CHAPTER TWO: LITERATURE REVIEW

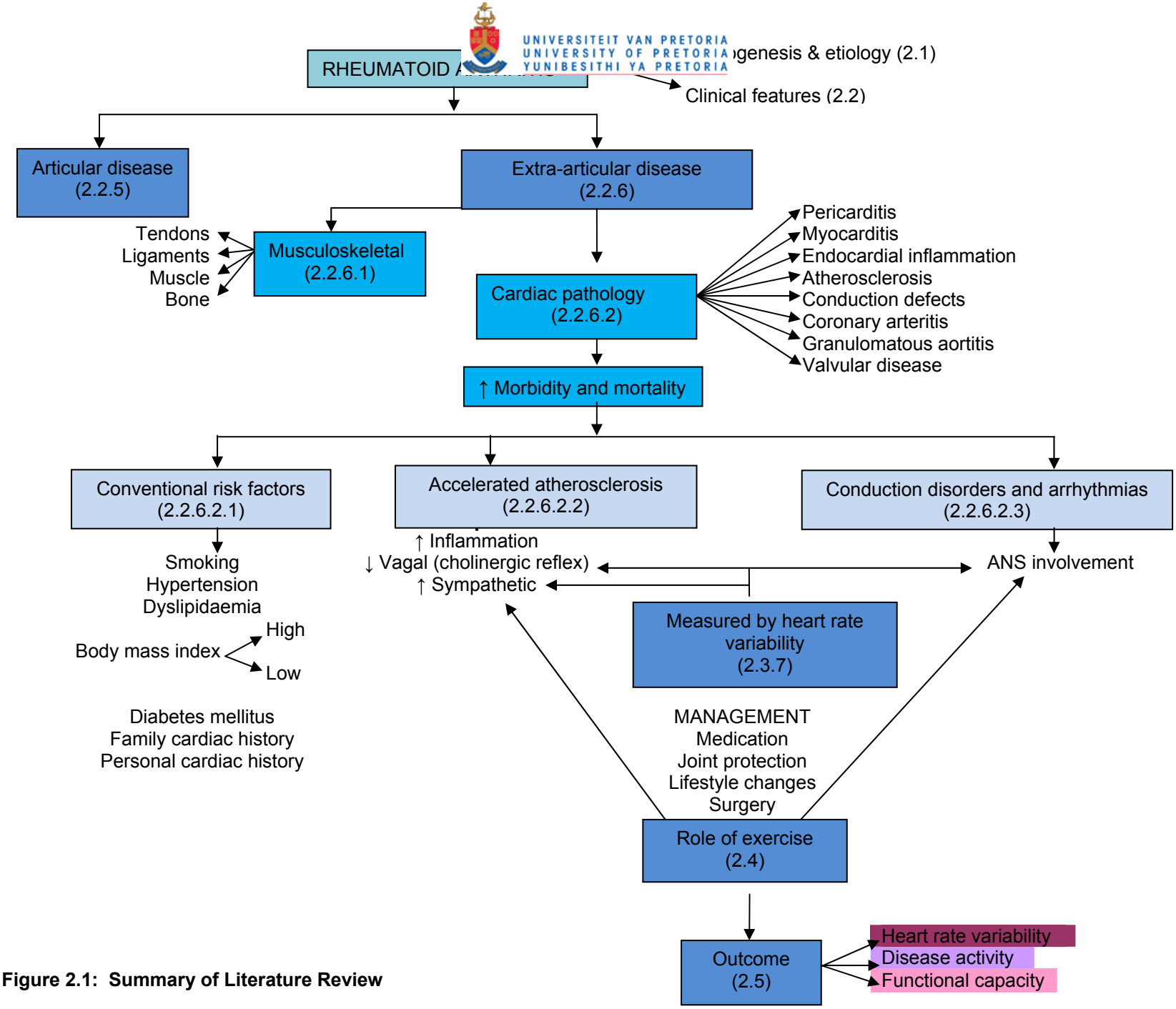

Figure 2.1: Summary of Literature Review

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic, inflammatory disease of unknown cause affecting 0.5%-1% of the world population. It is the most common inflammatory arthritis. Although considered a disease of the joints, a variety of extra-articular manifestations are caused by abnormal immune responses. The etiology of RA is still unknown and why the synovium is the primary target remains a mystery. The synovial cells can act like a localized tumor; invading and destroying articular cartilage, subchondral bone, ligaments and tendons. Early intervention to reduce synovitis has an important impact on morbidity and mortality[1].

2.1 PATHOGENESIS AND ETIOLOGY

There are a number of factors that may play a role in the pathogenesis and etiology.

2.1.1 ROLE OF IMMUNITY

Both the adaptive and innate immune responses are part of the initiation, propagation and maintenance of the auto-immune process of RA.

The immune mechanisms are complex and numerous. All cell types, including dendritic cells, macrophages, fibroblasts, T-cells and B-cells are involved.

Cytokine pathways show abnormal production and regulation in RA, with macrophages and synovial fibroblasts being the main producers of pro-inflammatory cytokines e.g. tumor necrosis factor (TNF)-alpha and interleukin-1.

High serum levels of autoantibodies like rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) are evident of the role of auto-immunity. It is suggested that synovial macrophages and fibroblasts may lose responsiveness to T-cells, thus becoming autonomous leading to pannus formation and ultimately destruction of cartilage and bone[1-3]. Figure 2.2 shows a schematic diagram of the immune mechanisms that likely play a role in RA.

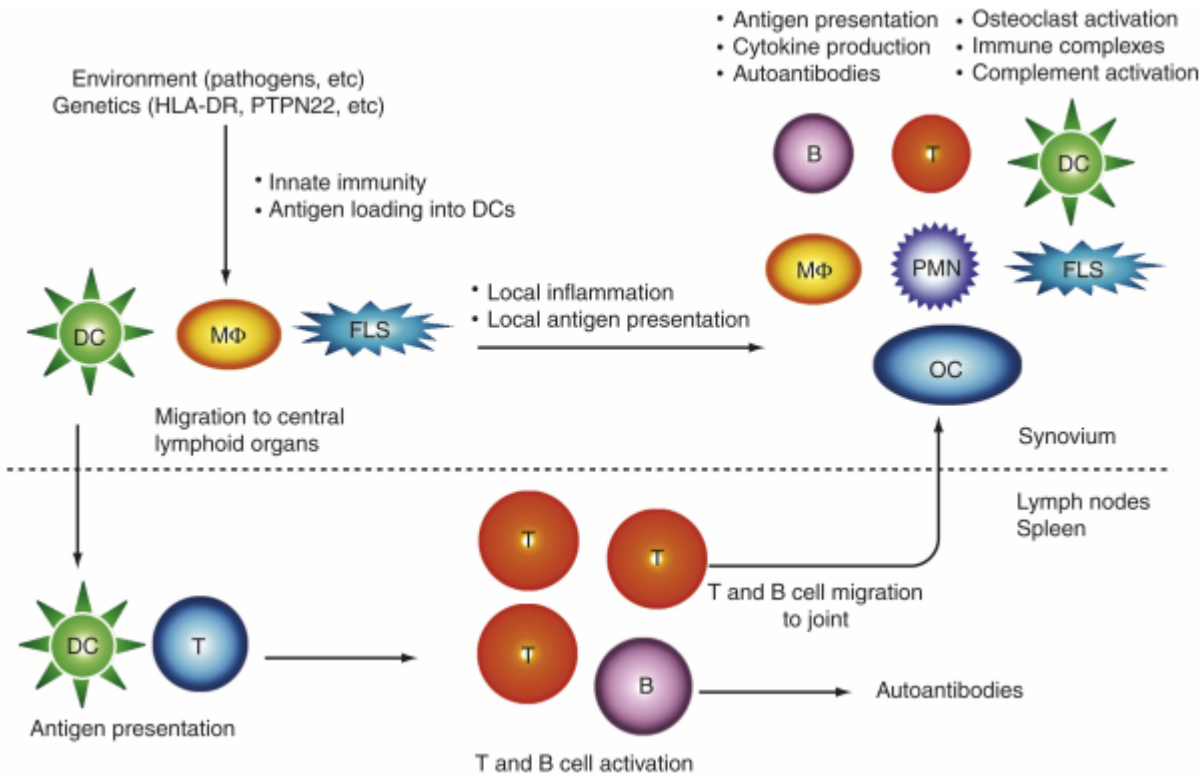

Figure 2.2: Immune mechanisms possibly playing a role in RA[1]

Schematic diagram of disease mechanisms that likely occur in rheumatoid arthritis. Innate immunity activates fibroblast-like synoviocytes (FLS), dendritic cells (DC), and macrophages (MΦ) in the earliest phases in individuals with underlying immune hyperreactivity as evidenced by the production of autoantibodies. The genetic makeup of an individual, including the presence of certain polymorphisms in genes that regulate immune responses, and environmental exposures are required. DC can migrate to the central lymphoid organs to present antigen and activate T cells, which can activate B cells. These lymphocytes can migrate back to the synovium and enhance adaptive immune responses in the target organ. In addition, repeated activation of innate immunity can lead directly to chronic inflammation and possibly antigen presentation in the synovium. In the latter phases of disease, many cell types activate osteoclasts (OC) through the receptor activator of nuclear factor κB (NFκB)/receptor activator of NFκB ligand (RANK/RANKL) system, although FLS and T cells likely provide the greatest stimulus. Autonomous activation of FLS also might contribute to this process.

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2.1.2 GENDER (HORMONAL)

As with many other auto-immune diseases, RA has a predominance in women. The female to male ratio is 2:1 to 3:1. The specific mechanisms for this are not clear, but exposure to estradiol seems to make autoantibody producing B-cells more resistant to apoptosis. The effect on the T-cells are more difficult to explain, because estrogen tends to favour T-lymphocyte differentiation towards T-helper type 2 cells which produces anti-inflammatory cytokines[1]. Various methods have been utilized to explore the role of

estrogens[4]. RA has a reduced incidence in women on contraceptives and it appears to be less active during pregnancy with recurrence in the post-partum period

2.1.3 TOBACCO

The best defined environmental risk factor for RA is smoking. In susceptible individuals this can possibly provide a stimulus for generation of anti-cyclic citrullinated peptide antibodies (anti-CCP)[5].The enzymatic conversion of protein-contained arginase residues to citrulline is the process of citrullination. The enzyme responsible for citrullination is peptidyl arginie deaminase (PADI). Citrullination of relevant self-proteins may induce autoantibody production. Also, it has been reported that environmental factors (e.g. smoking) may cause enhanced cell apoptosis and that citrullination occurs in dying cells. Therefore smoking may result in high cittrulline levels in broncho-alveolar lavage fluids[6]. Citrullinated peptides have been found in broncho-alveolar lavage samples of smokers.

2.1.4 INFECTION

The first clear description of RA in Europe appears to be that of Landré-Beauvais (1772-1840). He believed that it was a variant of gout. No convincing evidence of RA could be detected in ancient skeletal remains from Europe, in contrast to those of Native Americans. A current line of thought suggests that an undefined environmental exposure (possibly an infectious agent) could cause RA in susceptible Europeans as genetic admixture at that time was relatively limited[1,7]. Table 2.1 gives a summary of the possible infectious agents that may play a role in the pathogenesis.

Table 2.1: Possible infectious causes of rheumatoid arthritis[1]

Infectious Agent	Potential Pathogenic Mechanisms
Mycoplasma	Direct synovial infection; superantigens
Parvovirus B19	Direct synovial infection
Retroviruses	Direct synovial infection
Enteric bacteria	Molecular mimicry (QKRAA)
Mycobacterium	Molecular mimicry (proteoglycans, QKRAA), immunostimulatory DNA
Epstein-Barr virus	Molecular mimicry (QKRAA)
Bacterial cell walls	Macrophage activation

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2.1.5 GENETICS

A shared epitope of the HLA-DR_4 cluster (HLA-DR beta *0401, 0404, or 0405) is carried by approximately 60% of patients with RA in the United States. HLA-DR_1 (HLA-DR beta *0101) also carries this shared epitope[3]. Polymorphisms on many other non-HLA genes e.g. the ones associated with PADI are currently under investigation[1].

2.2. CLINICAL FEATURES

2.2.1 PREVALENCE AND INCIDENCE

RA is the most prevalent chronic inflammatory arthritis affecting 0.5-1% of the world population. All races are affected, although some, like the Chinese to a lesser extent (0.3%) and others like the Pima Indians (5%), more so. A prevalence of 0.9% has been reported in an urban black South African (SA) population. However, some rural areas in SA reported hardly any cases[8,9]. Females are affected more commonly with estimated incidences based on European and North American studies being 24-60 / 100 000 for females and 15-26 / 100 000 for males[10]. RA can occur at any age, but the incidence increases with age[11,12].

2.2.2 PATTERNS OF ONSET

2.2.2.1 Insidious onset

In 55-65% of cases the onset is slow over weeks to months. Initial symptoms can either be systemic or articular. Morning stiffness (lasting at least 30-45 minutes) can be the first symptom and is an important sign of inflammatory arthritis.

2.2.2.2 Acute onset

8-15% of patients have an acute onset of disease. Symptoms peak within a few days. Fever can be a prominent sign and vasculitis or sepsis must be ruled out.

2.2.2.3 Intermediate onset

Symptoms develop over days to weeks in 15-20% of cases. Systemic complaints are more on the foreground than in insidious type of onset[13].

2.2.2.4 Unusual patterns (variants) of disease[14]

2.2.2.4.1 Palindromic

Symptoms include pain, swelling and erythema of joints or peri-articular tissues that worsen over hours to a few days. In reverse sequence, symptoms resolve without leaving residual effects. 50% of patients will continue to develop RA.

2.2.2.4.2 Rheumatoid Nodulosis

A variant disorder with subcutaneous nodules, recurrent pain and swelling in different joints, and subchondral bone cysts on imaging.

2.2.2.4.3 Arthritis Robustus

More common in men, with proliferative synovitis and deformity, but with little pain and even less disability.

2.2.2.4.4 RA and Paralysis

In patients with strokes, cerebral palsy, poliomyelitis etc, joints are spared on the paralysed side.

2.2.3 CLASSIFICATION

In 1987 classification criteria were developed by the American College of Rheumatology (ACR) to distinguish non-RA from established RA[15]. Table 2.2 gives a summary of the 1987 revised criteria.

Table 2.2: The 1987 revised criteria for the classification of rheumatoid arthritis (traditional format)*

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

*For classification purposes, a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is *not* to be made.

PIP Proximal interphalangeal joint
MCP Metacarpophalangeal joint
MTP Metatarsophalangeal joint

Reprinted from Arthritis Rheum. 1988 Mar;31(3):315-324. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Copyright notice 2011. With permission from John Wiley and Sons

If at least 4 of the 7 criteria are present for at least 6 weeks it is 77-95% sensitive and 85-98% specific for RA. It is however important not to exclude the diagnosis on this alone as it is not a diagnostic tool for early disease[11]. More recently the 2010 ACR-EULAR classification criteria for RA was published[16].

2.2.4 CONSTITUTIONAL SYMPTOMS

Patients often present with constitutional symptoms including malaise, weight loss, loss of appetite, fever, fatigue and myalgia[11].

2.2.5 JOINT INVOLVEMENT

Joint involvement is the characteristic feature of RA. Well-documented descriptions of specific joint involvement were mostly reported in the decades before 1980. Stress put on individual joints by the patient as well as the intensity of the disease and its chronicity determines the effect of synovitis on joints[14].

The disease usually affects the joints in a symmetrical pattern, but an asymmetrical pattern does not exclude the diagnosis. Small joints of the hands and feet are most commonly affected with larger joints becoming involved at a later stage[11,17]. Table 2.3 gives an overview on the joint distribution in acute flare-ups.

Table 2.3: Distribution of joints involved in attacks based on a cumulative experience with 227 patients[14]

Joint Involvement	% Patients (Mean)	% Patients (Range)
MCP, PIP	91	74-100
Wrists	78	54-82
Knees	64	41-94
Shoulders	65	33-75
Ankles	50	10-67
Feet	43	15-73
Elbows	38	13-60
Hips	17	0-40
Temporomandibular	8	0-28
Spine	4	0-11
Sternoclavicular	2	0-6
Para-articular sites	27	20-29

MCP Metacarpophalangeal
PIP Proximal interphalangeal

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Affected joints show inflammation with warmth, swelling, tenderness and decreased range of motion (ROM). RA results in characteristic deformities if inflammation is not controlled, including:

- boutonniere and swan-neck deformities
- ulnar deviation
- hammer toes
- joint ankylosis

2.2.6 EXTRA-ARTICULAR MANIFESTATIONS

The severity and duration of the disease in general determines the number and severity of extra-articular features. These are associated with excess mortality[11,18]. A summary of these extra-articular features is found in Table 2.4.

Table 2.4: Extra-articular features of rheumatoid arthritis

Pulmonary	On post-mortem up to 75 %
Pleural effusions/pleurisy	Most common. Often asymptomatic, small effusions. Unilateral or bilateral. Usually exudates - mixed cell counts, high LDH, low glucose. Presence of multi-nucleated giant cells highly specific.
Nodules	Mainly seropositive patients with widespread synovitis and nodules. Usually asymptomatic. Peripheral or pleural in location.
Pulmonary Fibrosis	Up to 6% of patients develop systematic fibrosis within 10 years of RA onset. Men >women. Association with nodules. Usually bibasal. May be asymmetrical. Larger proportion may be asymptomatic. Contribution of methotrexate therapy debated.
Obstructive airways disease	Associated with inflammation, constrictive bronchiolitis, crico-arytenoid joint involvement. Up to 50% bronchiectasis on CT scan.
Bronchiolitis oblite-rans organizing pneumonia (BOOP)	Associated with fever and constitutional symptoms.
Shrinking lung syndrome, pulmonary arteritis and primary pulmonary hypertension are very rare.	
	On post-mortem up to 50%.
Cardiac	
Coronary artery disease	RA is an independent risk factor, particularly with persistently elevated ESR/CRP. Increased risk of cardiovascular death - myocardial infarction.
Pericarditis	Mainly seropositive patients with widespread nodules. Usually asymptomatic.
Valvular abnormalities, myocarditis and arteritis/aortitis are rare.	
Heamatological	
Anaemia	Correlates with disease activity. Abnormal iron utilization. Inhibition of erythropoiesis.
Thrombocytosis	Correlates with disease activity
Leucopenia	Felty's syndrome - in association with splenomegaly. May also have thrombocytopenia. Variant may have neutropenia without splenomegaly. Increased risk infection and lymphoproliferative disease including malignancies.
Lymphadenopathy	Common with active disease, can be associated with splenomegaly.
Neurological	
Mononeuritis multiplex/sensory neuropathy	Associated with RA vasculitis (<1%)
Nerve impingement	Secondary to joint inflammation and destruction. Peripheral nerves and nerve roots.
Cervical cord compression	Secondary to atlanto-axial or sub-axial subluxation due to erosive/destructive disease of the spine. Less commonly seen with aggressive early treatment of active RA. Important to consider pre-procedures requiring sedation where the neck may be subjected to extension (e.g. intubation, endoscopy).
Vasculitis (<1%)	Typically affecting smaller vessels with skin manifestations; leucocytoclastic vasculitis, capillaritis, chronic skin ulcers, infarcts (nail-fold infarct in up to 5%, does not seem to be associated with poorer outcome). Vasculitis can affect larger vessels and is more common with Felty's syndrome. Joint disease may not be active. Contributes to renal, neurological, cardiac and gastrointestinal complications. Associated with high RF levels and cryoglobulins.
Liver	Elevated liver function tests are not uncommon and parallel disease activity. Can be difficult to distinguish from drug effects (NSAIDs or DMARDs). Generally is due to drug treatment liver function should improve with discontinuation of the drug. Hepatomegaly can occur with Felty's syndrome. Rarely nodular regenerative hyperplasia can occur.
Renal	Renal abnormalities more commonly secondary to drug effects (NSAIDs, some DMARDs). Rarely low-grade membranous nephropathy, glomerulitis or vasculitis can occur with RA. Nephrotic syndrome is seen with secondary amyloidosis - less common now with adequate inflammation control.
Ocular	Keratoconjunctivitis sicca is most common, associated with xerostomia from secondary Sjögren's syndrome in up to 10% of patients. Episcleritis can occur with active RA. Scleritis indicates associated vasculitis and if persistent can result in scleromalacia, though seen less commonly with adequate inflammation control. Glaucoma and cataracts can occur as a result of drug therapy corticosteroids.

CT, computed tomography; DMARDs, disease-modifying antirheumatic drugs; LDH, lactate dehydrogenase; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RF, rheumatoid factor

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2.2.6.1 Muskuloskeletal involvement

RA causes various physical impairments in those suffering from the disease, including:

- inhibition of muscle contraction secondary to joint effusion
- muscle atrophy due to decreased activity levels, leading to a further decline in muscle strength and contributing to limitations in function, fatigue and deformities
- loss of joint motion
- reduced aerobic capacity as a result of systemic disease and decreased activity levels[19].

Most patients have muscle weakness, but only a few have muscle tenderness with elevated muscle enzymes[14]. Recent studies have described at least 5 different types of muscle involvement in RA:

1. Chronic myopathy (probably the end stage of inflammatory myositis)
2. Active myositis and muscle necrosis
3. Peripheral neuromyopathy
4. Atrophy of Type II fibers with diminution of muscle bulk
5. Steroid myopathy.

Other commonly described musculoskeletal manifestations include tenosynovitis and associated tendon rupture as well as carpal tunnel syndrome[3].

A further problem is bone loss due to systemic disease and/or glucocorticosteroid treatment, increasing the risk for stress fractures, fractures and generalized osteoporosis[20].

2.2.6.2 Cardiac involvement

RA can affect the cardiac system in many ways and many of these features are only found at post-mortem[11]. All structures can be involved, e.g. the pericardium (pericarditis), myocardium (myocarditis) and the endocardium (endocardial inflammation, valvular disease). Some other recognized cardiovascular (CV) diseases include:

- Atherosclerosis

- Conduction defects
- Coronary arteritis
- Aortitis[14].

Alamanos et al in their research made the statement that people with RA die prematurely[21]. Meune et al reported a 60% increase in risk of CV death in RA patients compared to the general population[22], while Aviña-Zubieta et al, after doing an observational meta-analysis reported that the increased mortality risk in RA patients are largely due to the higher rate of CV death[23].

There is thus a growing body of evidence recognizing the excess cardiovascular risk in patients suffering from RA[24-27]. Figure 2.3 illustrates the complex interactions between RA characteristics, CV risk factors and other determinants in developing CV disease.

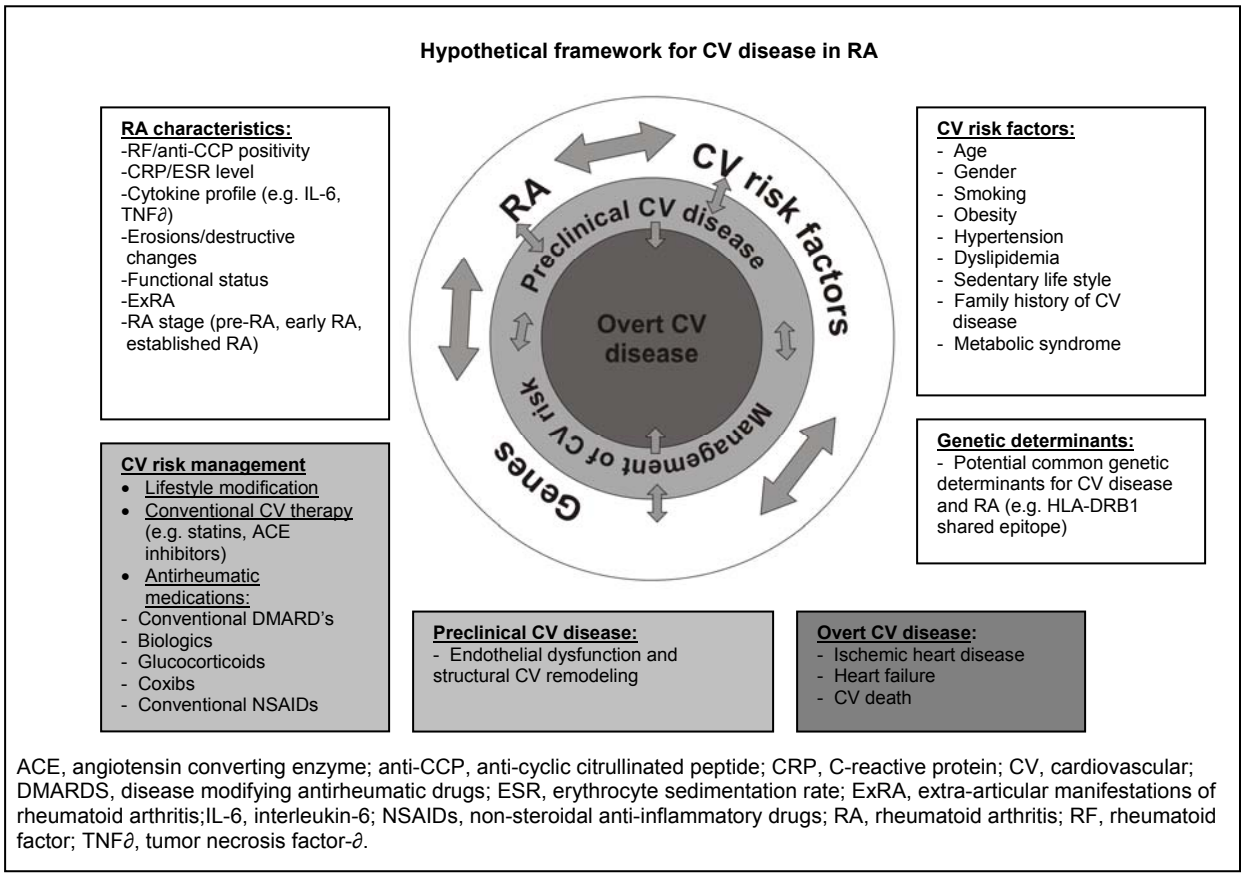

Figure 2.3: The complex interactions between RA characteristics, cardiovascular risk factors, genetic determinants and therapies on the development of preclinical and overt cardiovascular disease in RA[28].

Myasedova E, Gabriel SE, Cardiovascular disease in rheumatoid arthritis: a step forward. Current Opinion in Rheumatology 2010, 22:342-347

Some of the hypotheses that have been generated to explain an increased risk of CV events are:

- Conventional risk factors
- Accelerated atherosclerosis and chronic inflammation
- Conduction disorders and arrhythmias

2.2.6.2.1 Conventional Cardiovascular Risk Factors

Gabriel in a recently published study evaluated the prevalence of traditional risk factors between RA and non-RA subjects. The prevalence did not appear to differ significantly at disease onset. Over the follow-up period when comparing RA and non-RA subjects for hypertension, high body mass index (BMI) or diabetes mellitus, there was also no significant difference. However, low BMI was significantly more common and hyperlipidaemia significantly less common comparing RA with non-RA subjects over time[27]. In Table 2.5 the prevalence of traditional risk factors are compared between RA (at disease onset) and non-RA patients:

Table 2.5: Prevalence of traditional cardiovascular risk factors at RA incidence in RA and non-RA patients[27]

Cardiovascular risk factor	RA Patients N%	Non-RA Patients N%	P Value
Cigarette smoking			<0.001
Never	285 (47)	341 (57)	
Former	148 (25)	118 (19)	
Current	170 (28)	144 (24)	
Hypertension	312 (52)	298 (49)	0.42
Dyslipidaemia	163 (49)	169 (52)	0.45
High BMI (>30 kg/m2)	71 (13)	68 (13)	0.98
Low BMI (<20 kg/m2)	73 (13)	63 (12)	0.50
Diabetes mellitus	44 (7)	41 (7)	0.74
Family cardiac history	287 (48)	284 (47)	0.86
Personal cardiac history	77 (13)	72 (12)	0.66

BMI, body mass index; RA, rheumatoid arthritis

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The authors next examined the impact of conventional risk factors on cardiovascular outcome, which was defined as a combined endpoint including heart failure, myocardial infarction and cardiovascular (CV) death. Interestingly, a threefold increased risk of CV

death was associated with a low BMI among RA patients. Lipids appeared to have a paradoxical effect, while the relative impact of the other risk factors (gender, smoking, personal- or family cardiac history, hypertension and diabetes mellitus) appeared to be significantly less in RA patients compared to non-RA patients (Figure 2.4).

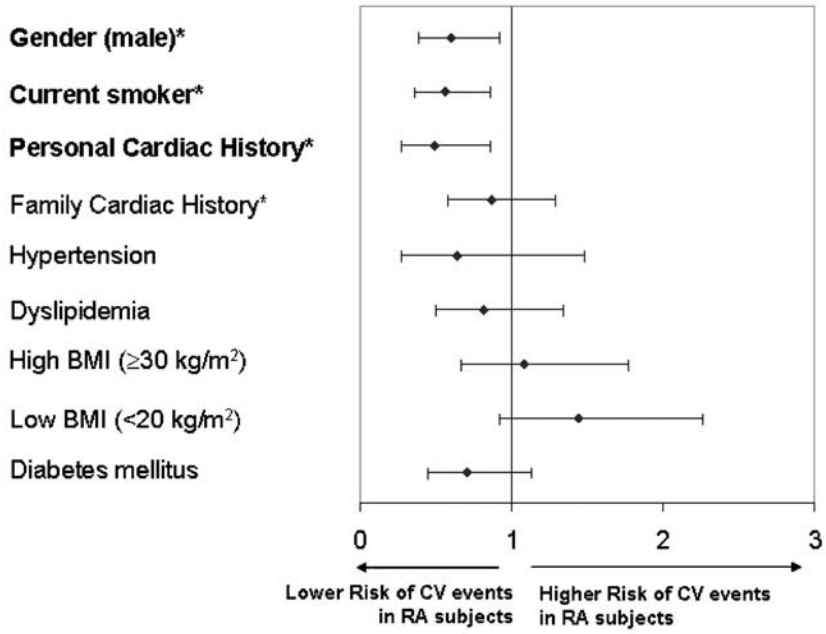

Figure 2.4: Relative impact of traditional CV risk factors on combined CV endpoint in RA and non-RA subjects[27]

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The above findings were noted by other authors like Kitas and Avina-Zubieta, as well as Maradit-Kremers et al who in their study concluded that "the risk of CV disease in RA precedes the American College of Rheumatology (ACR) criteria-based diagnosis of RA, and the risk cannot be explained by an increased incidence of traditional CV disease risk factors in RA patients", [23,29,30]. Myasoedova commented that RA not only represents an important modifier of conventional CV risk factors, but also has a role to play as an independent risk factor[28].

2.2.6.2.2 Accelerated atherosclerosis and chronic inflammation

There is compelling evidence that chronic inflammation has a pivotal role in the etiopathogenesis of atherosclerosis[31]. Several recent studies demonstrated the independent association of inflammatory indicators and RA towards an increased risk for CV disease[27,32-35]. RA activity and severity, high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), ACPA and HLA DRB_1 gene are statistically significantly associated with increased risk of CV events[33,34,36-39].

The Autonomic Nervous System (ANS) is one of a variety of neuronal pathways that have been implicated in modulating inflammation[40]. The "cholinergic anti-inflammatory pathway" is a well studied mechanism where signals transmitted via the vagus nerve control the release of cytokines, reducing the production of pro-inflammatory cytokines by an α-7 nicotinic acetylcholine receptor (α7nAChR) dependent mechanism, and therefore ameliorating inflammatory disease[41-43].

Recent studies have shown improved survival in animal models of inflammation by stimulation of the vagus nerve via electrical or pharmacological methods[42,44-46]. Goldstein et al in a prospective observational study found that RA patients had an increase in high mobility group box-1 ($HMGB_1$) – a pro-inflammatory cytokine – and a decrease in cholinergic anti-inflammatory pathway activity as measured by heart rate variability (HRV). They postulated that it would be interesting to consider if subclinical CV disease is the result of increased inflammation secondary to decreased vagus nerve activity[47].

2.2.6.2.3 Conduction disorders and Arrhythmias

Conduction disturbances arise through impaired conduction or abnormalities of intrinsic automaticity[48]. As the heart is richly innervated by efferent and afferent sympathetic and vagal fibers, it is highly susceptible to autonomic influences[49]. Zipes et al had already in 1995 described the autonomic modulation of cardiac arrhythmias. Electrophysiological mechanisms underlying disrhythmogenesis are influenced by increased sympathetic and decreased vagal tone[50,51].

2.3 AUTONOMIC DYSFUNCTION IN RA

Autonomic dysfunction in patients with RA, has been studied. The literature was reviewed by searching different databases and consulting standard textbook references. The search was conducted to cover a period of 48 years (1963-2011). Databases included Ovid Medline, Pubmed, Scopus, Google Scholar. Textbooks consulted included Kelly Harris' Textbook of Rheumatology, Dieppe's Rheumatology, Mathias CJ Bannister's Autonomic failure: a textbook of clinical disorder of the autonomic nervous system (1999) and E Oribe's Testing autonomic function, from Handbook of clinical neurology, 1999, p595-647. Figure 2.5 shows the route that was followed for the literature review.

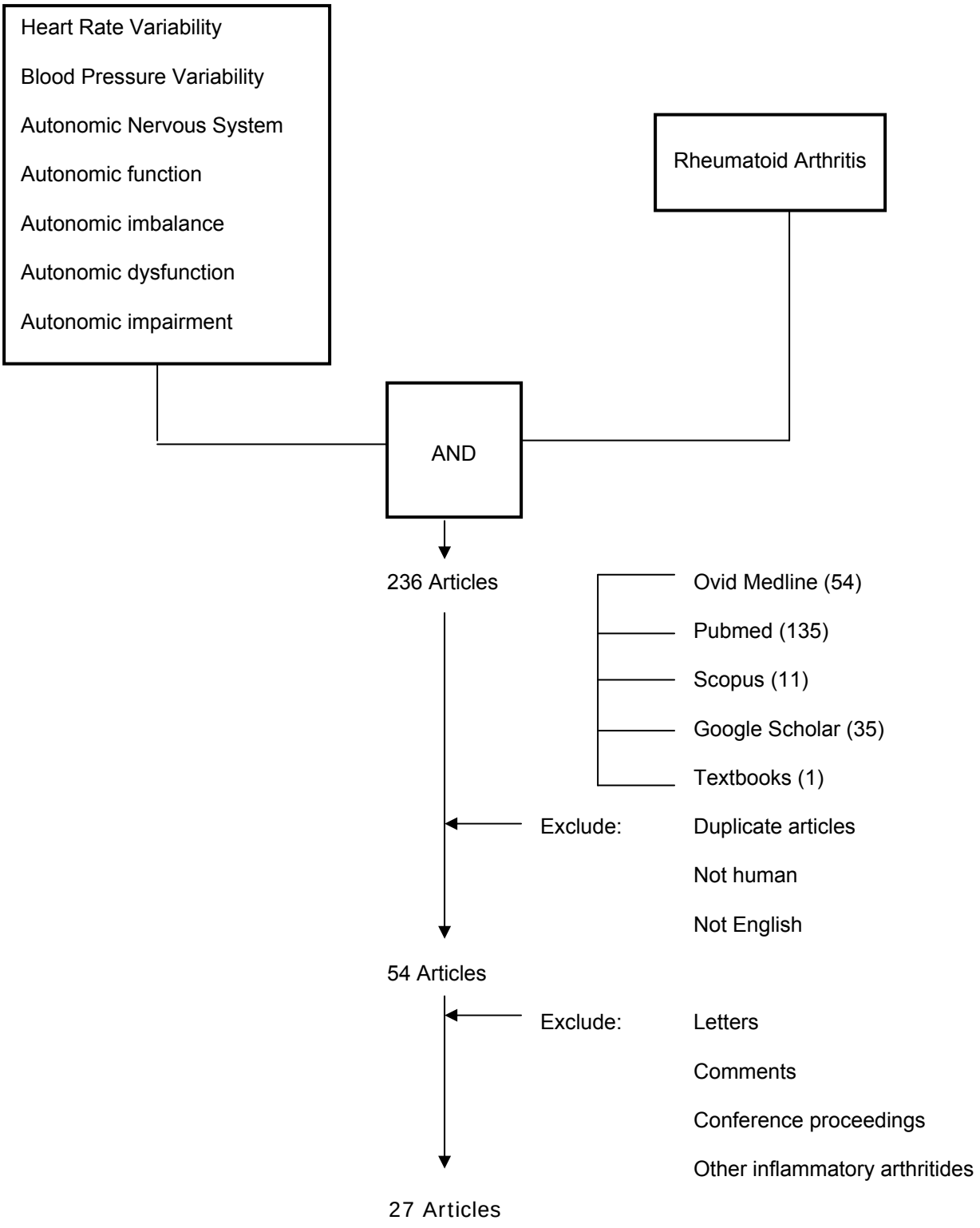

Figure 2.5: Database Search (1963-February 2011)

The 27 articles will now be discussed. The measurements utilized and background of each article is summarized in Table 2.7 which can be found at the end of the chapter.

2.3.1 SWEAT RESPONSES (SYMPATHETIC INVOLVEMENT)

In 1965 Bennett undertook a study to determine the presence, extent and location of autonomic nerve involvement in adult subjects with RA. He studied 18 RA patients with peripheral neuropathy, 8 patients with uncomplicated RA and 13 non-RA subjects. The thermo-regulatory sweating response to warm water immersion and the local sweating response to intradermal injection of acetyl choline and faradic stimulation were tested. In the Control Group (CG), areas of deficient sweating were small and symmetrical. In the uncomplicated RA group 6 of the 8 patients showed sweat responses similar to the CG, with 2 patients showing larger areas of sweat loss. In the RA group with peripheral neuropathy there was sweat loss in areas corresponding to those of cutaneous sensory impairment. It was concluded that clinical sensory neuropathy in RA is usually accompanied by an autonomic neuropathy of postganglionic type[52]. Kalliomaki et al performed axon reflex sweating tests in 100 RA patients and 100 non-RA patients with mental disorders. The number of patients reacting negatively to the test was significantly higher ($p<0.01$) in the RA group. These findings were only found in the female patients and the authors wrote that their observations suggested impaired axon reflex sweating (i.e. sympathetic involvement) in females suffering from RA[53].

2.3.2 CARDIOVASCULAR REFLEX TESTS (CRT)

Ewing described a test battery to evaluate cardiac autonomic function[54-56]. This battery tested the parasympathetic nerve function as follows:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing

and the sympathetic nerve function:

i. Blood pressure response to standing
ii. Blood pressure response to sustained handgrip.

These measurements were adopted by some authors to test for autonomic dysfunction in RA patients[57-59] while other used shorter or modified versions[60-68].

In 1979 Edmonds published his findings of autonomic neuropathy in RA. They investigated the cardiovascular reflexes, only using the tests described for parasympathetic nerve function. The conclusion was that significantly more patients with RA had abnormal autonomic function when compared to the control groups. They also felt that these abnormal cardiovascular reflexes could not be ascribed by other cardiac abnormalities found in RA patients (like pericarditis) and that autonomic neuropathy on its own might be a complicating factor leading to increased morbidity and mortality in RA[62]. Leden in 1983 assessed autonomic nerve function in RA of varying severity by means of deep breathing and an orthostatic test. Irrespective of disease severity all RA patients had increased resting heart rates. Only patients with severe RA showed significant abnormal responses to orthostatic stress, suggesting autonomic neuropathy[63].

Observing only parasymphatic nerve function, Piha could not show abnormalities in the cardiovascular reflexes of RA patients comparing 34 of them to 76 diabetes patients and 67 healthy controls. They suggested that the elevated resting heart rate in RA patients could be due to physical deconditioning and concluded that their data indicated that the parasympathetic pathway mediating cardiovascular reflexes via the vagus nerve is intact in RA[67]. Toussirot also only reported on parasympathetic involvement. A significant difference was found for Valsalva manoeuvre comparing RA patients to healthy subjects ($p<0.01$), but there was no correlation with inflammatory markers, presence of RF, disease duration or degree of joint destruction[68].

Bekkelund in 1996 compared RA subjects (n 43) to controls (n 61). They used 4 of the 5 tests described by Ewing, including:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing
iv. Blood pressure response to standing.

Cardiovascular reflexes were equal in the 2 groups, contradicting some of the other reports. They suggested that the high variability in the assessments of ANS between studies may be due to non-standardised test procedures as well as the choice of the statistical test used[60]. Maule et al in their study using CRT wanted to assess autonomic nervous function in a group of patients with Systemic Lupus Erythmathosus (SLE), RA and a matched healthy population. At the same time they assessed for the presence of circulating autoantibodies directed against sympathetic and parasympathetic nervous structures. Similar to Toussirot, they did not find any correlation between autonomic dysfunction and disease duration. They did however confirm autonomic nervous function impairment in connective tissue disease and this was significantly associated with the presence of autoantibodies to autonomic nervous structures[65]. Like Maule, Louthrenoo included SLE, RA and healthy controls, and they correlated ANS function as measured by CRT, to clinical features. 47% of the RA patients had symptoms suggesting ANS dysfunction. They confirmed Maule and Toussirot's findings that there was no correlation between ANS dysfunction and disease duration, or raised ESR[64].

Sandhu used 5 tests as described by Ewing to investigate autonomic cardiovascular reflexes in RA patients with reference to age, presence of RF and disease duration. The RA group comprised of 62 and the healthy CG of 41 subjects. Compared to the CG the RA group had significantly lower values for the following:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing
iv. Blood pressure response to sustained handgrip.

When age was taken into account the group <60 years of age showed significant differences for the same measurements as for the whole group compared to the CG. The group >60 years of age showed a significant difference only for the blood pressure response to sustained handgrip. Contrary to previous authors' findings, Sandhu reported a positive correlation for ANS impairment and presence of RF as well as disease duration[57]. A further study was performed by Stojanovich, who evaluated cardiovascular ANS function in patients with SLE, RA, Sjögren syndrome, scleroderma

and Polymyalgia Rheumatica (PMR). They correlated the ANS function to clinical features. They reported that in all tests higher percentages of the different patient groups demonstrated abnormal results compared to the controls ($p < 0.05$). No correlation was found between ANS dysfunction and disease duration, clinical manifestations or disease activity[58].

Bidikar investigated sympathetic nervous system involvement in RA. 50 RA patients were compared to 50 healthy controls. Compared to the controls the RA patients had a significant higher resting HR and blood pressure (BP). Significant differences were also shown for the sympathetic autonomic function tests between the two groups[61].

2.3.3 FOUR TASKS INDICATING AUTONOMIC FUNCTION

Geenen et al investigated the responsiveness of the ANS in RA of recent onset. The two groups (RA 21; CG 20) were subjected to 4 tasks presented in a fixed order: film watching and mild physical exercise to assess the parasympathetic system; and cognitive discrimination and the Stroop test for sympathetic activation. The patients showed normal responses to film watching and mild physical exercise, but diminished responses to cognitive discrimination and the Stroop test. According to them this implies normal parasympathetic activity but diminished sympathetic activity. They concluded that already in early disease there is evidence for diminished autonomic responsiveness, while baseline ANS levels may only deteriorate in the course of the disease. Their patients (recent onset disease) had normal resting heart rate, but they commented on the hypothesis of Piha that elevated heart rate levels might be due to physical deconditioning and that this may be a reversible phenomenon that can be rectified by exercise[69].

2.3.4 PRE-EJECTION PERIOD AND RESPIRATORY SINUS ARRHYTHMIA

In 2004 Dekkers published results on autonomic nervous system involvement in recent onset RA. Subjects with RA (n 25) were compared to healthy controls (n 28). The pre-ejection period (reflecting sympathetic nerve activity) and respiratory sinus arrhythmia (reflecting para-sympathetic nerve activity) were measured. The findings were in agreement with those of Geenen with abnormal sympathetic nervous system activity but normal parasympathetic nervous system activity in RA of recent onset. They did comment however that the environment was not standardized and this could have influenced the sympathetic nervous system activity[70].

2.3.5 SYMPATHETIC SKIN RESPONSE AND RR-INTERVAL VARIATION

In 1993 Tan decided to investigate autonomic function in RA patients with methods previously described by Shahani[71,72]. Sympathetic skin response (SSR) is an indicator of sympathetic nervous system function and RR-interval variation (RRIV) tests vagal function. Both tests were normal in the healthy CG (n=30). The RA group (n=30) had abnormal SSR's in 6 patients and abnormal RRIV's in 8 patients. Only 5 patients had complaints of clinical dysautonomia, leading to their conclusion that ANS dysfunction is frequent in RA patients even in the absence of clinical dysautonomia[73]. Gozke took this a step further and examined RA patients without clinical dysautonomia. Using the same methods as Tan et al they could not prove sympathetic involvement, but in 50% of RA cases the RRIV values were decreased [74].

2.3.6 PUPILLOGRAPHY

By using an infrared light reflection method, one can measure both parasympathetic function (constriction latency and latency of maximum constriction velocity) and sympathetic function (dilatation latency). Barendregt used this method to study autonomic dysfunction in 18 RA patients with ocular dryness, 18 RA patients without ocular dryness and 33 healthy controls. Constriction latency and maximum constriction velocity latency were prolonged in RA patients with ocular dryness compared to the other two groups ($p < 0.05$). Dilation latency did not differ between the three groups, neither was any correlation found between pupillography and age, disease duration or DAS score[75]. Schwemmer et al used a combination of pupillography and cardiovascular reflex tests to assess the prevalence and the characteristics of autonomic dysfunction in RA. This was followed by a longitudinal study to investigate if disturbed autonomic function is linked to higher mortality. Autonomic dysfunction was demonstrated in 60% of patients, with the prevalence for pupillary autonomic dysfunction (PAD) 15 out of 30 (50%) and for cardiac autonomic dysfunction (CAD) 6 out of 30 (20%). During the longitudinal study (8 years observation), 4 out of 30 patients died. The non-survivors did not differ at baseline with regards to age, gender, disease duration, swollen joint count, tender joint count, Visual Analogue Scale (VAS) for pain, Physician's Global Assessment, or medicine from survivors. Both CAD and PAD were

more frequent in non-survivors, perhaps indicating that autonomic dysfunction might be linked to higher mortality [76].

2.3.7 HRV

HRV has previously been shown to be a practical, reproducible and non-invasive method to detect early ANS impairment. Already in 1965 quantitative markers for autonomic homeostasis by HRV were recognized as a meaningful measurement. Since then it has been used to determine ANS dysfunction in fetal distress, diabetic autonomic neuropathy and RA[77].

Rhythmic contributions from sympathetic and parasympathetic activity modulate the heart rate and it modulates the RR-intervals between the QRS complexes on an electrocardiograph (ECG). Sympathetic activity shortens the RR-interval (tachycardia response) while parasympathetic activity lengthens the RR-interval (bradycardia response)[77]. Low variability implies poor or inhibited ability to maintain internal homeostasis. Commonly used methods to evaluate HRV are time domain analysis, frequency domain analysis and non-linear Poincare analysis. A detailed description of each of these measurements will follow in the chapter on Methodology.

Evrengul was one of the first authors applying this method to assess the autonomic function in patients with RA. They used time domain and frequency domain analysis in 42 RA patients and 44 healthy subjects. Recordings were obtained over an hour. Results conflicted between time and frequency domain parameters, but they defended this by pointing out that frequency domain analysis are more precise than time domain analysis by referring to work done by Fei in1996 and Howorka in 1998[78,79]. They concluded that their data suggested “an increase in sympathetic control of the heart rate in patients with RA”. No correlation between HRV parameters and stage of RA, disease duration or ESR was found[80]. Anichkov followed suit and investigated HRV parameters in RA patients, however recordings were obtained over 24 hours. Compared with controls, all time domain and Poincare parameters were significantly lower in RA patients. Contrary to most other studies already discussed they found a positive correlation between autonomic dysfunction and disease activity[81].

$HMGB_1$ is a pro-inflammatory cytokine and increased expression in synovium of RA patients has been shown. The cholinergic anti-inflammatory reflex (vagus nerve dependent) inhibits the release of $HMGB_1$ in experimental disease models[82]. Goldstein

et al did a study in RA patients where the results indicated that elevated levels of $HMGB_1$ correlated with depressed levels of vagus nerve activity as measured by time domain and frequency domain analysis[47]. The same group in another study on RA patients hypothesized that cytokine release can be suppressed by adding cholinergic agonists to whole blood cultures stimulated with endotoxin, even if vagus nerve activity is significantly reduced. Although their results showed reduced vagus nerve activity in the RA group compared to the healthy group, there was a significant age difference ($p<0.05$) with the RA group being older than the CG. This might have affected the result favouring the RA group, but previous authors[57,81] did not find age in RA patients to be a confounding factor. In the second phase of the study they proved their hypothesis to be correct[83].

Aydemir published a study on the cardiac autonomic profile of RA and SLE patients. They utilized both cardiac reflex tests and heart rate variability parameters. The groups consisted of 36 RA, 38 SLE and 40 Control subjects. The results showed that autonomic dysfunction is common in patients compared to controls, with RA patients having abnormal results in 61-75% of cases. There was a significant association between the different methods utilised. They found no relation between autonomic dysfunction and autoantibody positivity, disease duration or disease activity, supporting other authors' findings [58,59,64,65,68,75,80]. Another author that made use of a combination of methods to assess ANS dysfunction in RA and SLE patients, is Milovanovic. They aimed to evaluate the presence and level of ANS dysfunction as well as to identify cardiovascular risk factors associated with sudden cardiac death. In all measurements abnormal findings were significantly higher in the patient groups, but prolonged QT's interval was only significant in SLE patients. Although both diseases were associated with depressed HRV, in the RA group vagal predominance was evident while in the SLE group it was mostly higher sympathetic activity. They pointed out that there are still great discrepancies regarding published data on autonomic nervous system function in immunologic disorders with findings ranging from normal to grossly abnormal[66].

Vlcek in a small study (8 RA and 8 Control subjects) aimed to assess symphatoneural and adrenomedullary reactivity to changes in body position. Blood samples for epinephrine, norepinephrine (NE) and a sympathetic co-transmitter Neuropeptide Y

(NPY) were drawn during the course of HRV measurements. Levels for epinephrine were lower at baseline (p 0.053) and to orthostatic response (p 0.079), while NE levels were higher at baseline (p 0.034) but with no difference to orthostatic response comparing the RA group with the controls. No difference was shown for NPY or HRV parameters between the two groups. The authors concluded that their study "showed increased basal sympathetic activity and a tendency toward smaller adrenomedullary response to orthostasis in RA patients"[84].

Holman conducted a study to predict anti-tumor necrosis factor treatment response by assessing the autonomic status of RA and psoriatic arthritis patients. Although the results suggested that autonomic status may influence outcome there are a few problems identified in this study:

i. Can response to treatment be compared between different diseases (i.e. pathogenesis differ)?
ii. HRV was measured by an assessment tool (Omegawave) not previously validated in pathological conditions[85].

2.3.8 HEART RATE TURBULENCE (HRT)

According to Avsar HRT has been considered to reflect cardiac autonomic activity. HRT is measured in two phases, namely:

i. Turbulence onset (TO) is a measure of the initial acceleration after a premature ventricular complex due to vagal inhibition.
ii. Turbulence slope (TS) measures the rate of sinus deceleration that follows sinus acceleration with both parasympathetic and sympathetic contribution.

The response of the sinus node to premature ventricular complexes is reflected by HRT, while HRV describes variations in both RR-intervals and instantaneous heart rate. In this study of 26 RA patients and 26 healthy controls TO and TS did not show significant differences between the two study groups[86].

2.3.9 SUMMARY OF LITERATURE ON AUTONOMIC DYSFUNCTION IN RA

In the 27 studies reviewed there were a total of 1232 subjects (males and females) in the patient group and 918 (males and females) in the control group. The mean age for the patient group was 51.8 years and for the control group 44.25 years. Although all studies aimed to assess autonomic dysfunction in patients with RA, different methods were utilized, including:

- Sweat response[52,53]
- Cardiovascular Reflex Tests[57-68]
- Divergent autonomic reactions to specific tasks[69]
- Pre-ejection period and respiratory sinus arrhythmia[70]
- Sympathetic skin response and RR-interval variation[73,74]
- Pupillography[75,76]
- Heart Rate Variability[47,59,66,80,81,83-85]
- Heart Rate Turbulance[86]

Autonomic dysfunction was reported by most authors, with only Piha, Bekkelund and Avsar reporting no difference between patients and healthy controls, and Vlcek observing only a trend (not statistically significant) of increased basal sympathetic activity. Authors concomitantly assessing disease activity, disease duration and presence of RF mostly agreed that these do not correlate with ANS dysfunction[58,59,64,65,68,75,80]. Sandhu and Anichkov reported a positive correlation[57,81].

Unfortunately due to different measurements used, one cannot compare one study to the next. Other problems identified include:

- All studies did not comment on exclusion criteria (i.e. co-morbid diseases like diabetes[56,87] and hypertension[88,89] as well as medications used e.g. anti-arrhythmics and β-blockers will influence autonomic function). Stojanovic even included patients with HT and DM.
- Environment was not stabilized in all studies[70].
- Male and female subjects were used in the same study. Previous studies showed differences in HRV between males and females[90-92].

- Different statistical methods were used, even for the same measurement e.g. heart rate variability.
- Large age differences between patients and controls, with the patients being older could have skewed data in favour of the patient group[93,94].

Measures of autonomic function as prognostic factor for treatment response to biologic drugs was only reported on by Holman, and Anichkov commented that prednisolone use did not affect their results. No substantial evidence could be found in the reviewed articles on possible impairment of ANS function due to use of disease modifying drugs. Furthermore, exercise intervention studies have shown positive changes in increased cardiovascular functioning as measured by HRV[95-97]. No such data could be found for RA patients, and Metsios et al in their published review in 2008 concluded that "surprisingly little has been investigated and published on the role of exercise as a means to control risk and manage CV disease in individuals with RA"[98].

2.4 ROLE OF EXERCISE

RA patients are usually sedentary, with patients tending to limit physical activity due to the perceived danger of eliciting pain or damaging their joints[99,100]. Although there is still no cure for RA, much can be done to manage the condition. High-grade systemic inflammation and its vascular and metabolic effects have received much attention. Despite compelling evidence that exercise can play a significant role in the physical and psychosocial health of the general population there were no studies found investigating exercise interventions in relation to CV disease in RA[98].

Metsios mentions that exercise has been identified as one of the most important behavioural strategies for CV disease prevention and that sedentary individuals (like RA sufferers) will benefit by just a slight increase in physical activity[98,101,102]. Up to now the main focus of exercise therapy has been to improve physical capacity and functional ability[99].

Studies on exercise intervention in RA patients used resistance training[99,103-111], or aerobic training[112-125], or a combination of strength and aerobic training[126-134]. Unfortunately training regimes, methodology and outcomes differ widely, making conclusions difficult[135]. In a review done by Hurkmans et al, published in the Cochrane Library, they only included 8 studies because methodological criteria differed so much[135].

Strength training on its own seems to have a positive effect on functional ability[136-138] and muscular strength[139]. Cycling, followed by aquatics, aerobic dancing and walking/running are most frequently used as the mode of exercise in aerobic training for RA patients[98]. Although weight-bearing (and therefore possible joint damage) is minimized due to buoyancy[113], Hurkmans et al in their review found that water-based training only showed limited evidence for a positive effect on aerobic capacity and muscle strength contrary to land-based exercise which showed moderate evidence[135].

No Randomised Control Trials (RCT) based on walking as the main focus have been conducted[98], while studies focusing on aquatics suggest improvement of aerobic

capacity[119,140,141], muscle strength[106,120] and psychological status[119]. Studies on combination training showed positive influence on both cardiorespiratory fitness and muscle strength[126,142].

Previous studies in non-RA groups demonstrated that endurance exercise will improve HRV (i.e. cardiac health)[143-149] while strength training can have the opposite effect[150]. Similar studies have not been done in the RA population.

Buccheit et al have shown that, in middle-aged subjects, moderate endurance exercise is associated with greater vagal tone while high intensity exercise is not[151]. This fact will be used in our study population because due to sore joints and stiffness, patients will comply better with moderate rather than high intensity exercise. Patients with late stage rheumatic disease and many joint deformities will not comply with an intense exercise programme. Therefore the study population for this study will be limited to class 1 and 2 disease according to the Classification of Global Functional Status of RA[152]. This classification can be viewed in Table 2.6.

Table 2.6: **Classification of global functional status in rheumatoid arthritis**

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities
Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Acovational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.	

Reprinted from Arthritis Rheum, 1992 May:35(5):498-502. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Copyright notice 2011. With permission from John Wiley and Sons

Iversen has shown that rehabilitation started early in disease is more effective[153], and Geenen et al have shown diminished ANS responsiveness in patients with early RA disease[69]. These facts further strengthen the motivation to recruit patients with early disease (class 1 and 2 patients).

Stenstrom and Minor investigated the evidence for the benefit of aerobic and strengthening exercise in RA. They drew recommendations for exercise intervention from this evidence based approach. For aerobic exercise they concluded that in the light of the reviewed studies, the intensity level should be moderate to hard (60-85% of heart rate maximum) performed 3 times weekly for a duration of 30-60 minutes. Exercise can be land- or water based and progressive adjustment of the intensity was recommended. For resistance training they concluded that the load level of strengthening exercises should be moderate to hard (50-80% of a maximal voluntary contraction) and performed 2-3 times per week. Exercises can be static or dynamic and performed with various types of equipment or against body weight. A progressive adjustment of load was recommended[100].

A further suggestion made by them was that it is important to start documenting exercise response in terms of the individual's characteristics, as response criteria have been published for drug trials but those are not specifically applicable to exercise studies[100].

2.5 ASSESSMENT OF DISEASE ACTIVITY

As rightly stated by Stenstrom there are no specific response criteria to measure outcome following exercise intervention in patients with RA[100]. The major target of therapeutic interventions is reduction of disease activity, but for the patient the most relevant outcome is functional capacity. Current measurements have been developed and validated for the purpose of facilitating clinical trial reporting, but Aletaha and Smolen mention that it is reasonable to use these same measurements for clinical practice[154].

International bodies introduced the term “core set” comprising of tender and swollen joint counts, global assessments by the patient and the assessor (mostly the physician), pain assessment by the patient, acute-phase response and a functional element[154].

For the purpose of this study, it was decided to make use of the following previously validated measurements, in order to address all elements of the core set:

- DAS_{28}[155-157].
- Visual analogue scale (VAS)[158-160].
- Health assessment questionnaire (HAQ)[161,162].

All of the above will be discussed in detail in the chapter on Methodology.

2.6 CONCLUSION

The literature review has shown:

- There are extra-articular manifestations associated with increased mortality in patients with RA
- Patients with RA have cardiac involvement, and the autonomic nervous system (ANS) may play a role
- ANS dysfunction has been proven in patients with RA, but different measurements were used and there are still uncertainties left

- Exercise can improve ANS dysfunction in the general population, in cardiac patients with hypertension and ischemic heart disease as well as in patients with diabetes mellitus
- No previous exercise studies have been done in an RA population to measure the effect, if any, on autonomic function.

Table 2.7: Studies on autonomic nervous system function in rheumatoid arthritis patients

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Film watching (P) Mild physical exercise (P) Cognitive discrimination (S) Stroop interference test (S)	Geenen (1996)	Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset	<1yr	21	20	EG 17 CG 16	4 4	55.7 (±16.5)	52.7 (±11.8)	Excluded - not specified	Responsiveness of ANS in RA of recent onset
Pre-ejection period (S) Respiratory Sinus Arrythmia (P)	Dekkers (2004)	Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease	<2 yr	25	28	EG 19 CG 20	6 8	55.2 (±13.0)	55.8 (±11.3)	Excluded - not specified	1. Assess ANS activity 2. Association with - disease activity - symptoms of RA
Sympathetic skin response (S) RR-Interval variation (P)	Gozke (2003)	Sympathetic skin response and R-R interval variation in cases with rheumatoid arthritis	Not mentioned	10	14	EG 10 CG 14	0	48.7 (±11.6)	44.6 (±10.6)	Clinical dysautonomia excluded	Assess ANS involvement

ANS	Autonomic nervous system	P	Parasympathetic
CG	Control Group	RA	Rheumatoid arthritis
EG	Experimental Group	S	Sympathetic

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Sympathetic skin response (S) RR-Interval variation (P)	Tan (1993)	Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function	90.2 months (7.5 yr)	30	30	EG 27 CG 26	3 4	51.3	50.4	Dysautonomia not excluded in EG. Neurological disease excluded inCG.	Assess ANS neuropathy in presence or absence of clinical dysautonomia
Pupillography CL (P) MCV (P) DL (S)	Barendregt (1966)	Parasympathetic dysfunction in rheumatoid arthritis patients with ocular dryness	EG1 22yr EG2 10 yr	EG1 18 (Dryness of eyes or mouth) EG2 18 (No dryness of eyes or mouth)	33	EG1 18 EG2 18 CG 33	0	EG1 62 EG2 55	57	Excluded: Neurological disease Amyloidosis, Renal failure DM Other diseases known to interfere with ANS Drugs interfering with ANS	Is abnormal ANS function associated with oral and ocular dryness?
Pupillography (P and S) Cardiovascular reflex tests (P)	Schwemmer (2006)	Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis - a cross-sectional and longitudinal study	EG1 6.7 yr EG2 6.4 yr EG3 8.6 yr	EG1 30 (All patients) EG2 26 (Survivors) EG3 4 (non-survivors)	0	EG1 17 EG2 16 EG3 1	13 10 3	EG1 52.2 (±1.9) EG2 51.6 (±2.1) EG3 56.5 (±2.2)	Not used	Excluded: CVD, Peripheralneuropathy Other diseases or drugs	1. Assess ANS dysfunction in RA patients. 2. Interview 8.3 years lateron mortality.

ANS	Autonomic nervous system	DL	Dilation latency	P	Parasympathetic
CG	Control Group	DM	Diabetes mellitus	RA	Rheumatoid arthritis
CL	Constriction latency	EG	Experimental Group	S	Sympathetic
CVD	Cardiovascular disease	MCV	Maximum constriction velocity		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Sweat response (S)	Bennett (1965)	Autonomic neuropathy in rheumatoid arthritis	Not mentioned	EG1 18 (RA neuro-pathy) EG2 8 (No RA-neuropathy)	13	EG1 10 EG2 7 CG 5	8 1 8			Neuropathy included	Determine ANS involvement in RA
Sweat response (S)	Kalliomaki (1963)	Axon reflex sweating in rheumatoid arthritis	Not mentioned	100	100	EG 70 CG 44	30 56	47.9	51.1	CG No somatic disease Psychiatric hospital patients	1) ANS involvement 2) Correlation with clinical signs of RA
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic S - Orthostatic Handgrip	Sandhu (2004)	The effects of age, seropositivity and disease duration on autonomic cardiovascular reflexes in patients with rheumatoid arthritis	Not mentioned	62	41	EG 39 CG 21	23 20	RA 63	50	Excluded: DM CVD Co-pathology likely to interfere with ANS Drugs likely to interfere with ANS	To investigate ANS in RA with reference to - age group - disease duration - disease activity - RF status
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic	Piha (1993)	Elevated resting heart rate in rheumatoid arthritis: possible role of physical deconditioning	15 (±9)	RA 34 DM 76	69	RA 34 DM 76 CG 69	0	RA 49 DM 43	43	Excluded: ANS conditions CVD	Assess ANS function i RA by comparing then to DM andControls

ANS	Autonomic nervous system	EG	Experimental Group	S	Sympathetic
CG	Control Group	P	Parasympathetic		
CVD	Cardiovascular disease	RA	Rheumatoid arthritis		
DM	Diabetes mellitus	RF	Rheumatoid factor		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic S - Orthostatic	Maule (1997)	Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures	9.3 (± 7.9)	RA 17 SLE 17	25	RA 17 SLE 17 CG 25	0	37 (±13.5)	31.9 (±11.2)	Excluded: DM Obesity Renal failure Chronic liver disease Arrhythmia Anaemia Anti-hypertensive treatment	1) Assess ANS functi in RA and SLE 2) Assess presence of Compliment fixing antibodies
Cardiovascular reflex tests P - Orthostatic Valsalva Deep breathing	Edmonds (1979)	Autonomic neuropathy in rheumatoid arthritis	Not mentioned	RA 27 OA 13	Old 13 Young 15			RA 54.6 OA 54.2	Old 51 Young 24.6	Exclude: Drugs influencing cardiovascular rhythm HT Anaemia Cardiac failure	Assessing integrity of ANS
Cardiovascular reflex tests (Tilt table) P - Deep breathing Orthostatic S - Orthostatic	Leden (1983)	Autonomic nerve function in rheumatoid arthritis of varying severity	20	17	24	EG 12 CG 8	5 16	56	53	Exclude: CVD Pulmonary disease Renal Disease	1) Assess ANS 2) Correlate ANS function with severity RA

ANS	Autonomic nervous system	EG	Experimental Group	RA	Rheumatoid arthritis
CG	Control Group	HT	Hypertension	S	Sympathetic
CVD	Cardiovascular disease	OA	Osteo-arthritis	SLE	Systemic lupus erythemathosus
DM	Diabetes mellitus	P	Parasympathetic		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Deep breathing Valsalva Orthostatic S - Orthostatic	Bekkelund (1996)	Autonomic nervous system function in rheumatoid arthritis. A controlled study.	13.6 (± 7.4)	43	61	EG 43 CG 61	0	44.4 (±8)	42.1 (±9.3)	Excluded: Somatic disease Psychiatric disease CTD Primary neurological disease Alcoholism Drugs interfering with ANS	1) Assess ANS 2) Pancreatic polypeptide (PP) association with abnormal ANS and disease activity
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic	Toussirot (1993)	Autonomic nervous system involvement in rheumatoid arthritis	6	50	82	EG 31 CG 49	19 33	55.6	47.2	Excluded: Dysautonomia Drugs interfering with ANS Anaemia Renal Disease DM Porphyria Parkinsons Polyneuropathy MS HIV infection Breathing failure Sympatectomy	Frequency of ANS dysfunction
Cardiovascular reflex test S - Orthostatic Handgrip Cold Press	Bidikar (2010)	Autonomic (sympathetic) nervous system involvement in rheumatoid arthritis patients	Not mentioned	50	50	Not mentioned	Not mentioned	20-60	20-60	History of dysauto-nomia. Treatment interfering with ANS.	To examine the frequency of sympathetic dysfunc in RA patients

ANS	Autonomic nervous system	DM	Diabetes mellitus	MS	Multiple sclerosis
CG	Control Group	EG	Experimental Group	P	Parasympathetic
CTD	Cardiac thoracic disease	HIV	Human immunodeficiency virus	S	Sympathetic

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascularreflex tests P - Orthostatic Valsalva Deep Breathing Insp : Exp S - Orthostatic Handgrip HRV Frequency domain	Aydemir (2010)	Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus	RA 11.2 (±10) SLE 6.9 (± 5)	RA 36 SLE 38	40	RA 30 SLE 32 CG 31	RA 6 SLE 6 CG 9	RA 48.7 (±12.5) SLE 38.4 (±11.3)	HCG 42.5 (±12.5)	Excluded: Pregnancy DM Uraemia Hepatic failure Porphyria Amyloidosis Alcoholism Ishchemic Heart Disease Cardiomyopathy Arrhythmia Cardiovascular incident Parkinson's Disease Multiple sclerosis Drugs interfering with blood pressure and heart rate Fibromyalgia Vasculitis Secondary Sjögrens	To define the frequenc and spectrum of ANS dysfunction in patients with RA
Cardiovascular reflex tests P - Deep breathing Orthostatic S - Orthostatic Handgrip	Louthrenoo (1999)	Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus	5.1	RA 34 SLE 37	62	RA 30 SLE 34 CG 50	4 3 12	RA 47.2 (±10.5) SLE 30.4 (±8.1)	47 (±10.6) 30.3 (±7.9)	Excluded: Hb<10 Pregnancy DM Renal disease Liver disease Parkinsons Amyloidosis CVD Neurological disease Drugs interfering with ANS	1) To evaluate cardiovascular ANS function in RA and SL 2) To correlate ANS function with clinical features

ANS	Autonomic nervous system	HCG	Healthy Control Group	S	Sympathetic
CG	Control Group	HRV	Heart rate variability	SLE	Systemic lupus erythemathesus
CVD	Cardiovascular disease	P	Parasympathetic	SSc	Systemic sclerosis
DM	Diabetes mellitus	RA	Rheumatoid arthritis		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic S - Orthostatic Handgrip	Stojanovich (2007)	Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases	9.5 (± 5.2)	RA 39 SLE 54 Sjö 20 PMR 8 SSc 4	35	RA 33 SLE 49 Sjö 19 PMR 6 SSc 3 CG 19	6 5 1 2 1 16	RA 58.1 (±12.2) SLE 46.3 (±12.50) Sjö 52.2 (± 12.4) PMR 68 (± 9.9) SSc 60 (±4.5)	52.3	Excluded: Pregnancy Renal insufficiency Liver Insufficiency Cardiac insufficiency Respiratory insufficiency Arrhythmia Acute thrombosis	1) Evaluate ANS function in RA/SLE/PMR/SSc/Sjö 2) Correlate ANS function with clinical features
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic S - Orthostatic HRV - Time domain - Frequency domain - Poincare analysis	Milovanovic (2010)	Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk	Not mentioned	SLE 52 RA 38	41	SLE 46 RA 32 CG 17	6 6 23	SLE 43.3 (±22.8) RA 56.3 (±13.1)	HCG 37.4 (±14.6)	Excluded: Pregnancy Renal insufficiency Liver Insufficiency Cardiac insufficiency Respiratory insufficiency Arrhythmia Acute thrombosis	To evaluate the presence and level of ANS dysfunction in patients with SLE and RA and to identify cardiovascular risk factors associated with sudden cardiac death
HRV - Frequency domain	Vlcek (2008)	Sympathetic nervous system response to orthostatic stress in female patients with rheumatoid arthritis	7.5 (± 0.9)	8	8	RA 8 CG 8	0	30.5 (±2)	30.5 (±1.4)	Not mentioned	To evaluate autonomic activity in RA patients, namely sympathoneur and adreno-medullary reactivity in changes to body position

ANS	Autonomic nervous system	P	Parasympathetic	Sjö	Sjögrens
CG	Control Group	PMR	Polymyalgia rheumatica	SLE	Systemic lupus erythemathosus
HCG	Healthy Control Group	RA	Rheumatoid arthritis	SSc	Systemic sclerosis
HRV	Heart rate variability	S	Sympathetic		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
HRV - Frequency domain	Holman (2008)	Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis	7.6 (± 6.4)	RA 25 PsA 8		26	7	48 (±13.9)		Not mentioned	To consider autonomic status as a predictor o anti-tumour necrosis factor treatment response for inflammatory arthritis
HRV (24hr) - Time domain - Poincare	Anichkov (2007)	Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients	4	23	23	EG 23 CG 23	0 0	48 (±7)	47 (±7)	Excluded: HT DM Angina Pectoris Previous MI Previous stroke Congestive heart failure Peripheral neuropathy Drugs for CVD	1) Assess ANS involvement 2) Relationship with disease related characteristics
HRV - Frequency domain - rMSSD	Goldstein (2007)	Cholinergic anti-inflammatory pathway activity and high mobility group box-1 (HMGB1) serum levels in patients with rheumatoid arthritis	13 yr	RA 13	HCG 11	RA 9 HCG 6	4 5	52	38	Smoking	To consider whether decreased activity in th cholinergic anti-inflammatory pathway occur in patients with
HRV - Frequency domain - Time domain	Bruchfeld (2010)	Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis	13.2 yr	RA 13	HCG 10	RA 9 HCG 5	4 5	52	32	Not mentioned	Hypothesize that the addition of cholinergic agonists to whole bloo cultures stimulated wit endotoxin can attenua cytokine release, even RA patients with significantly reduced vagus nerve activity

ANS	Autonomic nervous system	DM	Diabetes mellitus	HRV	Heart rate variability	RA	Rheumatoid arthritis
CG	Control Group	EG	Experimental Group	HT	Hypertension	rMSSD	Root of the average squares of differences between neighbouring NN intervals
CVD	Cardiovascular disease	HCG	Healthy Control Group	PsA	Psoriatic arthritis		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
HRV (1hr) - Time domain - Frequency domain	Evrengul (2004)	Heart rate variability in patients with rheumatoid arthritis	6.5	42	44	EG 31 CG 31	11 13	48 (±10.4)	45 (±8.4)	Excluded: ANS dysfunction Previous MI HT DM Pulmonary disease Drugs interfering with ANS	Assess ANS involvement
HRT	Avsar (2010)	Cardiac autonomic function in patients with rheumatoid arthritis: heart rate turbulence analysis	Not mentioned	RA 26	HCG 26	Not mentioned		56 (±10)	55 (±9)	Excluded: Angina Pectoris MI Heart failure HT DM Valvular heart disease Non-sinus rhythm Hyper thyroidism Left ventricular hypertophy Electrolyte disturbances Chronic renal failure Hepatic failure Smokers Cardio-active drug use	To determine if HRT changes in patients with RA in comparison with healthy controls
			TOTALS:	1232	918			51.79	44.28		

ANS	Autonomic nervous system	HCG	Healthy Control Group	HT	Hypertension
CG	Control Group	HRT	Heart rate turbulence	MI	Myocardial infarction
DM	Diabetes mellitus	HRV	Heart rate variability	RA	Rheumatoid arthritis
EG	Experimental Group				

BIBLIOGRAPHY

1. Firestein GS. Etiology and pathogenesis of rheumatoid arthrits. In: Firestein GS, Kelley WN. Kelley's textbook of rheumatology. 8th ed. Philadelphia: Saunders/Elsevier; 2009. p.1035-1086

2. Firestein GS, Zvaifler NJ. How important are T cells in chronic rheumatoid synovitis?: II. T cell-independent mechanisms from beginning to end. Arthritis Rheum. 2002 Feb;46(2):298-308.

3. Rheumatoid Arthritis Available at: http://emedicine.medscape.com/article/331715-overview#showall.

4. Lang TJ. Estrogen as an immunomodulator. Clin.Immunol. 2004 Dec;113(3):224-230.

5. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, Kloppenburg M, de Vries RR, le Cessie S, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. Ann.Rheum.Dis. 2006 Mar;65(3):366-371.

6. Van Venrooij WJ, Pruijn GJM. Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. Arthritis Res 2000 May;(2):249-251

7. Harris ED. Rheumatoid arthritis. Philadelphia: Saunders; 1997. p 41-48

8. Kalla AA, Tikly M. Rheumatoid arthrtitis in the developing world. Best Pract Res Clin Rheumatol 2003 17(5):863-875.

9. Mody GM, Meyers OL.Rheumatoid arthrtis in Blacks in South Africa. Ann Rheum Dis1989;48:69-72

10. Hochberg MC, Silman AJ, Smolen JS. Rheumatology. 4th ed. : Elsevier; 2008.

11. Jeffery RC. Clinical features of rheumatoid arthritis. Medicine 2010 4;38(4):167-171.

12. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality. Am.J.Epidemiol. 1980 Jan;111(1):87-98.

13. Fleming A, Benn RT, Corbett M, Wood PH. Early rheumatoid disease. II. Patterns of joint involvement. Ann.Rheum.Dis. 1976 Aug;35(4):361-364.

14. Harris ED, Firestein GS. Clinical features of rheumatoid arthritis. In: Firestein GS, Kelley WN. Kelley's textbook of rheumatology. 8th ed. Philadelphia: Saunders/Elsevier; 2009. p.1087-1118

15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-324.

16. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria. Arthritis Rheum 2010 Sep;62(9):2569-2581

17. O'Dell JR. Rheumatoid Arthritis: The Clinical picture. In: Koopman WJ, Moreland LW, editors. Arthritis and Allied Conditions: Textbook of Rheumatology. 15th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 1165-1194.

18. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J.Rheumatol. 2002 Jan;29(1):62-67.

19. Hicks JE. Rehabilitation strategies for patients with rheumatoid arthritis. J Musculoskel Med 2000 Apr;17(4):991-204.

20. Haugeberg G, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. Arthritis Rheum. 2002 Jul;46(7):1720-1728.

21. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin.Arthritis Rheum. 2006 Dec;36(3):182-188.

22. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009 Oct;48(10):1309-1313.

23. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008 Dec 15;59(12):1690-1697.

24. Nurmohamed MT. Cardiovascular risk in rheumatoid arthritis. Autoimmun.Rev. 2009 Jul;8(8):663-667.

25. John H, Kitas G, Toms T, Goodson N. Cardiovascular co-morbidity in early rheumatoid arthritis. Best Pract.Res.Clin.Rheumatol. 2009 Feb;23(1):71-82.

26. Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. Circ.J. 2009 Jun;73(6):977-985.

27. Gabriel SE. Heart disease and rheumatoid arthritis: understanding the risks. Ann.Rheum.Dis. 2010 Jan;69 Suppl 1:i61-64.

28. Myasoedova E, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: a step forward. Curr.Opin.Rheumatol. 2010 May;22(3):342-347.

29. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann.Rheum.Dis. 2011 Jan;70(1):8-14.

30. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005 Feb;52(2):402-411.

31. Ross R. Atherosclerosis is an inflammatory disease. Am.Heart J. 1999 Nov;138(5 Pt 2):S419-20.

32. Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am.J.Cardiol. 2008 Sep 15;102(6):755-760.

33. Rho YH, Chung CP, Oeser A, Solus J, Asanuma Y, Sokka T, et al. Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1580-1585.

34. Liang KP, Kremers HM, Crowson CS, Snyder MR, Therneau TM, Roger VL, et al. Autoantibodies and the risk of cardiovascular events. J.Rheumatol. 2009 Nov;36(11):2462-2469.

35. Provan SA, Angel K, Odegard S, Mowinckel P, Atar D, Kvien TK. The association between disease activity and NT-proBNP in 238 patients with rheumatoid arthritis: a 10-year longitudinal study. Arthritis Res.Ther. 2008;10(3):R70.

36. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Jacobsen SJ, Roger VL, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. Ann.Rheum.Dis. 2007 Jan;66(1):76-80.

37. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum. 2008 Feb;58(2):359-369.

38. Lopez-Longo FJ, Oliver-Minarro D, de la Torre I, Gonzalez-Diaz de Rabago E, Sanchez-Ramon S, Rodriguez-Mahou M, et al. Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Rheum. 2009 Apr 15;61(4):419-424.

39. Tomasson G, Aspelund T, Jonsson T, Valdimarsson H, Felson DT, Gudnason V. Effect of rheumatoid factor on mortality and coronary heart disease. Ann.Rheum.Dis. 2010 Sep;69(9):1649-1654.

40. Waldburger JM, Firestein GS. Regulation of peripheral inflammation by the central nervous system. Curr.Rheumatol.Rep. 2010 Oct;12(5):370-378.

41. Tracey KJ. The inflammatory reflex. Nature 2002 Dec 19-26;420(6917):853-859.

42. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000 May 25;405(6785):458-462.

43. Bernik TR, Friedman SG, Ochani M, DiRaimo R, Susarla S, Czura CJ, et al. Cholinergic antiinflammatory pathway inhibition of tumor necrosis factor during ischemia reperfusion. J.Vasc.Surg. 2002 Dec;36(6):1231-1236.

44. Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, et al. Pharmacological stimulation of the cholinergic antiinflammatory pathway. J.Exp.Med. 2002 Mar 18;195(6):781-788.

45. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 2003 Jan 23;421(6921):384-388.

46. Pavlov VA, Ochani M, Yang LH, Gallowitsch-Puerta M, Ochani K, Lin X, et al. Selective alpha7-nicotinic acetylcholine receptor agonist GTS-21 improves survival in murine endotoxemia and severe sepsis. Crit.Care Med. 2007 Apr;35(4):1139-1144.

47. Goldstein RS, Bruchfeld A, Yang L, Qureshi AR, Gallowitsch-Puerta M, Patel NB, et al. Cholinergic anti-inflammatory pathway activity and High Mobility Group Box-1 (HMGB1) serum levels in patients with rheumatoid arthritis. Mol.Med. 2007 Mar-Apr;13(3-4):210-215.

48. Seferovic PM, Ristic AD, Maksimovic R, Simeunovic DS, Ristic GG, Radovanovic G, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. Rheumatology (Oxford) 2006 Oct;45 Suppl 4:iv39-42.

49. Wang W, Ma R. Cardiac sympathetic afferent reflexes in heart failure. Heart Fail.Rev. 2000 Mar;5(1):57-71.

50. Hutchins GD, Miller MA, Zipes DP. Neurocardiac imaging. In: Zipes DP, Jalife J. Cardiac electrophysiology : from cell to bedside. 5th ed. Philadelphia, PA: Saunders/Elsevier; 2009.p391-403.

51. Ellenbogen KA, Stambler BS, Wood MA. Atrial tachycardia. In: Zipes DP, Jalife J. Cardiac electrophysiology : from cell to bedside. 5th ed. Philadelphia, PA: Saunders/Elsevier. p 589-603

52. Bennett PH, Scott JT. Autonomic neuropathy in Rheumatoid Arthritis. Ann.Rheum.Dis. 1965 Mar;24:161-168.

53. Kalliomaki JL, Saarimaa HA, Toivanen P. Axon reflex sweating in rheumatoid arthritis. Ann.Rheum.Dis. 1963 Jan;22:46-49.

54. Ewing DJ. Cardiovascular reflexes and autonomic neuropathy. Clin.Sci.Mol.Med. 1978 Oct;55(4):321-327.

55. Ewing DJ, Campbell IW, Murray A, Neilson JM, Clarke BF. Immediate heart-rate response to standing: simple test for autonomic neuropathy in diabetes. Br.Med.J. 1978 Jan 21;1(6106):145-147.

56. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br.Med.J.(Clin.Res.Ed) 1982 Oct 2;285(6346):916-918.

57. Sandhu V, Allen SC. The effects of age, seropositivity and disease duration on autonomic cardiovascular reflexes in patients with rheumatoid arthritis. Int.J.Clin.Pract. 2004 Aug;58(8):740-745.

58. Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich B, et al. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases. Lupus 2007;16(3):181-185.

59. Aydemir M, Yazisiz V, Basarici I, Avci AB, Erbasan F, Belgi A, et al. Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus. Lupus 2010 Mar;19(3):255-261.

60. Bekkelund SI, Jorde R, Husby G, Mellgren SI. Autonomic nervous system function in rheumatoid arthritis. A controlled study. J.Rheumatol. 1996 Oct;23(10):1710-1714.

61. Bidikar MP, Ichaporia RB. Autonomic (sympathetic) nervous system involvement in rheumatoid arthiritis patients. Indian J.Physiol.Pharmacol. 2010 Jan-Mar;54(1):73-79.

62. Edmonds ME, Jones TC, Saunders WA, Sturrock RD. Autonomic neuropathy in rheumatoid arthritis. Br.Med.J. 1979 Jul 21;2(6183):173-175.

63. Leden I, Eriksson A, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand.J.Rheumatol. 1983;12(2):166-170.

64. Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. QJM 1999 Feb;92(2):97-102.

65. Maule S, Quadri R, Mirante D, Pellerito RA, Marucco E, Marinone C, et al. Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures. Clin.Exp.Immunol. 1997 Dec;110(3):423-427.

66. Milovanovic B, Stojanovic L, Milicevik N, Vasic K, Bjelakovic B, Krotin M. Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. Srp.Arh.Celok.Lek. 2010 Jan-Feb;138(1-2):26-32.

67. Piha SJ, Voipio-Pulkki LM. Elevated resting heart rate in rheumatoid arthritis: possible role of physical deconditioning. Br.J.Rheumatol. 1993 Mar;32(3):212-215.

68. Toussirot E, Serratrice G, Valentin P. Autonomic nervous system involvement in rheumatoid arthritis. 50 cases. J.Rheumatol. 1993 Sep;20(9):1508-1514.

69. Geenen R, Godaert GL, Jacobs JW, Peters ML, Bijlsma JW. Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset. J.Rheumatol. 1996 Feb;23(2):258-264.

70. Dekkers JC, Geenen R, Godaert GL, Bijlsma JW, van Doornen LJ. Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. Clin.Exp.Rheumatol. 2004 Jan-Feb;22(1):63-70.

71. Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch.Neurol. 1990 Jun;47(6):659-664.

72. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response--a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J.Neurol.Neurosurg.Psychiatry. 1984 May;47(5):536-542.

73. Tan J, Akin S, Beyazova M, Sepici V, Tan E. Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function. Am.J.Phys.Med.Rehabil. 1993 Aug;72(4):196-203.

74. Gozke E, Erdogan N, Akyuz G, Turan B, Akyuz E, Us O. Sympathetic skin response and R-R interval variation in cases with rheumatoid arthritis. Electromyogr.Clin.Neurophysiol. 2003 Mar;43(2):81-84.

75. Barendregt PJ, van der Heijde GL, Breedveld FC, Markusse HM. Parasympathetic dysfunction in rheumatoid arthritis patients with ocular dryness. Ann.Rheum.Dis. 1996 Sep;55(9):612-615.

76. Schwemmer S, Beer P, Scholmerich J, Fleck M, Straub RH. Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis - a cross-sectional and longitudinal study. Clin.Exp.Rheumatol. 2006 Nov-Dec;24(6):683-689.

77. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996 Mar 1;93(5):1043-1065.

78. Fei L, Copie X, Malik M, Camm AJ. Short- and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. Am.J.Cardiol. 1996 Apr 1;77(9):681-684.

79. Howorka K, Pumprla J, Schabmann A. Optimal parameters of short-term heart rate spectrogram for routine evaluation of diabetic cardiovascular autonomic neuropathy. J.Auton.Nerv.Syst. 1998 Apr 30;69(2-3):164-172.

80. Evrengul H, Dursunoglu D, Cobankara V, Polat B, Seleci D, Kabukcu S, et al. Heart rate variability in patients with rheumatoid arthritis. Rheumatol.Int. 2004 Jul;24(4):198-202.

81. Anichkov DA, Shostak NA, Ivanov DS. Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients. Int.J.Clin.Pract. 2007 May;61(5):777-783.

82. Taniguchi N, Kawahara K, Yone K, Hashiguchi T, Yamakuchi M, Goto M, et al. High mobility group box chromosomal protein 1 plays a role in the pathogenesis of rheumatoid arthritis as a novel cytokine. Arthritis Rheum. 2003 Apr;48(4):971-981.

83 Bruchfeld A, Goldstein RS, Chavan S, Patel NB, Rosas-Ballina M, Kohn N, et al. Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis. J.Intern.Med. 2010 Jul;268(1):94-101.

84. Vlcek M, Rovensky J, Blazicek P, Radikova Z, Penesova A, Kerlik J, et al. Sympathetic nervous system response to orthostatic stress in female patients with rheumatoid arthritis. Ann.N.Y.Acad.Sci. 2008 Dec;1148:556-561.

85. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton.Neurosci. 2008 Dec 5;143(1-2):58-67.

86. Avsar A, Onrat E, Evcik D, Celik A, Kilit C, Kara Gunay N, et al. Cardiac autonomic function in patients with rheumatoid arthritis: heart rate turbulence analysis. Anadolu Kardiyol Derg. 2011 Feb;11(1):11-15.

87. Figueroa A, Baynard T, Fernhall B, Carhart R, Kanaley JA. Endurance training improves post-exercise cardiac autonomic modulation in obese women with and without type 2 diabetes. Eur.J.Appl.Physiol. 2007 Jul;100(4):437-444.

88. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension 1998 Aug;32(2):293-297.

89. Virtanen R, Jula A, Kuusela T, Helenius H, Voipio-Pulkki LM. Reduced heart rate variability in hypertension: associations with lifestyle factors and plasma renin activity. J.Hum.Hypertens. 2003 Mar;17(3):171-179.

90. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, et al. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin.Auton.Res. 2001 Apr;11(2):99-108.

91. Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindblad LE, Jensen-Urstad M. Heart rate variability in healthy subjects is related to age and gender. Acta Physiol.Scand. 1997 Jul;160(3):235-241.

92. Huikuri HV, Pikkujamsa SM, Airaksinen KE, Ikaheimo MJ, Rantala AO, Kauma H, et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 1996 Jul 15;94(2):122-125.

93. Reardon M, Malik M. Changes in heart rate variability with age. Pacing Clin.Electrophysiol. 1996 Nov;19(11 Pt 2):1863-1866.

94. O'Brien IA, O'Hare P, Corrall RJ. Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. Br.Heart J. 1986 Apr;55(4):348-354.

95. Pagani M, Somers V, Furlan R, Dell'Orto S, Conway J, Baselli G, et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension 1988 Dec;12(6):600-610.

96. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992 Jun;85(6):2119-2131.

97. Malfatto G, Facchini M, Bragato R, Branzi G, Sala L, Leonetti G. Short and long term effects of exercise training on the tonic autonomic modulation of heart rate variability after myocardial infarction. Eur.Heart J. 1996 Apr;17(4):532-538.

98. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Treharne GJ, Panoulas VF, Douglas KM, et al. Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. Rheumatology (Oxford) 2008 Mar;47(3):239-248.

99. Ekdahl C, Andersson SI, Moritz U, Svensson B. Dynamic versus static training in patients with rheumatoid arthritis. Scand.J.Rheumatol. 1990;19(1):17-26.

100. Stenstrom CH, Minor MA. Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. Arthritis Rheum. 2003 Jun 15;49(3):428-434.

101. Duscha BD, Slentz CA, Johnson JL, Houmard JA, Bensimhon DR, Knetzger KJ, et al. Effects of exercise training amount and intensity on peak oxygen consumption in middle-age men and women at risk for cardiovascular disease. Chest 2005 Oct;128(4):2788-2793.

102. Fletcher GF. The antiatherosclerotic effect of exercise and development of an exercise prescription. Cardiol.Clin. 1996 Feb;14(1):85-95.

103. Hakkinen A, Hakkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. Scand.J.Rheumatol. 1994;23(5):237-242.

104. Hansen TM, Hansen G, Langgaard AM, Rasmussen JO. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. Scand.J.Rheumatol. 1993;22(3):107-112.

105. Ekdahl C, Ekman R, Petersson I, Svensson B. Dynamic training and circulating neuropeptides in patients with rheumatoid arthritis: a comparative study with healthy subjects. Int.J.Clin.Pharmacol.Res. 1994;14(2):65-74.

106. Stenstrom CH, Lindell B, Swanberg E, Swanberg P, Harms-Ringdahl K, Nordemar R. Intensive dynamic training in water for rheumatoid arthritis functional class II--a long-term study of effects. Scand.J.Rheumatol. 1991;20(5):358-365.

107. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford) 2002 Feb;41(2):157-166.

108. Munneke M, de Jong Z, Zwinderman AH, Ronday HK, van Schaardenburg D, Dijkmans BA, et al. Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. Arthritis Rheum. 2005 Jun 15;53(3):410-417.

109. Marcora SM, Lemmey AB, Maddison PJ. Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. J.Rheumatol. 2005 Jun;32(6):1031-1039.

110. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Ronday KH, Lems WF, et al. Long term high intensity exercise and damage of small joints in rheumatoid arthritis. Ann.Rheum.Dis. 2004 Nov;63(11):1399-1405.

111. Nordemar R. Physical training in rheumatoid arthritis: A controlled long-term study. II. Functional capacity and general attitudes. Scand.J.Rheumatol. 1981;10(1):25-30.

112. Lyngberg K, Danneskiold-Samsoe B, Halskov O. The effect of physical training on patients with rheumatoid arthritis: changes in disease activity, muscle strength and aerobic capacity. A clinically controlled minimized cross-over study. Clin.Exp.Rheumatol. 1988 Jul-Sep;6(3):253-260.

113. Bilberg A, Ahlmen M, Mannerkorpi K. Moderately intensive exercise in a temperate pool for patients with rheumatoid arthritis: a randomized controlled study. Rheumatology (Oxford) 2005 Apr;44(4):502-508.

114. Noreau L, Martineau H, Roy L, Belzile M. Effects of a modified dance-based exercise on cardiorespiratory fitness, psychological state and health status of persons with rheumatoid arthritis. Am.J.Phys.Med.Rehabil. 1995 Jan-Feb;74(1):19-27.

115. Harkcom TM, Lampman RM, Banwell BF, Castor CW. Therapeutic value of graded aerobic exercise training in rheumatoid arthritis. Arthritis Rheum. 1985 Jan;28(1):32-39.

116. Noreau L, Moffet H, Drolet M, Parent E. Dance-based exercise program in rheumatoid arthritis. Feasibility in individuals with American College of Rheumatology functional class III disease. Am.J.Phys.Med.Rehabil. 1997 Mar-Apr;76(2):109-113.

117. Daltroy LH, Robb-Nicholson C, Iversen MD, Wright EA, Liang MH. Effectiveness of minimally supervised home aerobic training in patients with systemic rheumatic disease. Br.J.Rheumatol. 1995 Nov;34(11):1064-1069.

118. Karper WB, Evans BW. Cycling program effects on one rheumatoid arthritic. Am.J.Phys.Med. 1986 Aug;65(4):167-172.

119. Hall J, Skevington SM, Maddison PJ, Chapman K. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. Arthritis Care Res. 1996 Jun;9(3):206-215.

120. Sanford-Smith S, MacKay-Lyons M, Nunes-Clement S. Therapeutic Benefit of Aquaerobics for Individuals with Rheumatoid Arthritis. Physiotherapy Canada 1998(Winter):40-46.

121. Perlman SG, Connell KJ, Clark A, Robinson MS, Conlon P, Gecht M, et al. Dance-based aerobic exercise for rheumatoid arthritis. Arthritis Care Res. 1990 Mar;3(1):29-35.

122. Baslund B, Lyngberg K, Andersen V, Halkjaer Kristensen J, Hansen M, Klokker M, et al. Effect of 8 wk of bicycle training on the immune system of patients with rheumatoid arthritis. J.Appl.Physiol. 1993 Oct;75(4):1691-1695.

123. Melton-Rogers S, Hunter G, Walter J, Harrison P. Cardiorespiratory responses of patients with rheumatoid arthritis during bicycle riding and running in water. Phys.Ther. 1996 Oct;76(10):1058-1065.

124. Danneskiold-Samsoe B, Lyngberg K, Risum T, Telling M. The effect of water exercise therapy given to patients with rheumatoid arthritis. Scand.J.Rehabil.Med. 1987;19(1):31-35.

125. Minor MA, Hewett JE. Physical fitness and work capacity in women with rheumatoid arthritis. Arthritis Care Res. 1995 Sep;8(3):146-154.

126. van den Ende CH, Hazes JM, le Cessie S, Mulder WJ, Belfor DG, Breedveld FC, et al. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. Ann.Rheum.Dis. 1996 Nov;55(11):798-805.

127. van den Ende CH, Breedveld FC, le Cessie S, Dijkmans BA, de Mug AW, Hazes JM. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. Ann.Rheum.Dis. 2000 Aug;59(8):615-621.

128. Stenstrom CH. Home exercise in rheumatoid arthritis functional class II: goal setting versus pain attention. J.Rheumatol. 1994 Apr;21(4):627-634.

129. Hakkinen A, Pakarinen A, Hannonen P, Kautiainen H, Nyman K, Kraemer WJ, et al. Effects of prolonged combined strength and endurance training on physical fitness, body composition and serum hormones in women with rheumatoid arthritis and in healthy controls. Clin.Exp.Rheumatol. 2005 Jul-Aug;23(4):505-512.

130. Hakkinen A, Hannonen P, Nyman K, Lyyski T, Hakkinen K. Effects of concurrent strength and endurance training in women with early or longstanding rheumatoid arthritis: comparison with healthy subjects. Arthritis Rheum. 2003 Dec 15;49(6):789-797.

131. Nordemar R, Berg U, Ekblom B, Edstrom L. Changes in muscle fibre size and physical performance in patients with rheumatoid arthritis after 7 months physical training. Scand.J.Rheumatol. 1976;5(4):233-238.

132. de Jong Z, Munneke M, Lems WF, Zwinderman AH, Kroon HM, Pauwels EK, et al. Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum. 2004 Apr;50(4):1066-1076.

133. Komatireddy GR, Leitch RW, Cella K, Browning G, Minor M. Efficacy of low load resistive muscle training in patients with rheumatoid arthritis functional class II and III. J.Rheumatol. 1997 Aug;24(8):1531-1539.

134. Hakkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. Arthritis Rheum. 2001 Mar;44(3):515-522.

135. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst.Rev. 2009 Oct 7;(4)(4):CD006853.

136. Hakkinen A, Sokka T, Kotaniemi A, Kautiainen H, Jappinen I, Laitinen L, et al. Dynamic strength training in patients with early rheumatoid arthritis increases muscle strength but not bone mineral density. J.Rheumatol. 1999 Jun;26(6):1257-1263.

137. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003 Sep;48(9):2415-2424.

138. Lyngberg KK, Harreby M, Bentzen H, Frost B, Danneskiold-Samsoe B. Elderly rheumatoid arthritis patients on steroid treatment tolerate physical training without an increase in disease activity. Arch.Phys.Med.Rehabil. 1994 Nov;75(11):1189-1195.

139. Hakkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P. Sustained maintenance of exercise induced muscle strength gains and normal bone mineral

density in patients with early rheumatoid arthritis: a 5 year follow up. Ann.Rheum.Dis. 2004 Aug;63(8):910-916.

140. Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989 Nov;32(11):1396-1405.

141. Suomi R, Collier D. Effects of arthritis exercise programs on functional fitness and perceived activities of daily living measures in older adults with arthritis. Arch.Phys.Med.Rehabil. 2003 Nov;84(11):1589-1594.

142. American College of Rheumatology Subcommittee on Rheumatoid Arthritis,Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-346.

143. Buchheit M, Gindre C. Cardiac parasympathetic regulation: respective associations with cardiorespiratory fitness and training load. Am.J.Physiol.Heart Circ.Physiol. 2006 Jul;291(1):H451-8.

1443. Aubert AE, Seps B, Beckers F. Heart rate variability in athletes. Sports Med. 2003;33(12):889-919.

144. Madden KM, Levy WC, Stratton JK. Exercise training and heart rate variability in older adult female subjects. Clin.Invest.Med. 2006 Feb;29(1):20-28.

146. Freeman JV, Dewey FE, Hadley DM, Myers J, Froelicher VF. Autonomic nervous system interaction with the cardiovascular system during exercise. Prog.Cardiovasc.Dis. 2006 Mar-Apr;48(5):342-362.

147. Bowman AJ, Clayton RH, Murray A, Reed JW, Subhan MM, Ford GA. Effects of aerobic exercise training and yoga on the baroreflex in healthy elderly persons. Eur.J.Clin.Invest. 1997 May;27(5):443-449.

148. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med. 2003;33(1):33-46.

149. Raczak G, Danilowicz-Szymanowicz L, Kobuszewska-Chwirot M, Ratkowski W, Figura-Chmielewska M, Szwoch M. Long-term exercise training improves autonomic nervous system profile in professional runners. Kardiol.Pol. 2006 Feb;64(2):135-40; discussion 141-2.

150. Melo RC, Quiterio RJ, Takahashi AC, Silva E, Martins LE, Catai AM. High eccentric strength training reduces heart rate variability in healthy older men. Br.J.Sports Med. 2008 Jan;42(1):59-63.

151. Buchheit M, Simon C, Charloux A, Doutreleau S, Piquard F, Brandenberger G. Relationship between very high physical activity energy expenditure, heart rate

variability and self-estimate of health status in middle-aged individuals. Int.J.Sports Med. 2006 Sep;27(9):697-701.

152. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992 May;35(5):498-502.

153. Iversen MD. Physical therapy for management of RA: rehabilitation measures are most effective when started early. J Musculoskeletal Med 2002;19(9):352-358.

154. Aletaha D, Smolen JS. Outcome Measurement in Rheumatoid Arthritis: Disease Activity. In: Hochberg MC, Silman AJ. et al, editors. Rheumatoid arthritis. Philadelphia: Mosby, 2009; p. 225-230.

155. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann.Rheum.Dis. 1990 Nov;49(11):916-920.

156. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-48.

157. Fransen J, Stucki G, van Riel PLCM. Rheumatoid arthritis measures: Disease Activity Score (DAS), Disease Activity Score-28 (DAS28), Rapid Assessment of Disease Activity in Rheumatology (RADAR), and Rheumatoid Arthritis Disease Activity Index (RADAI). Arthritis Care & Research 2003;49(S5):S214-S224.

158. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983 May;16(1):87-101.

159. Huskisson EC. Measurement of pain. Lancet 1974 Nov 9;2(7889):1127-1131.

160. Scott J, Huskisson EC. Vertical or horizontal visual analogue scales. Ann.Rheum.Dis. 1979 Dec;38(6):560.

161. Pincus T, Summey JA, Soraci SA,Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum. 1983 Nov;26(11):1346-1353.

162. Ramey DR, Raynauld JP, Fries JF. The health assessment questionnaire 1992: status and review. Arthritis Care Res. 1992 Sep;5(3):119-129.