8.3.2.2 Sudeck's syndrome

Sudeck's syndrome – the posttraumatic atrophy of extremity – is known more than 200 years. It is an acute localized bone atrophy accompanied with inflammatory alterations in the surrounding soft tissues. The underlying cause of Sudeck's syndrome are circulatory disorders in the affected region of extremity induced by reflex action. The pain stimuli after the trauma induce by reflex action an increase in the tonus of adrenergic nervous system leading to local spasm of venules and resulting in blood stasis in capillaries. During the persistence of circulatory disorder dystrophy of all tissue layers is developing. At further stage local excessive bone resorption occurs owing to the osteoclast accumulation in the site of impairment which leads to the painful posttraumatic osteoporosis. The pain progressively rises, hence the circulus vitiosus closes sustaining the disorder of vasoregulation up to the last ischaemic stage. The affected extremity does not bear longer any loading and the following immobilization further impairs the tissue metabolism. Atrophy of the bone and soft tissues associated with contractures may lead to complete loss of functional ability.

Diabetic osteopathy seems to be similar to the Sudeck's syndrome. The underlying cause of this type of osteopathy are as well the disorders of circulation.

8.4 Disorders of joints

8.4.1 Some remarks on anatomy and physiology

Most of the permanent joints in the body are synovial. In **synovial joints** the ends of the bones are covered with smooth hyaline articular cartilage. The joint is lubricated by a thick synovial fluid and is enclosed by a flexible articular capsule. The four basic structures of a synovial joint are the synovial cavity, the articular cartilage, the articular capsule and ligaments. All the tissues of synovial joints receive nutrients from blood vessels, except the articulating portions of the articular cartilages, disks and menisci.

Synovial cavity contains folds of **synovial membrane** that secretes the thick synovial fluid lubricating the synovial cavity. It is an adapted connective tissue, the cells are covered with small villi. The surface of synovial membrane is smooth, moisty and sheeny. Synovial membrane also plays an important role in exchange of substances between the joint and blood vessels and participates in the nutrition of cartilages. The cells on the surface of synovial membrane- the lining cells produce hyaluronic acid important for the exchange of proteins between synovial membrane and joint cavity. There exist two types of these cells.

- Type A – these cells are very simillar to macrophages and contain a lot of cytoplasmatic lysosomes.
- Type B – they are very close in their structure to cells acting in proteosynthesis. The synovial membrane participates also in elimination of waste products of joint metabolism.

The metabolic activity of synovial membrane is very low, but it can be rised in pathologic conditions, e.g. in rheumatoid arthritis. The increase in metabolic activity is accompanied by proliferation of lining cells. It is assumed that the proliferation of lining cells is the determinig factor of raised metabolism in inflammatory processes of synovial membrane.

The *synovial fluid* is a clear, viscous, ambercollored liquid present in human joints in small amounts. It has two essential functions:

1. the participation in the nutrition of cartilages,
2. lubrication of the synovial cavity.

The composition is the same as that of interstitial fluid except of the presence of hyaluronic acid. Hyaluronic acid is responsible for the viscosity rate in synovial fluid. Decrease in viscosity is typical for inflammatory processes of joints. In noninflammatory processes the viscosity increases and in haemorrhagic conditions the viscosity value varies. A part of calcium present in the synovial fluid is bound with hyaluronic acid in form of calcium hyaluronate which represents an important buffer system for maintenance of slightly alkalic pH in synovial fluid. The normal pH range in synovial fluid is 7.31 to 7.64. All

the components of synovial fluid except hyaluronic acid are products of plasma filtration. The normal synovial protein level represents one third of plasma protein level, no fibrinogen and other coagulation factors are found. The concentration of lipids is very low compared with plasma, it rises in pathologic conditions. Electrolytes are distributed between plasma and synovial fluid according to electrolyte balance principles Chlorides and bicarbonates are present in synovial fluid in higher concentration, anorganic phosphorus in the same and natrium, potassium and ionized calcium in lower concentrations as in serum. The concentrations of other substances (glucose, uric acid) are the same as in serum. The synovial fluid cell count is similar to that of interstitial fluid. Mononuclear phagocytes, mainly responsible for the elimination of detritus, predominate. Besides cells irregular amorphous particles are present which are probably fragments of articular cartilage and fibrous fragments of synovial membrane. The amount of detritus in synovial fluid depends on the degree of degenerative changes.

Degenerative disorders of joints are characterized by clear synovial fluid without spontaneous coagulation. In inflammatory diseases the effusion is turbid with increased white cell count and polymorphonuclear leukocyte predominance, the protein is elevated and viscosity is low.

Articular cartilage is a smooth and sheeny surface of the bones facing the synovial cavity. Because of its thickness and elasticity it acts like a shock absorber, it mitigates mechanical stress when the joint is loaded. With increasing age its elasticity decreases. The articular cartilage itself is insensitive to pain, since it has no nerve supply, it has also no blood supply. Its basic components are cells, fibres and matrix. The matrix is composed of collagen and proteoglycans captured in collagen web. Proteoglycans are responsible for load whithstand and elasticity, collagen provides tensile strength. When the cartilage is loaded, proteoglycans are compressed and water is released. After removal of pressure water returns and the cartilage increases its volume. This mechanism is essential for cartilage elasticity.

Besides articular cartilage within some joints there are articular disks. These disks may act as shock absorbers to reduce the effect of shearing upon a joint and to prevent jarring between bones. They also adjust the unequal articulating surfaces of the bones.

Articular capsule is a fibrous capsule that lines the synovial cavity in the noncartilaginous parts of the joint. The inner linning of the capsule is the synovial membrane, the outer layer is a fibrous membrane which reinforces the capsule. The articular capsule is lax and pliable and permits considerable movement.

Ligaments are fibrous thickenings of the articular capsule. Most of them are inelastic, but yet are pliable enough to permit considerable movement. They prevent excessive movement and strain. They are richly supplied by sensory nerves and in this way they prevent a person from stretching the ligaments excessively.

Two other structures associated with joints are bursae and tendon sheaths. Bursae resemble flattened sacs and are filled with synovial fluid. They are helpful in elimination of friction arising by muscle rubbing against another one. They facilitate the movement of muscles over bones.

Tendon sheaths are modifications of bursae They are also filled with synovial fluid and their function is to reduce friction so that the tendos can slide easily.

8.4.2 Degenerative disorders of the joints

8.4.2.1 Osteoarthritis

Osteoarthritis, or degenerative arthritis is the most common form of arthritis. It is a slowly progressive degeneration of the articular cartilage that generally is manifested in the weight-bearing joints such as the hip, knee and lumbar region of vertebral column and in fingers of elderly individuals. The disease is not a single nosologic entity, but rather a group of disorders that have in common the mechanical destruction of a joint.

It was often called degenerative joint disease because of the progressive degradation of articular cartilage that leads to joint narrowing, subchondral bone thickening, and eventually, a nonfunctioning, painful joint. Although it is not primarily an inflammatory process, a mild inflammatory reaction may occur within the synovium. Ostephytes, large peripheral nodules of bone represent the bones attempt to grow a new articular surface. In the early stages the cartilage is thicker than normal because of chondrocyte replication, but with progression the degree of cell replication is not enough to keep pace with the continuing stress and the joint surface thins

down, the cartilage softens and the integrity of the surface is breached. Remodeling and hypertrophy of bone are also major features. There are also important changes of soft tissue present. They include chronic synovitis and thickening of the joint capsule and periarticular muscle wasting, which may further restrict the movement.

The factors that play a major role in the etiology of osteoarthritis include:

1. an increased unit load on the joint
2. inferior material properties of the cartilage.

The increased unit load may result from a number of factors, but it is often attributable to incongruties of the joint secondary to various pathological conditions. For example, in congenital hip dysplasia the socket of the acetabulum is shallow, covering only 30 to 40 % of the femoral head (normally 50 %). As a result there is less surface area covered by cartilage and an increased load on articular cartilage. Some congenital disorders, slipped capital femoral epiphysis and other similar conditions may lead to increased joint congruity and to concentration of dynamic loads. In general, the earliest progressive degenerative changes occur at those sites within the joint, which are subject to greatest compressive loads. So, the mentioned subtle congenital or developmental changes in combination with repetitive impact loading can soon lead to joint failure. Repetitive overloading can often lead to osteoarthritis at specific sites related to vocational or avocational overload (e.g., ankles of ballet dancers, metacarpophalangeal joints of boxers, knees of basketball players).

The inferior material properties of the cartilage are related to the biochemical structure. As mentioned above, the articular cartilage is composed of two major macromolecular species: proteoglycans (PGs), which are responsible for stiffness of the tissue and its ability to withstand load, and collagen, which provides tensile strength and resistance to shear. There are lysosomal proteases present within the cells and matrix of normal articular cartilage, but their low pH optimum asures that their proteoglycanase activity will be confined to intracellular sites. However, cartilage also contains a family of metalloproteinases, which can degrade all the components of the extracellular matrix at neutral pH. Very important role in the biochemical processes of cartilage degradation seems to play interleukin 1 (IL-1), a cytokine produced by mononuclear cells and synthesized by chondrocytes. IL-1 stimulates the synthesis and secretion of latent metalloproteinases and tissue plasminogen activator. In addition to its catabolic effects, at concentrations even lower than those needed to stimulate cartilage degradation, IL-1 suppresses PG synthesis by chondrocyte, inhibiting matrix repair. The activity of these potentially very destructive substances is limited by at least two inhibitors:tissue inhibitor of matalloproteinase and plasminogen activator inhibitor 1, both synthesized by the chondrocyte. If they are destroyed or present in insufficient concentrations, the cartilage degradation by these substances is started.

Chondrocyte metabolism in normal cartilage can be modulated also directly by mechanical loading. Whereas static loading and prolonged cyclic loading inhibit synthesis of Pgs and protein, loads of relatively brief duration may stimulate matrix biosynthesis.

8.4.2.2 Pathophysiology of cartilage changes in osteoarthritis

The biochemical changes of osteoarthritis primarily involve proteoglycans. There is a decrease in proteoglycan content and aggregation. There exists a strong evidence supporting the concept that lysosomal and neutral metalloproteinases are responsible for much of the loss of cartilage matrix in osteoarthritis. It is not sure whether their synthesis is stimulated by IL-1 or other factors, but an imbalance appears to exist between the levels of active enzymes and their inhibitors. This leads to serious loss of cartilage matrix and so alters the important properties of the cartilage.

The collagen fibres are thicker than normal and there are apparent changes in their arrangement present, but no alterations in collagen content occur.

In the early stages of osteoarthritis, synthesis of matrix by chondrocytes is augmented, presumably as a reparative reaction. This marked biosynthetic activity may lead to an increase in PG concentration, which may be associated with thickening of the cartilage and maintain the joint in a reasonable functional state for years, however the repair tissue is often inferior to normal hyaline cartilage. As the osteoarthritis progresses, protein synthesis tends to decrease, suggesting that the cell reaches the point where it

fails to respond to reparative stimuli. The cell metabolism gradually diminishes, as does cell replication and end stage osteoarthritis develops with full loss of cartilage.

The most common form of osteoarthritis is **idiopathic (primary) osteoarthritis**, in which no predisposing factor is apparent. But several *risk factors* may play important role in the development of the disease. The most important are the age, female sex, race, genetic factors, major joint traumas, repetitive stress, obesity, congenital/developmental defects, prior inflammatory joint diseases and metabolic/endocrine disorders.

The age represents the most powerful risk factor in osteoarthritis. With increasing age progressive rise in incidence of osteoarthritis occurs. In radiographic survey the prevalence in women older than 65 years was 68 %.

Genetic predisposition plays important role in generalized primary osteoarthritis with HeberdenŽs nodes(osteophytes at the distal interphalangeal joints in the fingers). The heredity is linked to one gene, dominant in women and recessive in men.

Obesity represents an important risk factor for knee osteoarthritis as recently was clearly proved.

Major trauma and repetitive overloading represent the most common risk factors for the development of osteoarthritis. Damage to the articular cartilage may occur at the time of injury or subsequently during use of the affected joint.

The leading **clinical feature** of osteoarthritis is joint pain. It is a deep, aching pain aggravated by joint movement and relieved at rest. The articular cartilage has no nerve supply, so other structures are responsible for joint pain in osteoarthritis. It can be the synovium – its inflammation due to cartilage particles, subchondral bone – its microfractures or medullary hypertension, osteophytes which stretche the periostal nerve endings, stretching of ligaments, muscle spasm and joint instability leading to stretching of the joint capsule or inflammation of capsule.

Other important clinical feature is stiffness of the joint upon arising in the morning or after a period of inactivity. Primary osteoarthritis has no systemic manifestations.

Secondary osteoarthritis has the same clinical pattern, but develops on the basis of preexisting underlying cause.

8.4.3 Inflammatory disorders of the joints

Rheumatoid arthritis

Rheumatoid arthritis is a systemic, chronic, inflammatory disease that involves the joints. Characteristic clinical feature of rheumatoid arthritis is persistent inflammatory synovitis which can lead to cartilage destruction and bone erosions. It usually involves matching joints on opposite sides of the body. Most susceptible are the peripheral jointsfingers, wrist and knee. The course of the disease is variable, and is often punctuated with remissions and exacerbations. The broad spectrum of clinical manifestations ranges from barely discernible and mild forms to severe, destructive, and mutilating disease.

Rheumatoid arthritis affects less than 1 % of the adult population, its incidence is greater in women than in men(with ratio 3 : 1). A genetic origin for the disease is suggested by the association of HLA-DR4 and related B cell aloantigen, HLA-DRW4, with severe seropositive rheumatoid arthritis in white people. As many as 70 % of patients with classic or definite rheumatoid arthritis express HLA-DR4 compared with 28 % of control individuals.

The cause of rheumatoid arthritis is unknown. Infectious bacteria or viruses have never been detected in the joints of patients with rheumatoid arthritis. It is thought that immunologic mechanisms play an important role in the pathogenesis of the disease.

It has been suggested that rheumatoid arthritis might be the manifestation of the response to an infectious agent in a genetically susceptible host. There have been suggested several causative agents, e.g. Mycoplasma, Epstein-Barr virus, cytomegalovirus, parvovirus and rubella virus but no convincing evidence supports this theory. The mechanism by which an infectious agent can cause RA remains also unclear.

One theory supposes a persistent presence of infection of articular structures or retention of microbial products in the synovial tissues which generates a chronic inflammatory process. Another possibility is that microorganisms might induce an immune response to components of the joint, because they disturb its integrity and reveal antigenic peptides. It can also be a break down in normal self-tolerance leading to reactivity to self-antigens in the joint or the infecting microorganism might prime the host to cross-reactive determinants expressed on joint struc-

tures. *In summary*, a pathogenetic theory maintains that, initially, in a joint or elsewhere, an unknown agent, possibly a virus, stimulates the formation of antibodies(immunoglobulins). These immunoglobulins act as a new antigens, triggering the production of autoantibodies reactive with the Fc portion of IgG (the rheumatoid factor). Immune complexes, which contain rheumatoid factors (IgG-IgG-RF, IgG-IgM-RF), are phagocytosed by leukocytes, which release lysosomal enzymes and other products. Similarly, mononuclear phagocytes within the synovium may also phagocytise the immune complexes. The rheumatoid synovium is characterized by the presence of a number of secreted products of activated lymphocytes, macrophages and other cell types. The local production of these *cytokines* appears to be responsible for many clinical manifestations of RA. These cytokines include those that are derived from T lymphocytes such as interleukin 2 (IL-2), IL-6, granulocyte-macrophage stimulating factor (GM-CSF), tumour necrosis factor a and transforming growth factorb, those originating from activated macrophages-including IL-1, tumour necrosis factor a, IL-6, IL-8, GM-CSF, macrophage CSF, platelet derived growth factor, insulin-like growth factor, and those secreted by other cell types in the synovium, such as fibroblasts and endothelial cells-IL-1, IL-6, IL-8, GM-CSF, macrophage CSF. The infiltrating T cells appear to be activated, since they express activation antigens such as HLA-DR and in addition they appear to have proliferated locally in the synovial tissue, perhaps in response to sequestered antigen.

The activity of these above mentioned cytokines is supposed to be responsible for many features of rheumatoid synovitis, such as **synovial tissue inflammation, synovial proliferation and cartilage and bone damage**, as well as **the systemic manifestations** of RA. On the other hand, local factors are produced that tend to slow the inflammation, such as transforming growth factor β, which inhibits many of the features of rheumatoid synovitis including T cell activation and proliferation.

It has been suggested that the *propagation* of RA is an immunologically mediated process, but the initiating stimulus has not been characterized. It is possible, that the *inflammatory process* is started by the CD4+ helper-inducer T cells infiltrating the synovium. Many findings support this theory, such as the predominance of CD4+ T cells in the synovium, increased amounts of IL-2 receptors, a product of activated T cells, in blood and synovial fluid and also administration of monoclonal antibodies against T cells or CD4+ T cell subset that has suppressed rheumatoid inflammation in some patients. T lymphocytes produce a number cytokines that can lead to activation of macrophages and also increased expression of HLA molecules, also cytokines which promote B cell proliferation and differentiation into antibody-forming cells. This results in the production of immunoglobulin and rheumatoid factor and in formation of immune-complex and consequent activation of complement and exacerbation of the inflammatory process by the production of anaphylatoxins, C3a and C5a. It is, however, unclear whether this represents a response to a persistent exogenous antigen or to altered autoantigens such as collagen, immunoglobulin, or one of the heat shock proteins. It could also be a persistent responsiveness to activated autologus cells that might occur as a result of Epstein-Barr virus infection or persistent response to a foreign antigen or superantigen in the synovial tissue.

The **exudative synovial fluid** in RA contains more polymorphonuclear leukocytes than mononuclear cells. The exudation is stimulated by a number of mechanisms. It is the local production of immune complexes which can activate complement and generate anaphylatoxins and chemotactic factors. Mononuclear phagocytes produce factors such as IL-1, tumour necrosis factor a and leukotriene B4 which can together with activated complement stimulate the endothelial cells of postcapillary venules to bind circulating cells. TNF-α, IL-8, C5a and leukotriene B4 stimulate the migration of polymorphonuclear leukocytes into the synovial site. Vasoactive mediators such as histamine produced by mast cells that infiltrate synovium may also facilitate the exudation of inflammatory cells into the synovial fluid as well as prostaglandin E2 with its vasodilatory effects. Polymorphonuclear leucocytes in the synovial fluid in RA are able to ingest the immune complexes and in this way produce reactive oxygen metabolites and other inflammatory mediators. *In summary*, changes in the synovial fluid include a massive increase in volume, increased turbidity, and decreased viscosity because the lysosomal enzymes degrade hyaluronate, the protein content is increased with relative in-

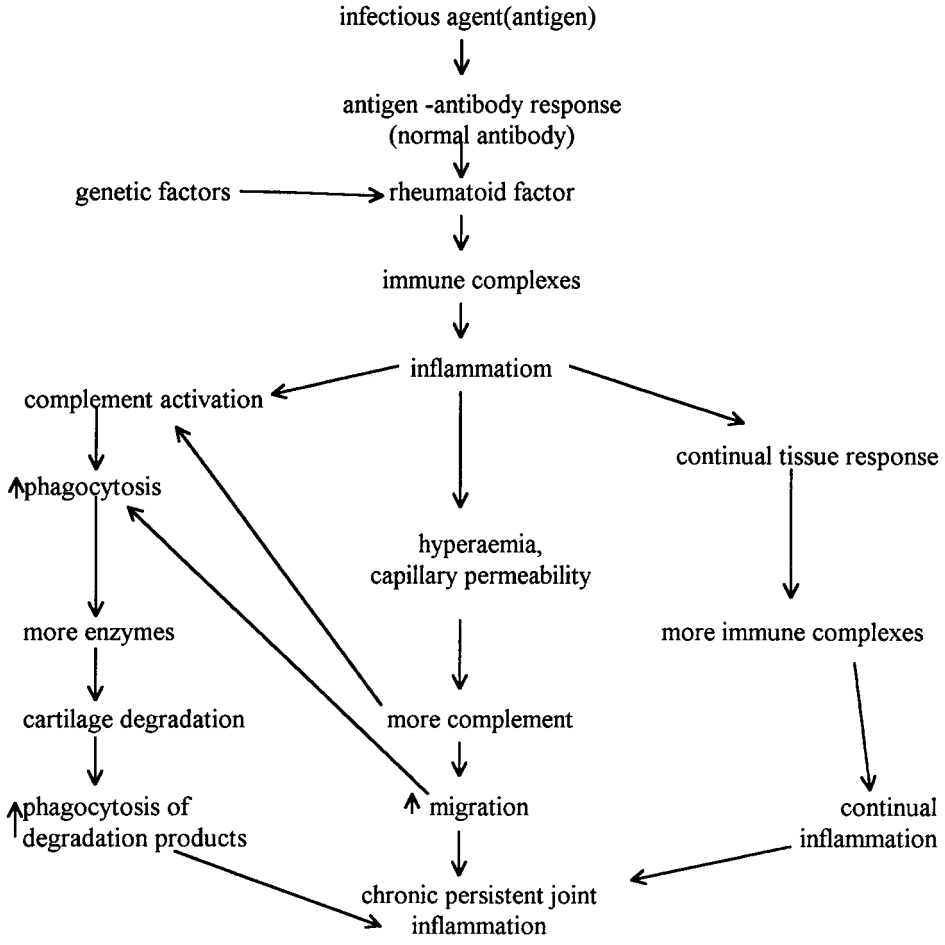

Figure 8.2: Pathogenesis of rheumatoid arthritis

creases in larger molecules, such as IgG. The number of white blood cells in the synovial fluid is markedly increased, with a polymorphonuclear predominance of about 70 %. The synovial fluid may also contain lymphocytes, macrophages, and the exfoliated lining cells of the synovium. Fragments of of synovial villi, fibrin and particles of collagen may be also present.

The pathomechanism of **bone and cartilage destruction** is not fully understood. The synovial lining cells, which are normally one to three layers thick, undergo hyperplasia and form layers 8 to 10 cells thick. As the synovium undergoes hyperplasia and hypertrophy, it creeps over the surface of the articular cartilage and adjacent structures. The inflammatory processes lead to formulation of *pannus*, vascular granulation tissue composed of proliferating fibroblasts, small blood vesels and variable number of mononuclear cells. Pannus produces a large amount of degradative enzymes such as collagenase and stromelysin, that may facilitate tissue damage. Very important role in the mechanism of bone and cartilage destruction play two cytokines, IL -1 and tumour necrosis factor α (TNF-α). They stimulate the pannus cells to produce collagenase and other

neutral proteases causing erosion of cartilage, activate chondrocytes in situ and stimulate them to produce proteolytic enzymes degrading the cartilage, they may activate osteoclasts and so cause demineralization of bone. The characteristic bone- loss of rheumatoid arthritis is juxta-articular, probably related to a factor elaborated locally by the rheumatoid synovium. The pannus invades the joint and subchondral bones and eventually the joint is destroyed and undergoes fibrous fusion, or ankylosis.

For **systemic manifestations** is the release of inflammatory substances, such as IL-1, TNF-α IL-6, from synovium responsible.

Since rheumatoid arthritis is a systemic disorder that predominantly affects the joints, the **clinical features** can be divided into two groups: articular manifestations and extraarticular (systemic) manifestations.

Articular manifestations are the result of inflammation of the joint structures. They involve pain in affected joints aggravated by movement, swelling, tenderness warmth and erythema of the affected joints. Almost invariable is morning stiffness with duration more than 1 hour. Initially motion is limited by pain, the inflammed joint is held in flexion to minimize distention of the capsule. Later, fibrous or bony ankylosis or soft tissue contractures lead to fixed deformities. Muscle atrophy and weakness develop as a result of motion restriction.

The majority of patients develop constitutional symptoms such as weakness, easy fatigability, anorexia, and weight loss.

Extraarticular manifestations involve rheumatoid nodules, rheumatoid vasculitis, pleuropulmonary manifestations and osteoporosis.

The **rheumatoid nodule** resembles a granulomatous reaction to a centrally located core of so-called "fibrinoid necrosis", which is a mixture of fibrin and other proteins, such as degraded collagen. Midzone consists of histiocytes arranged in a radial, or palisading fashion. Granulation tissue forms outer zone. These nodules are usually located on periarticular structures, extensor surfaces and in other areas of pressure, but they can also develop in visceral organs. The most common locations are the olecranon bursa, the proximal ulna, the Achilles tendon, and the occiput.

Vasculitis may affect virtually any organ, it can produce myocardial infarction, cerebrovascular occlusion, renal failure or mesenteric infarction.

8.4.4 Arthritis urica (gout)

Gout represents a heterogenous group of diseases in which the common denominator is an increased serum uric acid level. Recurrent attacks of acute arthritis are associated with the deposition of urate crystals in and about the joints of the extremities. The most striking feature of gout is the acute attack of monarticular arthritis.

Hyperuricaemia, or increased serum uric acid level, is defined as a plasma urate concentration greater than 420 μmol/L. It can be the result of increased production of urate, decreased elimination of uric acid, or combination of these two processes. Increased uric acid level in serum leads to formation of crystals and their tissue deposition.

8.4.4.1 Increased production of urate

In order to understand the pathogenesis of gout, a brief discussion of purine metabolism is necessary. Uric acid is produced by the oxidation of hypoxanthine and xanthine, catalyzed by xanthine oxidase. These purines arise either from the breakdown of endogenous nucleic acids, or the catabolism of dietary purines, or as a result of an increased synthesis of purines in the liver, caused by loss of regulation in several steps. Each of these three processes can lead to overproduction of uric acid.

Conditions such as leukaemic blast crises, cytotoxic therapy for malignancy, haemolysis, or rhabdomyolysis, which are characterized by rapid cell turnover, proliferation or cell death, lead to accelerated purine nucleotid metabolism and in this way to uric acid overproduction. Accelerated breakdown of ATP is the cause of hyperuricaemia in myocardial infarction, smoke inhalation, strenuous physical exercise or status epilepticus. Diet provides an exogenous source of purines. Foods rich in nucleic acid content such as liver or kidney, have a significant effect on the serum urate level.

Biosynthesis of purines takes place in the liver. The formation of a purine ring is an 11-step process. The first step is catalyzed by amidophosphoribosyltransferase (amidoPRT) activity. The rate of purine biosynthesis is determined, for the most part, by this enzyme, which is regulated by the substrate

phosphoribosylpyrophosphate(PRPP) which stimulates the reaction and the end products of biosynthesis that inhibit the reaction. One of the causes of gout is the increase in activity of the enzyme PRPP synthetase which leads to increased PRPP production and accelerated de novo biosynthesis. It is an inborn error of metabolism with overproduction of purines, hyperuricaemia, hyperuricaciduria and development of gout before the age of 20. The disorder is X-linked similarly as hypoxanthine phosphoribosyltransferase(HRTP) deficiency that also causes hyperuricaemia, hyperuricaciduria and gout because of urate overproduction. HRTP catalyzes the combination of the purine bases hypoxanthine and guanine with PRPP to form the respective ribonucleotides. In HRTP deficiency PRPP is accumulated and provides increased substrate for amidoPRT and de novo synthesis which leads to increased urate levels. In addition, decreased formation of ribonucleotides decreases feedback inhibition on amidoPRT.

8.4.4.2 Decreased elimination of uric acid

Since renal excretion is an important regulator of serum levels of uric acid, renal abnormalities may affect its metabolism. Urate is completely filtered by the glomerulus and reabsorbed in the proximal nephron. It is then secreted at a more distal site in the tubule and, in turn, is partially reabsorbed. Decreased urate clearence is caused by all diuretics(except spironolactone), low doses of aspirin, pyrazinamide, ketone bodies, lactate and chronic lead nephropathy. Diuretic therapy leads to enhanced reabsorption of uric acid distal to the site of excretion. Renal insufficiency can decrease urate clearence as a result of impaired glomerular filtration. Decreased proximal tubular secretion of urate may cause the hyperuricaemia in individuals with gout and no evidence of urate overproduction, and also causes the secondary hyperuricaemia of acidosis.

Combination of these two mechanisms may also contribute to hyperuricaemia as it is in deficiency of glucose-6-phosphate, hereditary fructose intolerance or excesive alcohol consumption.

8.4.4.3 Pathogenesis

Acute gout is the result of the interaction between urate crystals and polymorphonuclear leukocytes. Urate crystals activate complement, Hageman factor and contact system of coagulation that leads to generation of bradykinin, kallikrein and plasmin. Urate crystals also react with neutrophils and it leads to release of lysosomal enzymes, oxygen-derived free radicals, collagenase and protease. These substances are responsible for the development of synovitis. When synovitis develops, larger molecules, such as lipoproteins, enter the joint space, bind to urate crystals, and perhaps, play a role in terminating the attack.

Tophi, aggregates of monosodium urate monohydrate crystals generally surrounded by foreign body giant cells, are formed in extraarticular and articular structures. They cause deformities and destruction of hard and soft tissues.

The typical course of the disease involves progression through asymptomatic hyperuricaemia, acute gouty arthritis, interval or intercritical gout, and chronic or tophaceous gout. Renal stones may occur in any stage except the first.

Acute gouty arthritis is a painful condition that usually involves one joint. The painful joint is accompanied by signs of intense inflammation : swelling, erythema, warmth, and exquisite tenderness. However, later in the course of the disease, polyarticular involvement with fever is common. Commonly the gouty attack begins at night, and the exquisitely painful, inflamed joint may simulate an acute bacterial infection. The duration of the attack is about 7–10 days. The first metatarsophalangeal joint is involved in over 50 percent of first attacks.

The **intercritical period** is the asymptomatic phase that represents the interval between the initial acute attack and subsequent attacks. These periods may last up to 10 years, but later attacks may be increasingly severe and prolonged.

Chronic gout is characterized by persistent polyarticular low-grade pain with attacks of acute pain. Tophi are present in the cartilage, synovial membranes, tendos and soft tissues and become apparent on physical examination.

Renal dysfunction, manifested by albuminuria, occurs in up to 90 % of patients and is due to crystal deposition in the renal interstitial tissue and obstruction of the collecting tubules by the uric acid crystals.