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# The Stress Response and Its Functional Implications in the Immune Response After Surgery in Patients with Chronic Inflammation Undergoing Arthroplasty

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## 1. Introduction

Surgical injury evokes an injury response involving immunologic mechanisms. Alterations in the immune response after surgery are recognized as physiological reactions of the organism to restore its homeostasis. The immune responses are characterized by the release of cytokines, inflammatory mediators and acute-phase proteins. The activation of immune cells is followed by the release of various cytokines as well as by a migration of leukocytes into inflamed tissues. Cytokines play roles in the immune response, inflammatory reaction and homeostasis maintaining. Alternations of cytokines concentration in patients with normal immune system function are probably not sufficient and temporary to cause the relevant immune problems postoperative. Moreover, this response is characterized by proper balance between pro-and anti-inflammatory cytokines. Conversely, in patients with chronic inflammatory state the surgery stimulated immune response can be an additional aggravating factor that can contribute to the weakening or pathological intensification of the response.

The surgery is associated with trauma-related immunological changes. The level of these immunological changes directly correlates with the degree of tissue damage. Both surgery and anesthesia are immunosuppressive factors, but regional anesthesia seems to be less than general anesthesia.

Rheumatoid arthritis is an autoimmune disorder characterized by immune-mediated chronic inflammation including a degradation of the connective tissue and bone. The chronic inflammatory state is related with a strong prolonged stimulation of the immune system including a release of the complete cytokines cascade and inflammatory mediators targeted against self cells. So suddenly and unexpectedly the friend turns into the enemy with a excited powerful destructive force.

## 2. The short overview of the immune system and stress response to a surgery

The surgery-associated tissue damage leads to the activation of the immune system and the inflammatory response. The bidirectional relationship between the neuroendocrine and

immune systems with the participation of common mediators seems to be essential for the mechanisms of the chronic inflammatory state including hormonal and immune changes. The tight coexistence of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA axis) is extremely important for damping as well as hastening the reaction of the immune system. The presence of the chronic inflammatory state is exactly with the dysfunction of the neuroendocrine-immune system. The crucial aims of the immune system are the organism protection by recognition and elimination of the antigens which are usually different various components but generally are infectious agents such as bacteria, viruses and fungi.

Two types of immunity can be distinguished from the immune system: the nonspecific (innate) and the specific (acquired) response. There are two forms of acquired response: the humoral and the cell-mediated.

### 2.1 The innate immunity

The innate immunity contains the following elements such as: the Langerhans cells inside the skin, the submucosal tissues of the respiratory and alimentary tracts, the complement system, the phagocytic cells (granulocytes and macrophages) and the glial cells. Lymphocytes, granulocytes and macrophages are responsible for the elimination of antigens. The initiation of the immune response has its own essential origin in the mononuclear phagocyte system (MPS) which is represented by monocytes and macrophages (both types of cells accumulate in the site of surgery). During the first step of immune response the antigen is absorbed by MPS cells and degraded into peptides in the intracellular compartments. The pathogen-associated molecular patterns (PAMPs) are the molecules associated with microorganisms which can be recognized by sophisticated presentation to the pattern-recognition receptors (PRR) and the Toll-like receptors (TLRs) situated on the membrane surface or inside of various cells. They have a unique ability of triggering innate immune responses. Toll-like receptors (TLR) belong to the PRR family and play a key role whilst the induction of the immune response. The TLRs are also expressed by immune cells and various other cells such as endothelium, muscle cells and adipocytes. It can be said they participate while both types of immune response especially during the induction and the regulation of T and B lymphocytes activation (Majewska & Szczepanik 2006).

### 2.2 The cells and mechanism of the acquired immunity

When the innate mechanisms are not enough to inactivate microorganisms then the proteins from pathogenic antigens are presented to molecules expressed on B or T cells becoming their activators. The process called the antigen processing and the presentation leads to the proliferation of the activated lymphocytes and is typical for the acquired immunity.

As the after-consequence of the response to signals from the mononuclear phagocytes the B lymphocytes differentiate into plasma cells. Moreover, T lymphocytes become active and start to release soluble factors known as cytokines (Stevenson et al., 1990).

Contrasted with innate **the acquired response** is a more sophisticated form of the immunity and requires a longer activation period. The main cells of the **acquired immunity** are both types of lymphocytes and also the antigen-presenting cells (APC) such as dendritic cell. Chronic inflammatory state can modify these elements and delay the triggering of the both mechanisms of the immune response. The primary role of the **B**

**lymphocytes/ plasma cells** is the synthesis and the secretion of antibodies associated with the components of the humoral response.

**Immunoglobulins (antibodies)** are formed by - two identical light (L) and the two identical heavy (H) chains. The main form of the immunoglobulins are described: one of them is presented on the membrane surface of the B cells as the antigen specific receptor (BCR). However, the other one exists as the soluble form and is produced by plasma cells. The biologic results of the antigen-antibody reactions include many consequences such as agglutination with soluble antigen, as well as precipitations and activation of complement that results in the neutralization of bacterial toxins and microorganisms activity.

The activation of the B cells starts through the B cell receptor (BCR) at the cell membrane and triggers the intracellular signaling pathways regulating the transcription of antibodies and cytokines genes (Coico & Sunshine 2009). The BCR has the exceptional ability to react with many different types of antigens such as peptides DNA, lipids and carbohydrates.

**The T lymphocytes** are a part of the **cell-mediated** immunity and their role is the cytokines production and support of the B cells activation. The T lymphocytes are divided into following subsets: *helper (Th)*, *cytotoxic (CTL)*, *regulatory (T reg)* and *memory (Tm)*. Similarly B cells and the T cells also have the antigen binding receptor on their surface (TCR) but in contrast to the BCR, the TCR interacts with small fragments of antigenic proteins called peptides which are presented on APC in association with class I and class II molecules included MHC.

**The major histocompatibility complex (MHC)** in the humans called human leukocyte antigen (HLA) has many different diverse immunological and non-immunological functions. The MHC is divided into two types of molecules encoded by the MHC classes: MHC class I and MHC class II. Both of them are recognized by different subsets of the T cells. The MHC class I molecules have the crucial task of the presentation of an antigenic protein to the T Cytotoxic lymphocytes (CD8+) while MHC class II presents an antigen to T Helper lymphocytes (CD4+). Molecules of MHC class I are found on the surface of all nucleated cells of human body while molecules of MHC class II are found on the surface of the APC (Coico & Sunshine 2009). The MHC complex includes the most polymorphic genomes in the human genomes with many consequences related to the transplantation and the autoimmune disease. It turned out that the human leukocyte antigen HLA-B27 is tightly correlated with the frequency of the spondylarthritis (Cauli et al., 2002; Jin & Wang, 2003). The adhesion molecules CD4+ and CD8+ are necessary to enhance the binding of the T cells and the APC. The expression of CD4+ and CD8+ is variable on the T cells. The normal ratio of CD4+ T cell to CD8+ T cells is approximately 2:1 in healthy population.

**The dendritic cells (DC)** are classical, the most potent APC and by this way they contribute to connection between the innate and acquire immune systems. The dendritic cells present the ability to initiate several immune responses such as stimulation of T and B lymphocytes and the resistance against various infections and cancer cells (Bodey et al., 1997).

**Cytokines** are produced by all cells of the human immune system. Cytokines form a complex network secretory molecules which exert their effects on the phases of the immune response. Cytokines are immensely responsible for the transduction of information among the immune system cells and are the very important components of the bi-directional communication between the immune and the neuroendocrine systems (Lisowska et al., 2008). Depending on the prevailing effects of inflammatory response they are called as a pro-inflammatory or anti-inflammatory. The pro-inflammatory cytokines are mainly

represented by interleukins: IL-1, IL-6, TNF, IL-2, IL-6, IL-8, IL-15. The examples of the anti-inflammatory cytokines are interleukins IL-4, IL-10, TGF- $\beta$ . Cytokines may act locally or systemically by cell to cell signaling. The action of cytokines can be described as autocrine, paracrine or endocrine. Some cytokines are known to act in either synergistic or antagonistic way. Cytokines may affect the action of each other which may give synergistic or antagonistic effect on the targeted cells. Both the synthesis and activity of cytokines are regarded at different levels. Different type of antagonistic molecules (e.g. soluble receptor, cytokine binding proteins, molecules that compete with cytokine for binding to the receptors) are produced to restrict their activities. The potent pro-inflammatory activities of cytokines are restricted by three major systems that can prevent uncontrolled excessive production of cytokines. These relate to their synthesis and release membrane receptors and intracellular signal transduction (Weber et al., 2010). Both overproduction and underproduction of cytokines and their receptors take place in many diseases with prevailed acute or chronic inflammatory state.

### **2.3 The interdependence between the neuroendocrine and the immune system whilst direct response to surgery stress**

The surgical stress" can be described as a various alterations inside organism undergoing surgical procedure. The tissue damage caused by surgery leads to activation of the immune system and the early inflammatory response and directly correlates with the degree of tissue damage. A full-fledged systemic inflammatory reaction results in stimulation of the four major programs: the acute-phase reaction, the sickness syndrome, the pain program and the stress response, mediated by the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. The cooperation between the autonomic nervous system and the hypothalamic-pituitary adrenal axis (HPA axis) is important to dampen the reaction of the immune system.

The response to trauma consists of the hormonal as well as the immunological and the metabolic responses. The host response is mainly characterized by increased secretion of various hormones such as: cortisol, catecholamines, ADH (antidiuretic hormone), glucagon and growth hormone.

The direct afferent impulses from surgery site release several factors which strongly activate hypothalamus for corticotropin releasing hormone (CRH) secretion which in turn stimulates the pituitary gland to release its typical hormones. The potent correlation exist between concentration of hormones such as ACTH, cortisol, ADH and intensity of the surgical stress. The neurogenic stimuli from surgery site can be ceased by central blockade such as the spinal and the epidural anesthesia. The immune system and the neuroendocrine system influence each other via molecules and receptors shared by both systems. Activation of the neuroendocrine system results in alteration of the host homeostasis and the immune response including cytokine production.

Somatostatin and catecholamines are the basic examples of the mentioned correlation. Somatostatin (SS) is an endogenous peptide widespread distribute related with five known somatostatin receptors (sst1-5) which are usually expressed on the surface of the immune cells and on central and peripheral neurons as well. The SS is found in the central nervous system, the gastrointestinal tract and endocrine glands. Moreover, macrophage, endothelial cells and lymphocytes express high affinity receptors for the somatostatin (Armani et al., 2007; Dalm et al., 2003; Ferone et al., 2006).

Norepinephrine and dopamine can also increase the activation and the proliferation of T cells. Moreover, norepinephrine modulates the innate immune response e.g. by the inhibition of tumor necrosis factor (TNF) synthesis. TNF and IL-1 $\beta$  are classical pro-inflammatory cytokines secreted mostly by monocytes (Torres et al., 2005).

The different types of stress is associated with high production of catecholamines and corticosteroids cause immunosuppression. Both hormones can inhibit the production of interferon gamma (IFN- $\gamma$ ) and simultaneously stimulate the production of the anti-inflammatory cytokines: IL-4, IL-10 by the T helper cells via adrenergic receptors. The stimulation of the  $\beta$ 2-adrenergic receptors on CD4(+) T lymphocytes cause the inhibition of their proliferation and the cytokines secretion (Riether et al., 2011; Salicrú et al., 2007).

The another example of bidirectional correlation between the immune and the neuroendocrine system is the ghrelin secreted primarily by the stomach and intestine cells. Although, it should be noted that the hypothalamus, the pituitary gland and the other peripheral organs can also be the source of the ghrelin. The ghrelin acts on the other, however expresses many immunological functions through the growth hormone receptor expressed in many immune cells include the T lymphocytes, the B lymphocytes, monocytes and neutrophils. In addition, the ghrelin is known as the anti-inflammatory mediator and seems to have an opposite effects to the TNF while modulation of the immune response (Baatar et al., 2009; Hattori, 2009).

Ghrelin acts on other immune cells such as the T lymphocytes, the B lymphocytes, monocytes and neutrophils via the growth hormone receptor via and shows the anti-inflammatory action in inflammatory response (Himmerich & Sheldrick, 2010).

**Metabolic response** is also induced by the surgery trauma: However, depressed during first hours after the surgery in next phase is characterized by increase of catabolism and hypermetabolism with gluconeogenesis lasting 3-4 days. Metabolic changes induced by the surgery trauma are the part of the systemic reaction that includes a wide range of endocrinological, immunological and hematological effects. Perioperative metabolic changes described as the hypermetabolism include rapid increased oxygen consumption. Postoperatively, hypermetabolism is associated with increased glucose serum level, lactates and free fatty acids. The electrolytes disturbance takes important part while the metabolic response. Lower serum potassium level is the predictor of a serious perioperative arrhythmia and hypoproteinemia as well as it can disturb the process of wound healing (Blackburn, 2011; Jakob & Stanga, 2010; Wahr, 1999).

#### 2.4 The inflammatory response

The inflammatory response is the fundamental type of response against various situation like e.g. trauma or infection and it is focused on stimulation of various parameters which are essential for the wound healing, the protection against infection and the maintenance of homeostasis. The acute inflammatory response to surgery trauma can be prescribed as the combination of the neurological stimulation with the metabolic changes trigger release of the molecules of the local inflammation such as histamine, kinins and prostaglandins with increasing capillary permeability which allows leucocytes and lymphocytes the infiltration into injury site. The pro-inflammatory cytokines such as IL-1, IL-6, TNF- $\alpha$  are released from immune cells, their concentration correlate with the length of surgery therefore they are considered as an indicator of stress severity (Cruickshank et al., 1990; Norman & Fink, 1997). The function of cytokines focusing on communication between cells in both the paracrine and the endocrine way. Pro-inflammatory cytokines (IL-6, TNF, IL-1) are potent

inducers of acute phase proteins (APPs). Among some (e.g. C-reactive protein (CRP), complement factors, fibrinogen, plasminogen CAPPs) are up-regulated while production of others (albumin, transferrin, antitrombin) decreased (Engler, 1995).

The long-lasting inflammatory process called chronic inflammatory response, itself is a organism wasting disease. The presence of the chronic inflammatory state is immensely associated with the dysfunction of the neuroendocrine-immune system. The neuroendocrine-immune disturbances also play an crucial role in the development of human autoimmune diseases such as the rheumatoid arthritis and the systemic lupus erythematosus and the others. During the chronic inflammatory stage all these systems have become deficient.

### 3. The short overview of the role of cytokines in rheumatoid arthritis

Inflammatory diseases such as arthritis share some common clinical characteristics including the degradation of the connective tissue and bone. The rheumatoid arthritis (RA) is the chronic inflammatory state characterized by synovial inflammation and progressive joint cartilage and bone destruction. The chronic inflammatory process with the continuous stimulation of synoviocytes directly leads to the hypertrophy of the synovial membrane and bone resorption. The development of RA is associated with the uncontrolled production of pro-inflammatory cytokines by the activated synoviocytes and the antigen stimulated lymphocytes. The cytokines mentioned below play significant role while both the development of the RA and the surgical stress response

**Interleukin -1** (IL-1) is produced by macrophages, monocytes and endothelial cells. The secretion of IL-1 is triggered by many factors including TNF and complements. The interleukin 1 (IL-1) family includes two forms of IL-1 (IL-1 $\alpha$ , IL-1 $\beta$ ), IL-1 receptors (RI, RII) and IL-1 receptor antagonist (IL-1Ra). Interestingly, the recent results of studies suggested that the interleukin-1 $\alpha$  (IL-1 $\alpha$ ) plays the neuroprotective role inside the damaged brain cells (Clausen et al. 2011). During the early stages of shock, the IL-1 $\beta$  is secreted from liver cells after the stimulation of noradrenalin, which may be the example of the relationship between neuro-immune systems (Zhou et al., 2005). In rheumatoid arthritis patients, the plasma and the synovial fluid concentrations of IL-1 are elevated and are correlated with various parameters of disease severity. The production of endogenous IL-1Ra appears to be insufficient to counteract IL-1 activity (Pritchard et al., 2008). It is also appeared that IL-1 $\beta$  has a significant impact on the process of damage and degradation of the cartilage in the pathogenesis of arthritis (Aida et al., 2006).

**Interleukin -6** (IL-6) is secreted by many cells types. In RA joints synoviocytes are the major source of IL-6. The production of IL-6 is induced by IL-1 and TNF. IL-6 is involved in development of immune response, inflammation and haematopoiesis. For instance, it regulates the growth and differentiation of the lymphocytes T and is considered as the a critical factor for B cells proliferation and stimulation of the immunoglobulin production. The serum elevation of IL-6 is noticeable in face of infections, inflammation and injury when IL-6 induces fever and production of acute phase proteins. Silverman et al. (28) recently demonstrated that IL-6 can directly stimulate the corticosteroid secretion from the adrenal cortex and there is evidence suggesting that it can also stimulate ACTH secretion from the pituitary gland (Silverman et al., 2004). IL-6 has also anti-inflammatory function by stimulation of monocytes to release anti inflammatory cytokines such as IL-10, IL-1Ra.

The receptor for IL-6 consists of two proteins: the chain  $\alpha$ , that can be expressed on membrane cell or in soluble form and subunit gp130 that belongs to proteins receptor for IL-6 in membrane cells. In contrast to most cytokines (e.g. TNF) soluble IL-6 acts as agonist but not antagonist.

IL-6 play important role in many inflammatory diseases. RA is characterized by the overproduction of IL-6. The very high level of IL-6 in the serum and synovial fluid is involved and correlated with clinical and laboratory indices (Lisowska et al., Dec 2007; Nishimoto, 2006).

The secretion of both, described cytokines (IL-1, IL-6) is stimulated by tumor necrosis factor (TNF).

**Tumor necrosis factor** - is produced by monocytes, macrophages, neutrophils, mast cells, fibroblasts, and the activated T cells.

TNF is a number of TNF family. The binding of TNF to its receptors TNFR1 and TNFR2 cause multiple effects including: the increase of inflammatory mediators (e.g. nitric oxide (NO), arachidonic acid pathway, the platelet activating factor (PAF) and intracellular adhesion molecules (ICAM)) (Lenzab et al., 2007; Lenz et al., 2007).

The increased expression of TNF occurs in the synovium of rheumatoid arthritis patients with following induction of its cells activities. TNF is thought to play the role key role in the local activation of immune cells and joint cartilage and bone destruction. Together with IL-1 TNF- $\alpha$  also induce an expression of adhesion molecules on the surface of the endothelial cells which is particularly important during the first stages of inflammation, because it enables the infiltration of leukocytes from the bloodstream into the tissues.

**Transforming growth factor - $\beta$**  (TGF- $\beta$ ) belongs to the TGF family cytokines. The TGF- $\beta$  plays crucial role in inhibition of the inflammatory reaction and autoimmune diseases. The TGF- $\beta$  plays the essential role in control and regulation of the lymphocytes proliferation, differentiation and survival. The TGF function including the antiproliferation activity on the T, B lymphocytes that can initiate and aggravate the disease. The TGF- $\beta$  is also an important regulator of the B cell activation and differentiation (Li et al., 2006). Most of the produced cytokines are not stored at all. Nevertheless there are produced and released as needed. However, transforming growth factor  $\beta$  is stored inside the mast cells and platelets (Sheran & Hall, 1997).

#### 4. The influence of regional anesthesia for stress surgery response

The choice of anesthesia type as well as technique relates to influence on the immune response and may be important in patients with immunological disorders. This situation occurs in patients with immune system deficiency. Patients suffer from immune system disturbances, due to autoimmune or cancer diseases, appear to require special consideration. Among this group of patients should be expected the pathological reaction of immune system or significant immunosuppression caused by the surgery trauma.

The imbalanced immune system can modulate the neuroendocrine system and inflammatory responses to the surgery trauma in terms of production of cytokines, immunoglobins, proliferation of lymphocytes, and phagocytosis monocytes/macrophages. The choice of regional anesthesia techniques allow to avoid the supply of volatile/intravenous anesthetics agents and the controlled ventilation procedures. Furthermore, the afferent nerves blockade is associated with attenuation of the hormonal response to the surgery stress. The regional anesthesia techniques have a significant effect on the immune



system which depends on both the nerve blockade and the administered local anesthetic drugs (Lisowska, 2008).

The results of study revealed the influence of the bupivacaine presence for the reduction of the synthesis of immunoglobulin IgG, IgM, IgA and enhancing the granulocytes phagocytosis. The epidural anesthesia with bupivacaine was associated with lower serum concentration of gammaglobulins (IgG, IgM, IgA) and the complement components C3 and C4 (Gajdosz, 1994).

Bupivacaine is the most popular, long acting local anesthetic with a wide range of administration for peripheral and central nerves blockades. Ropivacaine is also a long acting local anesthetic drug similar to bupivacaine in terms of pharmacological activity, but in contrast to is characterized by the lower cardiotoxicity. Lidocaine is the most often and widely used local anesthetic for the peripheral nerves blockades especially in the combination with the bupivacaine for more beneficial balance of duration and onset. Lidocaine is also classified as an anti-arrhythmic agent. Bupivacaine in comparison with the lidocaine shows more potent effect on the function of leukocytes. However, the ropivacaine has been shown its anti-inflammatory properties related to the inhibition of leukocyte function such as the rolling/ adhesion which accompanies the early stage of the local inflammatory response. Moreover, both the ropivacaine and lidocaine could inhibit the CD11b/CD18 up-regulation and the L-selectin down-regulation on neutrophils migration between endothelial cells. There has been found that the effect of the lidocaine was 2.5 times lower than the ropivacaine (Martinsson et al., 1997; Zhang et al., 2000).

The extent of nerves blockade, occurs due to regional anesthesia, appears to have an influence on the neuro-endo-immune response intensity. The endocrine - metabolic stimulation following the surgical procedure can be inhibited by the afferent nerves blockade. The blockade of motor, sensory and afferent sympathetic fibers leads to resulted in predominance of parasympathetic system resulting changes in circulation. The intensified circulation may reduce the release of cytokines associated with the tissue ischemia and hypoxia but from the other site a marked low perfusion triggers cytokines burs following hypoxia. The degree of blood flow distribution is directly related to the level of the blockade. It was shown that usage of continuous epidural anesthesia reduced the hormonal stress response and improved the protein metabolism, but it didn't play any significant role in the stimulation of inflammatory response (Kehler, 2000). Although in comparison with general anesthesia, the epidural anesthesia demonstrate less effect on the activity of natural killer cell (NK), T and B cells (Tonnesen et al., 1988).

The spinal anesthesia is considered as the standard procedure for the orthopedic surgery. The choice of the central blockade is influenced with many benefits such as reduced risk of the postoperative cardiovascular, pulmonary and thromboembolic complications. The prolonged analgesia which spreads onto post operative period is also worth to be emphasized. The patients who underwent surgery with the spinal anesthesia would require greatly less opioids which action is not neutral to the immune system. Further advantages of the regional anesthesia, especially in the RA patients, has ability to avoid the difficult and traumatic intubation. The majority of patients with advanced RA demonstrated the atlanto-axial instability with the great risk of spinal cord compression (Lisowska et al., Jan 2007; 2008).

Many studies have revealed that the regional anesthesia can attenuate the perioperative immunosuppression related to the stress surgery. There are evidences demonstrating a greater number of the Th1 compare to Th2 (CD4+ T and CD8+ T cells) and increased the

neutrophil activity in patients with the spinal anesthesia compare to general anesthesia. The Th1/T2 (CD4+ T/ CD8+ T) balance is necessary for the immune response - both the humoral and the cell-mediated. The Th1 cells produce the interferon gamma and are responsible for the cell-mediated immunity. The Th2 cells produce interleukin-4 and are more effective in inducing the humoral immunity. Cytokine concentration is altered during the surgery as well as anesthesia, which may effects the Th cell predominance with consequences for immune responses.

The advances in the knowledge on the T helper 1 (Th1) and T helper 2 (Th2) cells revealed that the Th1 cells produce cytokines that stimulate the proliferation of CTLs while Th2 cells produce cytokines that are responsible for the activation of the humoral immune response in healthy people. The use of regional anesthesia allows the weakening of the immunosuppression caused by the operational trauma, which is evidenced by studies demonstrating a greater proportion of the Th1 to Th2 and increased neutrophils activity in patients received spinal anesthesia (Erskine et al., 1992; Erskine et al., 1994; Le-Cras et al., 1998).

It has also been demonstrated the beneficial effect of the spinal anesthesia on the immune system regards with its activity and the relationship with the incidence of cancer metastasis. Compared with the general anesthesia using volatile agents, the spinal anesthesia caused significantly less immunosuppressive effects with less postoperative incidences of metastasis in patients underwent surgery. That confirms the beneficial effects of the regional anesthesia on the immune system and the relationship between its activity and the incidence of cancer (Bar- Yosef et al., 2001; Wada et al., 2007).

## **5. The stress response and its functional implications in the immune response after surgery in patients with chronic inflammation (clinical study)**

The connection between the surgery stress and the immune system has been presented in numerous publications and while many aspects of the subject have been discussed, most research has been devoted mainly to patients whose immune system works properly. In the available literature there is little information on the impact of the surgery stress on the immune system in patients with a chronic inflammation which in the light of the accepted hypothesis should contribute to the modulation of the immune system response to the surgery stress. Therefore it can be assumed that the development of the stress surgery response should be altered by abnormalities of immune system associated with chronic inflammation. The previous results had reported by author et al. partially helped to confirm the chronic inflammatory state ability to modify of the response of the immune system to surgery trauma (Lisowska et al., 2008). In view of the fact that many of earlier evaluated patients presented significant advanced chronic inflammatory process that reflected in the high activity disease being evaluated the Disease Activity Score-28 (DAS28) based European League Against Rheumatism (EULAR) response criteria (Fransen & van Riel, 2009). DAS28 seems to be correlated with severity of inflammation; therefore, the immune response to surgery was evaluated in the patients with the different disease activity.

### **5.1 Material and methods**

Patients:

The 37 patients with long term rheumatoid arthritis scheduled for knee arthroplasty under spinal anesthesia. Hyperbaric bupivacaine in dose 4 mg was used in all cases.

Standard monitoring including continuous electrocardiogram, noninvasive automated blood pressure and pulse oxymetry. Cardiovascular and respiratory monitoring was continued at the time following surgery. All patients were transferred in the postoperative care unit after the operation.

Crystalloids, colloids were used perioperatively. Homologous blood was used for transfusion depending on the patient's requirements.

Patients with long-term steroids therapy received additional steroid doses during postoperative period in a predefined regiment.

Thromboprophylaxis with low-molecular weight heparin was given.

All patients received antibiotic prophylaxis with Cephazolin 1g on induction and 1 g eight-hourly within 3-5 days.

For postoperative pain relief, they were given standard analgesic drug consisting of opioid and paracetamol.

The tourniquet was used in all patients. Tourniquet pressure was 350 mmHg.

Exclusion criteria included an ASA $\geq$ 3, BMI $>$ 30 (obesity), Hb $\leq$ 9g/dl, treatment with biologic agents, allergy to local anesthetics, contraindications to spinal anesthesia.

The duration of RA was evaluated and the Disease Activity Score-28 (DAS28) was calculated for all patients before operation. The set of questionnaires was used, the Disease Activity Score-28 was assessed by the number of swollen and tender joints, erythrocyte sedimentation rate (ESR, mm/h) and general health assessment on a visual analog scale (VAS).

During observation the normally physical examination of respiratory system was performed in all patients. No patient had significant tachycardia, tachypnea or other symptoms of atelectasis. Moreover, none of patient complained of sharp pain burning sensation in urine tract that might be a sign of infection and no patient had documented wound complication during observations.

Patients were divided into two groups depending on the activity of the disease being evaluated DAS28. The patients with DAS-28 score lower than 5.0 were classified into the group 1 (G1) and the patient with DAS28 score $\geq$ 5 were classified into the group 2 (G2).

Blood samples:

Samples of venous blood were taken before induction of anesthesia (a baseline sample-0 h) and at 6, 12, 24, 36 hours (6h, 12h, 24h, 36h) after the end of surgery. Blood was collected in 5 ml pyrogen-free tube, the samples were centrifuged at 3000 rpm for 10 min then serum was separated and stored at -70°C for future analysis.

The serum concentration of interleukins IL-6, TGF- $\beta$  and C-reactive protein (CRP) were determined in all patients. Serum CRP was determined rapidly after obtaining.

The serum concentration of IL-6 was determined with a commercially available using ELISA kits (R&D System).

TGF- $\beta$  was determined with using DuoSet ELISA kits (R&D System). All determinations were performed according to the manufacturer's instructions.

CRP was determined using routine diagnostic test (dry chemistry) in analyzer Vitros 250.

Statistical analysis of results was performed using a standard computer application Statistica version 9. Continuous parametric data were assessed using one-way analysis of variance (ANOVA). Statistical significance was considered at the  $p \leq 0,05$

The study was approved by the medical Ethics Committee of the Institute of Rheumatology and informed written consent was obtained from each patient all the patients.

**5.2 Results**

The study population consisted of 37 patients (35 women, 2 men) with a primary diagnosis of rheumatoid arthritis underwent total knee arthroplasty under spinal anesthesia. ASA physical status II.

Patients were divided into two groups depending on the activity of the disease being evaluated DAS-28. Group 1 (G1) DAS-28 <5, group 2 (G2) DAS-28≥5

	Group 1	Group 2	P value
Number of patients	17	20	
Age (yr)	56.56.8±11.2	61.4±5.9	0.02
RA duration (yr)	18.5±7.3	20.2±8.2	0.61
DAS-28	4.09±0.59	5.9±0.75	0.39
Intravenous fluids (ml)	crystalloids: 3300± 376	crystalloids: 3300±316.0	0.5
	coloids: G1 500	coloids: 530±129	1.0
Tourniquet duration (min)	86.6±14.6	95.3±13.5	0.77

Data are mean ±SD or n

Table 1. Characteristics and surgical data of patients divided into DAS-28 groups (G1, G2)

Details of 37 patients studied are shown in Table 1. The significant difference was observed in relation to age between groups. By contrast, there were no significant differences between groups in terms of volume given fluids and tourniquet duration.

With regard to the DAS, the difference between groups is not statistically significant but this difference is particularly shown in the clinical observation.

No significant differences were observed with cardiovascular parameters between groups during observation: MAP (p=0.61) and SaO2 (p=0.98). MAP: G1: 89.6±11, G2: 86.7±10.2 and SaO2: G1 97.2±1.3 G2 96.5±1.3, the values are mean ±SD.

Analysis of concentration level of IL-6 shown statistically significant difference between groups ( $F_{v1=1, v2=171} = 41.23, p < 0.0001$ ). There was no found significant differences in concentration level of IL-6 in time segments ( $F_{v1=4, v2=171} = 0.13, p = 0.9721$ ). No interaction time and groups for IL-6 ( $F_{v1=4, v2=171} = 0.15, p = 0.9650$ ).

The concentration of IL-6 before operation was particularly higher in patients in G2. Moreover, a comparison of value of IL-6 concentration thirty-six hours after surgery with baseline value indicated small increase of IL-6 in patients in this group.

Taking into consideration the range of IL-6 value it can be concluded that the concentration of IL-6 was kept on the similar levels after operation.

There were none changes in concentration of IL-6 during observation in patients in G1 (Fig. 1).

In terms of TGF-β concentration, the analysis of results shown no statistically significant variation of mean value across time ( $F_{v1=4, v2=168} = 0.29, p = 0.8867$ ). There was no found the significant difference between groups ( $F_{v1=2, v2=168} = 2.79, p = 0.0966$ ). However, in opposition to IL-6, in both group the values of TGF-β measured at 36 hour were lower in comparison with preoperative values (Fig.2).

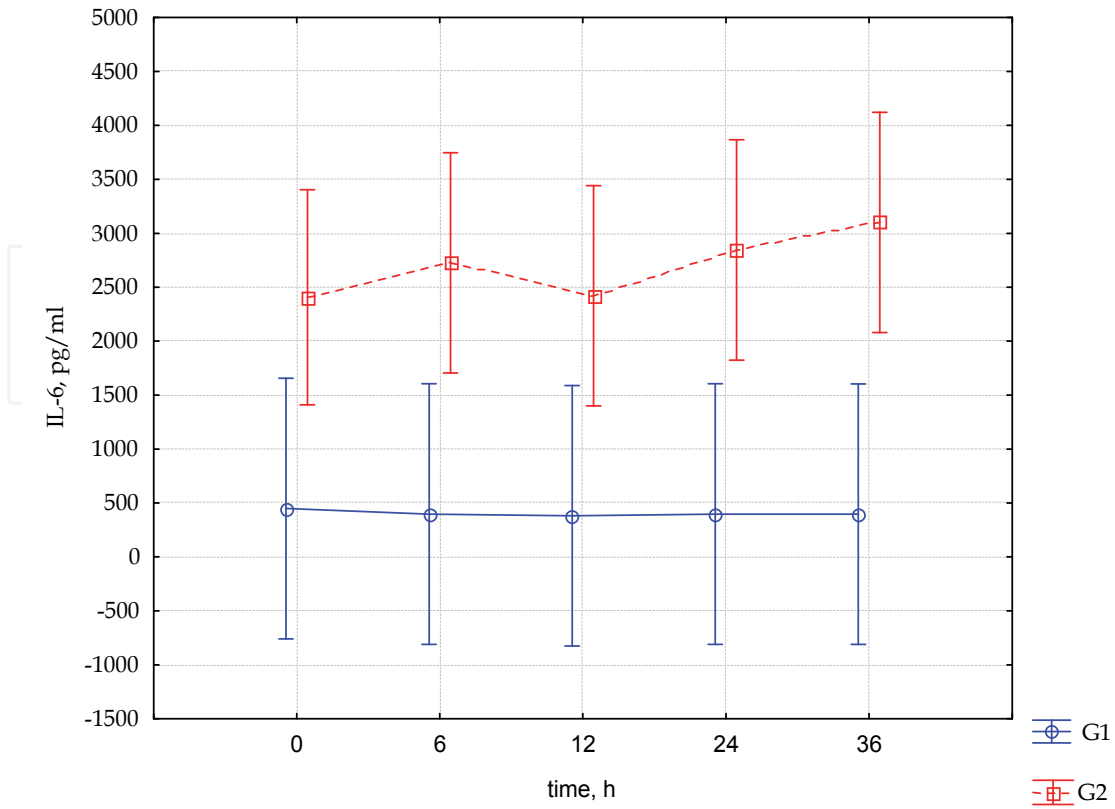


Fig. 1. Changes in serum IL-6 level against time in group G1 and G2. Presented values are mean.

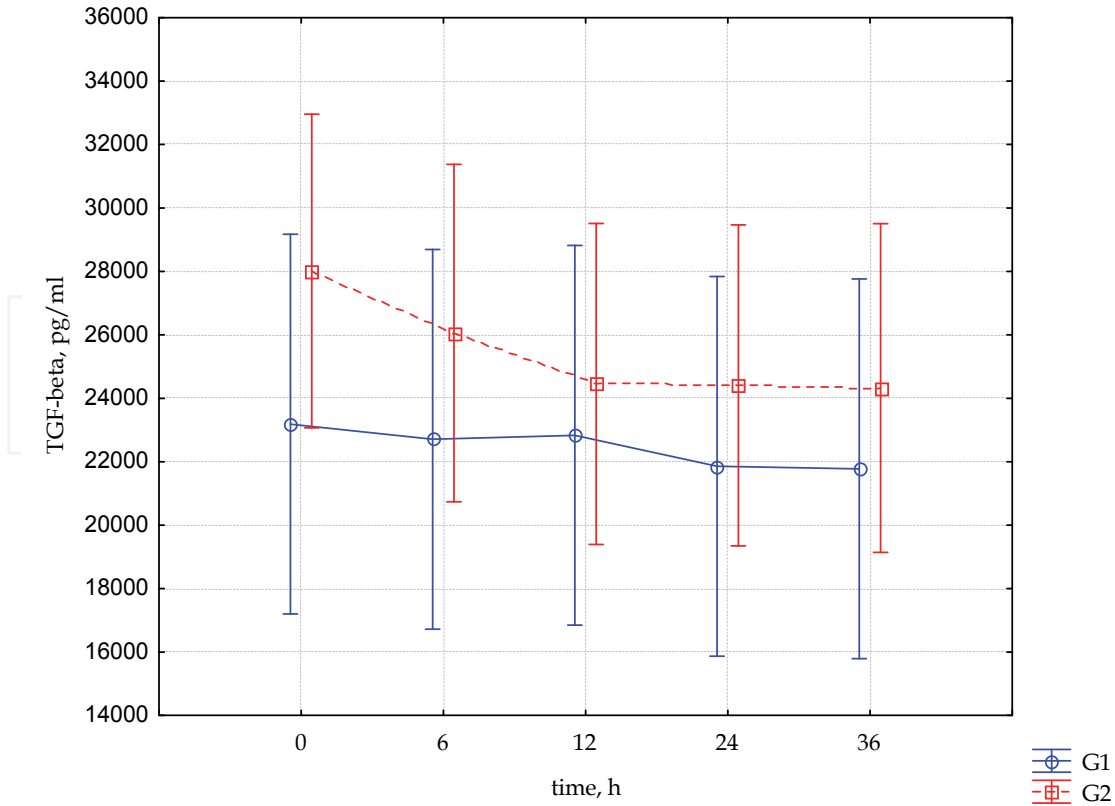


Fig. 2. Mean serum levels of TGF-β at predefined time in group G1 and G2.

The analysis of results of serum CRP concentration shown statistically significant variation  $p < 0.005$  across time ( $F_{v1=4, v2=160} = 26.56, p < 0.0001$ ) in both groups.

No significant difference was observed in CRP serum concentration between groups across time ( $F_{v1=2, v2=160} = 4.10, p = 0.0446$ ). In all patients the concentration of CRP systematically increased during observation with the peak level at 36 hour (Fig. 3).

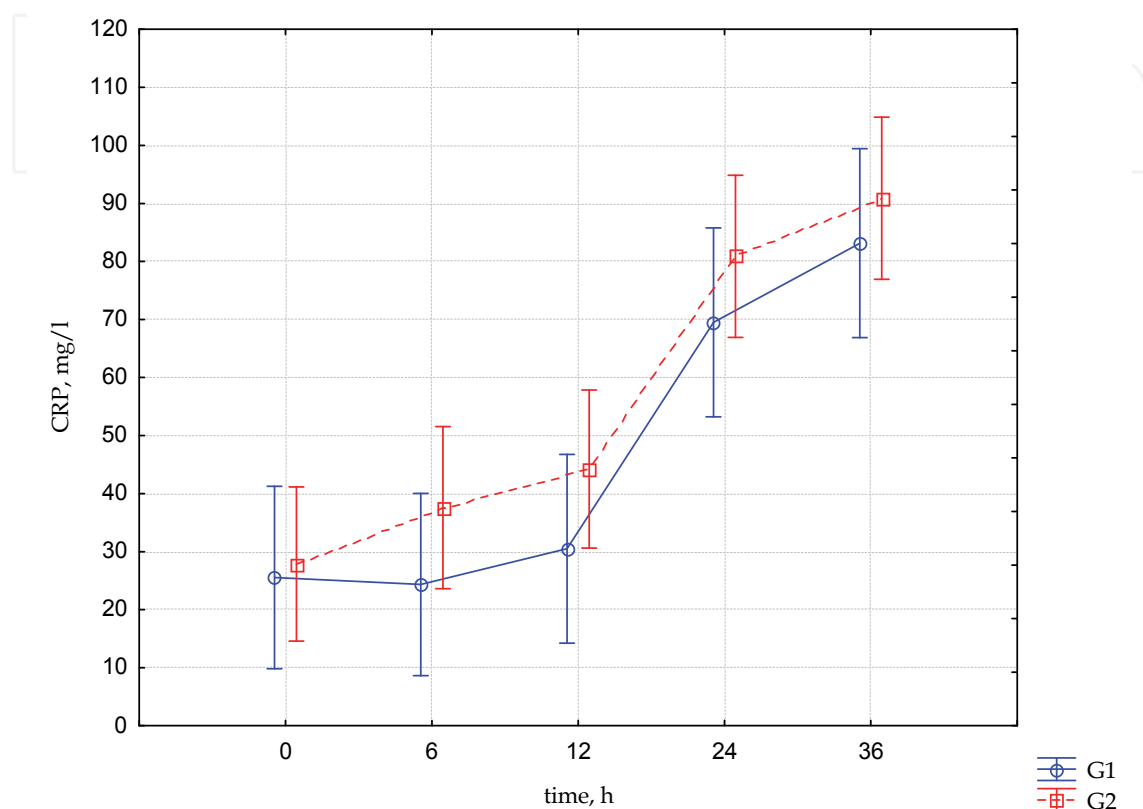


Fig. 3. Changes in serum CRP concentration against time in group G1 and G2. Data are mean

### 5.3 Discussion

No significant difference ( $p > 0.05$ ) in DAS 28 was shown between groups. However, these differences were strongly marked in a clinical picture. The patients with higher DAS 28 demonstrated significantly more swollen and painful joint counts that related to disability and progression of joint damage.

High, as well as the very high, the cytokines concentration such as IL-6 and TGF- $\beta$  was observed in all patients before the surgery. The disease severity common with degenerative joint changes were directly influence on the high cytokines concentrations. This also consistent with previous publications demonstrated the high serum IL-6 level in patients with chronic inflammatory disease (Kaneko et al., 2000; Desgeorges et al., 1997). The preoperative stress has also been proposed as one of factor could affect the IL-6 level (Hirano et al. 1988; Tanno et al., 2004). However, taking into consideration the very high baseline level of IL-6 the stress factor did not seem play significant role in this study. Besides that, the preoperative stress response was reduced with midanium premedication in all patients before the surgery. The autoimmune disease severity, as well as joint cartilage

catabolic damages could directly influence on the very high preoperative serum TGF- $\beta$ 1 level. The cytokines familiar with the growth factors group are major factors responsible for the metabolic processes of chondrocytes, consequently for their homeostasis (Shin-Han et al. 2009). TGF- $\beta$  have role in recruiting immune cells to site of injury and facilitates wound healing by influence for connective tissue remodeling relates with fibroblast proliferation and the synthesis of a number of extracellular matrix proteins (Cutroneo, 2007). Data on dynamic changes of postoperative serum concentration of tested cytokines showed not significant differences ( $p > 0.05$ ). Indeed, the postoperative results of cytokines concentration (IL-6 and TGF- $\beta$ ) revealed the insignificant changes in both groups of patient, regardless the disease severity. The one of possibly explanation for this finding is the significant impairment of inflammatory response due to autoimmune disease. In contrast, many reports have demonstrated the dynamics of the IL-6 increase after surgery in groups of patients with normal immune system (Minetto et al., 2006; Demura et al., 2006; Cruickshank et al., 1990).

The CRP levels significantly increased after surgery. The peak level occurred at 36 hour. The changes were similar for both groups. CRP is most important factor involved in inflammatory response and may reflect the surgical magnitude. Its concentration is normally less than 10 mg/L. In this study, the elevated levels of CRP before surgery could be evidence of confirm the chronic inflammatory state. The concentration of CRP revealed no significant differences between groups.

Regional anaesthesia decreases the neuroendocrine response but does not influence on the inflammatory response (Moor et al., 1994; Naito et al., 1992; Høgevold et al., 2000). Both, the regional and general anaesthesia does not significantly influence on the postoperative immunosuppression decrease [Kawasaki et al., 2007]. As the matter of fact, the postoperative changes demonstrated in this study may reflect the modulation of immune response to stress surgery due to the chronic inflammatory response.

The tourniquet time seemed not to have an influence on the serum cytokines level dynamic changes. The average tourniquet time was 86.6 in group 1 and in group 2 was 95.3 minutes. The tourniquet time longer than 105 minutes was found as statistically significant according to the results of previous study (Tak et al., 2000).

## 6. Conclusion and future research

Data on the dynamic changes of postoperative serum concentration of tested cytokines revealed the impairment response of the immune system to surgical stress, regardless of the intensity of disease activity.

Together, the evidence presented above suggests that it may be possible to identify patients likely to develop a more intensive problems with wound healing and postoperative complications. In conclusion the abnormal immune system with chronic inflammatory process due to autoimmune disease can attenuate the cytokines response to surgery.

The future experiments has to be enlarged on the other immunological response factors evaluations including endothelial dysfunction factors. The chronic inflammatory response influence on the wound healing process has to be evaluate in details. Thus, the major role of the growth factors while fibroblastic proliferation reactions as the key pathogenic factor during rheumatoid arthritis has to be initially evaluated.

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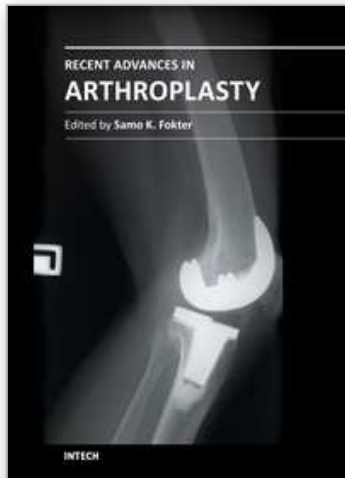
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## **Recent Advances in Arthroplasty**

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The purpose of this book was to offer an overview of recent insights into the current state of arthroplasty. The tremendous long term success of Sir Charnley's total hip arthroplasty has encouraged many researchers to treat pain, improve function and create solutions for higher quality of life. Indeed and as described in a special chapter of this book, arthroplasty is an emerging field in the joints of upper extremity and spine. However, there are inborn complications in any foreign design brought to the human body. First, in the chapter on infections we endeavor to provide a comprehensive, up-to-date analysis and description of the management of this difficult problem. Second, the immune system is faced with a strange material coming in huge amounts of micro-particles from the tribology code. Therefore, great attention to the problem of aseptic loosening has been addressed in special chapters on loosening and on materials currently available for arthroplasty.

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