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# The Pathogenetic Link Between Stress and Rheumatic Diseases

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## 1. Introduction

### 1.1 Definition of stress

Hans Selye was the first to define stress as a non-specific response of the body to any demand made upon it (1936). It has been demonstrated that Selye's theory about the effects of stress is applicable to any type of stress (Stojanovich & Marisavljevich, 2008). Key organ of stress processes is the brain. It determines what individuals will experience as stressful, it orchestrates how individuals will cope with stressful experiences, and it changes both functionally and structurally as a result of stressful experiences (McEwen & Gianaros, 2011).

Stress begins with a stimulus (stressor) that causes a reaction in the brain (stress perception), which subsequently activates physiologic systems in the body (stress response). The stress response system reacts with the release of neurotransmitters (norepinephrine etc.) and hormones (cortisol etc.) which serve to send an efferent message from the brain to the periphery in order to modulate the stressful event (Cutolo & Straub, 2006).

It is clear that stress, originating in the cortex of the brain, must be converted into somatic signals, which can modulate the immune system or pain perception. These somatic signals typically start off in the highest centres of the autonomic nervous system (ANS) and the endocrine system within the hypothalamus (Cutolo & Straub, 2006). Selye was the first to describe the system by which the body copes with stress: the hypothalamus-pituitary-adrenal system (HPA) (Stojanovich & Marisavljevich, 2008). The hypothalamus has close connections to the limbic system, which is responsible for the emotionalisation of psychological stress (whether it is perceived as positive eustress or negative distress). The major neuroendocrine response mediating stress adaptation relies on the activation of the HPA axis by stimulating corticotropin releasing hormone (CRH) and vasopressin (VP) from parvocellular neurons of the hypothalamic paraventricular nucleus. This leads in turn to stimulation of pituitary adrenocorticotrophic hormone (ACTH) secretion and increases in glucocorticoid secretion from the adrenal cortex. Basal production of glucocorticoids and its hypothalamic regulators together with transient increases during stress are essential for neuronal plasticity and normal brain function. While activation of the HPA axis is essential for survival during stress, chronic exposure to stress hormones can predispose to psychological, metabolic and immune alterations (Aguilera et al., 2011).

Selye is considered to be the first to demonstrate the existence of a particular stress disease, the stress syndrome, or the general adaptation syndrome (Stojanovich & Marisavljevic, 2008). These processes can be adaptive in the short term and may contribute to the dysregulation of the hormone status if persisting for a longer time. Moreover, they are involved in bidirectional signalling between the brain and the body as well as in stress-related mental and physical health conditions (McEwen & Gianaros, 2011). The chronic stress-induced dysregulation appears to be of sufficient magnitude to impact health (Gouin et al., 2008).

Recent advances in psychoneuroimmunology have provided insight into the complex mechanisms by which stressors might affect the homeostasis and the body's immune system (de Brouwer et al., 2010). Stress challenges the organism's homeostatic mechanisms, triggering a cascade of events that should, normally, maintain or allow a return to equilibrium (Pêgo et al., 2010). Psychological stress can influence immunoregulatory circuits and the course of an inflammatory disease (Marshall GD Jr, 1997). Furthermore, cytokines generated by the immune system influence hormonal secretion and the central nervous system, producing specific behavioural changes accompanying infectious and inflammatory diseases (Straub et al., 2008). Psychological distress and immune dysregulation have been linked to each other in chronic stress, in disease and other major life events.

It was shown that psychological stress is also thought to contribute to the aetiology, maintenance and exacerbation of rheumatic diseases (de Brouwer et al., 2010). Stress has been studied in several autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) (Cutolo & Straub, 2006). Growing evidence supports the hypothesis that alterations of the stress response and interactions between the neuroendocrine and immune systems contribute to the pathogenesis of rheumatic diseases (Chikanza et al., 1992).

## 2. Neurotransmitter-cytokine relationship

The stress response is mediated by the sympathetic nervous system and it results in the release of some neurotransmitters (epinephrine, norepinephrine) that regulates the immune system at regional, local, and systemic levels (Felten et al., 1988).

Immune organs including thymus, spleen, and lymph nodes are innervated by sympathetic nerves (Felten et al., 1988). Interruption of sympathetic innervation of immune organs has been shown to modulate the outcome of, and susceptibility to, inflammatory and infectious disease. Denervation of noradrenergic fibres of lymph nodes is associated with exacerbation of inflammation (Lorton et al., 1996), whereas systemic sympathectomy or denervation of joints is associated with decreased severity of inflammation (Eskandari et al., 2005).

Immune cells also express neurotransmitter receptors, such as adrenergic receptors (alpha- or beta- subtype) on lymphocytes that allow them to respond to sympathetic neurotransmitters (Elenkov & Chrousos, 1999). Neural influences on the immune response may be due to direct synapse-like nerve-lymphocyte connections (Mix et al., 2007). Through stimulation of adrenergic receptors locally released norepinephrine or circulating catecholamines affect lymphocyte traffic, circulation, and proliferation, and, in turn, modulate cytokine production as well as functional activity of various lymphoid cells (Elenkov et al., 2000; Straub et al., 2000; Madden et al., 2001).

Cytokines are important factors connecting and modulating the immune and neuroendocrine systems (Elenkov, 2005). Furthermore, cytokines and their receptors are expressed in the neuroendocrine system and exert their effects both centrally and peripherally (Benveniste et al., 1998). Systemic cytokines can affect the brain through several mechanisms, including active transport across the blood-brain barrier, through leaky areas in the blood-brain barrier in the circumventricular organs or through the activation of neural pathways such as the vagal nerve (Eskandari, 2005). For example, IL-6 and tumour necrosis factor (TNF)- $\alpha$ , released during an immune response and inflammation activate the central components of the stress system, alter neurotransmitter networks activity and induce fever, sleepiness, fatigue, loss of appetite and decreased libido. In addition, they activate the hepatic synthesis of acute phase proteins—changes referred to as ‘sickness behavior’ and ‘acute-phase response’, respectively (Elenkov, 2005).

Otherwise, administration of interleukin (IL)-1 in the periphery increases the turnover of norepinephrine in the hypothalamus; intracerebroventricular and peripheral injection of interferon (IFN)- $\alpha$  or IL-1 $\beta$  produces a long-lasting increase of the sympathetic activity of the splenic nerve and an increased turnover of norepinephrine in the spleen (Elenkov, 2000). Furthermore, it was shown that monoamine neurotransmitters, released in stress situations, represent a tonic sympathetic control on cytokine production and on the balance of pro-inflammatory/anti-inflammatory cytokines (Szelényi & Vizi, 2007).

Autoimmune diseases are characterized by common alterations of the T-helper (Th)1 versus Th2 cells and a shift towards pro-inflammatory cytokines. In RA the balance is skewed towards Th1 and an excess of IL-12 and TNF- $\alpha$  production, whereas Th2 activity and the production of IL-10 appear to be deficient (Segal et al., 1998).

Neurotransmitters, through stimulation of the beta 2-adrenoreceptors ( $\beta$ 2AR)-cAMP-protein kinase A pathway, inhibit the production of type 1/proinflammatory cytokines, such as IL-12, TNF- $\alpha$ , and IFN- $\gamma$  by antigen-presenting cells and Th1 cells, whereas they stimulate the production of type 2/anti-inflammatory cytokines such as IL-10 and transforming growth factor- $\beta$ . Through these mechanisms endogenous catecholamines may cause a selective suppression of Th1 responses and cellular immunity and a Th2 shift towards dominance of humoral immunity (Madden et al., 1995, Elenkov et al., 2000). On the other hand, in certain local responses and under certain conditions, catecholamines may actually boost regional immune responses through induction of IL-1, TNF- $\alpha$ , and IL-8 production. Thus, activation of the sympathetic nervous system during an immune response might be aimed to confine the inflammatory response on the local level through induction of neutrophil accumulation and stimulation of more specific humoral immune responses. However, systemically the SNS may suppress Th1 responses and thus protect the organism from the detrimental effects of pro-inflammatory cytokines and other products of activated macrophages (Elenkov et al., 2000). Otherwise, norepinephrine and epinephrine, through stimulation of classic cytoplasmic/nuclear glucocorticoid receptors and  $\beta$ 2-AR, respectively, suppress the production of IL-12 by antigen presenting cells (APCs) being the main inducer of Th1 responses (Elenkov et al., 2005). It was shown that an increase in disease activity among RA patients was associated with an increase in the level of stress experienced by these patients, suggesting that a stress induced increase in norepinephrine release might activate naive Th1 cells and/or increase their activity (Kin & Sanders, 2007).

Since  $\beta$ 2-ARs are expressed on Th1 cells, but not on Th2 cells (Sanders et al., 1997), catecholamines do not affect directly the cytokine production by Th2 cells. In murine and human systems  $\beta$ 2-AR agonists inhibit IFN-gamma production by Th1 cells, but do not affect IL-4 production by Th2 cells (Borger et al., 1998; Wahle et al., 2006). However, neurotransmitters through stimulation of  $\beta$ 2-AR up-regulate the production of the anti-inflammatory cytokine IL-6 and IL-10 by APCs (Elenkov, 2005). Administration of a  $\beta$ 2AR antagonist or a  $\beta$ 2AR agonist prior to or during the development of arthritis inhibits or exacerbates disease pathology, suggesting that NE stimulating  $\beta$ 2AR on naive T and/or Th1 cells modulate IFN-gamma production. As with the in vitro findings, the in vivo effects were found to depend on the time point when norepinephrine was released during the course of a disease (Kin & Sanders, 2007). The increased responsiveness of T cells from RA patients to  $\beta$ 2AR stimulation following NE exposure might exacerbate IFN-gamma production and promote conditions for RA development and progression. Therefore, NE, which normally participates in a CD4<sup>+</sup> T cell response to maintain homeostasis by enhancing the baseline immune cell-regulated IFN-gamma response, may cause disease progression when the regulatory conditions controlling sympathetic nervous system/  $\beta$ 2AR activity have changed (Kin & Sanders, 2007).

Otherwise, between RA patients and controls there was a highly significant distortion in the distribution of the beta2AR polymorphisms at codon 16 and to a lower extent at codon 27 contributing together with the human leukocyte antigen (HLA)-DR alleles to the genetic background of RA. Furthermore, polymorphisms of the beta2R gene may modulate the expression of anti citrullinated peptide (anti-CCP) antibodies further supporting the close interplay between the autonomic nervous system and the immune system (Malysheva et al., 2008). Single nucleotide polymorphisms have been found to be associated with the  $\beta$ 2AR expressed by cells of RA patients, suggesting that a change in the  $\beta$ 2AR structure on a naive T and/or Th1 cell may heighten the level of cell responsiveness to NE (Kin & Sanders, 2007).

In patients with RA, experimental stress did not change levels of inflammatory markers (IL-2, soluble IL-2 receptor, IL-4, IL-10 and IFN- $\gamma$ ) but TNF- $\alpha$ . Results for IL-6 were inconsistent (S.de Brouwer, 2010). In patients with SLE, experimental stress did not change levels of cytokines and other inflammatory markers (IL-2, IL-6, IL-10, IFN- $\gamma$ ,  $\beta$ -adrenoceptors), although levels of IL-4 increased after stress (Jacobs et al., 2001). Patients with SLE differed from controls in their response to stress, having a larger increase in IL-4, smaller IL-10 and IFN- $\gamma$  responses, and fewer  $\beta$ -adrenoceptors on monocytes (S. de Brouwer, 2010). In patients with JIA, stress did not affect IL-8 production, but increased IL-6 production (Roupe et al., 2000). However, in healthy subjects stress increased IFN gamma and IL-10 levels (Jacobs et al., 2001; Motivala et al., 2008). Thus, although experimental stress does not seem to influence levels of certain cytokines and inflammatory markers in patients with rheumatic diseases (for example, sIL-2, IL-8, IL-10, IFN- $\gamma$ ,  $\beta$ -adrenoceptors), it does cause specific changes in c-reactive protein (CRP) and TNF- $\alpha$  in patients with RA, changes in IL-4 in patients with SLE, and changes in IL-6 in patients with JIA. These changes are not observed in controls (S. de Brouwer, 2010). Finally, the pharmacological manipulation of the sympathetic-immune interface is reviewed with focus on new therapeutic strategies using selective  $\alpha$ (2)- and  $\beta$ (2)-AR agonists and antagonists and inhibitors of phosphodiesterase type IV in the treatment of experimental models of autoimmune diseases (Elenkov et al., 2000).

### 3. Integration of stress hormones, cytokines and neurotransmitters

Perception of an external stressful stimulus prompts the activation of various physiological systems that together define the body's stress response, which is aimed at re-establishing homeostasis (S. de Brouwer, 2010). Central to the maintenance of homeostasis is an appropriate response of the HPA axis as well as the sympathetic nervous system (Dunn & Swiergiel, 2008; Eskandari et al., 2003.). From animal models of arthritis as well as from clinical studies in RA patients a central role of the HPA axis in onset and severity of RA was suggested (Chikanza, 1992). In these patients an inadequate secretion of cortisol in the setting of a sustained inflammatory disease has been observed (Vassilopoulos & Mantzoukis, 2006). A hypoactive stress system may facilitate or sustain the Th1 shift in Th1-mediated RA. A suboptimal production of cortisol is involved in the onset and/or progression of RA. Patients with RA have "inappropriately normal" or low plasma cortisol levels in the setting of severe, chronic inflammation, characterized by increased production of TNF- $\alpha$ , IL-1 and IL-6. This may actually facilitate or sustain the pro-inflammatory shift in this disease (Elenkov, 2005). The HPA axis has been evaluated in multiple forms in former studies of RA patients. Assuming that an inflammatory process up-regulates HPA axis function, cortisol levels are inappropriately normal in RA patients when cytokine levels are increased (Straub et al., 2008). The proposed defect could reside at various levels of the HPA axis, i.e. the hypothalamic level, the pituitary, and the adrenal gland. However, results of HPA axis tests in RA patients were inconclusive since steroid treatment, drugs including disease modifying antirheumatic drugs (DMARD) and disease duration might interfere with the results leading to conflicting results for ACTH levels and cortisol response in RA patients (Eijsbouts, 2005).

Experimental psychosocial stress consistently increased autonomic activity, blood pressure and catecholamine levels in patients with RA and SLE, and increased neuroendocrine variables (cortisol and ACTH) in patients with RA. Furthermore, after such stress exposure an increase in IL-4 level in patients with SLE, an increase in TNF- $\alpha$  in RA patients, and inconsistent findings for IL-6 were observed (S. de Brouwer, 2010). Exercise stress was characterised by decreased levels of cortisol whereas ACTH levels and growth hormone levels increased. Moreover, this stress elicited a different cytotoxic T cell response in patients with RA and SLE (Pool et al., 2004; Kurtais et al., 2006).

The stress hormones, supposedly acting via  $\beta$ - and  $\alpha$ -adrenergic as well as glucocorticoid receptors, down-regulate immune and inflammatory processes; however, these processes also influence the central nervous system (Ader et al., 1995; MacEwen, 1998). Circulating cytokines and activated immune cells, markers of inflammation, activate both (intermediates of) the HPA axis and the autonomic nervous system. Chronically elevated levels of cytokines, as occur during long-term inflammation, might lead to changes in HPA axis and ANS activity (Chrousos, 1995). Otherwise, circulating hormones or locally released neurotransmitters regulate major immune functions, such as antigen presentation, antibody production, lymphocyte activity, proliferation and traffic, and the secretion of cytokines including the modulation of Th1 or Th2 cytokine responses. During inflammation, activation of the stress system, through induction of a Th2 shift protects the organism from systemic "overshooting" with Th1/pro-inflammatory cytokines. Under certain conditions, however, stress hormones, substance P, adenosine triphosphate (ATP) and the activation of CRH/substance P-histamine axis may actually facilitate inflammation, through induction of

IL-1, IL-6, IL-8, IL-18, TNF- $\alpha$  and CRP production. Thus, a dysfunctional neuroendocrine-immune interface associated with abnormalities of the 'systemic anti-inflammatory feedback' and/or 'hyperactivity' of the local pro-inflammatory factors may play a role in the pathogenesis of autoimmune diseases (Elenkov, 2008).

Cytokines signalling to the brain can not only activate the HPA axis but also facilitate pain and induce a series of mood and behavioural responses generally termed sickness behaviour (Watkins & Maier, 2000). Cytokines, such as IL-1, IL-6, and TNF- $\alpha$ , are also produced in the brain (Sebire, 1993). These brain-derived cytokines can stimulate the HPA axis. For example, IL-1 stimulates the expression of the gene encoding CRH and thereby the release of the hormone from the hypothalamus, the release of AVP from the hypothalamus, and the release of ACTH from the anterior pituitary, IL-2 stimulates AVP secretion from the hypothalamus, IL-6 and TNF- $\alpha$  also stimulate ACTH secretion. Otherwise, in chronic inflammation there seems to be a shift from CRH-driven to arginine vasopressin (AVP)-driven HPA axis response (Eskandari, 2005).

CRH is the strongest known activator of the HPA axis which has been functionally implicated in the regulation of many endocrine functions, such as glucocorticoid release from the adrenal gland and associated endocrine-immune responses (Elenkov, 2008). CRH not only activates the pituitary-adrenal axis but also sets in motion a coordinated series of behavioural and physiologic responses, suggesting that the central nervous system may coordinate both behavioural and immunologic adaptation during stressful situations (Sternberg, 1992; O'Connor, 2000). CRH is positively regulated by catecholaminergic system (Eskandari, 2005). During an immune response certain cytokines, such as IL-1, IL-6, and TNF- $\alpha$  can signal the brain, which via a complex CRH-dependent pathway, triggers activation of both the SNS and the HPA axis (Elenkov, 2000).

Recently several polymorphisms in the highly conserved regulatory region of the CRH gene were described with the gene being located on chromosome 8q13. Three polymorphisms co-segregated absolutely resulting in two alleles A1 and A2 with a further polymorphism being assigned as alleles B1 and B2. Population investigations demonstrated a distortion in the distribution of the resulting compound alleles A1B1, A2B1 and A2B2 between RA patients and healthy controls (Baerwald et al., 1997). In vitro studies revealed a different regulation of the CRH gene by these polymorphisms (Wagner et al., 2006). Furthermore, it was shown that the stress induced response of cortisol is differentially modulated by CRH promoter polymorphisms in RA patients. Thus, during insulin hypoglycemia test RA patients bearing the A2B2 allele exhibited an earlier CRH as well as ACTH peak compared to A1B1 positive patients. The integrated cortisol response to hypoglycemia expressed as area under the curve was significantly lower in RA patients with the A1B1 allele than in RA patients with the A2B2 allele. Moreover, there was a significant difference in the molar ratio cortisol to ACTH between controls and RA patients underlining the dissociation of the pituitary and the adrenal gland in patients with RA (Malysheva et al., 2011).

#### 4. Environmental factors in stress – disease interaction

The concept of environment included different factors that could disturb the homeostatic state of health (Parniapour, 1990). A growing body of research in rheumatic diseases highlights the importance of environmental influences to the contribution of stress on

disease activity of rheumatic diseases. These influences include factors such as emotional distress, coping, and familial factors (Anthony & Schanberg, 2007), diet, and some socio-economic factors (such as level of education, area of residence and income) may affect levels of pain and physical disability experienced by rheumatic patients (Symmons, 2003; Kobayshi et al., 2008).

#### 4.1 Family factors

It was shown that the family environment is important in juvenile rheumatic diseases. Thus, diagnosis of a rheumatic disease in children was associated with depression in the mother and a composite measure of parental (mother and father) distress and passive coping. Children's emotional and behavioural functioning was not related to medical diagnosis, however, a mother's depression and parental distress were associated with a child's behavioural problems. This kind of distress was associated with child functioning and interventions to ameliorate parental distress may have beneficial effects on the children's behaviour and on parent's reactions to their children (Frank et al, 1998). Furthermore, the social environment was found to operate on the core health outcome, i.e. pain severity in rheumatic diseases. Not only the status of being married but also the quality of the relationship in terms of long-term stress and emotional support may be useful prognostic factors in rheumatic diseases. Patient reports of negative spouse behaviour (such as avoidance and critical remarks) and baseline depression predicted worse pain outcome, and this association remained significant in analyses controlling for baseline pain. The level of formal education showed a weak correlation to disability, emotional support, and pain. Daily emotional support and social life domains associated with positive affect had an indirect influence on outcome. The absence of strong rather than weak social ties was the component of the loneliness construct linked to pain. These associations between social prognostic factors and pain severity, however, were mediated by psychological functioning at baseline (Waltz et al., 1999).

#### 4.2 Socioeconomic status

One more important factor of environment is socioeconomic status. Although RA occurrence is more frequent in lower socioeconomic parts of the population, it was not identified as a significant risk factor in RA (Damjanovic et al., 2009). Otherwise, there is a lack of good quality studies of the epidemiology of rheumatic diseases in developing countries. It appears that a threshold level where higher socio-economic status is associated with reduced prevalence of rheumatic disease is not reached in developing countries. Therefore, differences in the prevalence between socio-economic groups can be undetected. A similar case can be made for overcrowding (Steer et al., 2002). However, the education level as risk factor is significantly related to RA occurrence (Damjanovic et al., 2009). Furthermore, socioeconomic disparities in patients with chronic musculoskeletal complaints leading to increased pain may be attributable to both greater frequency of stressful financial events as well as greater vulnerability to economic hardship for those at the lower end of the socioeconomic spectrum. Conditions of economic hardship and daily ratings of financial worry both had significant detrimental effects on daily pain. Participants with greater levels of economic hardship reported greater pain severity in response to daily financial worries than their counterparts with little or no economic hardship. Further, participants in the

sample who were not employed and who reported higher levels of economic hardship exhibited the most pain reactivity in response to daily financial worries. Economic hardship was associated not only with greater exposure to daily financial worries but also with greater vulnerability to pain on days when daily financial worries were experienced (Rios & Zautra, 2011). A prospective cohort study (1958 British Birth Cohort Study) demonstrated that the prevalence of shoulder, forearm, low back, knee and chronic widespread pain at 45 years generally increased with lower social class. Persons in the lowest social class (compared to the highest) experienced nearly a threefold increase in the risk of chronic widespread pain (relative risk: 2.9, 95% CI 1.8 to 4.6). Social class during childhood also demonstrated a relationship with most regional pain and chronic widespread pain. With the exception of forearm pain, the magnitude of effect of childhood social status on reporting of pain in adulthood was less than that of adult social status. On multivariable analysis these relationships were partly explained by poor adult mental health, psychological distress, adverse life events and lifestyle factors (Macfarlane, 2009). Furthermore, there was an association between socioeconomic status, occupation, and hospitalization for RA. A total of 13,820 male and 14,509 female hospitalizations for RA were analysed during the study. Men and women with an education level > 12 years had a significantly decreased incidence ratio. Occupation also played a role in these items studied with an increased incidence ratio among farmers, miners and quarry workers, electrical workers, other construction workers, and engine and motor operators for men. Among women, assistant nurses and religious, juridical, and other social-science-related workers had significantly increased incidence ratio in all 3 cohorts (Li et al, 2008).

#### 4.3 Education and life style

It was proposed that such environmental factor as level of education was significantly inversely associated with the risk of RA, with a 2-fold lower risk of RA among those with the highest education compared with those having the lowest level of education. On the other hand, it is hypothesised that RF-positive and RF-negative RA have different "aetiologies" with factors related to educational level predominantly associated with the risk of RF-positive RA (Pedersem et al., 2006).

Diet and food life style could also be an important environmental factor contributing to rheumatic diseases. For example, diet, nutrition, and weight loss have shown promise in alleviating some of rheumatic burden. These lifestyle changes may give patients a feeling of control over their disease as well as a non-pharmacologic means of treatment. In particular the role of the Mediterranean diet has to be recognised as a protective factor against RA (Li & Micheletti, 2011). The goals of dietary therapy in rheumatic diseases are alleviation of under- and malnutrition, inhibition of inflammation, prophylaxis of osteoporosis, as well as recognition and treatment of nutrient sensitivities or intolerances. Inhibition of inflammation in these patients is improved by modulating the omega-3/omega-6 fatty acids ratio in the diet. Reduction of dietary arachidonic acid is recommended. This polyunsaturated fatty acid is the main precursor of pro-inflammatory mediators which interact with chemokines and cytokines. Simultaneously, intake of anti-inflammatory omega-3 fatty acids is increased. Studies have shown that this dietary regimen results in an amelioration of symptoms in patients with inflammatory rheumatic diseases (Adam et al., 2009).

The role of other types of environmental stress was studied in patients with different autoimmune diseases as well. For example, cognitive stressors elicited changes in leukocyte/lymphocyte counts, subsets of lymphocytes, and CRP levels in patients with RA (Geenen, 1998; Veldhuijzen van Zanten, 2005), and changes in leukocyte counts and cytotoxic T cell numbers in patients with SLE (Hinrichsen, 1992). It has recently been demonstrated that thermal stress (Spa therapy) induces a reduction in the circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), IL-1 $\beta$  and TNF- $\alpha$ , important mediators of inflammation and pain in patients with rheumatic diseases (Fioravanti, 2011). It was shown that environmental desiccating stress can be involved in the pathogenesis of chronic dry eye syndrome by exposing shared epitopes in the cornea, conjunctiva, and the lacrimal gland that induce pathogenic CD4+T cells leading to lacrimal keratoconjunctivitis, which under normal circumstances is restrained by CD4(+)CD25(+) forkhead/winged helix transcription factor(+) regulatory T cells (Niederkorn et al., 2006).

#### 4.4 Climate conditions

Some other environmental factors such as weather conditions and climate could be also important in rheumatic pain. For example, persons with osteoarthritis in urban Chicago exhibited more weather sensitivity than their rural counterparts in Grand Forks, North Dakota. Multiple regression analysis revealed that precipitation affected pain for urban subjects who identified weather as a pain-generating factor; barometric pressure, relative humidity and sunshine were significant factors influencing pain-related stress. Wind speed correlated with pain and pain-related stress; relative humidity and precipitation correlated with pain-related stress for urban subjects who did not perceive weather as a problem. Specific weather variables were not identified as affecting rural subjects' pain. However, temperature and barometric pressure affected pain-related stress in rural subjects who perceived weather as a problem (Laborde et al., 1986). However, one systematic review of nine longitudinal observational studies (up to September 2009) dealing with the association of weather variables (temperature, relative humidity and atmospheric pressure) and severity of pain in RA could not demonstrate any significant effects. Individual analyses from two studies indicate that pain reporting in a minority (< 25%) of RA patients is influenced by temperature, relative humidity or atmospheric pressure. The studies to date do not show any consistent group effect of weather conditions on pain in RA. There is, however, evidence suggesting that pain in some individuals is more affected by the weather than in others, and that patients react in different ways to various weather conditions. Thus, the hypothesis that weather changes might significantly influence pain reporting in clinical care and research in some patients with RA cannot be rejected (Smedslund & Hagen, 2011). Otherwise, one population-based study demonstrated that pain is not an inevitable consequence of climatic conditions. Persons were less likely to report pain on days with > 5.8 h of sunshine and with average temperature of > 17.5°C underlining a strong relationship between lack of sunshine, lower temperatures and pain reporting (Macfarlane et al, 2010). Interestingly, 84% of RA patients believe in an association between weather and rheumatism, while 57% claimed to have ability to forecast weather. The maximum contribution of weather on symptoms was 17.1 %. Of interest, the belief about a presence of an association between weather and arthritis was found to be stronger than its statistical power (Cay et al., 2011).

#### 4.5 Cultural difference

In addition, cultural differences in experiencing individual stress in RA patients were observed. In one study covering Polish and German RA patients it was demonstrated that in both countries, mental as well as physical health deteriorated resulting in about 50% of patients requiring support in everyday activities. 95% of Polish and 62% of German patients felt rejected from social activities. For the psychological stress perceived, functional capacity class 3 and male gender were shown to be predictive in Polish patients and living in a small town in German patients. In the Polish group, the tertiary/bachelor level of education was linked with lower distress level. RA has a serious impact on the mental health owing to a great disease burden (Bugajska et al., 2010).

#### 4.6 Other factors

Interestingly, during a 15-year follow-up study of 74 female patients with RA two categories of RA were identified: a disease form less connected with genetic factors and more influenced by major psychodynamic conflict situations ('major conflict group') and a second form more associated with hereditary predisposition and less influenced by environmental psychosocial changes ('non-conflict group') (Rimón & Laakso, 1985). In addition, a patient's perspective of the causes and consequences of RA could underline the role of environmental factors in disease. Two descriptive categories of patient's understanding of disease could be identified: the category 'consequences beyond personal control' comprised not having a clue, being exposed to climatic change, being genetically exposed and unexpected effects of events; the category 'overloaded circumstances' involved work and family-related strain. Consequences beyond personal control implied that the patients could not prevent the disease and expressed their lack of understanding as to why they contracted it. Overloaded circumstances were described as strained situations that were both work and family factors related and could be influenced by the patient. Reasoning along these lines it is concluded that understanding the patients' own view of disease is needed in order to achieve a more successful medical care model (Bergsten et al., 2009). Identifying of how these factors contribute to the development of autoimmune diseases may further lead to better explaining the pathogenesis of rheumatic diseases (Symmons, 2003; Kobayshi et al., 2008).

Finally, in one recent study of patients with psoriatic arthritis environmental factors such as lifting heavy loads of at least 100 pounds/hr (OR 2.8, 95% CI 1.51-5.05), infections that required antibiotics (OR 1.7, 95% CI 1.00-2.77), and injuries (OR 2.1, 95% CI 1.11-4.01) were associated with the occurrence of arthritis. No association was found between psoriasis arthritis and alcohol consumption, vaccination, and female hormonal exposures (Eder et al., 2011).

### 5. Rheumatic diseases as a model of stress induced disease

Despite more than twenty years of stress research in rheumatology, it is not completely understood whether stress induced neuroimmune dysfunctions play a causal role in the aetiology of rheumatic diseases or, in turn, rheumatic disease could change the stress reaction and thereby changing disease activity and worsening the outcome. However, epidemiological research increasingly suggests that exposure to traumatic stressors and psychological trauma is related to increased health care utilisation, adverse health outcomes,

the onset of specific diseases including rheumatic diseases, and premature death (Boscarino et al., 2004; Sommershof et al., 2009).

### **5.1 Stress as pathogenetic factor of autoimmune diseases**

From results of 27 studies evaluating more than 3,000 patients with RA it was recognised that stress is an important risk factor in the pathogenesis of autoimmune diseases. Major life events (e.g. death of a spouse, severe long-term illness of a spouse, loss of a parent, divorce of parents, death of a parent or severe disease of a parent) lead to an intense release of stress mediators (large time integral of released neurotransmitters and hormones), whereas in minor life events (daily hassles with small intensity) only short-lived surges of neurotransmitters and hormones are expected. Therefore, it is suggested that neurotransmitters such as norepinephrine or stress hormones such as cortisol might have different effects on immune/inflammatory responses at high and low concentrations present during short or extended periods of time, respectively. Long-lasting (chronic) stress may lead to pro-inflammatory effects since no adequate long-term responses of stress axes (anti-inflammatory) are to be expected (Cutolo & Straub, 2006). Furthermore, major life events and chronic minor stress seem to be important factors in juvenile chronic arthritis and are significantly associated with the onset of the rheumatic disease. With respect to RA, stress may be a provoking factor. However, during the course of the disease, minor stress could aggravate SLE and RA (Herrmann et al., 2000). In contrast, strong major stress, which is likely accompanied by a large and long-lived release of stress axes mediators, was associated with a decrease in disease activity (Cutolo & Straub, 2006).

#### **5.1.1 Early life stress**

One study (follow up 1980 till 1996) examining the risk of RA in parents after the death of a child does not support an association between severe psychological stress and RA. The relative risk of first hospitalisation for RA was 0.88 [95% CI 0.63-1.24]. The risk was close to 1 throughout the 18 years of follow-up (Li et al., 2005). Recent findings are consistent on the impact of early life stress on subsequent inflammatory responses. A predominant role for parent distress in children's adjustment to juvenile rheumatic disease was shown (Ryan et al., 2010). In one retrospective cohort study (follow-up 1995/1997 through 2005) of 15,357 adults it could be demonstrated that 64% adults reported early life stress with at least one adverse childhood experience (ACE), including childhood physical, emotional, or sexual abuse; witnessing domestic violence; growing up with household substance abuse, mental illness, parental divorce, and/or an incarcerated household member. The event rate (per 10,000 person-years) for a first hospitalization with any autoimmune disease was 31.4 in women and 34.4 in men. First hospitalizations for any autoimmune disease increased with increasing number of ACEs ( $p < 0.05$ ). Persons with equal or more than 2 ACEs were at a 100 % increased risk for rheumatic diseases compared to persons without any ACE ( $p < 0.05$ ) (Dube et al., 2009). Patients with juvenile idiopathic arthritis reported having pain, stiffness, and fatigue on  $> 70\%$  of days, with significant variability in symptom levels. Furthermore, significant same-day relationships between stress, mood, and disease symptoms were revealed. Specifically, daily fluctuations in both stress and mood were predictive of increased pain, stiffness, and fatigue. Increases in daily stress, mood, and disease symptoms were also significantly related to decreased participation in social

activities on a day-to-day basis (Schanberg et al., 2005). However, one study does not support the hypothesis that stressful life events and adverse childhood experiences play an aetiologic role in the development of rheumatic disease. The number and timing of occurrence of stressful life events, as well as their subjective immediate impact, did not differ between participants who developed RA and their matched controls. Termination of pregnancy was the only specific event individually associated with a higher risk of developing RA (OR 3.74; 95% CI 1.4-9.9). Negative childhood experiences were not associated with the risk of RA. However, RA cases reported significantly slower adaptation to the effects of adverse events than controls (Carette et al., 2000).

### 5.1.2 Posttraumatic stress disorder

Some studies have demonstrated a link between the traumatic stress exposures and posttraumatic stress disorder (PTSD) to rheumatic disorders. Recent findings indicate that victims of PTSD exhibit higher numbers of circulating T-cell lymphocytes and lower cortisol levels, suggesting that chronic sufferers of PTSD may be at risk for autoimmune diseases. In addition, patients with comorbid PTSD were more likely to have clinically higher T-cell counts, hyper-reactive immune responses on standardized delayed cutaneous hypersensitivity tests, higher immunoglobulin-M levels, and lower dehydroepiandrosterone levels (Stojanovich, 2008). It was also suggested that PTSD symptoms, as measured by impact of events scale, are strongly linked to chronic widespread pain (Arguelles, 2006). Otherwise, in one twin pair's study it was shown that PTSD symptoms were associated with onset of adult RA. Even after adjustment for familial/genetic factors and other confounders, an association between PTSD symptoms and RA remained (Boscarino et al., 2010). Furthermore, cross-sectional data from the 2002 National Health Interview Survey, an in-person household interview survey, in adults with ( $n = 6,829$ ) and without ( $n = 20,676$ ) arthritis demonstrated that the prevalence of severe psychological distress (SPD) in adults with arthritis is significantly higher than in adults without arthritis (5.6 % vs. 1.8 % and 26.2 % vs. 10.7 %,  $P < 0.001$ , respectively). In adults with arthritis, SPD was significantly associated with younger age, lower socioeconomic status, divorce/separation, recurrent pain, physical inactivity, having functional or social limitations, and having comorbid medical conditions. Adults aged 18 to 44 years were 6.5 times more likely to report SPD than those 65 years or older, and adults with recurrent pain were 3 times more likely to report SPD than those without recurrent pain. Serious psychological distress affects persons with arthritis and should be addressed in their treatment. Younger adults with arthritis, and those with recurrent pain or either functional or social limitations, may be at higher risk for SPD (Shih M, et al., 2006).

### 5.2 Stress and modulation of rheumatic disease activity

It was shown that perceived stress could be a predictor of rheumatic activity (Curtis et al., 2005). Otherwise, psychological stress is thought to aggravate disease activity in RA, although the physiologic mechanisms are not clear. Thus it was shown that brief psychological stress can trigger increased production of TNF-alpha of stimulated monocytes in RA patients. The use of TNF-alpha antagonists protects against stress activation of cellular markers of inflammation in RA patients (Motivala et al., 2008). In two prospective studies on RA, disease flare-ups were linked to a higher number of interpersonal minor

stressors few days prior to the visit (Cutolo & Straub, 2006). In addition, it was shown that stress is a potentially important risk factor for the onset of adult Still's disease. Stressful life events (OR 2.56; 95% CI 1.18 to 5.52) in the year preceding the onset was significantly associated with increased risk for adult Still's disease (Sampalis et al., 1996). Likewise, a longitudinal study over a period of 5 years showed that RA patients with a higher daily stress level at baseline had a poorer outcome and significantly more bony erosions after 5 years. Therefore, long-lasting (chronic) stress may lead to proinflammatory effects because no adequate long-term responses of stress axes (HPA - anti-inflammatory) are to be expected. Only 5 studies on about 150 RA patients did not support the link between minor stress and disease flares (Cutolo & Straub, 2006). However, it was shown that psychological distress and social support are more important than objectively assessed disease status in determining marital and sexual satisfaction in patients with RA (van Lankveld et al., 2004).

In RA patients pain was the predominantly perceived stressor followed by limitation in mobility, difficulties in carrying out activities of daily living, helplessness, dependency on others, threat to self-esteem, interference in social activity, interference in family relationships, difficulties performing at work, and discomfort of the treatment (Mahat, 1997). Interestingly, perceived stress had the strongest relationship with psychological well-being of rheumatic patients (Treharne et al., 2007).

In a large population-based case-control study (1996–2003) with incident cases of RA (1,221 cases and 1,454 controls) it could be shown that high psychological stress of job demands tended to be associated with a decreased risk of RA (OR = 0.8; 95 % CI = 0.6 - 1.0). Interestingly, low decision latitude was associated with an increased risk of RA (self-reported data: OR = 1.6; 95 % CI = 1.2 - 2.2). Self-reported job strain was associated with a 30% higher risk of RA, compared with relaxed working conditions (Bengtsson et al., 2009).

Similarly, in patients with osteoarthritis the relationship between social support, stress and functional status was of major importance. Thus, physical disability was associated with being older and having less tangible support; psychological disability was correlated with being younger, caucasian, and having less support; and pain was associated with being younger, caucasian and having less education. Self-esteem appeared to be the most, and appraisal the least, consistent social support dimension when predicting functional status. While exposure to stressors negatively affected functional status, its impact was greatest with respect to psychological disability (Weinberger et al., 1990).

## 6. Therapeutic interventions

Rheumatic diseases represent an important public health burden. To reduce the social and economic impact of these pathologies, an appropriate management of these conditions should be encouraged based on the use of established intervention strategies, including stress reduction approaches (Ottonello, 2007).

### 6.1 Psychological approach

In a recent metaanalysis of efficacy of psychological interventions in the treatment of RA patients 31 studies with 2021 patients could be included. There is consistent supportive evidence for the efficacy of disclosure therapy and cognitive behavioural therapy followed

by maintenance therapy. Similarly, there is an evidence for improvement with behavioural therapy (> 6 weeks duration) in the short-term but conflicting evidence for its long-term efficacy. While there is some evidence for improvement with biofeedback-based interventions and relaxation therapy, there is conflicting evidence for the benefits of counselling, psychotherapy, mindfulness and meditation, and behavioural therapy of less than 6 weeks duration (Dissanayake & Bertouch, 2010).

One possibility to reduce stress for patients with rheumatic diseases is cognitive-behavioural therapy aimed at minimisation of pain episodes and stressful events, improving quality of life and involving education, training in various types of relaxation approaches and other coping skills. Ideally the application of these skills includes the patient's home and work environment. It was shown that cognitive-behavioural therapy and stress management may be useful adjuvant therapy when treating the disease symptoms of children with polyarticular arthritis (Schanberg et al., 2005). Otherwise, patients with RA under greater perceived stress who do not use active coping strategies appear to be at risk of psychological comorbidity and may therefore benefit from interventions teaching specific active coping strategies (Treharne et al., 2007). A significant relationship between specific stressors and utilisation of coping strategies could be demonstrated: interference in family relationships and use of evasive coping strategies ( $p < 0.05$ ), threat to self-esteem and use of both evasive and emotive coping strategies (Mahat, 1997). Interestingly, an active behavioural coping buffered an association of stress with depression, while active cognitive coping buffered the effect of baseline stress on life satisfaction after 6 months of intervention. Patients with RA under greater perceived stress who do not use active coping strategies appear to be at risk of psychological comorbidity and may therefore benefit from interventions teaching specific active coping strategies (Treharne et al., 2007). Optimistic and confronting coping strategies were found most frequently and perceived to be most effective against distress (Herrmann et al., 2000). Furthermore, a sample of patients with RA who completed a stress management training program (such as self-efficacy, coping strategies, and helplessness) had a decrease of pain and depression due to beneficial changes in the arenas of self-efficacy (the belief that one can perform a specific behaviour or task in the future), coping strategies (an individual's confidence in his or her ability to manage pain), and helplessness (perceptions of control regarding arthritis) (Rhee, 2000).

Moreover, several studies suggest that the cognitive-behavioural approach is efficacious in RA and osteoarthritis in improving not only the psychological adjustment during the course of the disease but also physical function (Ottonello, 2007). It was demonstrated that psychosocial intervention (conventional psychotherapy or assertion/relaxation training) leads to improvement in functional status or disease activity of RA patients (Strauss et al., 1986). Moreover, cognitive-behavioural therapy and mindfulness interventions that target responses to chronic stress, pain, and depression reduce pain and the pro-inflammatory IL-6 improving the quality of everyday life for adults with RA (Zautra et al., 2008).

Otherwise, cognitive behavioural interventions to facilitate patient adjustment could usefully include not only management of stress and its appraisal but also utilisation of social support resources (Curtis et al., 2005). Several longitudinal studies have demonstrated that stress appraisal and resultant coping responses affect health outcome and health-related quality of life in women. In addition to problem-focused coping, women often use distraction methods, seeking social support and faith or religious coping. Psychological

interventions in chronic medical conditions need to move beyond education and incorporate more cognitive behavioural components, at the same time addressing women's specific needs. Coping behaviours in response to the negative threat of a chronic or severe medical illness serve to reduce psychological distress (Rao, 2009). One of the important factors to sustain a psychological well-being is the social background; in particular functioning of the family is of outstanding importance for clinical and psychological outcomes (Herrmann et al., 2000). On the other hand, personality and social relationships play an important role in almost every aspect of stress and coping. Daily process methods are particularly useful in elucidating how these factors might influence both responses to and outcomes of stress (DeLongis & Holtzman, 2005). Furthermore, a randomized clinical trial to evaluate a psychological intervention and social support program in RA patients showed that the psychological intervention produced significant reductions in patients' pain behaviour and disease activity. Significant reductions were also observed in trait anxiety after treatment and at 6-month follow-up. The social support program produced a significant reduction in trait anxiety after treatment only (Bradley et al., 1987). Moreover, in the European Research on Incapacitating Diseases and Social Support cohort of patients with early RA it was demonstrated that patients with a greater amount of specific social support or a stronger specific support network experienced less functional limitation and less psychological distress (Demange et al., 2004). Controlled studies of RA patients demonstrated that the ability of self-management behaviours (accommodation, active remediation, perseverance) can decrease impact of RA-related stressors (pain, fatigue, physical limitations, joint changes, and symptom unpredictability) to perform life activities ( $p < 0.01 - 0.0001$ ) (Katz et al., 2005).

## 6.2 Muscle relaxation training

Otherwise, supervised muscle relaxation training exercised 30 minutes, twice a week for 10 weeks in individuals with RA indicated improvements in the training group regarding self-care according to the Arthritis Impact Measurement Scales 2, and in recreation and pastimes according to the Sickness Impact Profile-RA ( $p < 0.05$ ) directly after the intervention. Mobility and arm function ( $p < 0.01$ ) according to the Arthritis Impact Measurement Scales 2, and muscle function of the lower limbs ( $p < 0.05$ ) were improved after six months of training (Lundgren & Stenström, 1999). There has been an increasing interest in meditation as a mind-body approach, given its potential to alleviate emotional distress and promote improved well-being in a variety of populations (Young, 2011). A randomized, waitlist-controlled pilot study of 4 month's Mindfulness-Based Stress Reduction program showed a significant decrease of psychological distress and strengthening well-being in patients with RA (Pradhan, 2007).

## 6.3 Tai chi

It was also shown that Tai chi is beneficial in stress inhibition increasing daily activities in RA patients. Tai Chi is a traditional Chinese art which combines a multimodal, complex intervention that may include interaction of physical, cognitive, and ritualistic components (including, for example, elements of musculoskeletal efficiency, breathing, mindfulness, psychosocial interactions, rituals, and environment) (Wayne & Kaptchuk, 2008). Two randomised clinical trials (RCTs) and three non-randomized clinical trials about efficacy of

Tai chi in RA were published. The included RCTs reported some positive findings for Tai chi on disability index, quality of life, depression and mood for RA patients. Two RCTs assessed pain outcomes and did not demonstrate effectiveness on pain reduction compared with education plus stretching exercise and usual activity control. Currently there are few trials testing the effectiveness of Tai chi in the management of RA (Lee et al., 2007). It was demonstrated that Tai chi practice lead to improved lower-limb muscle function, confidence in moving, balance and less pain during exercise and in daily life, stress reduction, increased body awareness at the end of intervention and at 12 weeks follow-up in patients with RA (Uhlig et al., 2010). Furthermore, in one randomised controlled trial there was an ACR20 (American College Rheumatology) response of 50 % in the Tai chi group compared with 0% in the control at 12 weeks ( $p = 0.03$ ). Tai chi had greater improvements in the disability index ( $p = 0.01$ ), vitality subscale of the Medical Outcome Study Short Form 36 ( $p = 0.01$ ) and the depression index ( $p = 0.003$ ). Similar trends to improvement were also observed for disease activity, functional capacity and health-related quality of life. It was concluded that Tai Chi appears safe and may be beneficial for functional class I or II RA (Wang, 2008). Despite certain limitations this exercise showed reduction of stress and improved quality of life and it can be recommended to patients with osteoarthritis and RA as a complementary and alternative medical approach (Wang, 2011). However, in the treatment of chronic conditions such as rheumatic diseases, particularly when it comes to complementary modalities such as tai chi, therapies are often used and studied in conjunction with other treatments. Although these heterogeneous interventions may better represent how care is delivered in real-world settings, they sometimes create problems when it comes to interpreting research findings (Yeh, 2008). Otherwise, the studies that are available are of low methodological quality. Taken together, evidence is not convincing enough to suggest that Tai chi is an effective treatment for RA. The value of Tai chi for this indication therefore remains unproven (Lee et al., 2007).

## 6.4 Yoga

Over the last 10 years, a growing number of research studies have shown that the practice of yoga can improve strength and flexibility, and may help control such physiological variables as blood pressure, respiration and heart rate, and metabolic rate to improve overall exercise capacity finally resulting in a benefit of yoga for people compromised by musculoskeletal disease (Raub, 2002). For example, it was demonstrated that 10-week yoga interventions in patients with RA significantly decreased the disability index, perception of pain and depression, and improved balance (Bosch et al., 2009). Another study of yoga showed improvements in mental health, vitality, and self-efficacy in a group of young patients with RA (age 18-36 years). Interviews demonstrated improvement in RA symptoms and functioning but uncertainty about whether the intervention affected pain (Ewans et al., 2010). Otherwise, it was indicated that 12 sessions of Raj yoga carried out bi-weekly might improve significantly disease activity and disability index (Badsha et al., 2009). Furthermore, hand grip strength of both hands, measured with a grip dynamometer, increased in normal adults and children as well as in RA patients, but not in the corresponding control groups. Adult female volunteers and patients showed a greater improvement than corresponding adult males. This gender-based difference was not observed in children (Dash & Telles, 2001). One pilot study of 8-week course of yoga in patients with osteoarthritis suggests that yoga may provide a feasible treatment option for previously yoga-naïve, obese patients > 50

years of age and offers potential reductions in pain and disability. Statistically significant reductions in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function, and Arthritis Impact Measurement Scales, patient and physician global assessments were demonstrated (Kolasinski et al., 2005).

### 6.5 Acupuncture

Acupuncture, which originated with traditional Chinese medicine, is another therapy option that reduces stress, relieves pain and promotes an increase in quality of life. Several systematic reviews have assessed the effectiveness of acupuncture for rheumatic conditions, often with contradictory conclusions. Relatively clear evidence emerged to suggest that acupuncture is effective for osteoarthritis, low back pain and lateral elbow pain to warrant positive recommendations of this therapy in routine care for such patients but being ineffective for RA (Ernst & Lee, 2010). In another systematic review it was shown that acupuncture with duration of 11 weeks results in a decrease in pain compared to controls; the mean or median changes of acupuncture-decreased tenderness of joints ranged from 1.5 to 6.5. In addition, a significant reduction of morning stiffness (mean change - 29 minutes) was noted, but the difference was not statistically significant versus controls. With regard to inflammatory markers, a reduction in erythrocyte sedimentation ratio (mean change - 3.9 mm/hour) and a CRP level reduction (mean change - 2.9 mg/dl) was observed. Despite some favourable results in active-controlled trials, conflicting evidence exists in placebo-controlled trials concerning the efficacy of acupuncture for RA (Wang et al., 2008). Regarding anaesthesia, supportive acupuncture treatment is performed for postoperative pain based on promising results of rigorous randomised trials. Many unresolved questions remain, such as regarding specificity of concepts, indications, and optimum dose (Stör & Irnich, 2009).

Individuals who are at risk to develop an autoimmune disease should be advised to refrain from lifestyle and activities that endanger their future health and quality of life. Different stress reactions should be discussed with patients, and obligatory questionnaires about trigger factors should include psychological stress in addition the usual suspects such as infection and trauma (Stojanovich et al., 2008). Stress reduction interventions can have a positive therapeutic effect in autoimmune disease patients leading to a reduction in the social and economic impact of rheumatic diseases. An appropriate management of these conditions should be encouraged based on the use of established intervention strategies. Physicians and patients should recognize the potential of stress to impact autoimmune diseases and that stress management should be integrated in a multidimensional treatment approach (McCray & Agarwal, 2011).

## 7. Conclusion

Rheumatic diseases are chronic inflammatory disorders of unknown aetiology and variable severity. It is now well known that several risk factors are contributing to aetiology and pathophysiology of rheumatic diseases, including genetic factors, sex hormones and environmental factors, e.g. infections and stress. An increasing number of studies could demonstrate that psychological stress and stress-related hormones are involved in immune modulation, which ultimately may result in autoimmune disease. Stress related hormones

exert numerous effects on various immune functions, e.g. chronic mild stress (family or occupational stress) lead to proinflammatory effects thereby increasing disease activity. Emotional stress could be shown to modulate pain reception and to modify quality of life in patients with rheumatic diseases. Furthermore, a positive correlation between stress levels and the onset of rheumatic diseases could be demonstrated. Unfortunately, not only stress causes disease, but the disease itself also causes significant stress in the patients disturbing the physiological stress response. In this respect, it could be demonstrated that coping strategies reduce stress episodes with a positive impact on disease activity in patients with rheumatic diseases. However, more studies are warranted to further explore the pathophysiological implications of stress on onset and activity of chronic autoimmune diseases. In particular stress is now recognised as an important risk factor for the onset and even more for the modulation of disease activity in different rheumatic diseases.

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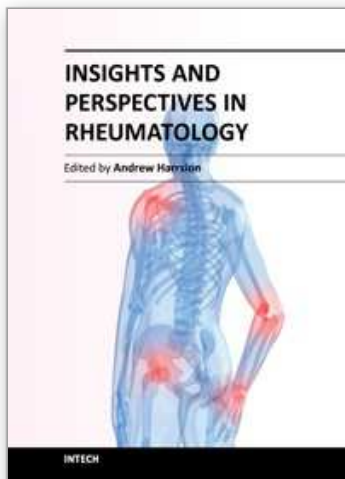
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This book offers a range of perspectives on pathogenesis, clinical features and treatment of different rheumatic diseases, with a particular focus on some of the interesting aspects of Sjögren's syndrome. It contains detailed and thorough reviews by international experts, with a diverse range of academic backgrounds. It will also serve as a useful source of information for anyone with a passive interest in rheumatology, from the genetic and molecular level, through to the psychological impact of pain and disability.

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