



MARKO H. NEVA

Cervical Spine Changes in Rheumatoid Arthritis



ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the small auditorium of Building B,
Medical School of the University of Tampere,
Medisiinarinkatu 3, Tampere, on November 30th, 2001, at 12 o'clock.

Acta Universitatis Tamperensis 834
University of Tampere
Tampere 2001

ACADEMIC DISSERTATION

University of Tampere, Medical School
Tampere University Hospital, Department of Surgery
Rheumatism Foundation Hospital, Heinola
Finland

Supervised by
Docent Markku Kauppi
University of Oulu
Docent Eero Belt
University of Tampere

Reviewed by
Docent Leena Laasonen
University of Helsinki
Docent Leena Paimela
University of Helsinki

Distribution



University of Tampere
Sales Office
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 215 6055
Fax +358 3 215 7685
taju@uta.fi
<http://granum.uta.fi>

Cover design by
Juha Siro

Printed dissertation
Acta Universitatis Tamperensis 834
ISBN 951-44-5200-3
ISSN 1455-1616

Electronic dissertation
Acta Electronica Universitatis Tamperensis 129
ISBN 951-44-5201-1
ISSN 1456-954X
<http://acta.uta.fi>

Tampereen yliopistopaino Oy Juvenes Print
Tampere 2001

With Love To Pia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred in the text by Roman numerals (I – V):

- I. Kauppi M and Neva MH (1998): Sensitivity of lateral view cervical spine radiographs taken in the neutral position in atlantoaxial subluxation in rheumatic diseases. *Clin Rheumatol* 17: 511-514.
- II. Neva MH, Kaarela K and Kauppi M (2000): Prevalence of radiological changes in the cervical spine - a cross sectional study after 20 years from presentation of rheumatoid arthritis. *J Rheumatol* 27: 90-93.
- III. Neva MH, Kotaniemi A, Kaarela K, Lehtinen J, Belt EA and Kauppi M. Atlantoaxial subluxations in rheumatoid arthritis associate with destruction of the peripheral and shoulder joints, and decreased bone mineral density. Submitted.
- IV. Neva MH, Myllykangas-Luosujärvi R, Kautiainen H and Kauppi M (2001): Mortality associated with cervical spine disorders: a population-based study of 1666 patients with rheumatoid arthritis who died in Finland in 1989. *Rheumatol* 40: 123-127.
- V. Neva MH, Kauppi MJ, Kautiainen H, Luukkainen R, Hannonen P, Leirisalo-Repo M, Nissilä M and Möttönen T, for the FIN-RACo Trial Group (2000): Combination drug therapy retards the development of rheumatoid atlantoaxial subluxations. *Arthritis Rheum* 43: 2397-2401.

ABBREVIATIONS

aAAS	anterior atlantoaxial subluxation
AADI	anterior atlantodental interval
AAI	atlantoaxial impaction
AC	acromioclavicular
ACR	American College of Rheumatology
BMD	bone mineral density
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
GH	glenohumeral
IQR	interquartile range
lAAS	lateral atlantoaxial subluxation
McG	McGregor method
MRI	magnetic resonance imaging
pAAS	posterior atlantoaxial subluxation
PADI	posterior atlanto-odontoid interval
r	correlation coefficient
R	Ranawat method
RA	rheumatoid arthritis
RF	rheumatoid factor
SAS	subaxial subluxation
SD	standard deviation
S-K	Sakaguchi-Kauppi method
WHO	World Health Organization

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory/autoimmune disease with an unknown etiology. The main target of rheumatoid inflammation is the synovial lining of joints. In addition, synovial structures of the cervical spine may become involved. Rheumatoid inflammation of cervical spine leads to increased laxity of ligamentous structures and joint capsules, and finally erosions of the facet joints. These changes may result in several cervical spine abnormalities, which are characteristic for RA.

The most important cervical spine changes in RA are anterior atlantoaxial subluxation (aAAS), atlantoaxial impaction (AAI) and subaxial subluxation (SAS). Already at an early stage of RA, increased laxity of transversal, apical and alar ligaments may allow atlas to glide forward in relation to axis, resulting in aAAS. The sustained inflammation of atlantoaxial and atlanto-occipital facet joints, in turn, leads to destruction of these joints, and to the development of AAI. Moreover, distortion of ligaments and joint capsules, and erosions in the facet joints below the second vertebra may lead to subluxations in the lower cervical vertebra, i.e. SAS. The prevalence of cervical spine changes in previous studies varies considerably and detailed studies on cervical spine changes in long-term RA have not been previously published. Severe cervical spine changes in RA may cause compression of brainstem or spinal cord leading to myelopathy and even para- or quadriparesis. Furthermore, several authors have reported death caused by compression of medulla.

The treatment of cervical spine disorders in RA is generally conservative, consisting of patient education, physiotherapy, collars, practical aids and symptomatic treatment. None of these treatments has been shown to retard the progression of cervical spine changes. Recently, aggressive drug therapy with

disease-modifying antirheumatic drugs (DMARDs) was shown to slow the progression of peripheral joint erosions. However, the effectiveness of anti-rheumatic drug therapies in the prevention of cervical spine changes has not been studied.

In the first study of the present thesis, the value of cervical spine radiographs taken in neutral position in the evaluation of aAAS was examined. Thereafter, the prevalences of different cervical spine changes in patients who had suffered from RA for 20 years was examined. In addition, the prevalence and severity of the most important cervical spine changes (aAAS, AAI and SAS) in these patients were compared to the occurrence and grade of destruction in peripheral and shoulder joints and to bone mineral density. To obtain more information on complications caused by cervical spine disorders in RA, mortality for cervical spine changes was studied. Finally, the efficacy of systemic drug therapy using a combination of DMARDs in the prevention of early cervical spine changes was evaluated.

REVIEW OF THE LITERATURE

1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune/inflammatory disease. Both genetic and environmental factors contribute to the generation of RA (Feldmann et al. 1996). Despite intensive research the triggering factor is still unknown. Following initial T-cell activation, multiple immunological cascades lead to chronic inflammation and hypertrophy of the articular synovium. Early clinical features of inflammation are pain, stiffness and swelling of the joints. Usually, small peripheral joints and wrists are affected first and thereafter the inflammation spreads into larger joints i.e. knees, hips, elbows and shoulders. Overgrowth of the hypertrophic synovium results in the formation of granulation tissue called pannus, which erodes adjacent cartilage and bone. Therefore, sustained inflammation process leads to progressive erosions of the articular cartilage and underlying bone, and finally to the destruction of several joints. Radiological joint destruction is often classified using a widely accepted method by Larsen et al. (1977). In addition, extra-articular manifestations such as rheumatoid nodules, vasculitis, pericarditis, pleuritis and peripheral neuropathy are found in a proportion of patients (Akil and Amos 1995a).

The diagnosis of RA is based on the 1987 revised classification criteria of the American College of Rheumatology (ACR; Arnett et al. 1988). No specific test for the diagnosis of RA is available. However, 70 to 80% of the patients have elevated rheumatoid factor (RF) levels in serum. The prevalence of RA is approximately 0.5 - 1.0% in adult Caucasian population. In Finland, the annual incidence of RA satisfying the ACR criteria is 39/100000 of the adult population (Kaipiainen-Seppänen et al. 1996).

No curative treatment for RA has been developed (Akil and Amos 1995b). Previously, treatment aimed at relieving the symptoms and non-steroidal anti-inflammatory drugs were the basis of medication. Thereafter, several drugs have been reported to suppress the inflammatory activity of RA, and thereby to retard or prevent joint destruction (Sokka 1999). These drugs include disease-modifying antirheumatic drugs (DMARDs) such as gold, antimalarials, D-penicillamine, sulphasalazine, methotrexate, azathioprine, cyclosporine, leflunomide and podofyllotoxine derivatives and, more recently, cytokine inhibitors such as neutralizing anti-tumor necrosis factor antibodies (Elliott et al. 1994). In addition, glucocorticoids have been reported to reduce the radiological progression of RA, but because of side-effects such as osteoporosis, their use have remained controversial (Kirwan 1995). In an attempt to treat patients with RA more effectively, new strategies have recently been tested. Fries (1990) described the continuous and serial use of DMARDs known as "sawtooth" strategy, which was reported to be beneficial in retarding peripheral joint destructions (Möttönen et al. 1996, Sokka et al. 1999). In addition, the combination of DMARDs has been shown to slow the radiographic progression and to increase the remission rate when compared with a single drug therapy (Boers et al. 1997, Möttönen et al. 1999).

2. Anatomy of the cervical spine

Human cervical spine consists of seven vertebrae C1 - C7 (Williams and Warwick 1980; Figure 1). The two most cranial vertebrae have special architectural design and the other five are constructed according to a common plan. In this small area between the skull and first thoracic vertebra, there are 16 serially arranged apophyseal (i.e. facet) synovial joints, 12 uncovertebral joints and six intervertebral discs (Bland and Boushey 1990).

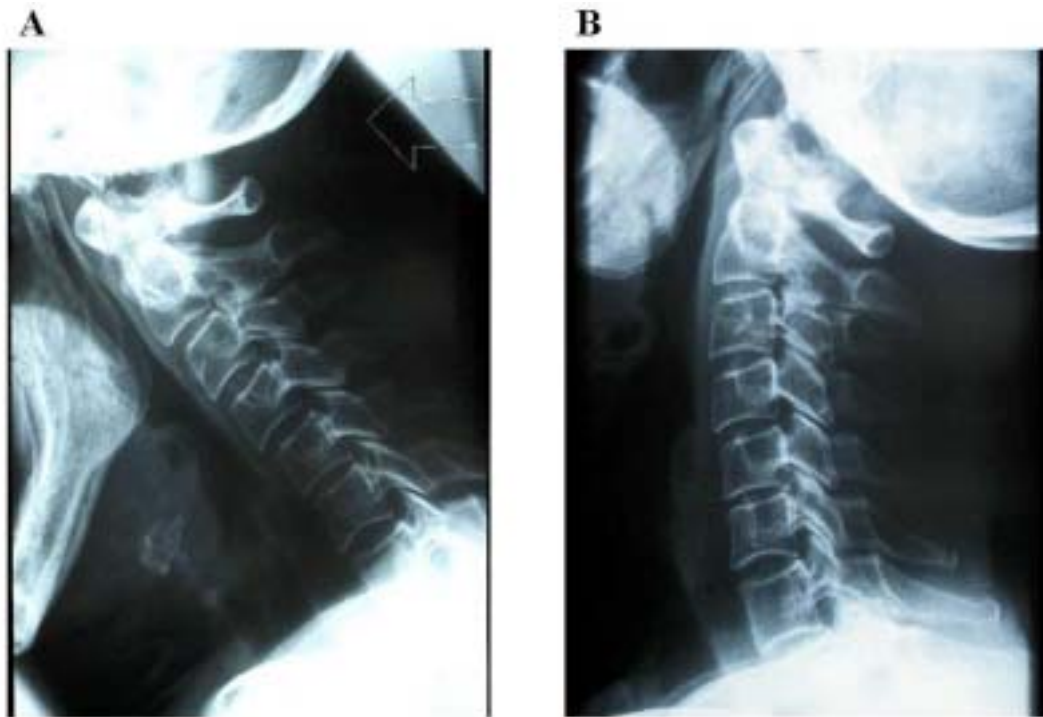


Figure 1. Radiographs of the normal cervical spine taken in flexion (A) and extension (B) position of neck.

The most cranial vertebrae "atlas" is a solid bone ring with two lateral pillars for the apophyseal joints (Figure 2). It carries the skull by two ellipsoid shaped joints, which allows only flexion and extension movement (Bland and Bousley 1987). The second vertebrae "axis" has a special structure called "odontoid process", which rises perpendicularly from midbody, acting as an eccentric pivot around which the atlas rotates. The odontoid process has articulation in the anterior surface with anterior arch of atlas and in the posterior surface with the transversal ligament. In addition, axis comprises two apophyseal joints with atlas and two with the third vertebra. Approximately 50% of head rotation occurs in the atlantoaxial joints and ~85% of the whole head and neck movement appears in the skull-atlas-axis complex (Bland 1974, Bland and Bousley 1987). Vertebrae from 3 to 7 all consist of body, pedicles, laminae, vertebral arches and spinous process. The size of the vertebrae increases from the top down, while the extent of rotation, flexion-extension and lateral flexion decreases.

The odontoid process is fixed to the anterior arch of atlas by a strong transverse ligament (Dickman et al. 1991; Figure 2, Figure 3). It allows rotational movement but prevents the atlas from slipping forward when the head is in flexion. In addition, the odontoid process is attached to the occipital bone by an apical and two alar ligaments, which increases the stability of both atlanto-occipital and atlantoaxial joints (Panjabi et al. 1991). The most important ligaments connecting vertebral bodies together are the anterior and posterior longitudinal ligaments, which continue as membrane-like structures to the occipital bone. Furthermore, the laminae of vertebrae are connected together by ligamenta flava.

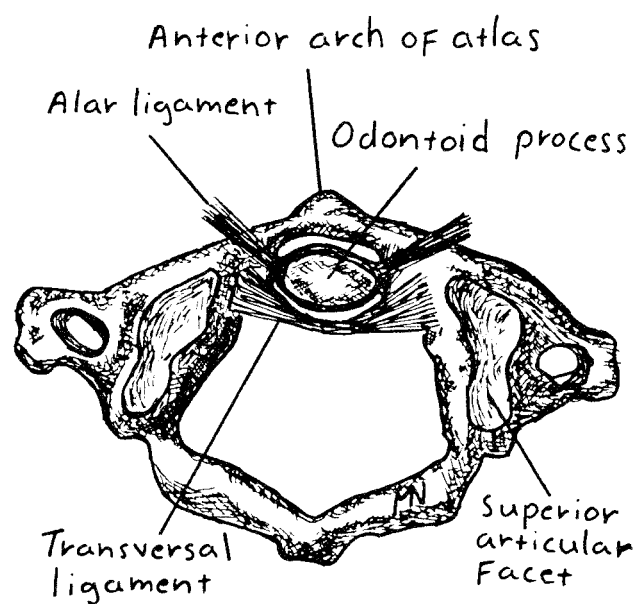


Figure 2. An illustration of the superior view of atlas and atlanto-odontoid joint.

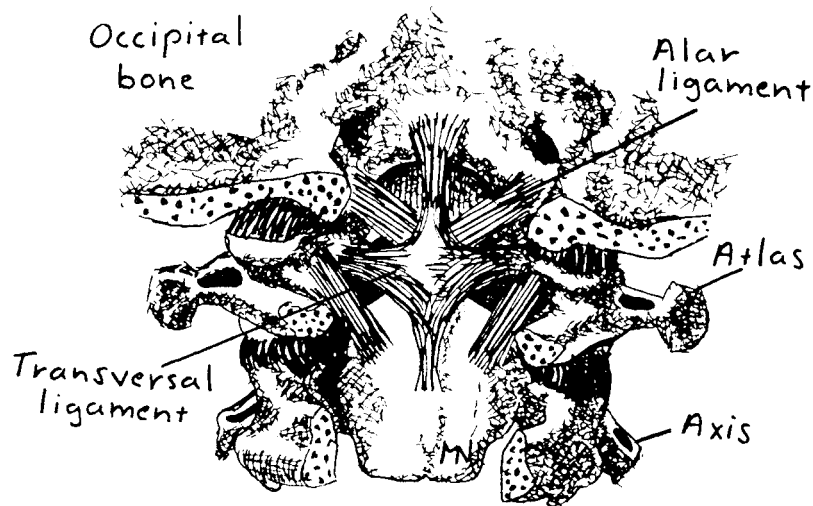


Figure 3. An illustration of the posterior view of the transversal and alar ligaments.

The junction of medulla oblongata and spinal cord is at the level of the odontoid process. Spinal cord is situated in the triangular cavity of the vertebral canal. The first and second spinal nerve roots exit the spinal canal posterior to the pedicles, whereas the lower nerve roots run through the intervertebral foramina. The blood supply of the spinal cord and spinal nerves comes from the anterior spinal arteries, vertebral arteries and posterior spinal arteries (Bland and Bousley 1987). The vertebral artery runs from the subclavian artery through the foramina transversaria of vertebrae and joins the opposite vertebral artery to form the basilar artery.

3. Cervical spine disorders in rheumatoid arthritis

3.1. Pathogenesis

The primary target of RA is the synovial lining of the joints. Cervical spine comprises multiple synovial structures including apophyseal, uncovertebral and atlanto-odontoid joints in a relatively small area, which makes it vulnerable for rheumatoid inflammation (Ball and Sharp 1971, Bland 1974).

Bland (1974), who dissected whole cervical spines which were removed post-mortem from nine patients with seropositive RA, observed synovial and granulomatous inflammation in both apophyseal and uncovertebral joints, even in patients without radiological changes. Rheumatoid granulomas invaded intervertebral discs as well as the space between the odontoid process and atlas. Furthermore, inflammatory lesions were found in transverse ligaments, articular capsules, periarticular tissues, posterior longitudinal ligament, dura and ligamenta flava. Moreover, inflammation had caused erosions in the cartilage and bone.

In a post-mortem study of Martel and Abel (1963), cervical spines of two patients with RA were dissected. They observed oedematous and lax transversal ligament. Increased ligamentous laxity allowed the atlas to glide anteriorly in relation to the odontoid process causing the most common rheumatoid cervical spine deformity, anterior atlantoaxial subluxation (aAAS; Halla et al. 1989; Figure 4). In a magnetic resonance imaging (MRI) study by Dickman et al. (1991), similar distortion and stretching of the transversal ligament was the main cause of aAAS in four patients with RA. Furthermore, in addition to changes in the ligamentous structures, inflammatory destruction in the bony attachments of transversal ligament and erosion in the posterior surface of odontoid process have been reported to cause aAAS (Eulderink and Meijers 1976). It should be noted that in healthy cervical spines complete cutting of the transversal ligament allows only ~4 mm atlantoaxial dislocation, further being prevented by the alar ligaments and joint capsules (Ball and Sharp 1971). Therefore, in severe atlantoaxial subluxation all these stabilising structures must be injured.

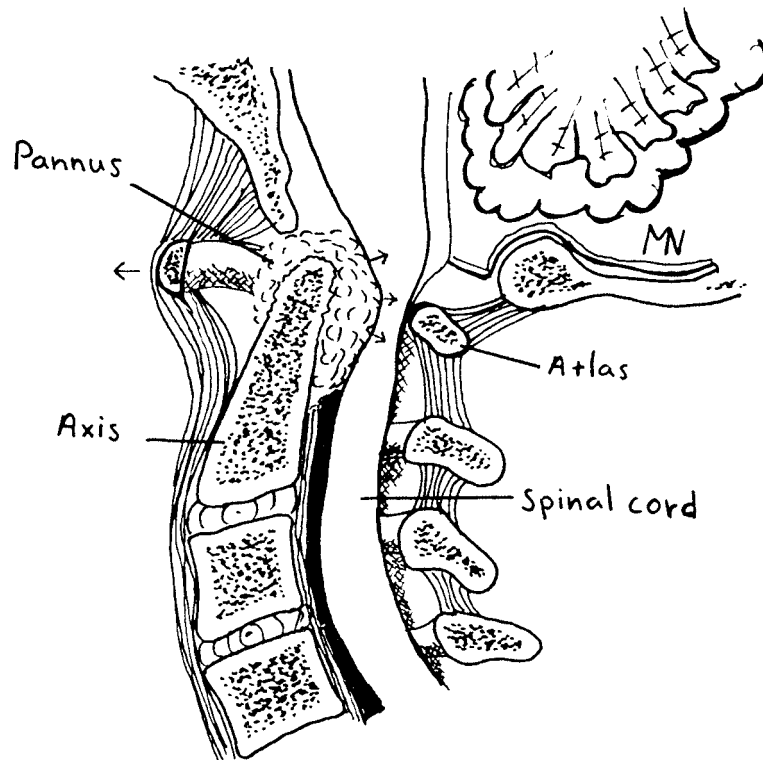


Figure 4. An illustration of the lateral view of the upper cervical spine demonstrating pannus formation and aAAS in a patient with rheumatoid arthritis.

Sustained rheumatoid inflammation of the atlantoaxial apophyseal joints causes cartilage destructions and finally bone erosions leading to atlantoaxial impaction (AAI; Kauppi et al. 1996; Figure 5), which has also been referred to as vertical atlantoaxial subluxation, basilar invagination or cranial settling. These changes may also result in lateral (LAAS) or rotational subluxations of atlas (Santavirta et al. 1987a). LAAS follows if erosions of the atlantoaxial joints lead to a lateral shift of atlas in relation to axis (Bunton et al. 1978, Burry et al. 1978, Bogduk et al. 1984). Rotational subluxation, in turn, is a persistent rotation of the atlas on the axis (Fielding and Hawkins 1977). In more severe cases the lateral masses of atlas and/or axis may collapse unilaterally or bilaterally leading to nonreducible rotational head tilt or to severe AAI, respectively (Eulderink and Meijers 1976, Halla et al. 1982, Santavirta et al. 1988a). As a result of severe AAI the odontoid process penetrates into the foramen magnum and may compress the brain stem (Eulderink and Meijers 1976, Mayer et al. 1976).

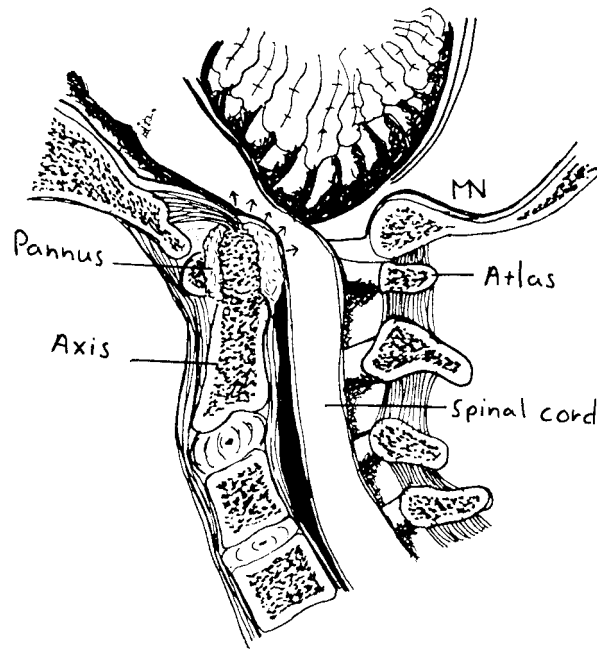


Figure 5. An illustration of the lateral view of the upper cervical spine demonstrating AAI and penetration of the odontoid process into the foramen magnum in a patient with rheumatoid arthritis.

Inflammation of the atlanto-odontoid joint may cause erosions in the anterior margin of odontoid process or even spontaneous fracture of it. As a result, atlas may glide posteriorly in relation to the anterior margin of the body of axis (Santavirta et al. 1985). This rare condition is known as posterior atlantoaxial subluxation (pAAS; Kauppi 1994). In addition, rheumatoid inflammation may involve cervical spine below the atlantoaxial region (Bland 1974, Eulderink and Meijers 1976). Inflammatory destruction of the intervertebral discs, distortion of ligaments and erosion of apophyseal joints may loosen intervertebral fixations and thereby permit movement between adjacent vertebral bodies causing subaxial subluxations (SAS; Ball and Sharp 1971, Hughes 1977). Furthermore, Bland (1974) reported that narrow disc spaces with little or no osteophytosis, vertebral plate erosions and generalised cervical spine osteoporosis are observed in patients with RA.

3.2. Symptoms and clinical findings

Neck pain is a common symptom in RA, regardless of the findings in cervical spine radiographs (Conlon et al. 1966, Mathews 1969, Stevens et al. 1971, Pellicci et al. 1981). However, pain is also the most common and earliest manifestation of cervical spine disorders (Pellicci et al. 1981, Halla and Hardin 1990, Rawlins et al. 1998). In addition to neck region, pain caused by cervical spine destruction may be experienced in occipital, retro-orbital or temporal areas (Sharp and Purser 1961, Bland 1974). In some patients it is intractable and resistant to conservative treatment (Slätis et al. 1989). Furthermore, patients may experience unpleasant feeling and crepitation in flexion-extension movement of the neck (Stevens et al. 1971). This symptom is caused by abnormal sliding between atlas and axis and may be demonstrated using the Sharp and Purser test (Sharp and Purser 1961). However, it is important to bear in mind that subluxations of the cervical spine do not necessary cause pain or other symptoms. In a study by Mathews (1969), two-thirds of patients with aAAS did not have neck pain. Moreover, Collins et al. (1991) reported that 50% of the patients with cervical spine instability were asymptomatic.

Patients with severe cervical spine disorders may present symptoms and signs caused by compression of the spinal cord, cervical nerve roots or cranial nerves (Santavirta et al. 1987a). In addition, penetration of the odontoid process through the foramen magnum may cause the compression of brainstem and even sudden death (Mikulowski et al. 1975). Neurological symptoms and signs have been reported to correlate poorly with the degree of atlantoaxial instability (Conlon et al. 1966, Mathews 1969, Rana et al. 1973, Floyd et al. 1989). However, these patients are often severely affected by RA and therefore the destruction of peripheral joints and generalised muscle atrophy may mask the symptoms caused by compression of spinal cord or spinal nerve roots. Moreover, neurological

examination of patients with mutilating RA may be difficult. The poor correlation between symptoms and the extent of cervical spine destruction increases the need for radiological examinations.

3.3. Radiological examinations

PLAIN RADIOGRAPHS

The primary radiological examinations of the cervical spine in patients with RA are plain radiographs (Braunstein et al. 1984; Figure 1). Radiographs of the cervical spine are generally taken using a 150 cm tube-to-plane distance. The standard cervical spine radiographs include anteroposterior, odontoid, lateral and oblique projections (Bland 1987b). The lateral view radiographs are most accurate for the evaluation of aAAS, pAAS, AAI and SAS. Instead, IAAS is diagnosed using radiographs taken in the odontoid projection (Burry et al. 1978). In the majority of rheumatological units lateral view radiographs are taken during full flexion and extension of the neck. Instead, in some other departments the lateral view radiographs of RA patients are still taken only in neutral position. Whether these two methods differ in the sensitivity for detecting rheumatoid changes has not been evaluated.

Sharp and Purser (1961) measured the distance between the anterior arch of atlas and the anterior surface of the odontoid process in lateral view cervical spine radiographs taken from a general population and from patients with RA. They demonstrated that in an adult population more than 3 mm separation is abnormal and it mainly associates with RA. Thereafter, more than 3 mm anterior atlantoaxial distances have been considered to indicate aAAS by the majority of the investigators (Smith et al. 1972, Park et al. 1979, Halla and Hardin 1990, Boden et al. 1993; Figure 6).

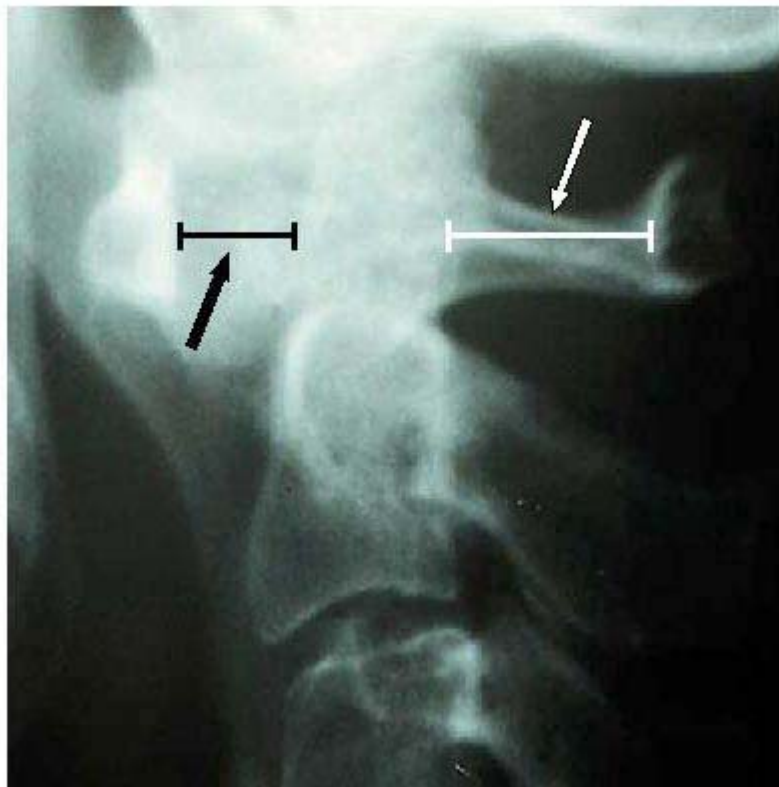
A**B**

Figure 6. Radiographs of the upper cervical spine of a patient with unstable aAAS taken in extension (A) and flexion (B) position of neck. In the radiograph taken during flexion anterior atlantodental distance (black arrow) has increased (8 mm) and posterior atlanto-odontoid interval (white arrow) has shortened (13 mm).

Unfortunately, anterior atlantoaxial interval correlates poorly with the occurrence of neurological deficits (Pellicci et al. 1981, Floyd et al. 1989, Rana 1989, Boden et al. 1993). Therefore, Boden et al. (1993) defined a new radiographic parameter i.e. the posterior atlanto-odontoid interval (PADI), which is the distance between the posterior aspect of the odontoid process and the anterior edge of the posterior arch of atlas in lateral view cervical spine radiographs. In their study, the sagittal diameter of the bony spinal canal was the most important predictor of paralysis and postoperative neurological recovery in patients with aAAS (Boden 1994). Values of 14 mm or less were determined to be critical for the development of irreversible myelopathic changes.

Several methods have been described for the evaluation of AAI in plain cervical spine radiographs taken in lateral projection (McGregor 1948, Ranawat et al. 1979, Redlund-Johnell and Pettersson 1984, Teigland et al. 1990). Kauppi et al. (1990) described a reproducible and simple method, in which the severity of AAI can be defined without previous radiographs (Figure 7). This Sakaguchi-Kauppi method was developed in particular for screening purposes and it evaluates the position of atlas in relation to axis. The method divides the severity of impaction to four grades (I-IV), grade I is defined as normal and grades II to IV as abnormal. Importantly, none of the methods used for the evaluation of AAI have been shown to be highly reliable in diagnosing the most severe complication of AAI, i.e. herniation of the odontoid process into the foramen magnum (Riew et al. 2001).

The severity of pAAS is defined by measuring how far posteriorly the posterior margin of anterior atlas arch is shifted in relation to the anterior edge of axis in lateral view cervical spine radiographs taken in extension (Kauppi 1994). Furthermore, lAAS is diagnosed if the lateral masses of atlas are lying 2 mm or

more laterally in relation to masses of axis in radiographs taken in the odontoid projection (Lipson 1984, Bland 1990).

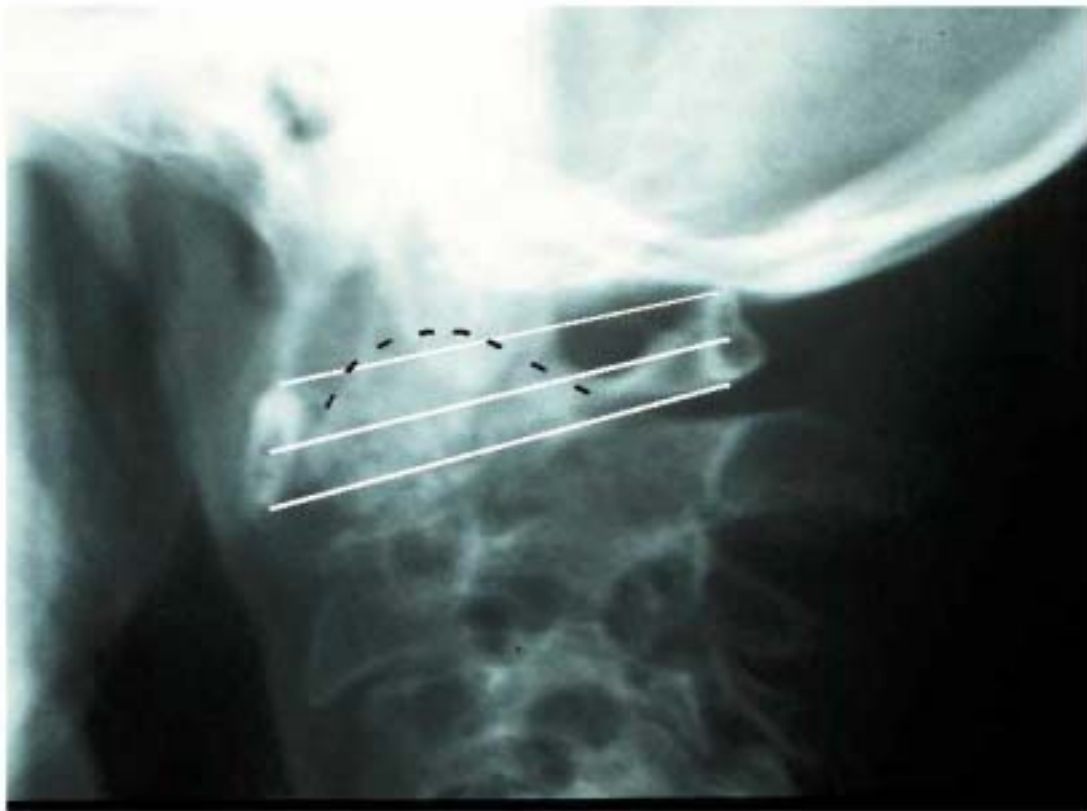


Figure 7. Radiograph of the upper cervical spine of a patient with AAI (Sakaguchi-Kauppi grade IV). Lateral masses of axis and atlas have collapsed and atlas has fallen to the level of the lower part of axis body. The dashed line marks the damaged superior facets of the axis and three straight lines represent the grading lines of Sakaguchi-Kauppi method.

White et al. (White et al. 1975, Panjabi et al. 1988) examined the instability of cervical spine and found that more than 3.5 mm horizontal distance between the posterior aspects of bodies of two adjacent vertebrae in lateral view radiographs causes mechanically unstable cervical spine (Figure 8). Thereafter, most authors have accepted subaxial distance of 4 mm or more as a pathological finding and some authors have chosen even a shorter distance to represent a pathological shift (Komusi et al. 1985, Santavirta et al. 1987a, Clark et al. 1989, Kauppi and Hakala 1994, Paimela et al. 1997).



Figure 8. Radiograph of the upper cervical spine of a patient with SAS. Third cervical vertebra has shifted 4 mm forward in relation to the fourth cervical vertebra (arrow) and end plate erosions are visible.

TOMOGRAPHIES, COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

The two-dimensional character of plain radiographs causes over-projection of structures and therefore in particular the atlanto-occipital and atlantoaxial facet joints are difficult to evaluate. Tomographies and panoramic zonography have been shown to give more detailed information on occipital condyles, the lateral masses of atlas and axis and atlantoaxial facet joints than conventional radiographs (Halla et al. 1982, Santavirta et al. 1988a). In addition to these structures, the bony spinal canal and often compression of the spinal cord can be observed using computed tomography (CT; Braunstein et al. 1984).

Tomographies and CT have been particularly valuable in the evaluation of the severity of AAI (Komusi et al. 1985, Boden 1994). However, after the development and increase in availability of MRI, the need for these examinations in clinical work has decreased. MRI provides detailed information on soft tissue lesions, pannus formation, vertebral subluxations and compression of the spinal cord, and is therefore the most important imaging method in patients with suspected spinal cord compression (Pettersson et al. 1988, Kawaida et al. 1989, Jacobsen and Riise 2000, Reijnierse et al. 2000).

3.4. Incidence and prevalence

The incidence of cervical spine disorders in early RA has been evaluated in two prospective studies (Table 1). Paimela et al. (1997) studied cervical spine changes in 67 patients with recent RA, who were prospectively followed up for a mean of 6.5 years. In a two years time, aAAS, AAI and SAS developed in 9%, 4% and 2% of the patients, respectively. At the end of the study aAAS, AAI and SAS occurred in 13%, 10% and 4% of the patients, respectively. Winfield et al. (1981) reported similar results in their follow-up study of 100 patients with early RA. After two years follow-up aAAS and SAS was observed in 10% and 19% of the patients, respectively. During the course of a mean follow-up time of 7 years 2 months, aAAS, AAI and SAS developed in 12%, 3% and 24% of the patients, respectively. It has to be noted that in the study of Winfield et al. the criterion for abnormal subaxial displacement was lower (>1 mm) than in the study of Paimela et al. (>3.5 mm) and thereby, the occurrence of SAS was higher in their study. Moreover, patients in the study of Paimela et al. were treated aggressively with DMARDs, whereas patients in the study of Winfield et al. received mainly gold, D-penicillamine or corticosteroids. Nevertheless, on the basis of these studies cervical spine changes develop early during the course of RA.

Table 1. Incidence of cervical spine subluxations in prospective follow-up studies.

Study	N	Mean follow-up time (years)	Incidence (%)			
			aAAS	AAI (McG)	SAS	aAAS, AAI or SAS
Rasker and Cosh 1978	62	15	42	32	-	-
Winfield et al. 1981	100	7	12	3	24	33
Corbet et al. 1993	64	15	-	-	-	19
Paimela et al. 1997	67	6.5	13	10	4	27

McG = McGregor method

The occurrence of cervical spine changes in late RA has been evaluated in two prospective studies (Table 1). Rasker and Cosh (1978) reported the incidence of cervical spine subluxations in 62 patients, approximately 15 years after disease onset. aAAS and AAI were detected in 26 (42%) and 20 (32%) patients, respectively. In another 15-year follow-up study, cervical spine subluxation developed in 12 (19%) of the 64 patients (Corbett et al. 1993). According to these two studies the occurrence of cervical spine involvement in late RA varies considerably.

Other studies on the occurrence of cervical spine disorders are cross-sectional evaluations of variable patient groups. In a community-based study, cervical spine radiographs of 98 RA patients with mean disease duration of 15.7 years were evaluated (Kauppi and Hakala 1994). aAAS, AAI and SAS occurred in 33%, 27% and 21% of the patients, respectively. Cervical spine disorders in 113 patients who had undergone total knee or hip arthroplasty were evaluated retrospectively in a study by Collins et al. (1991). The duration of disease varied from 4 to 60 years. aAAS, AAI and SAS were detected in 49%, 12% and 21% of

the patients, respectively. Pellicci et al. (1981) evaluated 106 patients out of total 163 patients after five years of complaints of pain in neck area. At the end of this symptom-based study, 70% of the patients had subluxation of the cervical spine.

In addition to these population-, arthroplasty-, and symptom-based studies several other cross-sectional evaluations have been done. Data of the patients, follow-up times and the occurrence of subluxations in these cross-sectional studies are presented in Table 2. When examining the results in Table 2, the reader should bear in mind that the diagnostic criteria of RA have changed during time and therefore the incidences of subluxations in earlier and more recent studies are not directly comparable. Although the occurrence of cervical spine changes has been evaluated in several studies, patient materials, follow-up times, types of evaluated disorders and even diagnostic criteria have varied considerably. The prevalence of detailed radiographic changes in long-term RA has not been reported.

Table 2. Prevalence of cervical spine subluxations in cross-sectional studies.

Study	N	Follow-up time in years Mean (range)	Incidence (%)			
			aAAS	AAI	SAS	aAAS, AAI or SAS
Conlon et al. 1966	333	(0-10+)	25	-	-	-
Mathews 1969 (Hospital outpatients)	76	(0-20)	25	8	-	-
Stevens et al. 1971 (Hospital outpatients)	100	11	36	-	-	-
Meikle and Wilkinson 1971	118	13	37	-	26	-
Smith et al. 1972 (Hospital inpatients)	962	(0-30)	-	-	-	16
Pellicci et al. 1981 (Symptom based)	106	24 (6-45)	58	9 (R)	25	70
Halla and Hardin 1990 (Neck-shoulder girdle signs or symptoms)	128	-	28	6 (McG)	9	-
Collins et al. 1991 (Arthroplasty based)	113	(4-60)	49	12 (McG/R)	21	61
Kauppi and Hakala 1994 (Community based)	98	16 (1.5-44)	33	27 (S-K)	21	52

R= Ranawat method, McG = McGregor method, S-K = Sakaguchi-Kauppi method

3.5. Associating clinical factors

Mathews (1969) examined RA patients of a hospital clinic and observed that aAAS was more frequent in patients with longstanding disease, joint erosions, rheumatoid nodules or positive RF. The same variables were reported to associate with deformation of the atlantoaxial facet joints (including vertical, lateral and rotational subluxations; Halla and Hardin 1990). Furthermore, the occurrence of SAS was shown to associate with peripheral erosions and longer duration of RA (Smith et al. 1972, Oda et al. 1995).

The involvement of cervical spine has been reported to occur already after one year of RA (Winfield et al. 1981, Paimela et al. 1997). The early development of cervical spine disorders has been compared to the progression of peripheral erosions in two studies (Winfield et al. 1983, Paimela et al. 1997). Winfield et al. followed up 100 patients with RA for an average of 9.5 years and found that in the majority of patients the timing and severity of the cervical spine subluxations coincided with the progression of peripheral erosions. In a similar 6.5 years follow-up study of Paimela et al., the progression of annual peripheral joint Larsen score was significantly faster in patients with involvement of the cervical spine than in the other patients, and this difference was already observed after one year of RA.

Oda et al. (1995) retrospectively examined the progression of cervical spine changes during a period of five years and observed that patients with highly erosive or mutilating peripheral disease showed accelerated progression of aAAS and AAI when compared to patients with less erosive disease. Furthermore, the presence of aAAS and longer atlantoaxial distance in late RA has been shown to correlate with the severity of erosions in the metacarpophalangeal joints and wrists and with the presence of rheumatoid nodules (Rasker and Cosh 1978).

Collins et al. (1991) reported 61% occurrence of aAAS, AAI or SAS in RA patients who had undergone total knee or hip arthroplasty, demonstrating an association between cervical spine disorders and destruction of large, central joints.

3.6. Bone mineral density

Bone mineral density (BMD) describes the bone strength and decreased BMD is associated with increased risk for fractures (Seeley et al. 1991, Kanis et al. 1994). In standard clinical practise BMD is usually determined as bone mineral content (bone mass) divided by area of measurement using X-ray bone densitometry. BMD is often expressed as a T-score, which represents the number of standard deviations (SD) from the mean peak bone mass. According to the 1994 World Health Organisation (WHO) definition, those with bone mass that is 2.5 SD or more lower than the mean value in young healthy women ($T\text{-score} \leq -2.5$) are classified as having osteoporosis (Kanis et al. 1994). An alternative approach is the use of Z-score, which is calculated as the number of SDs from the mean BMD of age- and sex-matched healthy controls.

A decreased BMD has been shown in a proportion of patients with RA or juvenile polyarthritis (Sambrook et al. 1987, Kotaniemi et al. 1993, Kröger et al. 1994, Haugeberg et al. 2000). Increased disease activity and/or glucocorticoids have been reported to decrease the BMD in both RA and in juvenile polyarthritis (Laan et al. 1993a, Laan et al. 1993b, Kotaniemi et al. 1999). However, these two factors are difficult to separate, because the use of the corticosteroids in RA may be an indicator of severe disease (Kröger et al. 1994).

Bland (1974) described osteoporosis as one of the diagnostic radiological features of rheumatoid cervical spine. Several other authors have observed

osteoporosis in post-mortem studies or in cervical spine radiographs (Ball and Sharp 1971, Meikle and Wilkinson 1971, Mikulowski et al. 1975). However, conventional radiographs are not very reliable in the evaluation of BMD, because over-exposure of the film may simulate osteoporosis (Komusi et al. 1985). Moreover, post-mortem studies generally include older patients and therefore the probability for osteoporosis for other reasons than RA is high.

The essential pathogenetic mechanism in the development of severe AAI is the collapse of lateral masses of axis and/or atlas (Santavirta et al. 1988a). Moreover, aAAS may develop following the destruction of bony attachments of the transversal ligament (Eulderink and Meijers 1976). Some authors have suggested that osteoporosis due to RA and corticosteroid treatment may weaken bony structures of the upper cervical spine and thereby promote the development of AAI or aAAS (Ball and Sharp 1971, Eulderink and Meijers 1976). However, the role of the corticosteroid treatment as a risk factor for cervical spine disorders is controversial (Conlon et al. 1966, Meikle and Wilkinson 1971, Stevens et al. 1971, Smith et al. 1972, Rasker and Cosh 1978, Rudge et al. 1981, Kauppi et al. 1991), and the association between BMD and cervical spine disorders in RA have not been studied.

3.7. Complications

The destructive changes in cervical spine and periodontoid pannus formation may cause the compression of brainstem, cranial nerves, spinal cord or nerve roots, resulting in a large variety of neurological symptoms and even sudden death (Davis and Markley 1949, Kataoka et al. 1979, Menezes et al. 1985, Santavirta et al. 1987a). The compression of brainstem or cranial nerves in RA is usually caused by the odontoid process, which has penetrated through foramen magnum (AAI), while horizontal atlantoaxial and subaxial subluxations (aAAS and SAS)

are the primary disorders causing spinal cord or nerve root compression leading to myelopathy or radiculopathy, respectively (Mayer et al. 1976, Hughes 1977, Menezes et al. 1985, Santavirta et al. 1988b, Zeidman and Ducker 1994, Rawlins et al. 1998). Spinal cord injury is either due to straight mechanical compression and destruction of cord or to vascular compression and ischaemic damage (Delamarter and Bohlman 1994, Mathews 1998). Dvorak et al. (1989) described increased risk for myelopathy in patients with spinal cord diameter less than 6 mm in MRI scan taken in flexion position of the neck. Moreover, a decreased angle between medulla and the upper cervical cord in MRI has been reported to associate with brainstem compression and myelopathy (Bundschuh et al. 1988). The symptoms in patients with spinal cord compression vary from mild subjective weakness to complete quadriplegia, and the neural involvement is usually progressive (Hopkins 1967, Nakano et al. 1978, Casey et al. 1996). The poor prognosis of patients with myelopathy was demonstrated in a study by Meijers et al. (1984), in which nearly 50% of the patients died within two years. In addition to compression of the nervous structures, AAI may impair either blood flow in the vertebral artery or circulation of the cerebrospinal fluid, leading to vertebrobasilar insufficiency or hydrocephalus, respectively (Robinson et al. 1986, Collee et al. 1987).

3.8. Mortality

The life expectancy of patients with RA has been reported to be significantly shortened when compared to general population (Vandenbroucke et al. 1984, Mitchell et al. 1986, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995). Already in 1949 Davis and Markley (1949) described fatal medulla compression caused by atlantoaxial subluxation and herniation of the odontoid process through foramen magnum. Since then several reports of fatal cervical spine disorders in RA have been published (Martel and Abel 1963, Smith et al. 1972, Meijers et al.

1984, Vandenbroucke et al. 1984). Mikulowski et al. (1975) performed a post-mortem study for 104 hospital inpatients with RA, and observed 10% mortality for medulla compression caused by cervical spine destruction. However, in epidemiological studies the role of cervical spine disorders as a cause of death in patients with RA has been minimal (Vandenbroucke et al. 1984, Mitchell et al. 1986, Wolfe et al. 1994). Furthermore, cervical spine involvement in patients with RA has not been reported to shorten life expectancy (Smith et al. 1972, Pellicci et al. 1981). Mortality due to cervical spine disorders has not been studied in a Finnish population.

3.9. Treatment

CONSERVATIVE TREATMENT

Treatment of cervical spine disorders in RA is generally conservative. The aim of non-surgical treatment of cervical spine disorders is to relieve symptoms and to retard the progression of the disease (Moncur and Williams 1988, Kauppi et al. 1998). Active conservative treatment consisting of patient education, physiotherapy, collars, practical aids, symptomatic treatment and active disease-modifying medication has been reported to significantly relieve chronic neck pain (Kauppi et al. 1998). Moreover, custom-made stiff collars and a special type "Headmaster" collar have been shown to restrict atlantoaxial subluxation in selected cases (Kauppi and Anttila 1995, Kauppi and Anttila 1996, Kauppi et al. 1999). However, none of these conservative treatment methods have been shown to prevent the progression of cervical spine involvement.

Recently, active treatment with a combination of DMARDs was reported to increase the rate of remissions and to retard the development of peripheral joint erosions in patients with RA (Boers et al. 1997, Möttönen et al. 1999). Furthermore, in a case report preoperatively administered intravenous

corticosteroid therapy significantly decreased the size of the pannus tissue in cervical spine (Louthrenoo et al. 1992). However, the effectiveness of drug therapies in the prevention of cervical spine destruction in RA has not been evaluated.

OPERATIVE TREATMENT

Surgical intervention may be needed in severe rheumatoid cervical spine abnormalities. The primary indications for operative treatment are myelopathy, neurological deficits and intractable pain resistant to conservative treatment (Conaty and Mongan 1981, Santavirta et al. 1990, McRorie et al. 1996, Grob et al. 1999, Christensson et al. 2000). Weissman et al. (1982) reported increased risk for spinal cord compression in patients with ≥ 9 mm aAAS or with less severe aAAS combined with AAI. Moreover, another study reported 10% mortality rate for cervical spine subluxations in hospital inpatients with RA (Mikulowski et al. 1975). To avoid irreversible neurological deficit or even sudden death, several authors have recommended prophylactic surgery for severe cervical subluxations in asymptomatic patients (Ranawat et al. 1979, Kankaanpää and Santavirta 1985, Santavirta et al. 1987b, Clark et al. 1989, Rana 1989, Papadopoulos et al. 1991, Boden et al. 1993). In these studies, the critical limit for the anterior atlantoaxial distance varied mainly between 8 and 10 mm (Ranawat et al. 1979, Santavirta et al. 1987b, Clark et al. 1989, Rana 1989). Moreover, prophylactic operations have been recommended in patients with severe AAI or with 4 mm or more SAS (Ranawat et al. 1979, Kankaanpää and Santavirta 1985, Clark et al. 1989, Kauppi and Hakala 1994). In a study by Boden et al. (1993), PADI was reported to be more reliable in predicting paralysis and postoperative neurological recovery than the extent of aAAS. They recommended consideration of surgical treatment if PADI was 14 mm or less.

After the development of MRI, clinical evidence of compressive myelopathy was shown to correlate better with the presence of spinal cord distortion in MRI than with the extent of subluxation in plain radiographs (Breedveld et al. 1987). Moreover, MRI has been helpful in determining the levels of surgical intervention in patients with multiple subluxations (Pettersson et al. 1988, Bell and Stearns 1991). Therefore, MRI together with conventional radiographs is the cornerstone of preoperative planning (Pettersson et al. 1988, Roca et al. 1993). Surgical management includes reduction and stabilisation of the spine, and decompression of the neural elements (Boden et al. 1993, Grob et al. 1999, Santavirta et al. 1990).

AIMS OF THE STUDY

The purpose of this thesis was to study certain clinically important aspects of cervical spine disorders in RA.

The specific aims were:

1. To examine the sensitivity of lateral view cervical spine radiographs taken in neutral position in the diagnosis of aAAS.
2. To determine the prevalence of cervical spine changes in patients after 20 years of RA.
3. To evaluate the clinical factors associating with cervical spine changes in late RA, and thereby identify patients with increased risk to develop these disorders.
4. To evaluate the mortality associated with severe cervical spine disorders in patients with RA.
5. To evaluate whether cervical spine changes in RA can be prevented with aggressive medical treatment.

PATIENTS AND METHODS

1. Patients

The objective of the present thesis was to study the diagnostical procedures, prevalence, associating clinical factors, mortality and treatment of cervical spine disorders in RA. For this purpose altogether four patient groups were studied.

1.1. Study I

This series consisted of 65 consecutive patients with unstable aAAS, who were collected between 1994 and 1995 at Rheumatism Foundation Hospital, Heinola, Finland. All patients had aAAS that was 5 mm or more in flexion and 3 mm or less in extension, and the shift between flexion and extension positions was 3 mm or more. Fifty-three patients were women and 12 men, and their mean age and duration of the disease were 51.9 (SD 12.4) and 19.5 (SD 9.5) years, respectively. The diagnosis was RA in 63 of patients, and the remaining two patients had chronic polyarthritis caused by psoriasis or mixed connective tissue disease resembling RA. Most patients had suffered pain in shoulder-neck region but none had presented neurological symptoms or signs of myelopathy.

1.2. Studies II and III

During 1973 - 1975, 118 patients with recent (Ö6 months) seropositive RA were recruited to a follow-up study at the Rheumatism Foundation Hospital. The selection criteria, data of collection strategy and characteristics of the patients have been previously described in detail (Kaarela 1985, Kaarela et al. 1993, Kaarela and Kautiainen 1997). All patients were \times 16 years old and in subsequent evaluations they fulfilled the 1987 ACR criteria for RA. Patients were clinically assessed at the beginning of the study and at 1, 3, 8, 15 and 20 years from entry. A total of 74 and 67 patients attended the 15- and 20-year check-ups,

respectively. During the follow-up period 34 patients died (none because of cervical spine disorder) and 17 patients failed to attend the 20-year check-up. These 67 patients formed the basic patient group of studies II and III. 56 patients were women and 11 men, and their mean age was 61.2 years (range 37 – 86). In addition to these 67 patients, cervical spine radiographs of two patients were received from another unit and they were included in study II.

Initially, the majority of patients in this series were treated with DMARDs, either with D-penicillamine, sodium aurothiomalate or chloroquine, or a combination of the latter two (Sokka et al. 1999). The combination therapy was prescribed to only ~5% of the patients during the first 8 years of the follow-up. Moreover, during the same follow-up time the proportion of non-DMARD-recipients increased considerably, finally exceeding approximately 40% of the patients. In addition to DMARDs, 56% of the patients were at least periodically treated with corticosteroids.

1.3. Study IV

Since 1966, the sickness insurance act in Finland has provided for the prescription of drugs free of charge for certain chronic diseases including inflammatory joint diseases (since amendment made in 1987, 90% of the costs have been reimbursed). The national sickness insurance program covers the entire population of Finland, and almost all patients with RA take advantage of it (Hakala et al. 1993, Myllykangas-Luosujärvi et al. 1995). Eligibility requires a comprehensive medical certificate written by the attending physician who is usually a rheumatologist and is approved by an expert adviser on the behalf of the sickness insurance scheme. In 1989, the total number of subjects who were registered for chronic inflammatory rheumatic diseases was 56175 (Myllykangas-Luosujärvi 1995).

All 48550 subjects who died in Finland during 1989 were identified by computer linkage with Finnish population registry, using the unique identification code assigned for each Finnish citizen. Altogether 1849 subjects (578 men and 1271 women) who died in 1989 were entitled to specially reimbursed medication for chronic inflammatory rheumatic diseases. The basic information was obtained from death certificates and from the certificates for drug reimbursement. In 1666 subjects (480 men and 1186 women), the diagnosis according to the sickness insurance file was RA. The causes of death of these 1666 patients were classified by the statistical office of Finland according to the rules of the WHO using the 9th revision of the international classification of diseases. This study included these 1666 patients with RA who died in Finland in 1989.

1.4. Study V

From April 1993 to May 1995, 199 patients with recent onset (<2 years) RA were recruited to a Finnish multicentre, parallel-group, follow-up study comparing the efficacy and tolerability of the combination-DMARD therapy (simultaneous sulphasalazine, methotrexate, hydroxychloroquine and prednisolone) with those of a single-DMARD (initially sulphasalazine with or without prednisolone) therapy. Oral prednisolone was prescribed for 63 patients in the single-therapy group (according to clinicians' decisions). The details of the study have been previously described (Möttönen et al. 1999). The patient selection criteria were: 1) fulfilling the classification criteria of the ACR for RA (Arnett et al. 1988), 2) age between 18 - 65 years, 3) duration of symptoms of <2 years, and 4) active disease with $\times 3$ swollen joints and at least three of the following: a) erythrocyte sedimentation rate (ESR) $\times 28$ mm/hour or C-reactive protein (CRP) level >19 mg/litre, b) morning stiffness of $\times 29$ minutes, c) >5 swollen joints, or d) >10 tender joints.

One hundred ninety-five patients started the trial (97 received combination and 98 single-drug therapy). Ten patients in the combination group and seven patients in the single-DMARD group withdrew from the study (eight refused to continue, data for six were omitted due to protocol violation, one withdrew due to intercurrent illness, one withdrew due to loss of treatment efficacy and one did not attend the follow-up visits). In addition, cervical spine radiographs of two patients in the combination-therapy group were not performed. Patients were clinically assessed at the beginning of the study and after 1, 3, 4, 5, 6, 9, 12, 18 and 24 months. Radiographs of the hands and feet were taken at baseline and after 24 months of follow-up. They were scored by the method of Larsen et al. (1977). RF was measured at the beginning of the study. The swollen joint count, tender joint count and several other variables including ESR and CRP were used for the evaluation of the disease activity (Möttönen et al. 1999).

2. Methods

2.1. Study I

Lateral view cervical spine radiographs of all 65 patients with unstable aAAS were taken in neutral, flexion and extension positions of the neck. The distance between the posterior aspect of anterior atlas arch and the anterior aspect of odontoid process (atlantoaxial distance) was measured. Atlantoaxial distance in flexion was chosen as the golden standard in the diagnosis of aAAS and its severity. The qualitative (diagnostic) and quantitative (ability to measure the true extent of aAAS) values of neutral position radiographs were assessed by comparing them with the respective flexion and extension radiographs.

2.2. Studies II and III

Cervical spine radiographs were taken from all 67 patients who attended the 20-year follow-up. In study II, these and radiographs of two additional patients were evaluated and the occurrences of aAAS, AAI, SAS and pAAS were recorded. The evaluation of IAAS was possible only in 52 cases, since proper openmouth radiographs were not available in 17 cases. Moreover, the extent of PADI was measured and the presence of subaxial disc space narrowings were recorded. Thereafter, patients with severe cervical spine changes were determined.

In study III, the occurrences of aAAS, AAI, SAS and disc space narrowings were compared to the presence and severity of peripheral, glenohumeral (GH) and acromioclavicular (AC) joint erosions, to the BMD of the lumbar spine and femoral neck and to the age of patients at disease onset. Because aAAS and AAI represent the most characteristic cervical spine disorders in RA, they were referred as atlantoaxial disorders in this study. The BMD of lumbar spine (L2 – 4) and femoral neck was measured from 53 and 57 patients at the 20-year check-up, respectively. Radiographs of hands and feet of all 67 patients taken at the 20-year follow-up and the shoulder radiographs of 61 patients taken at the 15-year check-up were graded in previous studies (Kaarela and Kautiainen 1997, Belt et al. 1998, Lehtinen et al. 1999, Lehtinen et al. 2000). The results of these studies were used for comparison.

2.3. Study IV

Death certificates and certificates for drug reimbursement of all 1666 RA patients who died in Finland in 1989 were evaluated (Figure 9). In addition, hospital records of patients who had died of cardiovascular diseases, neoplasms, RA, respiratory diseases, gastrointestinal diseases, accidents or intoxication, genitourinary diseases, infections, amyloidosis or central nervous system

diseases, as well as those of patients who had mental diseases or were treated at the Rheumatism Foundation Hospital (altogether 853 patients) were collected from hospitals throughout Finland. Thereafter, all cervical spine radiographs that were available and the detailed clinical histories of the patients with diagnosed cervical spine disorder were evaluated separately. The evaluated abnormalities in cervical spine radiographs were aAAS, AAI and SAS. In addition, the extent of PADI was measured.

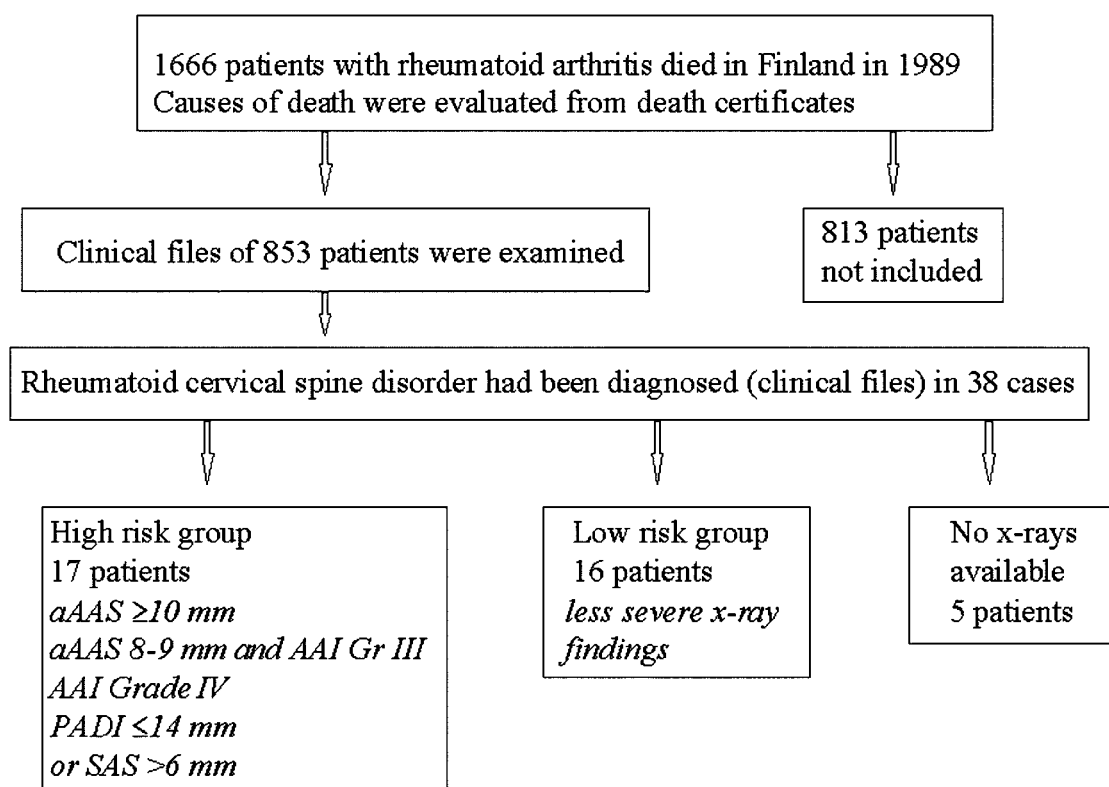


Figure 9. Schematic presentation of the distribution of patients among the study groups (study IV).

To investigate whether the extent of cervical spine changes correlated with the death history, the patients were divided into three groups on the basis of the radiographic evaluation of the cervical spine. In the "high risk group", the cervical spine changes were determined severe enough to carry a high risk for fatal complications. These criteria are defined in a section below (radiography).

In the "low risk group", the radiographic findings were less severe. Patients with a diagnosed cervical spine disorder, whose radiographs were destroyed after death and thus were not available, formed the third group. Classification into high and low risk groups was made without any knowledge of the clinical history.

2.4. Study V

After two years follow-up, cervical spine radiographs were taken from 176 of total 178 patients (85 allocated to the combination-therapy and 91 to the single-therapy group). These radiographs were evaluated and the occurrence and severity of subluxations (aAAS, AAI and SAS) were compared to the strategy of therapy, peripheral joint destruction and clinical and laboratory variables describing the disease activity.

2.5. Radiography

The cervical spine radiographs were taken in lateral (during flexion and extension) and odontoid projections, using a 150 cm tube-to-plane distance. In addition, lateral view radiographs taken in neutral position were included in study I. The definitions, diagnostical methods and criteria for the characteristic rheumatoid cervical spine changes aAAS, AAI, SAS, pAAS and lAAS, as well as the measurement of PADI have been specified in the Introduction. For simplicity, AAI was classified under cervical spine subluxations throughout the present thesis. The criteria for severe radiological subluxations used in study II is based on the indications for surgery as previously defined by several authors (Ranawat et al. 1979, Santavirta et al. 1987a, Boden et al. 1993, Kauppi and Hakala 1994). These criteria included aAAS ≥ 9 mm, aAAS 6 – 8 mm combined with AAI, SAS > 5 mm or PADI ≤ 14 mm. In study IV, the inclusion criteria for the "high risk" group were stricter than those in study II in order to only include patients with very probable spinal cord or brainstem compression (Boden 1994). These criteria

were: aAAS ≥ 10 mm, aAAS 8 – 9 mm combined with AAI S-K grade III, AAI S-K grade IV, SAS >6 mm and PADI ≤ 14 mm.

Radiographs of hands and feet (studies III and V) were taken in the dorsovolar projection (Kaarela and Kautiainen 1997, Belt et al. 1998). The Larsen grades for the 1st to 5th metacarpophalangeal joints, wrists and 2nd to 5th metatarsophalangeal joints (20 joints) were assigned and added together to form the Larsen score of 0 to 100. Shoulder radiographs (study III) were taken in the following standard positions: patient supine, slightly turned (20 degrees) to the imaged side, and the arm in external rotation, palm facing upwards (Lehtinen et al. 1999, Lehtinen et al. 2000). The sums of the left and right GH or AC joint Larsen grades were calculated to describe the destruction of these central joints (i.e. range of the joint destruction varied from 0 to 10).

2.6. Bone mineral density

BMD of the lumbar spine (L2 – 4) and femoral neck was measured using dual X-ray bone densitometry. The BMD is described as a Z-score, which represents the number of SDs from the mean, weight adjusted, BMD for persons of the same age and sex.

2.7. Statistics

The descriptive values of variables which followed a normal distribution were expressed as the mean and SDs, and statistical comparison between the groups was performed using Student's t-test. If the variables did not have a normal distribution or were ordinal, the descriptive values were expressed as the median and interquartile range (IQR) or range, and statistical comparison between the groups was performed using Mann-Whitney U-test. Frequencies and percentages were analysed by chi-square test or Fischer's exact test. The normality of

variables was evaluated by the Kolmogorov-Smirnov test, with a Lilliefors significance test or Shapiro-Wilk test. Correlation coefficients were calculated by the Pearson or Spearman method. The most important descriptive values were expressed as 95 percent confidence interval (95% CI). The α level was set at 0.05 for all tests.

RESULTS

This section reviews the main results of the five studies included in this thesis. Further details are presented in the original articles.

1. Cervical spine radiographs taken in neutral position in the evaluation of aAAS (study I)

The significance of lateral view cervical spine radiographs taken in neutral position in the evaluation of aAAS was studied in 65 patients. In this series, all patients had unstable aAAS, with an average of 6.4 (SD 1.8) mm difference in atlantoaxial distance between flexion and extension radiographs. The mean atlantoaxial distances in flexion, extension and neutral position were 7.4 (SD 1.5) mm, 1.1 (SD 0.9) mm and 4.1 (SD 3.1) mm, respectively. The differences in atlantoaxial distances between these three positions were statistically significant ($p < 0.0001$). Atlantoaxial distance in neutral position was similar to that measured during flexion in 22 (34%) patients, pathological but shorter than that measured during flexion in 12 (18%) patients and normal (i.e. 3 mm or less) in 31 (48%) patients. Therefore, the sensitivity of neutral position radiographs in the diagnosis of AAS was 52% (95% CI 39.5-64.9) and in measuring the true extent of abnormality it was 34% (95% CI 22.6-46.6).

2. Prevalence of and clinical factors associating with cervical spine changes (studies II and III)

2.1. Prevalence of cervical spine changes

Radiological changes in the cervical spine were evaluated in 69 patients with seropositive RA followed prospectively for 20 years. Altogether 29 (42%) patients presented subluxation in the cervical spine. The diagnosis of aAAS, AAI,

and SAS was made in 16 (23%), 18 (26%), and 13 (19%) of the patients, respectively. IAAS was recorded in 3/52 (6%) patients and none of the patients had pAAS. Narrow subaxial disc spaces were observed in 45 (65%) patients, with an average of three disc space narrowings per patient. The most common level for this finding was disc space C5 - 6 (84% of the patients with disc space narrowing), whereas changes in the C2 - 3 disc space were the most rare (38% of the patients with disc space narrowing). Ten patients presented aAAS only in flexion whereas in six patients aAAS was also observed in extension. All these six patients also had AAI, which represents the erosive character of a stable aAAS. Severe cervical spine abnormalities were observed in seven (10%) patients. The details of patients with severe cervical spine changes are presented in Table 3. None of the patients had undergone operations due to cervical spine disorders.

Table 3. Age, sex and cervical spine findings in 7 patients who had severe cervical spine changes after 20 years of rheumatoid arthritis.

Patient	Age (years)	Sex	AADI flexion, mm	AADI extension, mm	AAI, S-K grade	SAS, mm	PADI, mm
1	64	F	1	1	I	CII-III 6	24
2	71	F	8	3	II	CIII-IV 5 CIV-V 6	16
3	61	F	6	1	II	0	20
4	57	F	6	6	II	CIII-IV 5	18
5	73	M	10	8	III	CIII-IV 5	15
6	65	F	15	9	II	CIV-V 5	11
7	47	F	9	8	II	0	18

AADI = anterior atlantodental interval, S-K = Sakaguchi-Kauppi method
Criteria for severe radiological cervical spine changes are defined in the Methods section in text (page 42).

2.2. Relationship between atlantoaxial disorders and the destruction of peripheral and shoulder joints

To better define patients with an increased risk for cervical spine disorders, the occurrence and severity of atlantoaxial disorders was compared to the destruction of peripheral and shoulder joints. A statistically significant relationship was observed between the presence of atlantoaxial disorders and the destruction of peripheral, GH and AC joints (Table 4). Moreover, the severity of destruction in these joints positively correlated to a certain extent with the severity of aAAS and AAI (Table 5).

Table 4. Larsen score/grade of peripheral, glenohumeral (GH) and acromioclavicular (AC) joints in RA patients with and without atlantoaxial disorders (aAAS or AAI).

	Patients without atlantoaxial disorders		Patients with atlantoaxial disorders		p value
	N	Median (IQR)	N	Median (IQR)	
Larsen score of peripheral joints (0-100)	45	33 (16, 48)	22	68 (47, 81)	0.001
Larsen grade of GH joints (0-10)	40	2 (0, 3)	21	4 (3, 7)	<0.001
Larsen grade of AC joints (0-10)	40	3 (1, 4)	21	5 (4, 7)	<0.001

Table 5. Correlation between the severity of atlantoaxial disorders (aAAS and AAI) and Larsen score/grade of the peripheral and shoulder joints.

Larsen score/grade	Atlantoaxial distance (mm) r (95% CI)	Severity of atlantoaxial impaction (S-K grade) r (95% CI)
Peripheral joints	.44 (.22 to .61)	.44 (.22 to .61)
Glenohumeral joints	.46 (.24 to .64)	.37 (.13 to .57)
Acromioclavicular joints	.40 (.17 to .60)	.41 (.18 to .60)

S-K = Sakaguchi-Kauppi method, r = correlation coefficient, CI = confidence interval

2.3. Association between atlantoaxial disorders and bone mineral density

To investigate the suspected influence of decreased BMD on the development of atlantoaxial disorders, BMD of patients with and without atlantoaxial disorders was examined. The BMD at the femoral neck was significantly decreased in patients with atlantoaxial disorders (Table 6).

Table 6. Lumbar spine and femoral neck Z-scores of bone mineral density (BMD) in RA patients with and without atlantoaxial disorders (aAAS or AAI).

	Patients without atlantoaxial disorders		Patients with atlantoaxial disorders		p value
	N	BMD Z-score Mean (95% CI)	N	BMD Z-score Mean (95% CI)	
Lumbar spine	37	0.45 (-0.20 to 1.11)	16	-0.35 (-0.97 to 0.27)	0.13
Femoral neck	40	-0.30 (-0.63 to 0.04)	17	-1.00 (-1.48 to -0.52)	0.019

BMD Z-score = number of SDs from the mean BMD of age- and sex-matched healthy controls, CI = confidence interval

However, the difference in the BMD of the lumbar spine between the two groups did not reach statistical significance. The results were similar even if patients with aAAS or AAI were evaluated separately.

2.4. Clinical factors associated with subaxial subluxations

In contrast to atlantoaxial disorders, no significant relationship was found between the occurrence of SAS and the destruction of peripheral, GH or AC joints, or BMD in the lumbar spine or femoral neck. However, the prevalence of SAS and subaxial disc space narrowing associated with the late onset age of RA. In patients with SAS, the mean age at the onset of RA was 48 (SD 8) years and in the other group 39 (SD 12) years ($p = 0.015$).

3. Mortality associated with cervical spine disorders (study IV)

The high frequency of severe cervical spine changes observed in study II prompted us to study the mortality associated with cervical spine disorders in RA. According to the official death certificates, rheumatoid cervical spine destruction was not an underlying, contributory or immediate cause of death in any of the 1666 patients with RA who died in Finland in 1989. Cervical spine disorder was diagnosed in 38 patients (nine males and 29 females; mean age 68 years, range 39 - 90 years) according to the clinical files of 853 patients (Figure 9). Thus, the prevalence of rheumatoid cervical spine disorders was only 4.5%. Six patients had undergone surgical operation of the cervical spine and one of those had been operated three times.

Cervical spine radiographs were available in 33 of these 38 patients. In 17 (52%) cases cervical spine changes (at least one abnormality, often several simultaneously) were determined to be severe enough to carry a high risk for fatal complications, and these patients formed the "high risk group". 16 patients had

less severe changes in their cervical spine radiographs and they were classified to have low risk for fatal complications ("low risk group"). Furthermore, cervical spine radiographs were not available from 5 patients with a diagnosed rheumatoid cervical spine deformity, and they formed the third group (no radiographs available).

There were no apparent differences in the gender, age or official main causes of death between these groups. Instead, the clinical histories of patients in the high risk group presented more evidence of possible complications caused by cervical spine changes than those of patients in the low risk group (Table 7). In the high risk group, three patients had quadri- or paraparesis, which was probably caused by rheumatoid cervical spine deformity. In addition, four patients died suddenly, one died due to a brain stroke, one patient died soon after a cervical spine operation and a further three patients also died postoperatively.

Table 7. The clinical history preceding the death of 38 RA patients with a diagnosed cervical spine abnormality.

Clinical history*	High risk group N = 17	Low risk group N = 16	No radiographs N = 5
Brain stroke	1	1	0
Non-ambulant patient	5	3	0
Paraparesis/quadriparesis	3	1	0
Sudden death	4	0	0
Postoperative death:			
Cervical spine operation	1	0	0
Other operation	3	2	1
Death from gastrointestinal disease	3	1	0
Uraemia	2	5	1
Pulmonary embolism	1	1	0
Sepsis/infection	3	7	2
Heart stroke	1	2	2

* Patients may have had several incidents simultaneously

4. Effect of combination drug therapy on the incidence of cervical spine changes (study V)

The effectiveness of combination-DMARD therapy versus single-DMARD therapy in the prevention of cervical spine subluxations was studied in 176 patients with a recent onset RA. At the baseline the patient groups were comparable with regard to the demographic, clinical, and radiographic variables (Möttönen et al. 1999). After two years, 6 (3.4%) of the 176 RA patients had aAAS (95% CI 1.3-7.3). AAI and SAS were recorded in 2 (1.1%) of 176 patients (95% CI 0.1-4.0) and 5 (2.8%) of 176 patients (95% CI 0.9-6.5), respectively. None of the cervical spine changes were severe (i.e. all aAAS and SAS distances were <6 mm and both AAI patients had grade II impaction). Eleven patients had only one disorder and one patient had a combination of aAAS (distance 4 mm) and AAI (grade II).

None of the patients in the combination-therapy group had aAAS (95% CI 0.0-4.2) or AAI (95% CI 0-4.3). The incidences of aAAS and AAI in the single-therapy group were 6.6% (95% CI 2.5-13.8) and 2.2% (95% CI 0.3-7.7), respectively. The difference in the aAAS incidence between the two treatment arms was statistically significant ($p = 0.029$). SAS was observed in 2 (2.2%) of the 91 patients (95% CI 0.3-7.7) in the single-therapy and in 3 (3.5%) of the 85 patients (95% CI 0.7-10.0) in the combination-therapy group.

Of the 6 patients with aAAS, 5 were females and 4 were RF positive. None of them had subcutaneous nodules. A positive correlation was found between the presence of aAAS and peripheral joint destruction (Larsen score) after 24 months follow-up ($p < 0.01$; Figure 10). In patients with aAAS the median Larsen score was 28 (6-38) and in the other patients it was 7 (0-53). None of the patients who had aAAS, AAI or SAS achieved remission during the study.

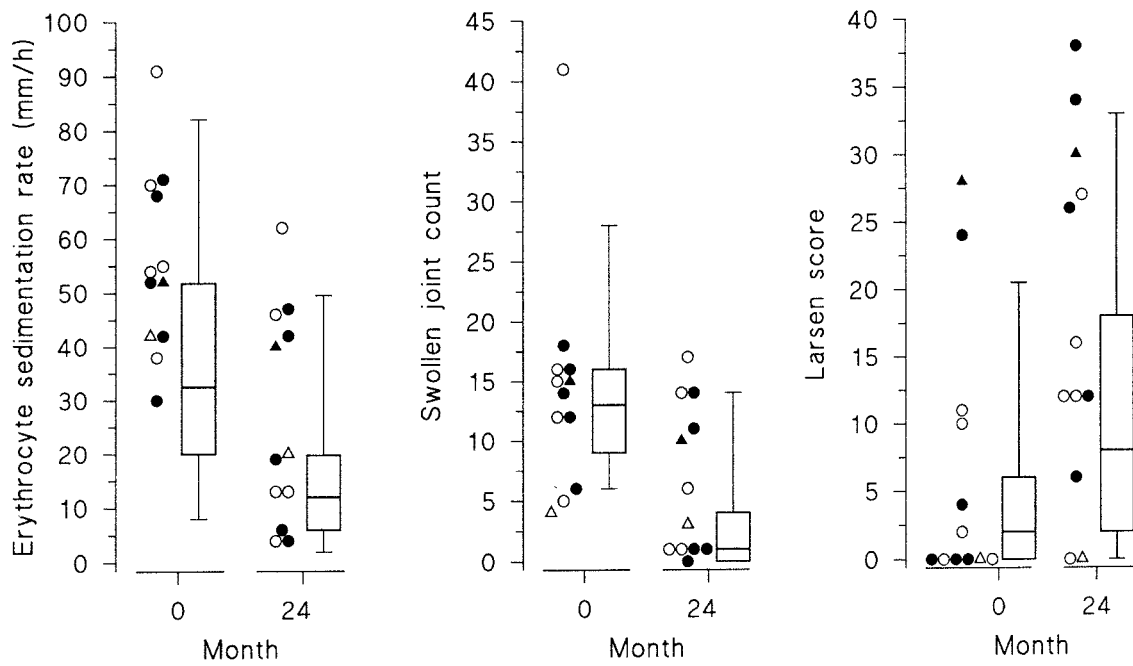


Figure 10. Erythrocyte sedimentation rate, swollen joint count, and Larsen score (0-100) in patients with cervical spine subluxations after two years of rheumatoid arthritis. Boxes show the distance between quartiles, with the median marked as a line, and “whiskers” show 5th and 95th percentiles of all 176 patients. \bullet = aAAS, \circ = AAI, \blacktriangle = SAS and \triangle = aAAS + AAI (study V).

DISCUSSION

The first study of the present thesis evaluated the diagnostic reliability of cervical spine radiographs of RA patients taken in the neutral position. Thereafter, the prevalences of different types of cervical spine changes were examined in patients with long-lasting RA. The results, which demonstrated high prevalence of subluxations including severe ones, prompted us to evaluate these patients further to distinguish those with an increased risk to develop cervical spine disorders. In addition, the mortality associated with cervical spine disorders was studied. Finally, we examined whether the development of cervical spine subluxations can be prevented with aggressive systemic drug therapy.

1. Radiographs taken in neutral position in the examination of cervical spine

In the departments of rheumatology the plain cervical spine radiographs of patients with RA are usually taken both in flexion and extension position of the neck. However, it is well known that in many other units the cervical spine radiographs of RA patients are mainly taken only in neutral position. The diagnostic significance of neutral position radiographs in the evaluation of aAAS, when compared with flexion position radiographs, has not been studied. We therefore wanted to examine the sensitivity of plain radiographs taken in neutral position in the diagnosis of aAAS and in the evaluation of its severity. In patients with unstable aAAS, the diagnostic sensitivity of lateral view radiographs taken in neutral position was only 52% when compared to radiographs taken in flexion. Moreover, in 66% of these patients the neutral position radiographs did not reveal the true severity of aAAS. Therefore, lateral view cervical spine radiographs of RA patients should always be taken during flexion and preferably also during extension of the neck. The significance of neck position in the radiological

examinations of cervical spine in patients with horizontal atlantoaxial instability has previously been described in MRI studies. In these patients MRI taken in flexion was reported to be more reliable in the detection of decreased spinal canal diameter and spinal cord compression than MRI taken in neutral position (Dvorak et al. 1989, Roca et al. 1993).

2. Early incidence, progression and late prevalence of cervical spine changes

Atlantoaxial subluxations have been reported to occur already after two years of RA (Mathews 1969, Meikle and Wilkinson 1971). In the study by Winfield et al. (1981), aAAS developed in 10 out of 100 patients during the first 2 years of RA (Table 8). Patients were treated mainly with penicillamine and gold. Paimela et al. (1997) reported similar frequency in patients who were treated with DMARDs according to "sawtooth strategy". After 2-years follow-up, the incidences of aAAS, AAI and SAS were 9%, 4% and 2%, respectively. These rates are in accordance with the results in study V, in which the incidences of aAAS, AAI and SAS in patients who were treated with a single-DMARD therapy were 6.6%, 2.2% and 2.2%, respectively.

The above results demonstrate that rheumatoid inflammation in the cervical spine occurs already at an early stage of RA. At the beginning, the inflammation affects the ligaments, articular capsules and other stabilizing structures of the cervical spine, resulting in increased laxity and thereafter the development of aAAS (Martel and Abel 1963, Bland 1974). Sustained inflammation of the atlantoaxial facet joints, in turn, leads to the erosions of these joints and results in AAI. Thereafter, the laxity of ligaments still allows atlas to glide forward in relation to axis, but the roughness of articular surfaces may reduce the movement causing stable aAAS (Kauppi et al. 1996).

Table 8. Early incidence and late prevalence of cervical spine subluxations in prospective studies.

Study*	N	Mean follow-up time (years)	Incidence/prevalence (%)			aAAS, AAI or SAS
			aAAS	AAI	SAS	
Winfield et al. 1981 Conventional therapy	100	2	10	-	19	-
Paimela et al. 1997 "Sawtooth" strategy	67	2	9	4 (McG)	2	-
Neva et al. 2000 (study V)						
Single DMARD	91	2	6.6	2.2 (S-K)	2.2	10
Combination of DMARDs	85	2	0	0 (S-K)	3.5	3.5
Corbet et al. 1993 Conventional therapy	64	15	-	-	-	19
Rasker and Cosh 1978 No data of therapy available	62	15	42	32 (McG)	-	-
Neva et al. 2000 (study II) Conventional therapy	69	20	23	26 (S-K)	19	42

*Studies are in order of follow-up time

DMARD = disease-modifying antirheumatic drug, McG = McGregor method, S-K = Sakaguchi-Kauppi method

This phenomenon was observed in study II, in which all patients with stable aAAS also presented AAI. Finally, the lateral masses of atlas and/or axis may collapse and increase the severity of AAI. Erosions of the facet joints are also the outstanding feature in the development of SAS (Ball and Sharp 1971). Therefore, both SAS and AAI predominantly occur after prolonged RA.

Cervical spine subluxations and atlantoaxial facet joint involvement have been reported to occur mainly at a later stage of RA (Mathews 1969, Smith et al. 1972, Halla and Hardin 1990). Corbet et al. (1993) reported 19% occurrence of cervical spine subluxations after 15 years follow-up (Table 8). Unfortunately, the types of subluxations were not specified. Rasker and Cosh (1978) reported significantly higher prevalences of cervical spine disorders during the same follow-up time. The rates of aAAS and AAI were 42% and 32%, respectively. The number of subluxations in total or the prevalence of SAS was not reported.

The variable results on the occurrence of subluxations and the absence of detailed information on different types of disorders in the above mentioned two follow-up studies encouraged us to examine the prevalence of cervical spine abnormalities in patients who had suffered from RA for 20 years. Altogether 42% of the patients presented cervical spine subluxations. The prevalences of aAAS, AAI and SAS were 23%, 26% and 19%, respectively. Bearing in the mind the pathogenetic process leading to AAI and SAS, it was somewhat expected that the increase in the occurrence of these abnormalities in longstanding RA was even more outstanding than the increase in the prevalence of aAAS. At this stage of RA, aAAS has progressed to AAI in the majority of patients with atlantoaxial disease.

In addition to the high prevalence of cervical spine subluxations, narrowings of disc spaces were frequently observed. However, both RA and osteoarthritis of

cervical spine may result in the development of narrow disc spaces as well as in SAS (Bland 1974, Bland 1987a). In study III, the occurrence of these disorders had a positive relationship with the late onset age of RA, indicating that these changes were more common in older patients, who often have degenerative changes in their cervical spine. Indeed, most of the disc space narrowings were located at level C5 – 6, a finding which is more characteristic for degenerative than rheumatoid disease. Moreover, SAS caused by RA may be difficult to distinguish from degenerative spondylolisthesis. Therefore, I suppose that in a significant proportion of the patients narrowings of disc spaces and SAS developed as a result of degenerative disease rather than RA.

Interestingly, the prevalence of severe cervical spine subluxations was high (10%). The criteria for severe subluxations were determined on the basis of operative indications previously defined by several authors (Ranawat et al. 1979, Santavirta et al. 1987a, Boden et al. 1993, Kauppi and Hakala 1994). Therefore, it seems that approximately 10% of patients with longstanding RA may need surgical intervention due to high risk for myelocompression. However, the radiographic indications for surgery are always relative and additional factors including the patients' general condition and symptoms influence the decision for surgical treatment. Moreover, in these patients MRI would give more accurate information on the risk for spinal cord compression and thereby help the clinician to choose between surgical and conservative treatment.

3. Clinical factors associating with cervical spine changes

The occurrence and severity of rheumatoid cervical spine subluxations have been reported to correlate with the severity of peripheral disease in early as well as in late stage of RA (Rasker and Cosh 1978, Winfield et al. 1983). A positive relationship between the occurrence and severity of late atlantoaxial disorders

(aAAS and/or AAI) and the degree of peripheral joint destructions was confirmed in study III, in which the duration of RA was 20 years. Moreover, the incidence of early (24 months) aAAS positively correlated with the severity of peripheral joint erosions in study V.

Association between the destruction of central joints and the prevalence of cervical spine changes in RA have been evaluated only in few studies (Kauppi et al. 1990, Collins et al. 1991). Collins et al. reported 61% occurrence of cervical spine subluxations in patients with RA who had undergone total hip or knee arthroplasty. Although pain in the neck and shoulder area is common in RA patients with or without cervical spine involvement, no studies considering the relationship between cervical spine disorders and destruction of shoulder joints have been published. In study III, we wished to evaluate whether patients with cervical spine changes also present destruction of shoulder joints. Interestingly, GH and AC joints were significantly more destructed in patients with atlantoaxial disorders than in other patients. This association is important to recognise when examining and treating pain in the neck and shoulder area in patients with RA.

The results presented in study III demonstrate that RA patients with destructive articular disease also have an increased risk for cervical spine involvement. Therefore, these patients should have cervical spine radiographs taken at regular intervals and the frequency should be determined by the clinical stage. In addition, excessive flexion-extension movements during intubation in general anaesthesia may cause myelocompression in patients with severe cervical spine changes (Matti and Sharrock 1998). Therefore, to avoid serious complications caused by compression of the spinal cord or brainstem during anaesthesia, cervical spine of patients with severe RA should be examined before major surgery.

Destruction of the bony attachments of the transversal ligament has been reported to cause aAAS. Moreover, collapse of the lateral masses of atlas and/or axis is a major cause for the development of severe AAI. Osteoporosis has been suggested to weaken all these structures, and thereby increase the risk for aAAS and severe AAI (Eulderink and Meijers 1976). However, the association between BMD and atlantoaxial disorders in RA have not been previously studied. In study III, we demonstrate decreased BMD of the femoral neck in patients with aAAS or AAI. However, the difference in BMD of the lumbar spine between patients with and without atlantoaxial disorders did not reach statistical significance. Osteophytes and end-plate erosions have been reported to influence spinal bone mass in elderly, postmenopausal women (von der Recke et al. 1996). The majority of patients in study III belonged to this category, and therefore in these patients femoral neck is more reliable than lumbar spine for the measurement of BMD. Our results demonstrate that RA patients with atlantoaxial disorders have also decreased BMD, and thereby support the notion that osteoporosis may promote the development of aAAS and AAI. However, to better understand the significance of low BMD in the development of atlantoaxial disorders, further studies are needed. Unfortunately, we could not evaluate the influence of corticosteroids on the development of atlantoaxial disorders in our study, since the patients had received different quantities of corticosteroids for variable periods during the long follow-up time.

4. Life-threatening complications caused by cervical spine disorders

Severe cervical spine destruction and pannus formation in RA may cause compression of neural and vascular structures in the area of spinal cord and brainstem (Delamarter and Bohlman 1994). Chronic compression of these structures may lead to myelopathy and eventually result in para- or quadriplegia

(Hopkins 1967, Nakano et al. 1978). These neurological symptoms reduce the patient's ability to move and may thereby cause life-threatening complications. Moreover, trivial traumas in daily life or intubation during anaesthesia may cause myelocompression in patients with severe instability or impaction of the upper cervical spine, and even result in sudden death (Bland 1974, Mikulowski et al. 1975, Nakano et al. 1978). Mikulowski et al. (1975) reported 10% incidence of fatal medulla compression caused by atlantoaxial disorders in post-mortem examinations of hospital inpatients with RA. Interestingly, the prevalence of severe cervical spine changes in our 20-years follow-up material was also 10% (study II). Taken together, these results suggest that severe cervical spine destruction with high risk for complications develop in approximately 10% of patients with long-term RA.

In study IV we evaluated the death certificates of all 1666 RA patients who died in Finland during one year. Surprisingly, not a single death was officially recorded as being caused by a cervical spine disorder. Four hundred fifty-three patients were autopsied, but unfortunately the examination of the upper cervical spine is not included in routine post-mortem examination. Because of this unexpected result, hospital records of 853 out of 1666 subjects were carefully evaluated. These patients included those who died of RA or amyloidosis and who were treated in the Rheumatism Foundation Hospital, indicating that the patients in this group suffered from more severe RA than those in the other group, and most probably the frequency of cervical spine changes was also higher in this group. According to hospital records, a cervical spine disorder was diagnosed only in 38 patients (4.5%), which is a considerably lower frequency than the prevalence in our 20-year follow-up study (study II) or in other previous studies (Tables 1 and 2). As demonstrated in study III, patients with severe cervical spine changes present also major destructions in the central and peripheral joints. The presence of mutilating peripheral disease may focus clinician's attention to the

condition of peripheral joints and therefore cervical spine involvement may remain unrecognised. Moreover, patients with less severe rheumatoid cervical spine changes are often asymptomatic (Mathews 1969, Collins et al. 1991). Therefore, I suppose that several cases with minor, but probably also some with severe cervical spine changes were not diagnosed in study IV, which supports the conclusion that cervical spine disorders were poorly diagnosed in Finland in 1980:es.

In radiographs of 17 patients out of the 38 patients with diagnosed cervical spine disorder, the cervical spine changes were severe enough to carry a high risk for the compression of spinal cord or brainstem. In addition, in several patients with severe cervical spine changes the clinical history preceding the death presented evidence of possible spinal cord or brainstem compression. In these patients, three quadri- or paraparesis, four sudden deaths, one brain stroke and four postoperative (one after cervical spine surgery) deaths were recorded. Therefore, although cervical spine disorders were not the official cause of death in any of these patients, further analysis suggested that severe cervical spine disorders contributed to the death of some patients. Previous epidemiological studies show that cervical spine involvement does not shorten the life expectancy in RA (Smith et al. 1972, Pellicci et al. 1981), and this conclusion is supported by our study. However, one has to bear in mind that in individual patients these disorders may cause severe and even life-threatening complications.

5. Drug therapy in the treatment of cervical spine changes

Peripheral erosions and cervical spine changes develop due to persistent rheumatoid inflammation. Both glucocorticoids and DMARDs regulate the inflammatory process. Active treatment with glucocorticoids or DMARDs has been shown to reduce the progression of peripheral destructions in RA (Kirwan

1995, Möttönen et al. 1996). Sokka et al. (1999) compared the radiological outcome of two RA cohorts treated either with conventional monotherapy or according to "sawtooth" strategy. After eight years follow-up the more extensively treated patients demonstrated significantly less destruction in their peripheral joints. In studies II and III we also showed that, in the same conventionally treated group of patients the occurrence of cervical spine changes was high and associated with the presence of destructions in both shoulder and peripheral joints.

Recently, aggressive therapy with a combination of DMARDs was reported to slow the progression of peripheral destructions when compared to treatment with a single DMARD (Boers et al. 1997, Möttönen et al. 1999). We therefore examined whether aggressive treatment with a combination of DMARDs also retards the development of cervical spine changes in patients with RA (study V). The incidence of cervical spine subluxations in patients treated with a single DMARD was in accordance with previous studies (Table 8). However, none of the patients in the group receiving a combination of DMARDs presented atlantoaxial subluxations, which are the most characteristic cervical spine changes caused by RA. In contrast, the incidence of SAS was similar in both treatment arms. However, SAS is also caused by degenerative diseases (Bland 1987a), and therefore the role of RA in the development of this disorder remains uncertain, as also demonstrated in study III.

The radiographic progression of peripheral joint destruction has been an important tool in assessing the effectiveness of systemic drug therapies in clinical studies. However, since local corticosteroid injections are effective in the treatment of peripheral joint synovitis (Green et al. 2001), they may also influence the development of erosions in these joints. In contrast, the joints of cervical spine are not routinely injected, and therefore this area may reflect the

systemic effect of drug therapy better than the peripheral joints. Therefore, in addition to radiographs of peripheral joints radiographic evaluation of the cervical spine may be informative in the assessment of the long-term effectiveness of anti-rheumatic drug therapies.

Previously, no conservative treatment has been reported to influence the development of cervical spine disorders in RA. We have presented the first study, which evaluates the effectiveness of systemic drug therapy in the prevention of cervical spine changes in patients with RA. These results confirm the clinical hypothesis that rheumatoid cervical spine changes can be prevented or retarded using aggressive treatment with a combination of DMARDs. In the future, aggressive medical treatment of RA patients may reduce the high incidence of cervical spine abnormalities demonstrated in study II, as well as the occurrence of severe abnormalities and possible life-threatening complications.

SUMMARY AND CONCLUSIONS

The purpose of this thesis was to obtain information on the diagnostical procedures, prevalence, associating clinical factors, mortality and treatment of cervical spine disorders in RA.

In the first study, the sensitivity of cervical spine radiographs taken in neutral position in the evaluation of aAAS was compared to the sensitivity of radiographs taken in flexion position. Using radiographs taken in neutral position aAAS was diagnosed only in 52% of patients who presented aAAS in radiographs taken in flexion. Moreover, the ability of neutral position radiographs to demonstrate the true extent of aAAS was significantly impaired further indicating that, cervical spine radiographs of RA patients should always be taken in flexion position of the neck.

The late prevalence of cervical spine changes was studied in 69 RA patients who were followed up for 20 years since the onset of the disease. aAAS, AAI and SAS were diagnosed in 23%, 26% and 19% of the patients, respectively. In addition, severe cervical spine changes with high risk for complications were recorded in approximately 10% of patients. Thereafter, the prevalence and severity of aAAS, AAI and SAS were compared with the occurrence and severity of peripheral and shoulder joint destruction, and BMD in the lumbar spine and femoral neck. Patients with aAAS or AAI presented significantly more erosions in peripheral, AC and GH joints. In addition, the severity of atlantoaxial disorders (aAAS or AAI) positively correlated with the grade of destruction in the evaluated joints. Moreover, BMD of the femoral neck was significantly lower in patients with atlantoaxial disorders than in the other group. These results indicate that cervical spine disorders are common in longterm RA and patients with severe RA have an increased risk for cervical spine involvement. They also

suggest that decreased BMD may influence the development of atlantoaxial disorders.

The mortality caused by cervical spine disorders was studied in RA patients who died in Finland during a period of one year. According to the death certificates, cervical spine disorders were not an official cause of death in any of these patients. However, a detailed examination of hospital records and cervical spine radiographs indicated that cervical spine disorders were poorly diagnosed in Finland in 1980:es, and in certain patients they most likely had resulted in life-threatening complications.

Finally, the effectiveness of combination-DMARD therapy in the prevention of rheumatoid cervical spine changes was studied. One hundred ninety-five patients with recent-onset RA were randomly assigned to receive either a combination of DMARDs or a single-DMARD therapy. After two years follow-up the incidences of aAAS and AAI were 6.6% and 2.2% in the single-therapy group, respectively, whereas none of the patients in the combination-therapy group presented these disorders. The difference in the occurrence of aAAS between the two groups was statistically significant. In conclusion these results suggest that cervical spine disorders caused by RA can be retarded or even prevented with aggressive systemic drug therapy.

ACKNOWLEDGEMENTS

The present study was carried out at the Rheumatism Foundation Hospital, Heinola in co-operation with the Department of Surgery, Tampere University Hospital and the Medical School, University of Tampere.

I am very grateful to Professor Markku Järvinen, a honorable and supportive person, for his encouragement to do scientific work and for offering me the possibility to undertake this thesis as well as my orthopaedic specialization at Tampere University.

My deepest gratitude goes to my supervisor Docent Markku Kauppi, who has been the best supervisor I can imagine. Years of clinical work and research experience on cervical spine disorders have given him an excellent knowledge of this topic. He always has a lot of great ideas for new studies and how to overcome the difficulties. His optimistic way of thinking and flexible character have greatly aided in completing this thesis. He has always been ready to help me, even at the expense of his family life.

My special gratitude is extended to Docent Eero Belt, my second supervisor. He has been very supportive during these years and his example has inspired me to carry on this work. He also has been an important person in introducing me to the field of orthopaedic and trauma surgery.

My warm thanks to the reviewers of this thesis, Docent Leena Laasonen and Docent Leena Paimela for their comments and constructive criticism.

I am deeply grateful to Mr. Hannu Kautiainen for his help in statistical work and graphics, as well as for constructive comments on this thesis.

I am indebted to Docent Kalevi Kaarela, the present head of the 20-year follow-up survey, for an optimistic support during these years, and to Docent Riitta Myllykangas-Luosujärvi for a possibility to co-operate in the evaluation of her mortality data.

I am grateful to Docent Timo Möttönen, the main organizer of the FIN-RACo trial, for providing me a chance to utilize this patient material. Warmest thanks also to the other members of the FIN-RACo trial group for co-operation, and in particular to Professor Marjatta Leirisalo-Repo, Professor Martti Nissilä, Docent Pekka Hannonen and Docent Reijo Luukkainen for revising the article with constructive criticism.

I wish to express my gratitude to Dr. Antero Kotaniemi and Dr. Janne Lehtinen, the co-authors of my original studies for their valuable help and collaboration.

I am also indebted to Mrs. Hannele Kalske, Head of the Rheumatism Foundation Hospital, and to Docent Isto Nordback, Head of the Department of Surgery, Tampere University Hospital, for providing facilities and working environment for this study.

Special thanks go to Docent Kimmo Vihtonen, Docent Ilkka Kiviranta and Dr. Mauri Kammonen for encouraging me in scientific work as well as in the field of orthopaedic surgery and for providing me the possibility to do research in addition to my clinical work.

My warmest thanks also to all colleagues at the Department of Orthopaedic Surgery in Rheumatism Foundation Hospital, and at the Departments of Surgery in Jyväskylä Central Hospital and in Tampere University Hospital, for collaboration and friendship and to all my good friends for relaxing activities during these years.

Very warm thanks to my parents Kerttu and Lasse, and to Marja, Seppo and Reijo, who have always supported me in my academic career.

During the last nine autumns I have shared a lot of colourful and unforgettable moments with my partner Pia Isomäki. Without her endless patience, understanding and love this thesis would have been a neverending story.

Last but not least, Rudolf Sebastian has opened my eyes to new areas of life.

This study was supported by the Rheumatism Foundation Hospital PATU Development Project, co-financed by the European Social Fund of the European Commission, by the Research Foundation of the Orthopaedic and Trauma Surgery in Finland and by the Medical Research Fund of Tampere University Hospital.

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ORIGINAL PUBLICATIONS (I, II, IV and V)