due to receptor functional deficit for LDL
  2. Alteration of VLDL metabolism and of triglycerides:
     - Increased hepatic synthesis of fatty acids and triglycerides by increasing acetyl-CoA carboxylase activity
     - VLDL catabolism deficiency induced by lipoprotein lipase and heparin loss (co-factor)
  3. Increased Lp(a) synthesis

- Consequences:
  - High atherogenetic risk
  - High incidence of coronary disease

Important!
Hypercholesterolemia in the nephrotic syndrome is NOT associated with clinical signs of dyslipidemias (e.g., xanthelasma, corneal arcus, xanthomas).

5. Hypercoagulability

- Cause: plurifactorial, determined by 5 major processes:
  1. Increased hepatic synthesis of coagulation factors:
     - moderate concentration increase of factors II, V, VII, VIII, X stimulated by hypoalbuminemia
  2. Hyperfibrinogenemia:
     - secondary to the increased hepatic globulin synthesis
  3. Increased platelet aggregation:
     - subsequent to the high serum level of free arachidonic acid that will be metabolised in thromboxane
  4. Coagulation inhibitor deficit:
     - urinary loss of antithrombin III
     - decreased concentration/activity of C and S proteins
  5. Fibrinolysis deficit:
     - increased α1-antiplasmin

- Consequences:
  - predisposition for spontaneous thrombosis
  - risk of pulmonary embolism