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Mortality and Causes of Death in Patients with Rheumatoid Arthritis

A Cross-sectional Population-based Study during the Years 1988-1999

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To My Family

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology associated with inflammation of joints and systemic features. Most previous studies have shown that mortality among RA patients is higher than that in the general population. RA patients have increased risk to die due to infections, cardiovascular diseases and renal diseases compared to the general population. There is also some evidence that RA patients carry a higher risk of developing lymphoproliferative malignancies. The purpose of this study was to evaluate the mortality and causes of death in a cross-sectional population-based material of RA patients and to compare the results to mortality among matched controls and the general population. Potential predictive factors for mortality were evaluated, including descriptive factors for disease severity, autoantibodies and previous medications, and especially renal findings.

In the first study (I) of this thesis mortality and causes of death among 1042 RA patients and 457 age- and sex-matched controls were analysed. RA patients had an increased mortality risk (standardized mortality ratio, SMR 1.37-1.71) compared to matched controls or the general population. They were at an increased risk of death from urogenital and gastrointestinal diseases, infections, respiratory diseases, hematopoetic malignancies and cardiovascular diseases, and a decreased risk of accidental death compared to the controls or the general population. Seven per cent of deaths among RA patients were due to amyloidosis.

The second study (II), including 604 RA patients, showed that renal amyloidosis was associated with over two-fold mortality (hazard ratio, HR=2.31, p=0.040), whereas histologically confirmed mesangial glomerulonephritis (MesGN) did not predict increased mortality in RA patients. Nephropathy presenting with combined hematuria and proteinuria, proteinuria and microalbuminuria was associated with increased mortality in RA patients.

In the third study (III) positive rheumatoid factor (RF) (particularly high IgA RF and IgM RF levels) predicted increased mortality in the RA population, the risk of death varying from 1.32 to 1.80 depending on the definition of RF positivity used. Positive anti- citrullinated cyclic peptide (anti-CCP) or antineutrophil cytoplasmic antibodies (ANCA) were not associated with mortality risk, but high anti-CCP levels predicted increased mortality (HR=1.68, p=0.034).

The results of fourth study (IV) showed that the mortality among RA patients treated with glucocorticoids over 10 years was increased (HR 1.69, p=0.011) compared to patients treated less than 10 years or patients not receiving glucocorticoid treatment. The increased mortality was related mainly to infections and complications of systemic amyloidosis.

In conclusion, increased mortality among RA patients compared to the general population was observed in the present as in previous studies, and the mortality risk was fairly similar to that previously reported. The results of the present study confirm that renal amyloidosis is associated with poor prognosis. MesGN was not associated with increased mortality, which supports observations of a favourable prognosis in MesGN. The present results also confirm previous findings that RF positivity indicates an increased mortality risk. In addition, this study is the first to establish a possible association between anti-CCP antibodies and mortality in RA patients.

CONTENTS:

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ABBREVIATIONS

AA   amyloid A

AAS   atlantoaxial subluxation

ACR   American College of Rheumatology

AFA   anti-filagrin antibodies

AKA   anti-keratin antibodies

ANA   anti-nuclear antibodies

ANCA   antineutrophil cytoplasmic antibodies

ARA   American Rheumatism Association

cANCA   cytoplasmic antineutrophil cytoplasmic antibodies

CCP   citrullinated cyclic peptide

CI   confidence interval

COPD   chronic obstructive pulmonary disease

COX-2   cyclooxygenase-2

CRF   chronic renal failure

CVD   cardiovascular diseases

DMARD   disease-modifying antirheumatic drug

DPA   d-penicillamine

ELISA   enzyme-linked immunosorbent assay

ESR   erythrocyte sedimentation rate

FS-WaRo   Waaler-Rose test

HAQ   Health Assessment Questionnaire

HLA   Human leucocyte antigen

HR   hazard ratio

ICD   International Classification of Diseases

IgA/G/M	immunoglobulin A/G/M
IL	interleukin
MesGN	mesangial glomerulonephritis
MGN	membranous glomerulonephritis
NSAID	non-steroidal anti-inflammatory drug
pANCA	perinuclear antineutrophil cytoplasmic antibodies
PAD	peptidyl-arginine deiminase
RA	rheumatoid arthritis
RF	rheumatoid factor
SAA	serum amyloid A
SMR	standardized mortality ratio
TNF	tumor necrosis factor
WHO	World Health Organization

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original communications, referred to in the text by the Roman numerals I-IV:

I.   Sihvonen S, Korpela M, Laippala P, Mustonen J and Pasternack A (2004). Death rates and causes of death in patients with rheumatoid arthritis: a population based study. Scand J Rheumatol 33:221-7.

II.   Sihvonen S, Korpela M, Mustonen J, Laippala P and Pasternack A (2004). Renal diseases as a predictor of mortality in patients with rheumatoid arthritis. Nephron Clin Pract 96:107-14.

III.   Sihvonen S, Korpela M, Mustila A and Mustonen J (2005). Predictive value of anti-cyclic citrullinated peptide antibodies, rheumatoid factor isotypes and antineutrophil cytoplasmic antibodies for mortality in patients with rheumatoid arthritis. J Rheumatol 32:2089-90.

IV.   Sihvonen S, Korpela M, Mustonen J, Huhtala H, Karstila K and Pasternack A (2006). Mortality in patients with rheumatoid arthritis treated with low-dose oral glucocorticoids. A population-based cohort study. J Rheumatol (33):1740-46.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease of unknown etiology affecting about 0.5-1.0 % of the adult population in Western countries (Hochberg and Spector 1990). Without treatment it leads to primarily progressive joint destruction, and in addition to work disability, deterioration of life quality, and even premature death. The inflammation of joints frequently occurs with extra-articular manifestations such as rheumatoid nodules, pericarditis, pleuritis and vasculitis (Turesson et al. 1999).

Disease outcome is multidimensional and comprises five main areas: death, disability, discomfort, iatrogenic complications and economic losses (Fries et al. 1980). Outcome can also be measured in terms of physical disability, pain, number of swollen or tender joints, radiological destruction of joints, social handicap and extra-articular morbidity and mortality (Isomäki 1992).

For more than 50 years, increased mortality has been reported in patients with RA compared with the general population (Cobb et al. 1954). In only a few recent studies has the survival of RA patients been no boorer than in the general population (Lindqvist et al. 1999, Kroot et al. 2000, Peltomaa et al. 2002). It has been estimated that severely disabled patients had a 5-year survival of less than 50%, which means a similar prognosis to that of 3-vessel coronary disease or stage IV Hodgkin`s disease at that time (Pincus et al. 1986). Most studies have demonstrated increased mortality due to infections, cardiovascular diseases, renal diseases and hemopoetic malignancies (Mitchell et al. 1986, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995b and c). Death from renal disease has been explained mainly by amyloidosis (Laakso et al. 1985, Mutru et al. 1985), while the role of other renal diseases such as mesangial glomerulonephritis (MesGN) has not been established. Also the treatment of RA can cause renal diseases such as membranous glomerulonephritis (MGN). The prognosis of drug-induced MGN is favourable in most cases, as it is usually reversible after cessation of the drug in question (Hall et al. 1987).

The factors influencing increased mortality are complex; including basic disease, its treatments and comorbidity. The purpose of this study was to evaluate mortality and causes of death in a population-based material of RA patients and to compare the results to mortality among matched controls and the general population. Potential predictive factors for mortality were evaluated from baseline data in 1988, including factors descriptive of disease severity, some immunological findings and previous medication, and especially renal findings.

REVIEW OF THE LITERATURE

1. Methodological aspects of survival research

The aim of mortality studies has been to assess mortality and causes of death in certain patient groups and to compare this to selected controls or to general populations.

Mortality can be reported as standardized mortality ratio (SMR), which is the ratio of the number of observed deaths in a study population to the numbers of expected based on population estimates of survival in groups of similar age and sex composition or expected numbers of deaths in an age- and sex-matched control group (relative risk) (Campbell 2001). Other ways to indicate the mortality are to calculate hazard ratios (HR) using the Cox proportional hazard model (regression analyses) or to report shortening of life-span in years (Campbell 2001). Mortality in different groups can also be expressed using survival curves (Kaplan-Meier) (Campbell 2001).

Data on causes of death can be based on death certificates, hospital records, autopsy reports, national mortality statistics or a hospital registry. Causes of death can be classified as underlying, immediate or contributive. The underlying causes of death are usually reported according to the International Classification of Diseases (ICD, World Health Organisation 1995), but authors may have used their own grouping (Cobb et al.1953). ICD has been regarded as in part illogical in application. For example, only systemic infections, contagious or epidemic diseases are classified under the category of infection and pneumonias under respiratory diseases.

The actual mortality of RA patients is in many ways difficult to determine. Study settings differ markedly in different studies, which makes comparison of mortality findings somewhat challenging. Reports based on national mortality statistics only are unreliable, in that RA is mentioned in only part of the death certificates (Allebeck et al. 1981, Symmons 1988). The classification of RA may also vary. The classification of American College of Rheumatology (ACR) has been widely used, but some authors have studied atypical groups (Isomäki et al. 1975, Vandenbrouke et al.1984). Any assessment of death risk in RA patients depends to a

considerable extent on the study cohort (population-based vs. hospital-based) and the choice of comparison group (matched controls vs. general population) and follow-up period (Table 1). In addition, the duration of RA before study are different. Few studies have followed early RA patients (symptoms less than one year at entry) (Rasker and Cosh 1987, Reilly et al. 1990, Corbett et al. 1993, Lindqvist et al. 1999, Sokka et al. 1999, Kroot et al. 2000, Peltomaa et al. 2002) and none until all patients have died. There are only few studies on mortality in RA in which causes of death are evaluated only from autopsies (Mutru et al. 1976, Boers et al. 1987, Suzuki et al. 1994). One Finnish group have examined the issue from a new perspective and reported causes of death in all RA patients who had died in Finland during a one-year period in 1989 and had been entitled under the nationwide sickness insurance scheme to reseive specially reimbursed medication (Myllykangas-Luosujärvi et al. 1995a-c).

Table 1. Standardized mortality ratios (SMR) in RA studies

Study, year	Country	N	SMR	Follow-up/years	Setting
Cobb et al. 1953	US	583	1.32	9	Clinical
Dutchie et al. 1964	UK	307	1.62	9	Clinical
Uddin et al. 1970	Canada	475	1.29	10	Clinical
Monson and Hall 1976	US	1035	1.86	12-42	Clinical
Lewis et al. 1980	UK	311	1.13	11	Clinical
Linos et al. 1980	US	521	1.16 (ns)	24	Community
Allebeck et al. 1981	Sweden	293	1.32	11	Community
Allebeck et al. 1982	Sweden	1165	2.48	7.5	Clinical
Pincus et al. 1984	US	75	1.31	11	Clinical
Prior et al. 1984	UK	489	2.98	11	Clinical
Mutru et al. 1985	Finland	1000	1.64	10	Clinical
Mitchell et al. 1986	Canada	805	1.51	12	Clinical
Reilly et al. 1990	UK	100	1.40	25	Clinical
Jacobsson et al. 1993	US	2979	1.28	2-25	Community
Wolfe et al. 1994	US, Canada	3501	2.26	9-35	Clinical
Myllykangas-Luosujärvi et al. 1995	Finland	1186	1.37 (F)	5	Community
Wallberg-Jonsson et al. 1997	Sweden	606	1.57	15	Clinical
Symmons et al. 1998	UK	448	2.70	16-22	Clinical
Gabriel et al. 1999	US	450	1.38	12-15	Clinical
Lindqvist et al. 1999	Sweden	183	0.87	9.8	Clinical
Sokka et al. 1999	Finland	135	1.28 (ns)	8-14	Clinical
Kvalvik et al. 2000	Norway	147	1.49	15	Clinical
Krause et al. 2000	Germany	256	2.6	7-15	Clinical
Björndal et al. 2001	Sweden	46817	2.03		Clinical
Cheata et al. 2001	UK	309	1.65	14	Clinical
Gordon et al. 2001	UK	289	1.30	10	Clinical
Riise et al. 2001	Norway	187	2.0	17	Clinical
Sanchez-Martinez et al. 2001	US	182	1.85	9	Community
Peltomaa et al. 2002	Finland	150	1.33(ns)	7-14	Clinical
Gabriel et al. 2003	US	609	1.27	40	Community
Minaur et al. 2004	UK	100	2.13	40	Clinical
Book et al. 2005	Sweden	152	1.56	20	Clinical

RA= rheumatoid arthritis, ns= non-significant, F= females

2. Mortality in RA patients

Despite differences in methodology, mortality rates in RA patients have generally been reported to be higher than those among the general populations (Cobbs et al. 1953, Monson and Hall 1976, Allebeck et al. 1982, Vandenbrouke et al. 1984, Mitchell et al. 1986, Myllykangas-Luosujärvi et al. 1995b, Gabriel et al. 1999, Kvalvik et al. 2000, Riise et al. 2001b) or matched controls (Koota et al. 1977, Allebeck et al. 1981, Mutru et al. 1985). However, some recent studies have indicated that mortality rates are not increased in RA patients (Lindqvist et al. 1999, Sokka et al. 1999, Kroot et al. 2000, Bjornadal et al. 2002, Peltomaa et al. 2002). SMR has varied from 1.13 to 2.98 depending on study design (Table 1). The risk of mortality has been found lower in population-based cohorts than in hospital-based cohorts (see Table 1). Few studies have attempted to evaluate the shortening of lifespan in years (Reach 1963, Vandenbroke et al. 1984, Mitchell et al. 1986, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995b). Estimates have ranged from three (Vandenbroke et al. 1984) to 18 year (Reach 1963). Myllykangas-Luosujärvi et al. (1995d) estimated that life expectancy is shortened by 4.5 years if a Finnish woman got RA at the age of 50.

2.1. Gender and mortality

Increased mortality in RA compared to the general population has been noted in both sexes (Monson and Hall 1976, Mutru et al. 1985, Mitchell et al. 1986, Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998, Wållberg-Jonsson et al. 1997, Riise et al. 2001b). Several studies have reported gender-specific mortality and noted a more higher mortality risk in females than in males (Koota et al. 1977, Allebeck 1982, Prior et al. 1984b, Wolfe et al. 1994, Gabriel et al. 1999, Kvalvik et al. 2000), but in many studies there have been no significant differences between the sexes (Cobb et al. 1953, Dutchie et al. 1964, Allebeck et al. 1981, Reilly et al. 1990, Leigh and Fries 1991). A review of 10 studies dealing with the influence of age and gender confirms that RA contributes to earlier mortality in both sexes (Anderson 1996).

2.2. Disease duration and mortality

The excess of mortality in RA has been related to longer duration of the disease (Symmons 1988, Erhardt et al. 1989, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995b, Wållberg-Jonsson et al. 1997, Bjornadal et al. 2002). Gabriel et al. (1999) noted that survival early in the course of RA may be comparable with that in the general population and may diverge only after a disease duration of over 10 years. In a cohort in Canada SMR increased from 1.5 to 2.25 during an 8 years follow-up (Mitchell et al. 1986, Wolfe et al. 1994). Causes of death are also different in early and late disease (Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998). Deaths due to infections, renal failure and lymphoma increase progressively with disease duration (Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998). In a study by Rasker et al. (1981) deaths in early RA were due to infections or vasculitis, while amyloidosis was the main cause of death when disease duration was exceeded 7.7 years.

3. Causes of death in RA patients

Most studies concerning RA have observed increased mortality from cardiovascular diseases, infections, renal diseases, hematopoetic malignancies and RA itself (Allebeck 1982, Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998). On the other hand, some reports suggest that RA patients die of the same causes as the general population, but at an earlier age (Duchie et al. 1964, Lewis et al. 1980, Allebeck et al. 1985).

3.1. Cardiovascular diseases

Cardiovascular diseases are the commonest cause of death both in RA patients and in general populations. In most studies an increased mortality has been found from cardiovascular diseases in RA patients compared to the population at large (Monson and Hall 1976, Allebeck 1982, Prior et al. 1984b, Jacobsson et al. 1993, Myllykangas –Luosujärvi et al. 1995c, Wållberg-Johnsson et al. 1997, Symmons et al. 1998), but not in all (Cobbs et al. 1953, Uddin et al. 1970,

Vandenbroucke et al.1984, Mitchell et al. 1986, Riise et al. 2001b). In a large series of 2262 deaths of RA patients, approximately 40% of deaths were due to cardiovascular diseases (Pincus et al. 1986). Myllykangas-Luosujärvi et al. (1995c) reported a 34% excess of death due to cardiovascular diseases in females with RA.

Potential mechanisms underlying cardiovascular comorbidies in RA would appear to be multifactorial. Cardiovascular diseases in RA patients may be consequence of the disease itself such as inflammation. Inflammation plays a central role in the pathogenesis of atherosclerosis (Ross et al. 1999, Abou-Raya and Abou-Raya 2006). Recent studies have shown that endothelial cell dysfunction not only occurs in the presence of classic risk factors but is also induced by bacterial products and especially inflammatory cytokines (Bacon et al. 2001). Several studies have demonstrated that markers of systemic inflammation in RA such as high erythrocyte sedimentation rate (ESR), high c-reactive protein (CRP) and swelling of joints, increase the risk of cardiovascular mortality (Wållberg-Johnsson et al. 1999, Ridker et al. 2000, Jacobsson et al. 2001, Goodson et al. 2005, Maradit-Kremes et al. 2005). Active RA leads to unfavorable lipid profiles, such as low plasma apolipoprotein A1 and very low high-density lipoprotein cholesterol level (Park et al. 1999), which improves with treatment of RA (Boers et al. 2003, Munro et al. 1997). Further, elevated concentrations of homocysteine, which may promote atherosclerosis and thrombosis, and an increased prevalence of insulin resistance have been found in RA patients (Duell et al. 1997, Roubenoff et al. 1997, Dessein et al. 2002). Another possible link between RA and atherosclerosis may be reduced physical activity. Smoking is associated with the development and severity of RA and it has been suggested that smoking among RA patients is more common than in the general population (Heliövaara et al. 1993, Silman et al. 1996).

Medications could produce CVD risk factors by increasing homocysteine levels (methotrexate, suphasalazine), promoting hypertension (leflunomide, cyclosporine, glucocorticoids, NSAID), and impairing lipid profiles (cyclosporine, gold, glucocorticoids) and promoting insulin resistance (glucocorticoids) (Maxwell et al. 1994, Munro et al. 1997, Hall and

Dalbeth 2005). Futhermore, it has recently been found that the COX-2 selective (cyclooxygenase-2) NSAIDs rofecoxib and celecoxib are associated with an increased risk of thromboembolic events (Fizerald 2004). On the other hand, hydroxychloroquine has been attributed a benefical effect on lipid profiles (Munro et al. 1997).

3.2. Gastrointestinal diseases

Excess mortality due to gastrointestinal diseases (i.e.peptic ulcers) in RA patients has been found in a numbers of studies (Monson and Hall 1976, Allebeck 1982, Prior et al. 1984b, Vandenbroucke et al. 1984, Mitchell et al. 1986, Wolfe et al. 1994, Wållberg-Jonsson et al. 1997). Most of these excess deaths were due to complications of peptic ulcers, which have generally been regarded as important complications of medication with non-steroidal anti-inflammatory drugs (NSAID) Gabriel et al. 1991, Myllykangas-Luosujärvi et al. 1995a). A prospective study of 1400 patients receiving glucocorticoid therapy showed an overall twofold risk of peptic ulcers. However, a multivariate analysis showed that concomitant use of NSAIDs explained the increased risk of ulcers (Piper et al. 1991). Also arteritis and secondary amyloidosis may cause intestinal perforations in some patients (Adler et al. 1962, Suzuki et al. 1994). In a series of 1 666 RA patients Myllykangas-Luosujärvi et al.(1995) reported increased mortality due to peptic and intestinal diverticulosis. They suggested that this was probably related to antirheumatic medication, i.e. NSAIDs.

3.3. Infections

Infections are still common cause of death in RA. Almost all studies have reported increased mortality from infections in RA patients compared to the general population (Cobbs et al. 1953, Allebeck 1982, Vandenbrouke et al. 1984, Mutru et al. 1985, Mithcell et al. 1986, Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998, Kvalvik et al. 2000). The numbers of deaths vary depending on whether the authors have used their own grouping concerning causes of death or

the ICD. The ICD classifies all infections except septicemia and epidemic infections under the organ category in which they occur. Pneumonia is therefore classified under respiratory diseases (WHO 1995).

Deaths due to infections have been found commonly in patients with long-standing RA (Symmons et al. 1988). The frequent use of immunosuppressive treatment and a primary or acquired defect in the immunological system have been considered possible explanations for the increased suscebtibility to infections in RA patients (Segal and Sneller 1997). Doran et al. (2002a) reported a 1.7 risk of infections in a cohort of 609 RA patients followed for 12.7 years compared to matched controls. The authors mentioned both the effect of medication and the immunomodulatory effect of RA itself as potential explanations for this risk (Doran et al. 2002b).

Most of the infections have in question been pneumonias (Cobbs et al. 1953, Prior et al. 1984b, Mitchell et al. 1986, Suzuki et al. 1994, Symmons et al. 1998, Kvalvik et al. 2000), and the proportion has varied for between 10% (Cobbs et al. 1953, Vandenbroucke et al. 1984, Reilly et al. 1990, Symmons et al. 1998) and 24% (Corbett et al. 1993) of all deaths. Also bacterial arthritis, bone and urinary tract infections and septicemia have been common (Vandenbrouke et al. 1984, Doran et al. 2002a).

3.4. Renal diseases

Earlier studies have demonstrated increased mortality due to renal diseases among RA patients (Cobb et al. 1953, Mutru et al. 1976, Koota et al. 1977, Allebeck 1982, Prior et al.1984b, Vandenbroucke et al.1984, Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1995, Symmons et al. 1998). Renal diseases accounted for between 2% (Reilly et al. 1990, Myllykangas-Luosujärvi et al. 1995b) and 20% (Mutru et al. 1985) of deaths in different studies. These figures also included deaths due to renal infections. Most of the investigators agree that this excess in renal

death is due mainly to amyloidosis (Mitchell et al. 1986, Reilly et al. 1990) if infections (Vandenbroucke et al.1984) are excluded.

In a Finnish case-control study comprising 1000 RA patients, renal failure was the cause of death in 20.5 % of patients (Mutru et al. 1985, Laakso et al. 1986). The most common kidney disorders were considered to be amyloidosis (43%), chronic nephritis and renal infections. Symmons et al. (1998) found in a cohort of 448 patients 10 deaths from renal diseases during a follow-up of up to 27 years, two of these being due to amyloidosis. The proportion of deaths due to amyloidosis has varied from three (Cobbs et al. 1953, Myllykangas-Luosujärvi et al. 1999) to eleven per cent depending on the study (Boers et al. 1986).

3.5. Malignancies

Malignant diseases would appear to be responsible for 8-20% of deaths in different reports on RA patients (Allebeck 1982, Vanderbroucke et al. 1984, Scott et al.1987, Jacobsson et al. 1993, Myllykangas-Luosujärvi et al. 1995b**,** Kvalvik et al. 2000). There is agreement that the incidence of other than hematopoetic malignancies is reduced or the same as in the general population (Uddin et al. 1970, Koota et al. 1977, Allebeck et al. 1981, Mutru et al. 1985, Mitchell et al. 1986, Reilly et al. 1990). Pincus et al. (1986) observed a decreased mortality from malignancies when they compared the attributed causes of deaths in 2262 RA patients from 13 reported studies with US general population data. In a large study of 11 683 Swedish RA patients a group under Gridley (1993) reported a reduced incidence of colorectal malignancies in RA patients compared to that in the general population. The authors suggest that the use of NSAIDs might protect from intestinal malignancies. Similar results have been also reported in earlier studies (Monson and Hall 1976, Isomäki et al. 1978, Allebeck 1982).

Although the overall incidence of malignancies is not elevated, there is evidence that RA patients run an excess risk of developing lymphoproliferative malignancies (Isomäki et al. 1978, Prior et al. 1984b, Gridley et al. 1993, Myllykangas-Luosujärvi et al. 1995b, Symmons et al.

1998, Thomas et al. 2003). One Finnish study group in a large register study found for the first time a greater risk of Hodgkin`s lymphoma, leukemia and myeloma in both in and females with RA (Isomäki et al. 1978). Prior et al. (1984a) analysed cancer morbidity and mortality in the UK and noted an increased liability to lymphoproliferative malignancies in RA patients. Recently a Swedish study group observed a two-fold risk of lymphomas in a population-based cohort of 76,000 RA patients compared to the general population (Ekström et al. 2003). The risk of developing lymphoma has been associated with an increasing duration of RA (Myllykangas-Luosujärvi et al. 1995b Symmons et al. 1998, Baecklund et al. 2006), disease activity and severity (Prior et al. 1984a, Gridley et al. 1993, Baeklund et al. 1998) and especially Felty`s syndrome (Gridley et al. 1994). There is also some evidence that the lymphoma risk is associated with Epstein-Barr virus infection (Kamel et al. 1993, van de Rijn et al. 1996), but this represents a minority of all lymphomas in RA (Kamel et al. 1998). Also the use of immunosuppressive drugs (i.e. methotrexate, atsathioprine, cyclosporine) has been proposed to be the cause of these types of malignancies, but results have been controversial (Lewis et al. 1980, Balthus et al. 1983, Prior et al. 1984a, Silman et al. 1988, Gridley et al .1994, Jones et al. 1996, Baecklund et al. 1998, van den Borne et al. 1998, Baecklund et al. 2006).

3.6. Respiratory diseases

Pulmonary manifestations in RA are numerous, including pleuritis, pleuropulmonary nodules, interstitial lung disease, bronchiectasis and bronchiolitis (Bois and Wells 2004). The proportion of deaths due to these disorders has, however, been small. Several drugs (e.g. methotrexate, gold sodium thiomalate, sulfasalazine, leflunomide, biologicals) may cause pulmonary complications which may occasionally lead to death (Bois and Wells 2004). Biological treatments may also reactivate tuberculosis (Hochberg et al. 2005). One study has shown that patients with both RA and bronchiectasis had a poor survival and the increased mortality risk was associated with

smoking, severe RA and glucocorticoid treatment (Swinson et al. 1997). Most respiratory deaths in RA are in fact due to infections, and this is discussed in greater detail in chapter 3.3.

3.7. Rheumatoid arthritis

It is generally agreed that certain manifestations of RA themselves may lead to death, namely vasculitis, systemic amyloidosis, rheumatic lung diseases and cervical cord compression syndromes (Mitchell et al. 1986). Severe systemic complications of RA except amyloidosis are, however, relatively rare and do not account for many deaths in RA cohorts (Symmons 1988).

The proportion accounted for by RA among all causes of death in previous studies has varied mainly by reason of difference of classification. In most studies causes of death have been reported according to underlying cause without taking into account the immediate or contributory causes of death, which may underestimate RA-related mortality. In addition, death certificates may be inadequately drawn up and RA is mentioned in only part of them. Reilly et al. (1990) found 19% of deaths to be due to RA and in a further 14% RA was a contributory factor. Thus one third of deaths were related to RA or its treatment. Most deaths in their study were due to infections or amyloidosis. Analyses of 233 deaths among 805 RA patients by Mitchell et al. (1986) showed that 20 deaths appeared to be basic disease-associated and 8 resulted from side effects of drugs. They observed that death certificates underreported death due to RA. In a series of 489 patients (184 deceased) in the United Kingdom, RA was mentioned as an underlying cause of death in 16% and as a contributing cause in 36% of death certificates (Prior et al. 1984). Myllykangas-Luosujärvi et al. (1995b) reported RA as an underlying cause of death in 12%. Infections and complications of amyloidosis were the most common mechanisms of death. In a Norwegian study, Riise et al. (2001a) found increased mortality in patients with atlantoaxial subluxation (AAS) compared to those without. Drug related deaths are discussed in greater detail in chapter 5.3. and amyloidosis as a cause of death in chapter 3.4.

3.8. Other causes

Several studies have reported decreased mortality due to accidental deaths in RA patients (Cobbs et al. 1953, Koota et al. 1977, Allebeck 1982, Vandenbroucke et al. 1984). Myllykangas-Luosujärvi et al. (2000) reported that RA patients carry a reduced risk of alcohol-related deaths (SMR 0.40).

4. Renal diseases in RA

4.1. Secondary renal amyloidosis

Systemic AA (amyloid A) amyloidosis is one of the most severe complications of RA. The most usual clinical manifestations of renal amyloidosis are proteinuria (often nephrotic syndrome) and renal failure (Boers et al.1987, Helin et al. 1993). Also hematuria or combined hematuria and proteinuria can occur (Korpela 1993, Helin et al.1995, Nakano et al. 1998).

Diagnosis is based on histological demonstration of amyloid in tissue. Amyloid is identified as hyaline, extracellular deposits, which after Congo red staining display green birefringence in polarized light (Puchtler et al. 1962). In renal tissue the initial deposits are usually found in the glomerular mesangium and in the basement membranes of small vessels (Helin et al. 1993). It is a result of systemic deposition of the acute-phase reactant SAA (serum amyloid A protein), the hepatic synthesis of which is induced by pro-inflammatory cytokines (Interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) -α). Levels of circulating TNF-α, IL-18 and soluble tumor necrosis factor receptor-1 (TNFR-1) are increased in RA patients with amyloidosis (Maury et al. 2002, Maury et al. 2003).

The risk of developing systemic amyloidosis is associated with disease severity and duration of RA (Boers et al.1987, Korpela 1993, Tiitinen et al. 1993, Nakano et al. 1998). In a Finnish study of 1666 RA patients deceased during the year 1989 the median duration between the onset of RA and clinical amyloidosis was 19 years (Myllykangas-Luosujärvi et al.1999). The

prevalence of histologically proven renal amyloidosis in renal biopsy materials has varied 0-46% (average 20%) (Pollak et al. 1962, Pasternack et al. 1967, Salomon et al. 1974, Helin et al. 1986, Korpela et al. 1990, Nakano et al 1998) and in autopsy materials 7-21% (Mutru et al. 1976, Boers et al 1987, Suzuki et al. 1994) depending on the study population and methods used. Differences in study design and selection of patients makes it difficult to determine the exact prevalence of amyloidosis in RA. There is some evidence to suggest that its incidence of in RA is decreasing in Finland (Laiho et al. 1999). The number of RA patients suffering from amyloidosis on dialysis treatment has decreased (Kaipiainen-Seppänen et al. 2000). It has been suggested that more aggressive treatment with cytotoxic drugs is the reason for the reduced incidence of amyloidosis (Laiho et al. 1999, Kaipiainen-Seppänen et al. 2000). One autopsy series has shown an increasing incidence of amyloidosis in Japan during 1975-1990 (Suzuki et al. 1994)

The survival of RA patients with renal amyloidosis is poor (Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1999). No curative treatment for amyloidosis is as yet available. However, open studies have suggested that effective treatment with immunosupressive drugs may slow the progression (Ahlmen et al. 1987, Berglund et al. 1993, Kaipiainen-Seppänen et al. 2000, Chevrel et al. 2001). The current treatment strategy is to reduce SAA values to under 10 mg/l in RA patients with amyloidosis (Gillmore et al. 2001). Recently it has been observed that TNF- α inhibitors suppress the production of SAA and are effective in suppressing proteinuria and stabilizing renal function in renal amyloidosis (Fernandez-Nebro A et al. 2005). The new anti-amyloid drug Fibrillex (1.3-propanedisulfonate) is an oral product for the treatment of AA amyloidosis preventing amyloid fibril formation. It has been tentatively shown to reduce renal failure and total mortality (Gorevic et al. 2005).

In a study of 1666 Finnish RA patients who had died in 1989, the lifespan of the patients with systemic amyloidosis was shortened by 7.7 years (Myllykangas-Luosujärvi et al. 1999). Also the survival rates of RA patients with amyloid nephropathy on dialyses and after renal

transplantation are lower than those of non-amyloidotic patients (Pasternack et al. 1986, Ylinen et al. 1992, Kuroda et al. 2006).

4.2. Mesangial glomerulonephritis

MesGN is the most common renal finding in RA and constitutes from one to two thirds of all renal lesions in RA (Korpela et al.1991, Helin et al.1995, Nakano et al.1998). A frequent histopathologic finding is mild mesangial hypercellularity with or without a slight increase in mesangial matrix (Helin et al. 1986, Korpela 1993, Helin et al.1995). The most common clinical abnormality is hematuria (Helin et al.1986, Korpela et al. 1997, Nakanoet al. 1998), but also combined hematuria and proteinuria or isolated proteinuria can occur (Korpela 1993, Helin et al. 1995) Renal function is usually normal (Korpela 1993, Helin et al.1995). An association between high rheumatoid factor (RF) titers and the occurrence of MesGN has been observed (Helin et al.1986, Pollet et al.1989, Korpela et al.1997). MesGN has no association with any disease-modifying drug (DMARD) treatment, but an association has been found between long-standing RA and MesGN (Korpela et al.1991, Helin et al.1995). Thus MesGN is related to the basic rheumatoid disease itself and could therefore be regarded as an extra-articular manifestation of RA (Korpela et al. 1997).

Isolated hematuria seems to be a favourable clinical sign in patients with MesGN, whereas proteinuria is associated with boorer prognosis (Korpela et al.1991). The effect of MesGN on mortality has not previously been assessed

4.3. Membranous glomerulonephritis

Membranous glomerulonephritis (MGN) has been a fairly common renal biopsy finding in RA patients (Helin et al. 1986, Korpela et al. 1990). It is usually regarded as a complication of treatment with gold salts (Hall 1988), auranofin (Plaza et al.1982) or d-penicillamine (DPA) (Neild et al. 1979). Proteinuria is the most common clinical abnormality in gold- or DPA-

induced MGN (Hall 1988, Korpela 1995), but microscopic hematuria alone or combined hematuria and proteinuria are also possible (Helin et al.1986). Renal function is usually normal. MGN may also occur in RA patients not on gold or DPA treatment (Honkanen et al. 1987).

The prognosis of drug-induced MGN is favourable in most cases, as it is usually reversible after the discontinuing of the drug in question (Hall et al. 1987).

4.4. Systemic rheumatoid vasculitis with rapidly progressive glomerulonephritis

Systemic rheumatoid vasculitis (i.e. necrotizing vasculitis), commonly associated with rapidly progressive glomerulonephritis, is a rare complication of RA (Kutznetsky et al. 1986). It usually occurs in patients with longstanding seropositive RA and RA with nodulis, and is associated with a wide range of other extra-articular manifestations, high levels of immunoglobulin G (Ig G) and IgM RFs, circulating immune complexes, cryoglobulinemia, and anticomplementary activity (Scott et al. 1981).

4.5. NSAIDs and the kidney

Treatment with NSAIDs can cause sodium retention, edema, hypertension and reversible renal failure (Blackshear et al. 1985). Analgesic nephropathy was originally ascribed to phenacetin toxity, but also occurred with other combinations of antipyretic analgesics, often in mixtures containing codeine or caffeine (Nanra 1983). The morphological characteristic of analgesic nephropathy is papillary necrosis followed by secondary cortical damage (Kleinknecht 1985). Clinical manifestations at presentation of the disease include sterile pyuria, hematuria and renal failure (Nanra 1983). Later, hypertension and progressive renal failure dominate the clinical picture (Nanra 1983). Since the withdrawal of phenacetin renal deaths due to analgesic nephropathy are less common or even absent (Kasanen et al. 1973, Mitchell et al.1986, Boers et al. 1987, Varis et al. 1988).

Acute interstitial nephritis is less common and contitutes an unpredictable adverse effect of NSAIDs. Usually the clinical picture is that of nephrotic syndrome with acute renal failure, less often as renal failure or nephrotic syndrome alone (Abraham and Keane 1984). Renal failure is in most cases reversible after the cessation of the drug involved (Abraham and Keane 1984).

Also the modern anti-inflammatory drugs, selective COX-2 inhibitors, are implicated as in causing nephrotoxity as often as the conventional NSAIDs (Gambaro and Perazella 2003).

4.6. Others

One study has recorded a high incidence of renal stones in RA patients (Ito et al. 1997). Other abnormalities reported in RA patients are a thinning of the glomerular basement membrane probably attributable to gold treatment (Saito et al.1995) and an increased occurrence of microalbuminuria (Pedersen et al. 1995). Disease- and treatment-related (i.e. gold) microalbuminuria has been noted in up to one quarter of RA patients, and may be a marker of disease activity (Pedersen et al. 1995).

Mitchell et al. (1986) found that proteinuria predicted mortality in a series of 805 RA patients. They thought that proteinuria represents disease severity, drug toxicity and comorbid conditions. Microalbuminuria is associated with increased mortality in patients with diabetes (Mogensen 1984) and in elderly people without diabetes (Damsgaard et al. 1990), but no such study has been conducted among RA patients.

5. Factors predicting mortality

5.1. Severity of RA

Although the reasons for increased mortality in RA are not completely understood, excess mortality is clearly related to indicators of disease severity. In several studies increased mortality has been associated with disease activity and severity, reflected by a high erythrocyte

sedimentation rate (ESR), low blood hemoglobin, a high number of swollen joints, severe radiological destruction and a high score in the Stoke index, the physician's and patients's global assessment of disease activity (Reilly et al. 1990, Pincus et al. 1994, Wolfe et al. 1994, Chehata et al. 2001, Jacobsson et al. 2001, Minaur et al. 2004, Book et al. 2005). Recently, a study of Goodson et al. (2005) found increased total mortality, and specifically CVD mortality to be associated with CRP levels in inflammatory polyarthritis.

It is well established that poor functional status, whether expressed as Steinbrocker functional grade or Health Assessment Questionnaire (HAQ), is associated with an increased risk of death (Pincus et al. 1984, Rasker et al. 1984, Leight and Fries 1991, Cobbert et al. 1993, Wolfe et al .1994, Söderlin et al. 1998, Book et al. 2005). HAQ seems to be the best clinical predictor of poor survival (Pincus et al. 1984, Leight and Fries 1991, Söderlin et al. 1998, Goodson et al. 2002, Wolfe et al. 2003). A study of 1 387 RA patients with a 20-year follow-up has shown that a change of one SD in HAQ resulted in a much greater increase in the odds ratio for mortality than global disease severity (HR 2.31 vs 1.83) (Wolfe et al. 2003).

Extra-articular manifestations such as subcutaneous nodules, pericarditis, pleuritis, amyloidosis, Felty´s syndrome and vasculitis have been associated with severe RA (Gordon et al. 1973) and the presence of RF (Jakle et al. 1985, Turesson et al. 2002), but not with disease duration (Turesson et al. 1999). An increased mortality risk has been associated with several extra-articular manifestations in most studies (Gordon et al. 1973, Scott et al. 1981, Erhard et al. 1989, Turesson et al. 1999 and 2002) but not all (Voskuyl et al. 1996).

5.2. Autoantibodies in RA

RA has been associated with several autoantibodies (Nakamura 2000). RF is the only serologic test routine used in RA assessment. Recently a new serologic diagnostic marker has been found for the diagnosis of RA, anti-cyclic citrullinated peptide (anti-CCP) antibody (Schellekens et al. 1998).

RF is an autoantibody directed against antigenic determinants on the Fc fragment of the IgG molecule, and was first described about 75 years ago (Waaler 1940). Depending on the test technique used, 60% to 80% of RA patients are RF-seropositive (Nakamura 2000). The techniques most commonly used have been Waaler-Rose (WaRo), latex fixation and immunoturbidimetry tests. All of which measure IgM-RF. Enzyme-linked immunosorbent assays (ELISA) can be used for the detection of RF isotypes. RFs are not specific for RA, but are also present in relatively high percentages in other autoimmune diseases and infections (e.g. hepatitis, tuberculosis) (Van Schaardenburg et al. 1993, Aho et al. 1994). Even 1-5% of healthy persons, particularly elderly individuals, are RF-positive (van Schaardenburg et al. 1993, Aho et al. 1994). Smoking is also associated with false-positive RF (Heliövaara et al. 1993). RF has been recognised as an important predictor of more severe disease, including extra-articular manifestations and bone erosions (Kaarela 1985, Reilly et al. 1990, van Schaardenburg et al. 1993, Kroot et al. 2000, Bukhari et al. 2002, Vencovsky et al. 2003). Positive RF has also predicted increased mortality in a number of studies (Allebeck et al. 1981, Vandenbrouche et al. 1984, Mitchell et al. 1986, Jacobsson et al. 1993, van Schaardenburg et al. 1993, Wolfe et al. 1994, Gabriel et al. 1999, Turesson et al. 2002). Some recent studies have found no such association (Riise et al. 2001b, Book et al. 2005, Nikolaisen et al. 2005). Mortality has been more pronounced with increasing titers of RF (Mitchell et al. 1986).

Anti-filaggrin antibodies (AFA) represent a group of RA-specific antibodies originally described in 1964 as anti-perinuclear factor (APF) and in 1979 as anti-keratin antibodies (AKA) (Nienhuis and Mandema 1964, Young et al. 1979). These antibodies have shown to be directed against filaggrin (Sebbag et al. 1995). It has recently been shown that they bind specifically to substrates containing the modified amino acid citrulline formed by a post-transcriptional modification of arginine residues by peptidyl-arginine deiminase (PAD) (Schellekens et al. 1998). Antibodies against cyclic citrullinated peptide (anti-CCP) were first reported in 1998 (Schellekens et al. 1998). Recent studies have indicated that modern anti-CCP antibody tests are

very highly specific for RA (95-98%) and have reasonable sensitivity (68-75%, 80% for second-generation test) (Bizzarro et al. 2001, Bas et al. 2001, Vencovsky et al. 2003). They can be detected at an early stage, even years before the appearance of clinical symptoms of RA (Rantapää-Dalqvist et al. 2003, Nielen et al. 2004). Compared with RF testing, testing for anti-CCP antibody yields fewer false-positive reactions in patients with rheumatoid diseases other than RA, in patients with infectious diseases and among aged patients (Schellekens et al. 2000, Palosuo et al. 2003). Smoking increases the prevalence of anti-CCP antibodies at least in RA patients with HLA-DRB1 shared epitope alleles (Linn Raker et al. 2005). Anti-CCP antibodies seem to predict the development of more severe RA with joint damage (Kroot et al. 2000, Bas et al. 2003, Meyer et al. 2003) and anti-CCP antibodies combined with RF appear to be an even better prognostic marker (Schellekens et al. 2000, Vencovsky et al. 2001, Meyer et al. 2003). Meyer et al. (2003) have shown that RF-negative patients with anti-CCP antibodies have more joint damage than RF-positive patients without anti-CCP antibodies. Similar results were obtained in a study of 715 RA patients of Vallbracht et al. (2004). The authors suggested that anti-CCP antibodies may be even better prognostic markers than RF. There have been no studies hitherto concerning mortality in anti-CCP antibody-positive and –negative RA patients.

Antineutrophil cytoplasmic antibodies (ANCA) are directed against lysosomal entzymes of human neutrophils and monocytes. They can be divided into two groups depending on their location: cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA). In RA patients ANCA mainly presents as a pANCA pattern and the prevalence has varied 18-50% in different studies (Röther et al. 1994, de Bandt et al. 1996, Mustila et al. 1997, Vittecoq et al. 2000). Target antigen specificity of pANCA in RA isfor most part unclear. Sera of RA patients can be positive simultaneously for several antigen specifities and the antibody levels are usually low (Mustila 2000). The possible pathogenetic role of ANCA in RA also remains obscure. Positive pANCA has been associated with long disease duration, high RF titers, positive ANA and advanced functional disability, but not with extra-articular manifestations (Röther et al. 1994, de Bandt et

al. 1996, Mustila et al. 1997). However, Mustila et al. (1997 and 2000) have shown positive pANCA to be associated with bone erosions in early RA and more severe and inflammatory active disease with nephropathy in later disease. Nonetheless, Vittecoq et al. (2000) found no association between ANCA and any clinical manifestation in RA patients with mild RA. No studies have been made on mortality among ANCA-positive and –negative RA patients.

5.3. DMARD treatment

Evidence is emerging that disease progression and mortality may be favourably affected by the use of DMARDs. The Finnish Rheumatoid Arthritis Combination Trial (FIN-RACo) indicated a substantial slowing of radiographic progression with efficacious treatment (Möttönen et al. 1999, Korpela et al. 2004). Pincus et al. (2005) showed that patients in an age- and sex-adjusted RA cohort in 1985 had more joint damage than patients in an aggressively treated cohort in 2000.

Lower mortality has been reported at least in RA patients receiving long-term intramuscular gold treatment (Lehtinen and Isomäki 1991), in patients with good response to metotrexate (Krause et al. 2000, Choi et al. 2002), and in patients treated with combination DMARD therapies (Sokka et al. 1999). Mortality analysis of the FIN-RACo trial is not yet available (Möttönen et al. 1999). In a study of Lewis et al. (1980), in which most of the patients were treated with cytotoxic drugs, SMR (1.13) was lower than in other mortality studies. The influence of biological treatments on bone erosions seems to be especially beneficial (Maini et al. 1998, Genovese et al. 2002), but effects on mortality could not be evaluated by reason of the short follow-up time.

Treatments may predipose patients to severe infections (biologicals, methotrexate, azathioprine, cyclosporine) and may increase the risk of malignancy (azathioprine, cyclosporine) (Mikuls 2003). Many drugs used in RA may cause fatal side-effects such as bone marrow suppression (methotrexate, sulfasalazine) or pulmonary fibrosis (methotrexate, leflunomidi, biologicals) (Felson et al. 1992). Such cases are relatively rare and information on them is based

mostly on case reports (de la Mata et al. 1995). A study of 551 RA patients has shown that methotrexate is a well-tolerated drug and the incidence of life-threatening side-effects was 1.7%, including one death (0.15%) due directly to methotrexate during a ten years` period (Kinder et al. 2005). In a series of 157 RA patients Allebeck et al. (1985) could not identify any drug use generally or any particular drug type which would have significantly increased mortality. Mitchell et al. (1986) estimated that 10% of excess deaths were treatment-related, mostly by gastrointestinal perforations caused by NSAID and glucocorticoids. Myllykangas-Luosujärvi et al. (1995a) analysed deaths attributable to different antirheumatic drugs among 1666 unselected RA patients who died in Finland during the year 1989. They noted that 47 death were attributable to antirheumatic drugs: 30 due to use of NSAIDs, 11 due to use of glucocorticoids. Two cases of fatal bone marrow depression were a consequence use of methotrexate and 2 sulfasalazine. One lymphoma was propably induced by azathioprine and one death was due to hydroxychloroquine intoxication. There were no deaths due to intramuscular gold.

In a study of 623 RA patients Landewe et al. (2000) noted that methotrexate treatment was related to increased mortality from cardiovascular diseases. However, Choi et al. (2002) subsequently reported opposite results; methotrexate improved survival by reducing the number of deaths due to cardiovascular diseases (CVD). These findings supported the hypothesis that suppression of systemic inflammation by methotrexate provides cardiovascular benefits which outweigh the risk related to hyperhomocystenemia.

5.4. Glucocorticoid treatment

The side-effects of glucocorticoids are numerous, including avascular necrosis of bone and, osteoporosis-related fractures. Treatment increases susceptibility to infections and may exacerbate the ulcerogenic propeties of NSAIDs (Piper et al. 1991). Increased mortality has been associated with glucocorticoid treatment in several studies (Pincus et al. 1987, Leight and Fries 1991, Cobbert et al. 1993, Wolfe et al. 1994), but not in all (Linqvist et al. 1999). Leight and

Fries (1991) analysed a sample of 263 subjects and observed that age, prednisone use, disability index and male gender predicted increased mortality. They conceded that prednisone use may simply have been a marker of increased disease activity. Scott et al. (1987) noted a 35% overall mortality by 20 years in a follow-up study of 112 RA patients receiving prednisone treatment. The investigators regarded glucocorticoid treatment as a contributory factor in 27% of deaths due to infections. Wolfe et al. (1994) showed the use of prednisone to be clearly a risk factor for higher mortality in RA regardless of age, sex or disease severity.

Glucocorticoids could be an independent contributor to the risk of coronary artery disease, or may simply modify other cardiovascular risk factors such as hypertension, insulin resistance and hyperlipidemia (Maxwell et al. 1994). Wållberg-Johnsson et al. (1997) reported that glucocorticoids increase the mortality due to cardiovascular diseases if given early in RA, but not when given extensively during the disease. They suggested that glucocorticoid treatment early in the disease possibly indicates an active disease type. Recently in a study by Ricon et al. (2004) glucocorticoid exposure was found to be associated with carotic artery plaque independent of the effects of traditional cardiovascular risk factors or severity of RA. On the other hand, glucocorticoids could also reduce the risk of atherosclerosis by controlling inflammation (van Doornum et al. 2000).

5.5. Genetic factors

Human leukocyte antigen (HLA)-DRB1 and DR4 have been shown to associate with a poor outcome of RA (Gontzales-Gay et al. 2004). HLA-DRB1*0404 seems to play a role in endothelial dysfunction and may increase the CVD risk in RA patients. (Gontzales-Gay et al. 2004). However, the role of genetic markers in the prognosis of RA remains unclear.

5.6. Others

Old age at the onset of RA has been a strong predictor of increased mortality (Mitchell et al. 1986, Leigh et al. 1991, Goodson et al. 2002, Peltomaa et al. 2002). Low sosioecomic status (Leight and Fries 1991), poor education (Pincus et al. 1985, Wolfe et al. 1994), never-married state (Leight and Fries 1991) and low body mass index (Kremers et al. 2004, Escalante et al. 2005) have also been related to an excess mortality risk.

PURPOSE OF THIS STUDY

Most previous studies of mortality have been based on hospital-recruited patients. There are no large population-based reports in which both RA patients and sex- and age-matched controls have been assessed from commencement of follow-up. In the present series mortality was analysed in a cross-sectional population-based cohort of RA patients and their age- and sex-matched controls to compare death rates and causes of death in these groups.

The specific aims of the present study were:

I: to assess the mortality in a population-based cohort of RA patients and their age- and sex-matched population-based controls and to compare death rates and causes of deaths in these groups.

II: to assess the mortality and causes of death among RA patients and controls with abnormal clinical renal findings and histologically confirmed renal diseases.

III: to assess the possible role of RF isotypes, ANCA and anti-CCP antibodies predicting mortality in RA patients.

IV: to assess the mortality in patients treated with low-dose oral glucocorticoids compared to those not on glucocorticoid treatment.

STUDY POPULATIONS AND METHODS

Figure 1. Schematic presentation of patients in the studies I-IV

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┌─────────────────────────────────────┐
│ 1051 persons had definite or classic │
│ RA in the city of Tampere in 1988    │
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Study I

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┌─────────────────────────────┐    ┌─────────────────────────────┐
│ 604 RA patients participated│    │ 438 RA patients were studied│
│ in the original study in 1988│   │ by evaluation of hospital records│
└─────────────────────────────┘    └─────────────────────────────┘
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Study II

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┌─────────────────────┐    ┌─────────────────────────┐
│ 103 patients had    │    │ 103 Age- and sex-       │
│ nephropathy in 1988 │    │ and disease duration-   │
│                     │    │ matched controls without│
│                     │    │ nephropathy were selected│
└─────────────────────┘    └─────────────────────────┘
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Study III

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┌─────────────────────────────────────────────────────┐
│ Autoantibodies were determined from baseline sera    │
│         a) RF isotypes in 206 patients               │
│         b) ANCA in 200 patients                      │
│         c) anti-CCP-ab in 184 patients               │
└─────────────────────────────────────────────────────┘
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Study IV

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┌─────────────────────────────────────────────────────┐
│ 395 patients were treated with glucocorticoids until 1999│
│         a) 276 less than 10 years                    │
│         b) 119 more than 10 years                    │
│ 209 patients received no glucocorticoids at all      │
└─────────────────────────────────────────────────────┘
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1. Populations

The study population was based on a prospective cross-sectional population-based study of renal and urinary tract diseases in RA patients (Korpela 1993). In 1988, according to the registry of the Social Insurance Institute of Finland, 1385 persons in the city of Tampere had been admitted to the 90% refund category for antirheumatic drug therapy for RA; 1051 persons (834 females, 217 males) had definite or classic RA according to the diagnostic criteria of the ARA (Ropes et al. 1958), and 1042 of them were invited to participate. Altogether 604 persons (470 females, 134 males) participated (participants) in the original study and 438 non-participants (357 females, 81

males) were studied retrospectively by evaluation of patient records (Korpela 1993, Figure 1). Age- and sex-matched controls for participating RA patients were invited from the remaining general population of Tampere. Controls were not presumed to be healthy, only patients with chronic inflammatory rheumatic diseases were excluded**.** A total of 457 age- and sex-matched controls (352 females, 105 males) took part (Figure 1). Only participant RA patients were included in the present studies II-IV, as no equally detailed data on autoantibodies, other diseases, severity of RA and previous treatments from disease onset to 1988 were available for non-participants.

1.1. Study I

The study population included both participant and non-participant RA patients and age- and sex-matched controls. The estimation of mortality and causes of death in the present study was thus based on 1042 patients (total RA population), representing 99,1% of the total RA population (n=1051) in Tampere in 1988.

In 1988, during the original cross-sectional study, the mean age of the participant RA patients was 59 ± 13 years (59 ± 12 among females, 58 ± 2 among males), 64 ± 15 for non-participants (65 ± 14 females and 60 ± 15 males), 61 ± 13 for all RA patients (61 ± 13 females, 58 ± 13 males), and 58 ± 12 years for controls (58 ± 12 females, 59 ± 12 males) in 1988. The duration of RA was 15 ± 10 years among participants and 17 ± 11 among non-participants, and 16 ± 10 years in all RA patients.

Mortality in the total RA population was compared to that in the general Finnish population and mortality among participant RA patients to that of age- and sex-matched controls. Age- and sex-matched death rates for the general Finnish population in 1997 were used to calculate the expected number of deaths.

1.2. Study II

In the original cross-sectional study in 1988 altogether 103 participant RA patients had clinical signs or symptoms of renal and urinary tract diseases (nephropathy group, Figure 1). Isolated hematuria was observed in 54, isolated proteinuria in 27, combined hematuria and proteinuria in 7, chronic renal failure, also including those with other abnormal renal findings (CRFtot), in 36 and isolated chronic renal failure without hematuria or proteinuria (CRFisol) in 15 RA patients. Microalbuminuria was observed in 34, histologically confirmed renal amyloidosis in 13 and MesGN in 17 patients. Among controls hematuria was observed in 39, proteinuria in 11, CRFtot in 32 and CRFisol in 16. Combined hematuria and proteinuria was not found in any, but microalbuminuria was observed in 27 controls. Charasteristics of RA patients in 1988 are shown in Table 2.

Mortality among RA patients and controls with abnormal renal or urinary tract findings was compared to that among subjects with normal urinalysis and serum creatinine.

1.3. Study III

Paired controls (matched for age, sex and duration of RA) were selected for the nephropathy group from the remaining RA patients with normal serum creatinine and urinalysis (Korpela 1993). The presence of RF, RF isotypes (IgA RF, IgG RF and IgM RF), anti-CCP antibodies and ANCA in patients in the nephropathy group and their paired controls were determined from serum taken during the cross-sectional study in 1988. Serum samples were available for RF isotype analyses in 206 cases, for ANCA in 200 and for anti-CCP antibodies in 184. RF was analysed in all 604 participant RA patients in 1988.

Mortality in RA patients with different antibodies was compared to that among patients without these antibodies.

1.4. Study IV

The study population here comprised of 604 RA patients who participated in the cross-sectional study in 1988. Altogether 395 (311 females, 84 males) had been treated with oral glucocorticoids until 1999. In the non-glucocorticoid group (n=209) RA patients were not treated with oral glucocorticoids or the duration of treatment was for less than one month, while in the glucocorticoid groups the treatment had been continued for at least one month, but less than 10 years (n=276), or for more than 10 years (n=119). Characteristics of RA patients with or without glucocorticoid treatment are shown in Table 2.

Mortality in RA patients treated with glucocorticoids (<10 or ≥ 10 years) was compared to that in the non-glucocorticoid group.

Table : Characteristics of RA patients in different study groups in 1988

	Study I		Study II		Study III	Study IV	
	Participant RA patients n=604	Non-participant RA patients n=438	with nephropathy n=103	without nephropathy n=103	with autoantibody determinations n=206*	with glucocorticoids n=395	without glucocortiocoids n=119
Age (median, years)	59	64	63	62	62	59	61
Sex (Female,%)	78	82	74	74	74	79	73
Disease duration (median, years)	15	17	16	14	15	15	16
ESR (median, mm/h)	29	na	36	27	33	33	23
HAQ (median,1-3)	0.58	na	0.81	0.51	0.72	0.69	0.38
RF (positive,%)	55	na	70	69	70	61	43

RF was considered positive if quantitative immunoturbidic assay was $\geq$30 U/ml or Waaler-Rose-test titers $\geq$ 64.

HAQ=Health Assessment Questionnaire, ESR=Erythrocyte sedimentation rate, na= information not available

*= RF isotype determinations in 206 patients, ANCA-ab in 200 patients and anti-CCP-ab in 184 patients

2. Methods

2.1. Evaluation of mortality and causes of death (studies I-IV)

All persons were tracked on data from the Statistics Finland for notification of death. The vital status of each person was determined on August 31st 1999 and dates of death were indentified.

Causes of death were derived from the official death certificates, autopsy reports and hospital records. Death certificates were available for 98% of cases among RA patients and 99% among controls. Autopsy was performed on 32% of RA patients and 45% of controls. The underlying, immediate and contributory causes of death were recorded from the death certificates. Causes of death were classified according to underlying cause defined by the WHO as "the disease or injury, which initiated the train of morbid events leading directly to death "and to the rules of the World Health Organisation (WHO) using the 10th Revision of the ICD (WHO 1995). In addition, the immediate causes of deaths were analysed to define for example the total proportion of infections and intestinal perforations. In only three cases were the causes of death changed and different from those in the death certificates. In 10 cases certificates were missing or incomplete and these were excluded from the analyses.

Mortality in the total RA population was compared to that in the general Finnish population. Age- and sex-matched death rates for the general population (from Statistics Finland) were used to calculate the expected number of deaths.

In the first original paper (study I) SMRs compared to the general population were partly miscalculated, producing higher mortality risk ratios than reported in this thesis. The error has been corrected and an erratum is appended.

2.2 Assessment of severity of disease and medications in RA patients (studies II-IV)

In 1988 the functional capacity of RA patients was assessed using a Health Assessment Questionnaire (HAQ) index (Fries et al. 1980). A continuous scale (0-3) of functional disability was used. The presence of subcutaneous nodules, comorbidity (diabetes, coronary artery disease, heart failure and hypertension), ESR and blood hemoglobin was registered in the cross-sectional examination in 1988. Use of DMARDs and oral glucocorticoids was carefully recorded from the time of the diagnosis to the check-up in 1988. Data on oral glucocorticoid treatment during the years 1988 to 1999 or time of death were collected as accurately as possible from hospital

records (study IV). For 48 RA patients it was not possible to gather any information on glucocorticoid treatment from the years 1988-1999. These patients were included in the group receiving glucocorticoid treatment for less than 10 years. In the present setting it was not possible to calculate the cumulative glucocorticoid dose.

2.3. Assessment of abnormal clinical signs or symptoms of renal diseases in 1988 (study II)

Screening was carried out by first morning urine sample, 8-hour urine collection and blood sample at the close of urine collection. Urine samples were studied with a dipstick (Nephur-7-Test, Boehringer Mannheim, Germany) and if positive, by microscopic examination of the sediment. Hematuria was defined as a positive dipstick result in two consecutive samples. Proteinuria was screened by dipstick and 24 hours` urinary collection if urinary albumin excretion was 15mg/8h or more. Proteinuria was defined as urinary at a protein excretion level of 150mg/24h or more. Chronic renal failure was defined as serum creatinine more than 100 µmol/l in females and 115 µmol/l in males in two consecutive samples. Microalbuminuria was defined as a urinary albumin excretion rate of 20-200 µg/min determined from overnight urine collection. Renal biopsy specimens were examined by light, immunofluorescence and electron microscopy. Diagnosis of MesGN was made if abnormal findings were noted using in at least two out of three methods: a) mild mesangial enlargement consisting of increased matrix and/or hypercellularity in light microscopy, b) granular mesangial deposits of immunoglobulins or C3 in immunofluorescence microscopy and c) small mesangial electron-dense deposits in electron microscopy (Helin et al. 1986).

2.4. Determination of RF isotypes, anti-CCP antibodies and ANCA (study III)

The presence of RF was determined by quantitative immunoturbidic assay (FS-RF, positive if $\geq$ 30 U/ml) (Melamies et al. 1986) and by Waaler-Rose- test (WaRo, positive if $\geq$ 64) (Froelich

and Williams 1980). The presence of IgA RF, IgG RF, IgM RF was determined by enzyme immunoassays (Teppo et al. 1986, Maury et al. 1988).

Anti-CCP antibodies were analysed using a second-generation ELISA assay (Euro-Diagnostica, Immunoscan RA, Mark-2). Results were considered positive if the antibody level was greater than 25 U/ml. Serum samples resulting with absorbances over the highest standard (1 600 U/ml) were diluted and reanalysed.

Indirect immunofluorescence employing ethanol and formalin-fixed human granulocytes was used as a standard method to detect ANCA (Wiik 1989). The different staining patterns of ANCA, i.e. cANCA and pANCA were indentified. Positive sera were titrated to endpoint and titers $\geq$ 50 were considered positive. In all pANCA-positive patients, antinuclear antibodies (ANA) were also determined. If positivity for ANA was observed, the patient was considered to be pANCA-positive only if the titer of pANCA was more than 2 dilution steps higher than the titer of ANA (Wiik 1980).

2.5 Statistical analyses (studies I-IV)

Data means were given for normally distributed variables and medians for skew-distributed continuous variables. For categorical variables percentages were used. Pairwise comparisons were made with independent sample t- tests (normally distributed variables) and Mann-Whitney U-test (skew-distributed). Kruskal-Wallis test was used to compare more than two groups. Chi-square test was used for categorical data.

SMRs with 95% confidence interval (95%CI) were calculated (study I). The risk of death was estimated by Cox proportional hazards survival analysis with follow-up time (time from original study to death) as response variable, and this is expressed as hazard ratio (HR) with a confidence interval (CI) of 95%. The multivariate Cox proportional hazards model quantifies the predictive values of each variable in the model when all variables are considered together. The forward selection method performed in stepwise manner was used. For example a positive coefficient for

age implies that older persons have a poorer survival prospect. An HR of 1.08, for example, indicates that a person 1 year older in age has an eight per cent increased risk of death. The multivariate models included age, sex, disease duration, subcutaneous nodules and HAQ.

All tests were two-sided and differences were considered significant at a p-value less than or equal to 0.05. Computation was carried out using SPSS for Windows statistical software (version 9.0-11.5).

3. Ethical considerations

The study protocol was approved by the Finnish Ministry of Social Affairs and Health.

RESULTS

1. Mortality (study I)

Increased mortality was observed in RA patients when compared to the general population or matched controls. SMR varied between 1.37 and 1.71 depending on study population and control group. Increased risk of death was observed in both sexes (1.34-1.74 for females, 1.49-1.67 for males). Mortality gradually increased during the follow-up time (Figure 2). The mortality among controls was lower than that in the general population (SMR 0.68).

1.1. Participant RA patients (n=604) compared to matched controls

A total of 160 (26%) patients had died, 109 (23%) females and 51 (38%) males. SMRs compared to age- and sex-matched controls was for all participant RA patients 1.71 (1.64-1.77), 1.74 (1.67-1.81) for females and 1.67 (1.64-1.72) for males. Using the Cox proportional hazards model, the sex- and age-adjusted mortality ratio in the participant RA population was 1.71 (CI 95% 1.29-2.27) compared to controls. The mean age at death was similar in both groups (75.7 vs 74.1 yrs, p= 0.26, Figure 3).

1.2. Total RA population (n=1042) compared to the general Finnish population

There were 384 (37%) deaths in the total RA population, 292 (35%) females and 92 (43%) males. SMRs compared to the general Finnish population were for the total RA group 1.37 (CI 95% 1.23-1.51), 1.34 (1.19-1.50) for females and 1.49 (1.20-1.83) for males, showing that both sexes carried out increased mortality risk compared to the general population. The mean age at death (76.5 yrs) was slightly higher in the RA population than in the matched controls (74.1 yrs, p=0.026).

1.3. Age- and sex- matched controls (n= 457) compared to the general Finnish population

During the follow-up, 71 (16%) deaths had occurred in the control group, 47 (13%) females, 24 (23%) males. SMRs compared to the general Finnish population were for the controls 0.68 (053-0.86), 0.65 (0.47-0.86) for females, and 0.71 (0.46-1.06) for males, showing that mortality among controls was lower than that in the general population in both sexes.
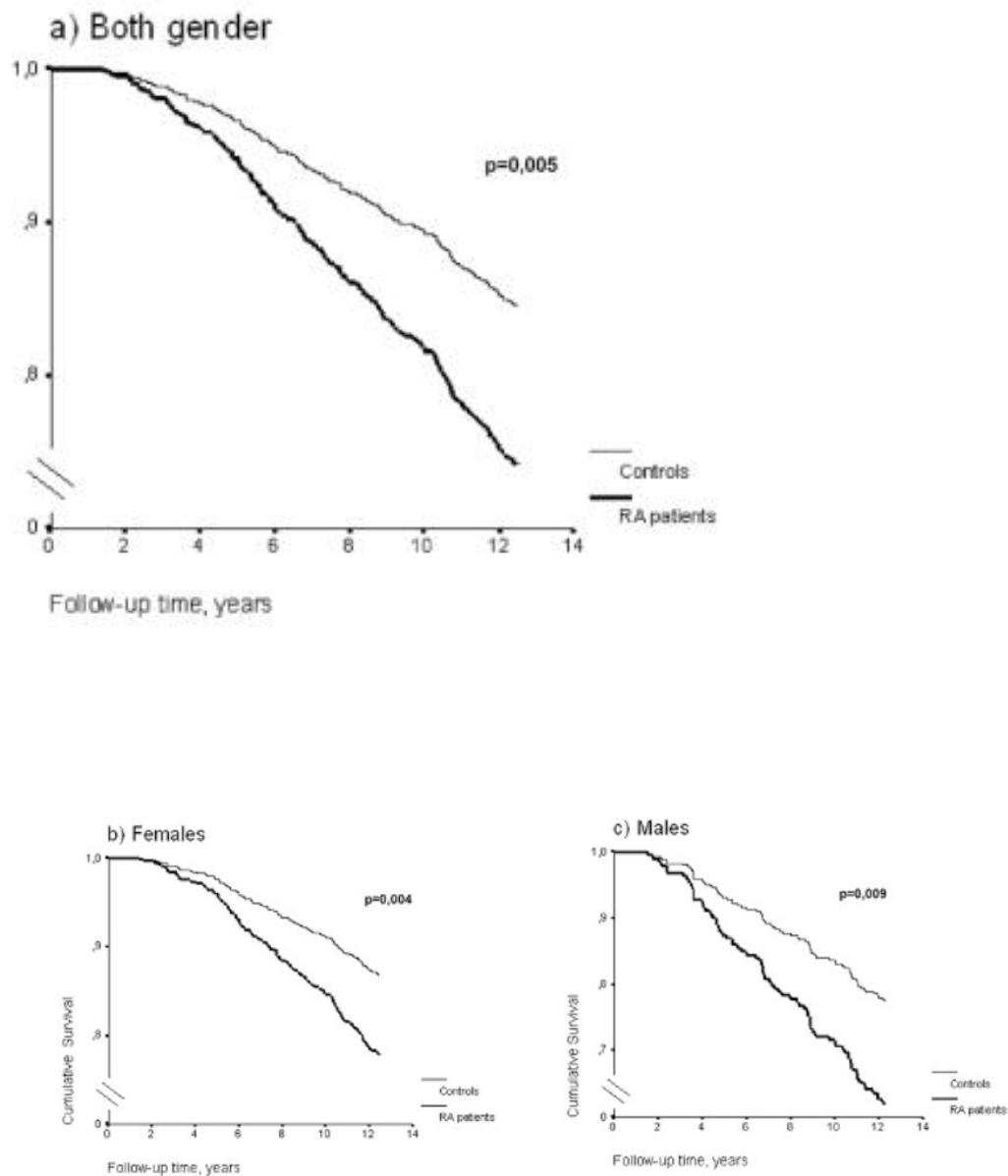
Figure 2a-c: Mortality in participant RA patients and matched controls

Figure 3: Age at death in participant RA patients and matched controls
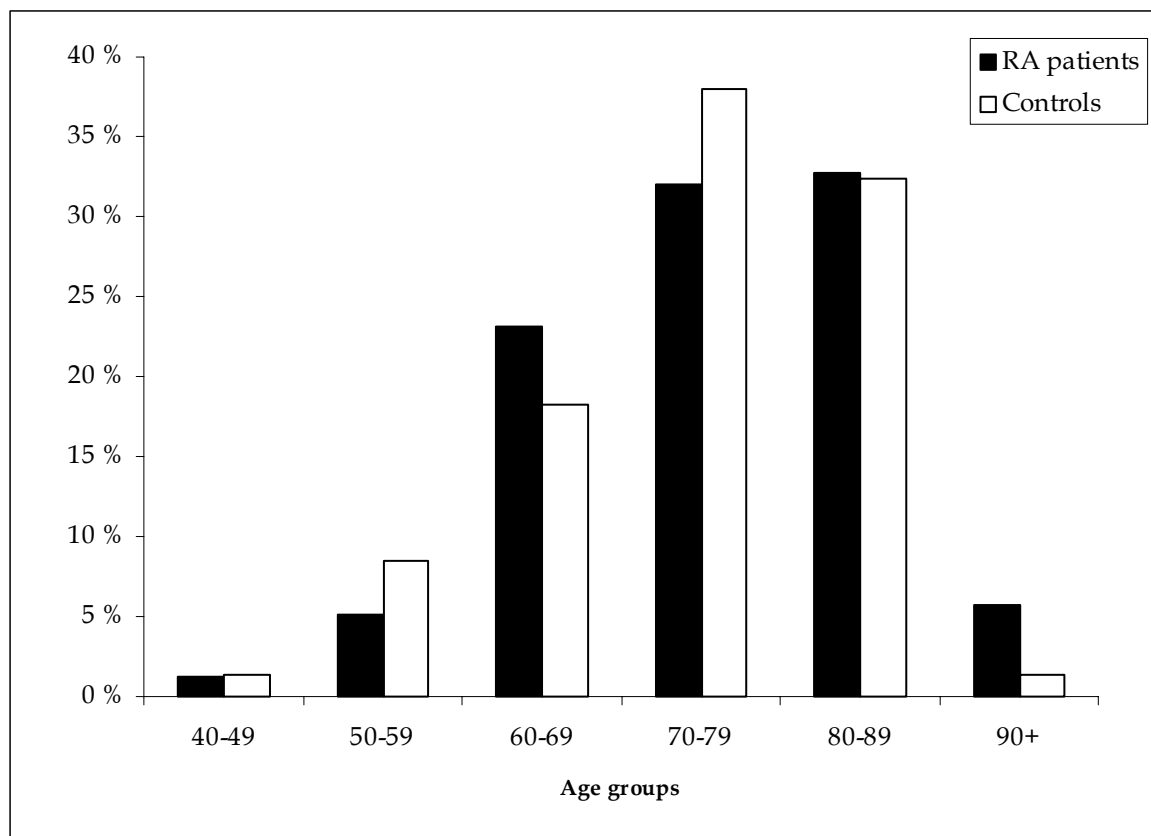
2. Causes of death

Over 40 % of deaths had occurred due to cardiovascular diseases and about 20% of the subjects had died of malignancies in every subgroup (Table 3). In this respect, there was no marked difference between the two RA subgroups, not between controls and the general population. RA patients were, however, at increased risk of death from urogenital and gastrointestinal diseases, infections, respiratory diseases, malignancies and cardiovascular diseases, and ran a decreased risk of accidental death compared to the general population or matched controls (Table 4).

Table 3: Underlying causes of death in RA patients and controls

ICD-code		Total RA patients N = 1042		Participant RA patients N = 604		Controls N=457	
		n	%	n	%	n	%
A00-A99	Infections	7	2	3	2	0	0
C00-C97	Malignancies	69	18	32	20	15	21
E00-E90	Endocrine	1	0.5	0	0	2	3
F00-F98	Mental	29	8	11	7	9	13
I00-I99	Cardiovascular	164	42	74	46	32	45
J00-J99	Respiratory	31	8	13	8	2	3
K00-K93	Gastrointestinal	18	5	5	3	2	3
M00-M99	Musculoskeletal	32	8	7	4	0	0
N00-N98	Urogenital	14	4	6	4	0	0
Q00-Q99	Congenital	2	0.5	0	0	1	1
S00-T98	Injuries	8	2	4	3	7	10
	Unknown	9	2	5	3	1	1
A00-T98	All categories	384	100	160	100	71	100

% = Number of deaths in particular category / total number of all deaths during 1988-1999

Table 4. Standardised mortality rates (SMR) in RA populations and controls compared to the general population or matched controls

ICD code		Total RA population vs. General population		Participant RA patients vs. Matched controls		Matched controls vs. General population	
		SMR	95%CI	SMR	95%CI	SMR	95%CI
A00-A99	Infections	4.12	1.78-8.13				
C00-C97	Cancers	1.20	1.02-1.52	1.61	1.48-1.76	0.61	0.34-1.00
E00-E90	Endocrine	0.30	0.01-1.68			1.54	0.19-5.60
F00-F98	Mental	1.29	0.84-1.86	1.11	0.95-1.28	1.43	0.66-2.72
I00-I99	Cardiovascular	1.23	1.05-1.43	1.75	1.65-1.85	0.66	0.45-0.93
J00-J99	Respiratory	1.16	1.01-1.76	5.00	4.35-5.72	0.23	0.03-0.84
K00-K93	Gastrointestinal	2.12	1.26-3.35	1.91	1.52-2.37	0.67	0.08-2.43
N00-N98	Urogenital	3.50	1.98-6.35				
S00-T98	Injuries	0.16	0.01-0.56	0.75	0.58-0.96	0.50	0.02-0.68
A00-T98	All categories	1.37	1.23-1.51	1.71	1.64-1.77	0.68	0.53-0.86

SMR=Observed mortality among RA patients and controls in relation to expected mortality in the general population or controls
CI = Confidence intervals, SMRs for infections, urogenital diseases were not calculated, as there were no deaths under these disease categories.

2.1. Cardiovascular diseases

RA patients had increased mortality from cardiovascular diseases (SMR 1.23-1.75, Table 4). Most of these deaths were due to ischemic heart disease in every subgroup; 89 in RA patients [45 in participants] and 22 in controls. Thirteen RA patients [5 participants] and one control had died of heart failure. Autopsy was performed in about 20% of these cases.

2.2. Gastrointestinal diseases

RA patients had increased mortality from gastrointestinal diseases (SMR 2.12-1.91, Table 4). In altogether eight cases peptic ulcers or intestinal perforations were the underlying cause of death. Intestinal perforation was recorded as an immediate cause of death in nine [4 in participants] RA patients and two controls. In three cases when intestinal perforation was the immediate cause of death, RA was recorded as an underlying cause. Four participant RA patients dying from intestinal perforation also had histologically confirmed amyloidosis. In three RA patients death was due to diverticulitis.

2.3. Infections

RA patients were at increased risk of dying from infections (SMR 4.12, Table 4). According to the underlying causes of death 26 RA patients [10 participants] and no controls had died of diseases in the infection category. If the immediate causes of death were also examined, altogether 109 RA patients [39 participants] and 15 controls had died due to infection. In the death certificates of RA patients only 17 deaths were recorded in the infection category and the remaining of the deaths due to infections were under other, particularly respiratory and urogenital categories. In RA patients 77% (72% participants) of infections comprised pneumonia and 15% (18% participants) septicemia. Among the controls 15 had died of pneumonia.

2.4. Renal diseases

Increased mortality in RA patients due to urogenital diseases (SMR 3.50, Table 4) was mainly due to amyloidosis. Eleven out of 14 RA patients had died of this cause. Three patients died due to chronic renal failure from other causes than amyloidosis. Autopsy was not performed in all of them, but they evinced no clinical signs of amyloidosis. There were no deaths attributable to urogenital diseases in the control group.

2.5. Malignancies

RA patients were at increased risk of dyinig from malignancies (SMR 1.20-1.61, Table 4). Deaths due to hematopoietic malignancies [lymphoma (n=8), multiple myeloma (n=3) and leukemia (n=2)] occurred more often in RA patients than in controls (p= 0,004), but there was no such difference in other sites or types of tumour. All patients who died from lymphomas had severe RA and long disease duration (over 15 yrs).

2.6. Respiratory diseases

Excess deaths from respiratory diseases in RA patients (SMR 1.16-5.00, Table 4) were mostly due to infections. Twenty out of 31 deaths were due to pneumonia, one to empyema. Two deaths were due to pulmonary fibrosis and the remainder to other causes (i.e. COPD, asthma). Two controls had died of respiratory disease: one of chronic obstructive pulmonary disease (COPD) and one of asthma.

2.7. Rheumatoid arthritis

RA was recorded as an underlying cause of death in 32 (8%) of the deceased persons and as a contributory cause of death in 76 (20%). Amyloidosis was recorded as an underlying cause of death in 11 RA patients, in 10 as an immediate cause of death and as a contributory cause in seven. Twenty-two patients had died due to end-stage renal amyloidosis, two from sepsis during

the dialyses, and one due to urinary bladder perforation. Thus 7% of deaths were related to amyloidosis in the total RA population. There was also one death recorded as due to systemic rheumatoid vasculitis and one pulmonary fibrosis due to gold sodium thiomalate as the underlying cause of death.

3. Renal disease as a predictor of mortality

Occurrences of different abnormal renal findings in the original study and mortality during the follow-up period are shown in Table 5. Mortality was increased in RA patients with combined hematuria and proteinuria (HR 4.45, p=0.005), with proteinuria (HR 3.45, p= <0.001), with chronic renal failure (CRFtot, HR 3.74, p=0.001) or with microalbuminuria (HR 2.77, p=0.002) when compared to RA patients with normal renal findings, whereas in those with hematuria (HR 1.49, p=0.132), isolated chronic renal failure (CRFisol, HR 1.71, p=0.147) the mortality rate was within the expected limits.

Table 5 . Number of deaths among RA patients and controls with clinical renal findings or histologically confirmed renal diseases

	RA patients (n= 604)			Controls (n=457)		
	patients in original material	deaths during follow-up		patients in original material	deaths during follow-up	
		n	%		n	%
Clinical findings						
Isolated hematuria	54	20	37	39	7	18
Chronic renal failure (CRFtot)	36	20	56	32	16	50
Microalbuminuria	34	16	47	27	3	11
Isolated proteinuria	27	14	52	11	3	27
Isolated chronic renal failure (CRFisol)	15	8	53	16	9	56
Bacteruria	15	4	27	12	2	17
Combined hematuria and proteinuria	7	4	57			
Pyuria	6	1	17	14	4	28
Histology findings						
Mesangial glomerulonephritis (MESGN)	17	4	24			
Amyloidosis	13	8	62			

Original material was screened in 1988. Follow-up was made until 1999.

Renal amyloidosis was associated with over two-fold mortality (HR=2.31, p=0.040), whereas MesGN (HR 1.61, p=0.426) was not associated with increased mortality. Similar results were obtained in the multivariate model. Among the controls, chronic renal failure (HR=3.33,

p=<0.001) was the only finding related to increased mortality when compared to those yielding normal renal findings.

Most of the deaths among RA patients with abnormal renal findings were due to cardiovascular diseases. In respect of other causes of death there were no marked differences between RA patients with or without abnormal renal findings. Amyloidosis was recorded in four and RA in two death certificates as an underlying cause of death in patients with histology-confirmed amyloidosis. In two death certificates cardiovascular disease was the underlying cause of death and there was no mention of amyloidosis or RA. Most deaths among controls with abnormal renal findings were due to cardiovascular diseases. In control subjects with hematuria the most common causes of death were cancers (one renal).

4. Autoantibodies and mortality in RA

At the time of the cross-sectional study in 1988 patients with positive RF and anti-CCP antibodies were older than those without. Also more severe RA was associated with positive RF and positive anti-CCP and pANCA antibodies (Table 6). Patients without anti-CCP determination (n=22) did not differ from thosein whom determination was made.

Of the 604 RA patients 55% were positive for RF using WaRo or FS-RF analyses, and the proportion rose to 59% if RF isotype analyses were taken into account. One hundred and twenty-two (66%) patients had anti-CCP antibodies; 34 (40%) the RF-negative patients were anti-CCP-positive and 12 (19 %) of RF-positive patients were anti-CCP-negative. In all, 134 (73%) patients had RF and/or anti-CCP antibodies and 50 (27%) were negative for these antibodies. Perinuclear ANCA (pANCA) was found in 29 (15%) and atypical cANCA in two patients.

Positive RF predicted increased mortality in the total RA population and the risk of death varied from 1.32 to 1.80 depending on the definition of RF positivity used (Table 7). In the multivariate model of the smaller cohort including only RA patients with anti-CCP antibody

determination (n=184), positive RF did not predict mortality. In this smaller cohort only high FS-WaRo titers were associated with increased mortality (Table 7).

High IgA RF and IgM RF levels predicted increased mortality (Table 7), whereas high levels of IgG RF did not. Even in the multivariate model including HAQ, high IgA RF levels were associated with higher mortality (Table 7).

Positive anti-CCP did not predict mortality, but high anti-CCP levels (over the median value of population ≥ 174 U/ml) were associated with increased mortality (HR=1.68, p=0.034, Table 7). In the RA severity-adjusted model such an association was not found. Neither positivity for pANCA nor high ANCA titers predicted mortality.

Table 6 : Characteristics of RA patients with or without different antibodies in 1988 and mortality during the follow-up time

	RF (n=604)			anti-CCP (n=184)			pANCA (n=198)		
	pos n=330	neg n=274	p=	pos n=122	neg n=62	p=	pos n=29	neg n=169	p=
Age (median, years)	59.7	57.3	0.021	63.9	58.7	0.005	59.9	62.3	0.301
Sex (Male,%)	24	20	0.161	26	26	0.915	14	28	0.111
Disease duration (median, years)	14.2	14.7	0.594	15.7	16.3	0.715	19.3	15.4	0.054
HAQ (median,1-3)	0.71	0.43	<0.001	0.88	0.54	0.001	1.11	0.68	0.003
RF (positive,%)				72*	19*	0.001	59*	56*	0.809
anti-CCP (positive,%)	88*	40*	<0.001				66*	56*	0.105
pANCA (positive,%)	15*	14*	0.710	17*	13*	0.105			
Mortality	32	21	0.003	41	31	0.171	41	38	0.720

Comparison between RA patients with and without different antibodies was made using Student´s t-test, Mann-Whitney-test variables)
(for continuous and the Chi-Square-test (for category variables). P-values less than 0.05 were considered significant.
RF=rheumatoid factor, anti-CCP=anti-cyclic citrullinated peptide antibodies, pANCA= perinuclear antineutrophil cytoplasmic antibodies.
RF was considered positive if quantitative immunoturbidic assay was >30 U/ml and/or Waaler-Rose-test titres > 64.
* percents were calculated only patiens with both antibody determination.

Table 7: Immunological features as predictors of mortality in patients with RA. Results of the univariate and multivariate Cox regressio analysis

		Univariate model			Multivariate models *		
Variable	N	HR	95% CI	p=	HR	95% CI	p=
Age (years)	604	1.09	1.07-1.11	0.001	1.09	1.04-1.09	0.001
Sex (male)	604	2.29	1.63-3.20	0.001	2.19	1.56-3.07	0.001
Disease duration (years)	604	0.96	0.94-0.98	0.001			
Immunological determinations							
RF (any of the five RF test positive)	604	1.80	1.28-2.53	**0.001**	1.55	1.10-2.19	**0.011**
RF (WaRo and/or FS-RF positive)	604	1.64	1.18-2.27	**0.002**	1.49	1.07-2.06	**0.017**
RF WaRo (positive)	604	1.32	0.95-1.82	0.089	1.57	1.13-2.19	**0.007**
FS-RF (positive)	604	1.63	1.18-2.24	**0.003**	1.41	1.01-1.95	**0.038**
RF WaRo (titer)	604	1.001	1.000-1.001	**0.004**	1.001	1.001-1.002	**<0.001**
FS-RF (level)	604	1.001	1.001-10..2	**<0.001**	1.001	1.001-1.001	**<0.001**
RF IgA (level)	206	1.005	1.002-1.008	**0.001**	1.003	1.002-1.008	**0.003**
RF IgG (level)	206	1.008	1.001-1.015	**0.049**			
RF IgM (level)	206	1.002	1.000-1.003	**0.024**	1.002	1.001-1.003	**0.006**
anti-CCP (positive)	184	1.44	0.85-2.44	0.176			
anti-CCP (level)	184	1.000	1,00-1.00	**0.010**	1.000	1,00-1.00	**0.044**
High anti-CCP level (present)	184	1.68	1.04-2.72	**0.034**	1.60	0.98-2.68	**0.057**
RF and/or anti-CCP positive	184	1.51	0.84-2.71	0.126			
pANCA (positive)	200	1.05	0.561-1.952	0.868			
pANCA (titer)	200	1.000	0.999-1.001	0.769			

HR= Hazard ratio, relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only.
95%CI= 95% confidence interval, N= number of patients with antibody determination, HAQ=Health Assessment Questionnaire
RF=rheumatoid factor, WaRo= Waaler-Rose test positive if titer $\geq$64, FS-RF= Quantitative immunoturbidic assay of RF positive if $\geq$30 U/ml
anti-CCP =anti-cyclic citrullinated peptide antibodies positive if >25U, pANCA=perinuclear antineutrophil cytoplasmic antibodies positive, if titer $\geq$50
Anti-CCP levels was divided into two categories using median level of population (174U) as cut-of value. High anti-CCP level means values over 174U.
*= age-, sex- and disease duration-adjusted multivariate model when each immunological test was at a time in the model .

5. Oral glucocorticoid treatment and mortality

Sixty-five per cent of the participating RA patients (311 females, 84 males) had been treated with oral glucocorticoids up to 1999; 276 less than 10 years and 119 more than 10 years. Age and sex ratios of RA patients were similar in all groups, but patients who had received glucocorticoids had a more severe disease (Table 2).

The mortality among RA patients treated with glucocorticoids for over 10 years (p=0.001) was increased and they died younger (73 vs.78 yrs, p=0.003) than patients treated for less than 10 years or patients not so treateed. Twenty-three per cent of RA patients had died by 1999 in the non-glucocorticoid group, 20% in the group receiving glucocorticoid treatment for less than 10 years and 45% in RA patients with over 10 years` treatment (p=0.001). Glucocorticoid treatment for one year increased the mortality risk by 17% (p=0.002) in the univariate model and by 14% (p=0.057) in the multivariate model. Long-term glucocorticoid treatment (over 10 years)

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increased the mortality risk by 69% (p=0.011) as compared to patients without the treatment in the multivariate model.

The major cause of death was cardiovascular disease in all groups. Underlying causes of death were more frequently classified under musculoskeletal and urogenital disease categories in RA patients treated with glucocorticoid for over 10 years. The increased mortality in these patients was related mainly to infections (p= 0.013) and complications caused by systemic amyloidosis (p<0.001). Moreover, deaths due to lymphoma were observed only in patients receiving glucocorticoid treatment (p=0.039).

DISCUSSION

1. Patient selection and methods

Most published mortality studies in RA have been hospital-based; there are no large population-based controlled studies where both RA patients and controls have been studied from the outset. In the present study both RA patients and matched controls comprised population-based groups. However, one limitation in this context was the rather low participation rate in the cross-sectional study in 1988. Non-participant patients may reprecent a potential source of bias in survey research. A Finnish study group has recently shown non-response to be an independent predictor of death (Kauppi et al. 2005). To minimize the selection bias in study I the mortality rate in the population-based cohort of RA patients (total RA population) was compared to that in the general population and mortality among the participating RA patients to that of their matched controls. Non-participants were older (64 ± 15 vs. 59 ± 13 yrs, p=0.005) and had longer disease duration than those participating (17± 11 vs. 15 ± 10 yrs, p=0.001) in 1988. Non-participant RA patients evinced increased mortality compared with participants, but causes of death were fairly similar.

The mean duration of RA was 16 years at commencement of follow-up in 1988 and the mean follow-up time from 1988 was 10.6 years. The average follow-up period from disease onset was thus almost 25 years, which is adequate to capture the long-term mortality.

In the present study causes of death were recorded from official death certificates, and also autopsy reports and hospital records were consulted. If national statistics are used to calculate the expected causes of specific death rates, then the causes of the observed deaths must also be taken from the death certificates, even if more precise information would be available from hospital records (Symmons 1995). It is then possible to calculate the cause-specific SMR. However, information in death certificates is not always accurate (Lindahl 1984). For example, RA is mentioned somewhat rarely (Allebeck et al. 1981). For this reason the hospital records were also

examined in the present study. In some cases there was some discrepancy between death certificate and hospital records. For example, pneumonia was recorded as the underlying cause of death although infection was a result of treatment of the basic disease, for example cancer. In such a case cancer was recorded as the underlying cause of death. The Statistical Office of Finland recodes causes of death on death certicicates according to the rules of WHO, using ICD 10 and the final code of a death is not always the same as that given on the death certificate. In the present study causes of death were not verified from the Statistical Office of Finland, which might have a minor effect on results.

2. Mortality

In the present study the mortality risk in the total RA population compared to the general population was lower (SMR 1.37) than that among the participant RA patients compared to their controls (SMR 1.71). The mortality among the participant RA patients was quite similar to that given in earlier reports (Mutru et al. 1985, Reilly et al. 1990, Wallberg-Jonsson et al. 1997, Kvalvik et al. 2000). Also the mortality among the total RA patients was similar to that in other population-based studies (Allenbeck 1982, Jacobsson et al. 1993, Myllykangas-Luosujärvi 1995b, Gabriel et al. 2003). However, mortality among the matched controls was lower than that in the general population (SMR 0.68). Similar results were obtained in a previous case-control study from Sweden (SMR 0.62 for females, 0.72 for males, Allebeck et al. 1981). This is as might be expected, as subjects with chronic inflammatory rheumatic disease were excluded.

Depending on the study in question the mortality risk of RA patients has varied from 0.87 to 2.98 (Table 1). Wolfe (1996) calculated from 10 studies a combined SMR of about 2.0 in RA patients. The risk has been lower in population-based cohorts (Linos et al. 1980, Allebeck et al. 1981, Jacobsson et al. 1993, Gabriel et al. 2003) than in hospital-based cohorts (Monson and Hall 1976, Prior et al. 1984,Wolfe et al. 1994, Symmons et al. 1998). One possible explanation for this is that patients in hospital cohorts have more severe disease than those in population-

based materials. Hospital-based studies probably overestimate the true shortening of life and population-based studies may underestimate it. Matched controls are probably more appropriate as a control population than the general population statistics, which also include patients with RA. On the other hand, study populations are generally smaller in matched cohorts than in population-based cohorts.

Some recent studies have indicated improved long-term outcome in RA patients (Lindqvist et al. 1999, Kroot et al. 2000, Peltomaa et al. 2002). In a study of 147 RA patients from Sweden with 8-13 years follow-up time the SMR was 0.87 (Lindqvist et al. 1999). In another larger study (n=622) from the Netherlands SMR was not increased, but the mean follow-up time was only 5.8 years (Kroot et al. 2000). These observations suggested that the improvement in survival might be due to the more aggressive antirheumatic treatment of RA in recent years. Some authors have surmised that RA has become a milder disease (Silman et al. 1989, Heikkilä and Isomäki 1994). Since the excess mortality in RA does not appear in early disease cohorts a short follow-up may not capture the excess. Other reports based on longer follow-up times have concluded that survival in RA has not improved (Gabriel et al. 1999, Gordon et al. 2001, Doran et al. 2002c). The finding reported by Gabriel et al. (1999) shows that mortality rates in RA have not substantially improved over the decades. They showed that three RA cohorts from different timepoints (1965, 1975 and 1985) all evinced increased mortality compared to that in the general population, while survival in the general population of similar age and sex distribution was improved in 1975 compared to 1965 and in 1985 compared to 1975. This improvement may thus be explained more by differences in study design than by any actual reduction in mortality rates. A large population-based register study of 46 917 RA patients in Sweden followed from 1964 to 1995 likewise showed increased mortality rates in RA patients compared with the general population (Bjornadel et al. 2002). However, the analysis revealed a decreasing mortality rate among RA patients since 1975.

Nowadays rheumatologists attempt to treat their RA patients earlier and more aggressively by using combination therapies, and i increasing evidence suggest that the outcome of patients with RA is nowadays more favourable than in previous decades. In new patient cohorts lower articular index, functional classes and radiographic progression have been reported, and the change has been associated with more widespred use of DMARDS and glucocorticoids (Bergström et al. 1999, Sokka et al. 1999, Korpela et al. 2004).

Mortality may be favourably affected by DMARDs, including intramuscular gold (Lehtinen and Isomäki 1991) and the commonly used metotrexate (Krause et al. 2000, Choi et al. 2002). A Finnish group has reported the cumulative mortality to be lower in patients treated with gold for over 10 years (25%) than in patients without this treatment (75%) (Lehtinen and Isomäki 1991). Krause et al. (2000) have shown that a good response to methotrexate during the first year is associated with prolonged survival. In a large study by Singer et al. (2003) mortality was significantly lower in the methotrexate-treated group than in those not so treated, with a mortality hazard ratio of 0.4. Lower mortality has also been reported in patients receiving modern combination therapies (Sokka et al. 1999). The FIN-RACo trial (Möttönen et al. 1999, Korpela et al. 2004) indicated a substantial slowing of radiographic progression, but the result of survival analyses are not yet available. The influence of biological treatments such as TNF-blockers on total mortality is not yet known, as the observation periods are too short.

In summary, increased mortality among RA patients compared to the general population was observed in the present study as elsewhere, and the mortality risk was fairly similar to that reported in earlier studies. The present results would indicate that any assessment of death risk in RA patients depends to a considerable extent on sampling procedures and the choice of comparison group and follow-up period. They nicely demonstrate how important it is also to analyse data on non-participants or drop-outs.

3. Causes of death

3.1. Cardiovascular diseases (CVDs)

CVDs were the most common causes of death in all patient groups in the present study. The excess mortality was due mostly to ischemic heart disease, and heart failure was also a more common cause of death in RA patients. Similar results have been recorded in earlier reports (Allebeck 1982, Mutru et al. 1985, Jacobsson et al. 1993, Wallberg-Jonsson et al. 1997, Goodson et al. 2002, Solomon et al. 2003). In only part of these studies were disease-specific SMRs calculated. Myllykangas-Luosujärvi et al. (1995c) observed a 34% excess of deaths due to CVDs in females with RA. Equal SMRs have also been noted in other reports on cohorts including both genders (SMR 1.45-1.77) (Allebeck 1982, Jacobsson et al. 1993). Symmons et al. (1998) reported the SMR for CVD-related mortality to be 2.2, and the same figure was obtained by Wolfe et al. (1994). SMRs for CVDs (1.23-1.75) in the present study were similar.

The potential mechanisms underlying cardiovascular comorbidities may be several in RA. The presence and/or severity of traditional CVD risk factors is increased in RA, for example pro-atherogenic lipid profiles (Park et al. 1999, Boers et al. 2003), insulin resistance (Svenson et al. 1987) and smoking (Heliövaara et al. 1993, Silman et al. 1996). There is no conspicuous increase in the prevalence of hypertension or diabetes (Solomon et al. 2003). Traditional risk factors alone cannot explain the increased risk of CVD in RA patients (del Ricon et al. 2001). The severity of RA correlates with the risk of CVD (del Ricon et al. 2001, Solomon et al. 2003). In a prospective study of 114 342 women with RA an over two-fold higher risk of myocardial infarction was associated with positive RF, subcutaneous nodules and bone erosions after adjusting for traditional CVD risk factors (Solomon et al. 2003). In a population-based study of 575 RA patients, the authors found that especially RF- positive patients have twice the risk of developing heart failure as compared to subjects without RA even after adjusting for CVD risk factors (Nicola et al. 2005). They suggested that the increased risk was attributable to systemic inflammation and drugs (NSAID, antimalarials, glucocorticoids). Several drugs (namely

methotrexate, suphasalazine, glucocorticoids) may further increase the risk by modifying CVD risk factors (hypertension, insulin resistance, hyperhomocytenemia) (Hall and Dalbeth 2005). The use of COX-2 inhibitors may also be associated with an increased CVD risk (Fizerald 2004).

Systemic inflammation may be regarded as accelerating the atherosclerotic process (Abou-Raya and Abou-Raya 2006). Endothelial activation not only occurs in the presence of classic risk factors but is also induced by inflammatory cytokines, including TNF-α and interleukin-1 (Bacon et al. 2001). Activation of adhesion molecules by cytokines, with concomitant leukocyte recruitment, may open up a potential access for lipids to the vascular wall (Bacon et al. 2001,van Doornum et al. 2002). It has been suggested that atherosclerosis represents a low-grade inflammatory condition associated with elevated levels of C-reactive protein, cytokines and fibrinogen. Levels of C-reactive protein have been associated with CVD risk in the general population and in patients with seropositive inflammatory polyarthritis (Ridker et al. 2000, Goodson et al. 2005). Moreover, some studies have shown that patients with one disease may be undertreated for other basic diseases (Kremers et al. 2003). Active treatment of RA is required and might reduce the risk of death due to CVD by controlling inflammation. Also prevention of cardiovascular risk factors should be borne in mind.

In summary, the present study confirms earlier findings. RA patients were liable to increased mortality due to CVDs and the risk was fairly similar to that previously was observed. However, long-term low-dose glucocorticoid treatment was not associated with increased CVD mortality.

3.2. Gastrointestinal diseases

In the present study RA patients had increased mortality from gastrointestinal diseases compared to the general population or the controls. The excess was mostly due to peptic ulcers and intestial perforations. The results are in accordance with those given in previous reports (Prior et al. 1984, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995a, Symmons et al. 1998). Peptic ulcers are

generally regarded as complications of NSAID use (Gabriel et al. 1991, Myllykangas-Luosujärvi et al. 1995a) and glucocorticoid treatment may exacerbate the ulcerogenic properties of these drugs (Piper et al. 1991). In the future frequent use of COX-2 selective NSAIDs and proton-pump inhibitors may reduce the risk (Fries et al 2004). Myllykangas-Luosujärvi et al. (1995b) found that diverticular disease, probably related to antirheumatic medication, is a more important cause of death in RA patients than is generally reported. Three RA patients in the present series died from diverticulitis. The effect of glucocorticoid treatment on peptic ulcers is discussed in greater detail in chapter 6.

In summary, the present study confirms earlier findings indicating, that RA patients have an increased mortality due to gastrointestinal diseases.

3.3. Infections

A high occurrence of deaths from infections was found in RA patients in the present cohort. Most deaths due to infections were of respiratory origin, which is in accordance with results reported in most previous papers (Cobbs et al. 1953, Vandenbrouke et al. 1984, Mutru et al. 1985, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995b, Wållberg-Jonsson et al. 1997, Kvalvik et al. 2001). The increased risk of dying from infections is associated with severe RA and partly with glucocorticoid treatment. A 40-year longitudinal study of a population-based cohort of RA patients showed that RA-related factors were significant predictors of infections (Doran et al. 2002a,b). These factors included markers of more severe RA such as RF, high ESR, extra-articular manifestations and poor functional capacity (Doran et al. 2002b). Other factors possibly influencing the risk of infections in RA patients are immobility, joint surgery, extra-articular manifestation, e.g. Felty`s syndrome (via leukopenia), and comorbidities (diabetes, chronic lung diseases) (Doran et al. 2002b). It is difficult to distinguish between the effects of RA and the iatrogenic effect of treatment. RA leads to alterations in cellular immunity, which may predispose patients to infections (Young et al. 1984). Immunomodulatory treatment (i.e.

methotrexate, azathioprine, cyclosporine, anti-TNF-α therapies) also further increases the risk (Brahm et al. 1997). The effects of glucocorticoids on the risk of infections are discussed in greater detail in chapter 6.

In summary, most previous studies have shown a high mortality due to infections in RA patients. The present results confirm this.

3.4 Renal diseases

In the present study increased mortality in RA patients due to urogenital diseases was mainly due to amyloidosis, which accords with the results of previous studies (Allebeck 1982, Prior et al.1984b, Vandenbroucke et al.1984, Laakso et al. 1986, Myllykangas-Luosujärvi et al.1995b). Renal diseases accounted for 3.6% of all deaths in the RA population, a slightly higher figure than in the study by Myllykangas-Luosujärvi et al. (1995b). Amyloidosis is discussed in greater detail in chapters 3.7. and 4.

3.5. Malignancies

In the present study about 20% of RA patients and controls died due to malignancies. Similar figures have been reported in earlier papers (Allebeck 1981, Vandenbrouke et al. 1984, Myllykangas-Luosujärvi et al. 1995b). In some reports RA patients seem to have a lower risk of colorectal cancers or a higher risk of lung cancer (Isomäki et al. 1978, Gridley et al. 1993). In the present study there were no such differences, which is in accord with the results reported by Myllykangas-Luosujärvi et al. (1995b).

RA patients here were at a slightly increased risk of dying from lymphoproliferative malignancies (especially lymphomas) as compared to the general population (p=0.004). A number of studies have shown that RA patients have an approximately a twofold or threefold risk of developing lymphomas compared with the general population (Isomäki et al. 1978, Prior et al. 1984a, Gridley et al. 1993, Ekström et al. 2003). All patients who died from lymphomas in

the present cohort had long-lasting, severe RA with high inflammatory activity and low functional capacity at the beginning of follow-up. Baeklund et al. (1998) in a case control study of 42 lymphomas have also shown a strong association between disease activity and the risk of developing lymphoma. This laibility has also been associated with increasing disease duration (Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998, Baecklund et al. 2006). There is some evidence that the risk of lymphomas in RA is independent of immunosuppressive treatment (Jones et al. 1996) or environmental risk factors (Ekström et al. 2003). At least no specific DMARDs have unquestionably been linked to an increased lymphoma risk. Silman et al. (1988) compared 202 RA patients receiving azathioprine and Balthus et al. (1983) 81 RA patients on cyclophosphamide treatment to matched RA controls not on cytotoxic treatment and found an increased risk of lymphoproliferative malignancies in the treatment groups. Methotrexate treatment has also been connected with lymphoma risk (Kremer et al. 1997. On the other hand, in a few other studies no correlation has emerged between a specific drug and lymphomas (Prior et al. 1985, Griedley et al. 1994, Wolfe 2003, Baecklund et al. 2006). Some lymphomas have been reported in patients with TNF-blocking therapies (Brown et al. 2002). Observation times for the TNF-blocking therapies are still short, but so far no clear risk of lymphoma has been observed (Baecklund et al. 2004 and 2006). In the present cohort all participant RA patients dying due to lymphoproliferative malignancies had been treated with glucocorticoids, but only one with cytotoxic drugs, namely methotrexate. The reason for the increased risk of lymphomas in RA remains unclear, but available studies tend to support the hypothesis that the severity of RA is associated with lymphomas rather than specific treatment regimens. It is conceivable that both too conservative and too aggressive immunosuppressive treatment may increase the risk of lymphomas in RA patients.

In summary, the present results confirm the previous finding that RA patients are at increased risk of dying from lymphoproliferative malignancies and the risk is associated with severe and long-lasting RA.

3.6 Respiratory diseases

Most of the deaths here due to respiratory disease were from infections. T proportion of pneumonias as the immediate cause of death averaged 20% and as underlying cause 5% in the present study. In earlier reports the corresponding proportion has varied from 11% to 24% (Cobbs et al. 1953, Vandenbrouke et al. 1984, Erhardt et al. 1989, Corbett et al. 1993, Symmons et al. 1998). One explanation for the pneumonias is that common subclinical pulmonary involvement in RA weakness airway host defences, making patients particularly susceptible to respiratory infections, and immunosuppressive treatment further increases the risk (Saag et al. 1997). In a recent study Young et al. (2006) observed that deaths due to pulmonary fibrosis were more common than expected. No association with treatment was found, but disease activity was higher in patients with fibrosis. In the present study only two patients died from pulmonary fibrosis, which in one case was due to gold treatment.

3.7. Rheumatoid arthritis

RA was recorded here as the underlying cause of death in 8% of all RA patients and as a contributory cause in 20%. Seven per cent of deaths were related to amyloidosis in the total RA population, which is within the range reported elsewhere. In one series of 583 RA patients, 3% had died of amyloidosis (Cobb et al. 1953). Koota et al. (1977) reported amyloidosis as cause of death in 8% and Myllykangas-Luosujärvi et al. (1995b) in 5.8% of patients. Boers et al. (1986) found histologically confirmed amyloidosis in 11% of autopsied patients. Other RA-related deaths due to systemic complications or DMARDs were rare in the present cohort. One patient died due to systemic rheumatoid vasculitis and one of pulmonary fibrosis due to gold sodium thiomalate.

There is some evidence to suggest that the incidence of amyloidosis in RA in Europe is decreasing (Laiho et al. 1999). The investigator found that annual figures for systemic amyloidosis decreased from 68 to 10 during the years 1987-1997. There is also one study from

Finland showing decreased mortality due to amyloidosis in juvenile chronic arthritis (Savolainen and Isomäki 1993). The declines have been attributed to more effective treatment of RA (Savolainen and Isomäki 1993, Sokka et al. 1999, Kaipiainen-Seppänen et al. 2000). One autopsy series showed an increasing occurrence of amyloidosis during 1975-1990 in Japan (Suzuki et al. 1994).

Estimation of whether the excess mortality should be attributed to RA itself, to its treatments, comorbidities or to combinations of these is a most difficult task. In only certain situations is it possible to attribute death entirely to a certain drug or disease; in most cases they have played a part, but not in themselves been sufficient cause. For example, death from gastrointestinal diseases may be related to treatment, especially to NSAIDs and glucocorticoids. However, patients with more severe disease use these more frequently. Thus, differences in the coding system of causes of death may underestimate the true proportion of RA-related deaths

4. Renal disease as a predictor of mortality

Patients with histologically confirmed renal amyloidosis in the present cohort had an over two-fold mortality compared to patients without nephropathy. In six out of eight deceased patients who died due to end-stage renal failure, RA or secondary renal amyloidosis was recorded as the underlying cause of death. Secondary amyloidosis has been found to be more common in patients with severe RA. Korpela (1993) found in a cross-sectional study that amyloidosis was associated with long-lasting inflammatory active RA, but in a series by Myllykangas-Luosujärvi et al. (1999) no clear correlation emerged between disease duration and amyloidosis. The prognosis of RA patients with secondary amyloidosis is poor. It has been estimated that their lifespan is shortened by 7.7 years (Myllykangas-Luosujärvi et al. 1999). The results of the present study confirm earlier findings.

This is the first long-term follow-up study on RA patients with MesGN. MesGN has been described as a frequent finding in a number of renal biopsy materials in RA patients with HU or

less frequently with PU (Pasternack et al. 1967, Hordon et al. 1984, Helin et al.1986). Earlier studies have shown that in most cases of MesGN renal function remains normal and the course of renal disease is favourable (Hordon et al. 1984, Kelly et al. 1988, Korpela et al. 1991). It has moreover been reported that isolated hematuria is a favourable clinical sign in patients with MesGN (Korpela et al. 1995). MesGN or hematuria were not associated with increased mortality in the present study, which is in keeping with the previous observations of a favourable prognosis in MesGN.

RA patients with proteinuria or combined hematuria and proteinuria carried an increased risk of dying compared to RA patients without nephropathy in the present study. Renal amyloidosis may explain this finding, in that proteinuria is a common clinical sign of amyloidosis and combined hematuria and proteinuria is also frequently a consequence of amyloidosis (Korpela 1993). In fact amyloidosis was observed in 13 patients, 9 of them having proteinuria and 2 combined hematuria and proteinuria. Patients with isolated chronic renal failure had a favourable prognosis. Besides this, in a cross-sectional study in 1988 isolated chronic renal failure was associated with ageing and hypertension (Korpela 1993).

In the present study microalbuminuria predicted increased mortality in RA patients, but not in controls. Damsgaard et al. (1990) reported a three-fold mortality in non-diabetic elderly people with microalbuminuria. Major causes of death were cardiovascular diseases in all patients. Yudkin et al. (1988) reported that microalbuminuria was a strong risk factor associated with ischemic heart disease in non-diabetic subjects. Unexpectedly little attention has been paid to microalbuminuria and mortality in RA, although this might be the first clinical sign in many renal diseases, for example amyloidosis.

5. Autoantibodies and mortality in RA

5.1. RF

The proportion of RF-positive patients in the present study was 55% (59% if all tests were taken into account), which was lower than generally anticipated (Nakamura 2000). On the other hand, 70% of RA patients with nephropathy and 69% without (paired controls) were RF- positive. The proportion of RF positivity in patients in whom RF isotypes, anti-CCP and pANCA were determined was similar to that in earlier reports. The cut-off level for FS-RF ($\geq$ 30 IU/ml) was higher than that generally used, which has an influence on the prevalence of seropositivity. It should also be noted that several of the DMARDs in use might have lowered RF levels (Paimela et al. 2001).

In the present series positive RF predicted increased mortality. The risk of death varied from 1.32 to 1.80 depending on the definition of RF positivity, and was slightly lower than previously reported (Gabriel et al. 1999, Glennås et al. 2000). In a smaller subgroup (only patients with anti-CCP antibody determination) high FS-WaRo titers predicted increased mortality. In the multivariate model including HAQ and rheumatoid nodules positive RF did not predict mortality. In previous studies increased mortality risk related to positive RF has varied considerably (OR 1.93,11.9) (Gabriel et al. 1999, Glennås et al. 2000). In some recent studies no association has emerged between RF and mortality (Riise et al. 2001a, Book et al. 2005, Nikolaisen et al. 2005). In a Norwegian study of 108 RA patients positive RF did not predict mortality (Nikolaisen et al. 2005). However, the follow up time was only 5 years and all three subgroups were small (n=24, 33, 51). In a study by Riise et al. (2001a) the study population was larger (n=187) and the follow-up time longer (mean 12 yrs), but the number of seronegative patients was small, making comparison difficult.

In the present context high IgA RF and IgM RF levels predicted increased mortality and a high IgA RF level was associated with increased mortality also in the multivariate model

including HAQ and rheumatoid nodules. In earlier mortality studies only IgM RF and not all RF isotypes have been determined (Reilly et al.1990, Jacobsson et al.1993, Wolfe et al. 1994, Glennås et al. 2000). Most show long-term joint destruction to be more severe in IgM RF-positive than -negative patients (Houssien et al.1998, Bas et al. 2000, Schellekens et al. 2000). Several have also shown that RA patients with increased IgA RF develop more severe disease with bone erosions and extra-articular manifestations than IgA RF-negative patients (Tuomi et al. 1988, Jonsson et al. 1995, Houssien et al.1998, Bas et al. 2003). Moreover, the combination of IgA RF and IgM RF positivity seems to predict an even more severe disease course (Houssien et al.1998).

RF can be associated with increased mortality either in being a marker of severe disease or by having direct pathogenetic effects. RF can initiate immune complexes by binding immunoglobulin and subsequently activating the complement cascade, including the release of chemotactic factors followed by the attraction of inflammatory cells into tissue (Dörner et al. 2004).

In summary, the present results confirm previous findings that RF positivity predicts an increased mortality risk. In this study especially IgA RF predicted an increased risk and the risk was correlated with levels of RF IgA.

5.2. Anti-CCP antibodies

The occurrence of anti-CCP antibodies in the present cohort (66%) was slightly higher than that found in previous studies (Meyer et al. 2002, Rantapää-Dahlqvist et al. 2003, Vencovsky et al. 2003, Forslind et al. 2004). Nineteen per cent of patients with RF were anti-CCP-negative and 40% without RF had anti-CCP antibodies. The proportion of RF-negative patients with anti-CCP antibodies was similar to that previously reported in RA (Kroot et al. 2000, Kastbom et al. 2004, Vallbracht et al. 2004).

Only high levels of anti-CCP antibodies (174 U/ml) predicted increased mortality in the present study. Anti-CCP has previously been found to be associated with a more severe disease course, including joint destruction (Meyer et al. 2002, Vencovsky et al. 2003, Forslind et al. 2004, Kastbom et al. 2004, Vallbracht et al. 2004) and has correlated highly with RF (Forslind et al. 2004, Kastbom et al. 2004). In the present cohort anti-CCP antibody determination was carried out in RA patients with nephropathy and their paired controls without nephropathy. In addition, the study population here consisted of RA patients with long disease duration. These circumstances might have a confounding effect on the results. Treatment could also have an effect on the levels of autoantibodies. For example, treatment with infliximab has been seen to reduce RF and anti-CCP antibody titers in a series of 43 RA patients, and the decrease was observed only in patients evincing a clinical response during the treatment (Alessandri et al. 2004). However, Kastbom et al. (2004) observed the mean level of anti-CCP antibodies declined, but anti-CCP antibody positivity remained unaltered for 3 years after the diagnosis of RA and commencement of DMARD treatment.

In summary, this present study is the first to establish a possible association between anti-CCP antibodies and mortality in RA patients. High anti-CCP antibody levels predicted increased mortality. The results support previous findings that anti-CCP antibodies are associated with severe RA.

5.3. ANCA

Neither ANCA positivity nor high ANCA titers were here related to mortality. The clinical significance of ANCA in RA has not been clearly established, and the association of pANCA with rheumatoid vasculitis remains controversial (Savige et al. 1991, Mulder et al.1993). pANCA positivity has been associated with high RF levels, long disease duration and advanced functional Steinbrocker grades (Röther et al. 1994). According to studies by Mustila et al. (1997 and 2000) positive pANCA was associated with bone erosions in early RA and more severe and

inflammatory active disease with nephropathy in later disease. No such association was subsequently found in a three-year prospective study of 91 RA patients with mild RA (Vittecoq et al. 2003).

In summary, ANCA was not associated with mortality. There are no previous reports on mortality in ANCA-positive or –negative RA patients.

6. Oral glucocorticoid treatment and mortality

Those RA patients in this cohort who received long-term glucocorticoid treatment evinced increased mortality due to infections and complications of systemic amyloidosis, which confirms findings in previous reports.

The propensity of glucocorticoids to predispose to infections is controversial and the mechanism involved is not competely understood (Da Silva et al. 2005). It has been suggested that the risk of infection is dependent on the dose and duration of glucocorticoid therapy (Dale et al. 1973). The relative risk of infections across a number of clinical settings was approximately two-fold compared to that in controls in a meta-analysis of 71 trials involving more than 2000 glucocorticoid-treated patients (Stuck et al. 1989). The risk varied according to type of disease treated. Five of the studies in question involved patients with various rheumatoid diseases and no increased risk of infections was found. In one study involving only RA patients the incidence of serious infections was slightly increased (Saag et al. 1994). Scott et al. (1987) regarded glucocorticoid treatment as a contributory factor in 27% of deaths due to infections in their series of RA patients. However, an increased mortality from infections in RA patients has been described in a series studied even before glucocorticoids came into use (Baum 1971). Glucocorticoid treatment may indicate severe RA, which itself predipose the patients to infections. In any case it seems that glucocorticoid treatment cannot alone explain the increased risk of dying due to infections, but might be a contributory factor in most cases.

In the present study cardiovascular deaths were more common in RA patients than in the general population or in the controls. However, CVD mortality was not increased in patients treated with glucocorticoids. Some earlier studies have suggested that glucocorticoid treatment is associated with accelerated arteriosclerosis (Nashel 1986, Maxwell et al. 1994, Maradit-Kremes et al. 2005). A large case-control study of 50 656 patients, including 1515 case-control pairs matched for RA, showed that patients receiving glucocorticoid treatment had a 25% higher risk of cardiovascular diseases, particularly heart failure and ischemic heart disease, after adjusting for confounders (Souverein et al. 2004). A study group from theUSA have shown that glucocorticoid use to be associated with an increased risk of cardiovascular death, even after adjusting for hypertension, diabetes and dyslipidemia (Maradit-Kremers et al. 2005). However, glucocorticoid treatment in patients with a history of CVDs reduced the risk of cardiovascular death. A Swedish study has shown that glucocorticoid treatment early in the course of RA increases the risk of cardiovascular events, but not if given extensively during the disease (Wållberg-Jonsson et al. 1999). These investigators also noted that in patients with RA and CVDs, glucocorticoids delayed the CV event. These findings suggest that the anti-inflammatory effect of glucocorticoids may be beneficial by merit of controlling inflammation (van Doornum et al. 2002). In any case the mechanisms linking glucocorticoid use and cardiovascular outcome are complex, perhaps reflecting a balance between adverse and potentially protective effects. Glucocorticoids could increase the risk of atherosclerosis via detrimental effects on lipids, glucose metabolism, and blood pressure and also reduce the risk by controlling the inflammation.

Four deaths in the present series were due to intestinal perforation in RA patients treated with glucocorticoids for over 10 years, compared to one among those who had not received glucocorticoids. Three of the four patients in question used both glucocorticoid and NSAID medications and all of them also suffered from amyloidosis. Intestinal perforations were thus not due solely to glucocorticoid treatment.

On the basis of animal studies conducted by Teilum (1952), glucocorticoid was thought to be conductive to the development of amyloidosis. Gardner (1962) compared post mortem the incidence of amyloidosis in patients with RA in the pre-glucocorticoid and glucocorticoid eras and found a 9.5% and 12.5 % incidence respectively. In the present study death due to amyloidosis was more frequent in RA patients treated with glucocorticoids, but this probably reflects the severity of the disease.

The potential toxicity of glucocorticoids is well documented (Caldwell et al. 1991). In spite of this, the role of glucocorticoids with regard to the balance between causing and preventing deaths in RA is unclear. Most studies have been retrospective and in such cases the cumulative dose of intermittent glucocorticoid users is difficult to estimate, in that prescriptions may not always be recorded in hospital reports. In the present study it was likewise not possible to calculate the cumulative glucocorticoid dose. Since in most cases glucocorticoids are used in more severe RA, estimation of their contribution to mortality is biased. It might be that patients on long-term glucocorticoid treatment simply had a more severe disease and were in any case at an increased risk of death, or the long-term glucocorticoid treatment in these patients relieved symptoms and signs of RA, but did not otherwise properly control the autoimmune inflammation.

In summary, RA patients with long-term glucocorticoid treatment in the present study had severe RA and evinced increased mortality due to infections and complications of systemic amyloidosis. These findings are accord with results given in previous reports.

SUMMARY AND CONCLUSIONS

1. RA patients from a cross-sectional population-based series had increased mortality compared to age- and sex-matched controls or the general Finnish population. RA patients had an increased risk of dying due to renal, gastrointestinal, respiratory and cardiovascular diseases, infections and hematopoetic malignancies. The mortality risk (SMR) varied between 1.37 and 1.71.

2. Nephropathy presenting with combined hematuria and proteinuria, proteinuria, microalbuminuria or histologically confirmed amyloidosis was associated with increased mortality in RA patients. In contrast, hematuria and histologically confirmed mesangial glomerulonephritis did not predict increased mortality. Among controls only chronic renal failure predicted increased mortality.

3. The presence of RF, particularly high IgA RF and IgM RF levels, predicted increased mortality in RA patients. Positive anti-CCP as a whole and ANCA were not associated with mortality risk, but high anti-CCP levels predicted increased mortality.

4. RA patients treated with low-dose oral glucocorticoids for more than 10 years evinced increased mortality compared to those who did not receive glucocorticoid treatment or in whom the duration of treatment was for less than 10 years. The increased mortality was related mainly to infections and complications of systemic amyloidosis.

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ORIGINAL COMMUNICATIONS

Death rates and causes of death in patients with rheumatoid arthritis: a population-based study

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Objective: To assess the mortality and causes of death in a cross-sectional population-based study of 1042 patients with rheumatoid arthritis (RA).

Methods: In 1988, 604 RA patients [470 females (F), 134 males (M)] and 457 age- and sex-matched controls (352 F, 105 M) were examined prospectively (participants) and 438 (183 F, 81 M) non-participant RA patients retrospectively. In 1999, vital status and causes of death were determined. Mortality in the total RA population was compared to that in the general population, and that among participant RA patients to their matched controls.

Results: A total of 384 (37%) RA patients and 71 (16%) controls died. RA patients had increased mortality compared to the general population (standardized mortality ratios SMR 2.64) or controls (1.71). This was observed in both sexes. Over 40% of deaths in all groups were due to cardiovascular diseases. RA patients were at increased risk of dying of urogenital, gastrointestinal, respiratory and cardiovascular diseases, infections, and cancers when compared to the general population or controls.

Conclusions: Our results show that a cross-sectional cohort of RA patients had an increased risk of death from various causes.

Many studies have established that patients with rheumatoid arthritis (RA) have a higher mortality than the general population (1–13); relatively few studies show the opposite results (14–17). Most reports show varying degrees of excess mortality and causes of death among RA patients. One reason for the differences in mortality rates may lie in differing patient recruitment and study designs. Mortality is generally lower in population-based (2, 6, 8, 10, 14, 18) than in hospital-based studies (2, 4–5, 9, 11–13).

It has been established that patients with RA often die of infections (5, 2–6, 9, 12–13, 16) and renal diseases (1, 2–5). Some papers also report an increased mortality from gastrointestinal (1, 2–4, 6, 9, 16) and respiratory diseases (3–4). Excesses in mortality due to cardiovascular diseases (1, 3–5, 8–9, 13, 16) and malignancies remain contradictory (1–2, 4, 16, 9, 13, 16). On the other hand, some studies suggest that the mortality among RA patients is increased, but causes of death are similar to those in the general population (15).

There are no large population-based studies in which both RA patients and sex- and age-matched controls have been studied from commencement of follow-up. We analysed the mortality in a cross-sectional population-based cohort of RA patients and their age- and sex-matched controls, and compared death rates and causes of deaths in these groups. We also analysed mortality in RA patients who did not participate in an original study in 1988, and compared the mortality in the total RA population to that of the Finnish population in general.

Materials and methods

Study population

In Finland, since 1966 certain chronic diseases, including chronic inflammatory rheumatic diseases, have qualified a patient to receive drug reimbursement. The sickness insurance scheme covers the entire population of Finland, and the register is maintained by the Social Insurance Institution. All inflammatory rheumatic articular diseases are grouped under the same code, including RA, juvenile chronic arthritis, ankylosing spondylitis, chronic reactive arthritis, and psoriatic arthritis. Systemic

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connective tissue diseases are grouped under another code. The decision on drug reimbursement is based on a certificate from a physician, which includes the history and clinical assessment of the disease, and the results of serologic and radiographic investigations. The certificate is approved by an expert adviser on behalf of the sickness insurance scheme.

The original cross-sectional study involved persons living in the city of Tampere (170 511 inhabitants in 1987, 3.5% of the population of Finland). According to the registry of the Social Insurance Institute of Finland (March, 1987), 1385 persons had been admitted to the 90% refund category for antirheumatic drugs therapy for RA. In 1987–88 re-evaluation of the original physicians' certificates, and supplementation where necessary by clinical examination and patient histories, confirmed that 1051 persons (834 females, 217 males) were suffering definite or classic RA according to the diagnostic criteria of the American Rheumatism Association (19).

In 1988, these patients with RA were invited to participate in a prospective study of renal and urinary tract diseases in patients with RA (20). Out of the 1051 RA patients selected for this study, 604 persons, (470 females, 134 males) were studied prospectively (participants) and 438 persons (357 females, 81 males) retrospectively (non-participants), by evaluation of patient records (20). The estimation of mortality and causes of death is thus based on 1042 patients, which represents 99.1% of the RA population. Age- and sex-matched controls were invited for those RA patients who participated in the study in 1988. Each RA patient was randomly assigned two control persons from the remaining general population of Tampere by computer, and if the first of these did not participate, the second was invited. Controls were not presumed to be healthy, but only patients with chronic inflammatory rheumatic diseases were excluded. A total of 457 age- and sex-matched controls (352 females, 105 males) were studied prospectively. The mean age of the patients was 59 ± 13 years for participants, 64 ± 15 years for non-participants, 61 ± 13 for all RA patients, and 58 ± 12 years for controls. The duration of RA was 15 ± 10 years for participants and 17 ± 11 for non-participants, and 16 ± 10 years for all patients. Age structure and duration of disease of the RA population were comparable to previous cross-sectional study populations (8, 21, 22). In the original prospective study, state of general health, renal and urinary tract diseases, treatments, and severity of RA were carefully recorded.

Establishment of mortality and causes of death

Information on the vital status on August 31st 1999 and times of death were evaluated from data from the Official Statistics of Finland. Causes of death were derived from the official death certificates, autopsy reports, and hospital records. Death certificates were available for 98% of the deaths of RA patients and 99% of deaths of controls. The underlying and immediate causes of death were recorded.

The causes of death were classified according to the rules of the World Health Organisation, using the 9th Revision of the International Classification of Diseases (ICD-9). Causes of death were missing for nine RA patients and one control because death certificates were incomplete or missing, or because an incorrect name was given in the records. Among RA patients, there were 365 (97%) deaths due to disease, nine (2%) due to injuries, one for an unknown reason, but no suicides. In the control group, 64 (91%) deaths were due to diseases, four (6%) due to injuries, and two had committed suicide. An autopsy had been performed on 121 (32%) RA patients and 32 (45%) controls. Autopsies are performed on about 30% of the deceased in Finland (Official Statistics of Finland).

Mortality in the total RA population was compared to that in the general Finnish population, and mortality among participant RA patients to that in age- and sex-matched controls. Age- and sex-matched death rates for the general Finnish population in 1997 were used to calculate the expected number of deaths. Standardized mortality ratios (SMRs) (the ratio of the observed to expected number of deaths) with 95% confidence interval (95% CI) were calculated for all causes together, and for the most frequent underlying causes separately. Patients for whom no death certificate was available were excluded from the analyses.

Kaplan–Meier plots were generated for the prospectively studied RA patients and controls, comparing survival for each year of follow-up. The Cox proportional hazards model was applied to evaluate the predictive value of age, sex, and subgroup. The data were recorded and statistical calculations performed using the SPSS/Win (Version 9,0) software. Ethical approval was obtained from the Finnish Ministry of Social Affairs and Health.

Results

Mortality

Total RA population (n=1042). There were 384 (37%) deaths in the total RA population, 292 (35%) females and 92 (43%) males. Their mean age at death was 76.5 ± 9.6 years and mean disease duration was 24.5 ± 11.2 years; the respective figures were 77.8 ± 9.2 and 25.6 ± 11.5 years for females, and 72.6 ± 9.9 and 20.9 ± 9.5 years for males. SMRs compared to the general Finnish population were for

males and females 2.64 (CI 95% 2.63–2.68), for females 2.53 (2.52–2.54), and for males 3.20 (3.11–3.30).

Participant RA patients (n=604). A total of 160 of the patients (26%) had died, 109 (23%) females and 51 (38%) males. Their mean age at death was 75.7±9.6 years, 77.3±9.6 for females and 72.4±8.8 for males. The mean duration of RA was 23.5±11.2 years, 24.6±11.7 for females and 21.2±10.0 for males. SMR compared to age- and sex-matched controls was 1.71 (1.64–1.77), 1.74 (1.67–1.81) for females and 1.67 (1.64–1.72) for males.

Controls (n=457). During the follow-up, a total of 71 (16%) deaths had occurred in the control group, 47 (13%) females, 24 (23%) males. Their mean age at death was 74.1±11.4 years, 75.8±11.6 for females and 70.5±10.4 for males. SMR compared to the general Finnish population was 0.98 (0.96–0.99), 0.83 (0.81–0.84) for females, and 1.49 (1.47–1.50) for males.

Using the Cox proportional hazards model, the sex- and age-adjusted mortality ratio in the total RA population was 2.26 (1.74–2.93), and in participant RA patients 1.71 (1.29–2.27) compared to controls. All values were statistically significant [probability (p)<0.001]. The cumulative survival curves in participant RA patients and controls are presented in Figure 1.

Causes of death

The underlying causes of death in the RA and control groups are set out in Table 1. The data show that >40% of deaths had occurred due to cardiovascular events in every subgroup. About 20% of the subjects had died of cancers. There were no marked differences between the two RA subgroups.

Table 2 shows the mortality risk among RA patients and controls expressed as SMR. RA patients were at increased risk of death from

Figure 1. Cumulative proportion surviving (Kaplan–Meier) of participant RA patients and controls.

urogenital and gastrointestinal diseases, infections, respiratory diseases, cancers, and cardiovascular diseases, and a decreased risk of accidental death. The mortality of participant RA patients compared to controls was fairly similar to that of the total RA population. The total mortality among controls was also very similar to that in the general population (Table 2).

Malignancies as cause of death. A total of 69 (18%) RA patients [32 (20%) participants] and 15 (21%) controls had died of malignancies, according to underlying cause of death. The median age at death was 74.5±8.2 years for RA patients (74.3±7.8 for participants) and 69.9±16.1 years for controls. Deaths due to haematopoietic malignancies [lymphoma (n=8), multiple myeloma (n=3) and leukaemia (n=2)] occurred more often among RA patients than among controls (p=0.004). There was no such difference in other sites or types of tumours.

Cardiovascular diseases as cause of death. There were 164 cardiovascular deaths among RA patients (74 participants) and 32 controls according to underlying cause of death. Eighty-nine RA patients had died of ischemic heart disease, 13 of heart failure, seven of other heart diseases, five of pulmonary embolism, 31 of cerebrovascular disease, and 19 of other vascular diseases. Twenty-two controls had died of ischemic heart disease, six of cerebrovascular disease, and two of other vascular diseases—one of heart failure and one of aortic valve stenosis.

Urogenital diseases as cause of death. Among RA patients, 14 had died of urogenital diseases, including renal amyloidosis in 11 patients and chronic renal failure from other causes in three patients, according to underlying cause of death. There were no deaths attributable to urogenital diseases in the control group.

Gastrointestinal diseases as cause of deaths. Gastrointestinal diseases were recorded as an underlying cause of death in 18 RA patients. There were six deaths due to duodenal or ventricular ulcer, two intestinal occlusions, two mesenteric thromboses, three diverticulitis, one oesophageal, and one colon perforation, as well as one case each of colitis, pancreatitis, and gall-bladder perforation. Two of the controls had died of duodenal ulcer.

Respiratory diseases as cause of death. In 31 RA patients, respiratory disease was recorded as an underlying cause of death: pneumonia in 20, chronic obstructive pulmonary disease (COPD) in five, pulmonary fibrosis in two, and asthma, emphysema, empyema, and pulmonary fibrosis in one patient each. Of the controls, two had died of respiratory disease: one of COPD and one of asthma.
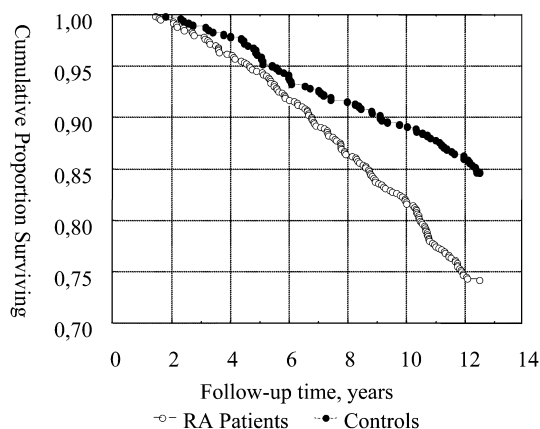
Table 1. Underlying causes of death in RA patients and controls.

ICD-code		Total RA population n=1042		Participant RA patients n=604		Controls n=457	
		n	*%	n	*%	n	*%
A00-A99	Infections	7	1.8	3	1.9		
C00-C97	Cancer	69	17.9	32	20.0	15	21.1
E00-E90	Endocrine	1	0.3			2	2.8
F00-F98	Mental	29	7.6	11	6.9	9	12.7
I00-I99	Cardiovascular	164	42.7	74	46.2	32	45.1
J00-J99	Respiratory	31	8.1	13	8.1	2	2.8
K00-K93	Gastrointestinal	18	4.6	5	3.1	2	2.8
M00-M99	Musculoskeletal	32	8.3	7	4.3		
N00-N98	Urogenital	14	3.6	6	3.8		
Q00-Q99	Congenital	2	0.5			1	1.4
S00-T98	Injuries	8	2.1	4	2.5	7	9.8
	Unknown	9	2.3	5	3.1	1	1.4
A00-T98	All categories	384		160		71	

*% = Number of deaths in particular category/total number of all deaths during 1988–99.

Table 2. SMR in RA populations and controls compared to the general population or matched controls.

ICD code		Total RA population / General population n=1042		Participant RA patients / Matched controls n=604		Controls / General population n=457	
		SMR	95%CI	SMR	95%CI	SMR	95%CI
A00-A99	Infections	6.47	6.25–6.57				
C00-C97	Cancers	2.40	2.38–2.42	1.61	1.48–1.76	0.85	0.84–0.86
E00-E90	Endocrine						
F00-F98	Mental			1.11	0.95–1.28		
I00-I99	Cardiovascular	1.91	1.89–1.92	1.75	1.65–1.85	0.88	0.87–0.89
J00-J99	Respiratory	2.51	2.49–2.55	5.00	4.35–5.72	0.34	0.33–0.36
K00-K93	Gastrointestinal	7.56	6.77–8.53	1.91	1.52–2.37	1.05	0.75–1.43
N00-N98	Urogenital	8.44	8.29–8.58				
S00-T98	Injuries	0.61	0.58–0.62	0.75	0.58–0.96	0.74	0.72–0.75
A00-T98	All categories	2.64	2.63–2.68	1.71	1.64–1.77	0.98	0.96–0.99

SMR = Observed mortality of RA patient and controls in relation to expected mortality in the general population, CI = Confidence interval.

Table 3. Infections as an immediate cause of death in RA patients and controls.

ICD-code		Total RA population n=1042	Participant RA patients n=604	Controls n=457
		n	n	n
A08	Gastroenteritis	1		
A24-A41	Septicemia	16	7	
A46	Erysipelas	1	1	
J11-J18	Pneumonia	84	28	15
J20	Bronchitis	3	2	
J86	Empyema	1		
N10	Pyelonephritis	3	1	
	All infections	109	39	15

Infections as cause of death. Altogether, 109 (28%) RA patients [39 (26%) participants] had died as a result of infection according to immediate cause of death (Table 3). On the death certificates, however, there were only 17 deaths recorded in the infection category (A00–A99). In addition to the infection category proper, many deaths had occurred due to infections in other main categories, particularly respiratory and urogenital diseases.

In RA patients, 77% (72% participants) of infections comprised pneumonia and 15% (18% participants) septicaemia. Females had died more often of septicaemia than males (4.8% versus 2.2%), but there was no such difference in deaths due to pneumonia (21.9% versus 21.7%). Among the controls, there were no deaths due to infections according to the infection category, but 15 (21%) subjects had died of pneumonia as an immediate cause of death.

RA-related causes of death. RA was recorded as an underlying cause of death in 32 (8%) persons, and as a contributory cause of death in 76 (19.8%). Amyloidosis was recorded as an underlying cause of death in 11 (3.1%) RA patients, in 10 (2.6%) subjects as an immediate cause of death, and as a contributory cause in seven (1.8%): therefore 28 patients (7.3%) died due to amyloidosis. Gastrointestinal bleeding or ulcer was mentioned as an underlying cause of death in six RA patients, and as a contributory cause of death in three. There was also one death recorded due to systemic rheumatoid vasculitis, and one pulmonary fibrosis due to gold sodium thiomalate as the underlying cause of death.

Discussion

In our study, SMR was 2.64 for the total RA population compared to the general population, and 1.71 for participant RA patients compared to the age- and sex-matched controls. This means that RA was associated with almost threefold mortality. Korpela (1988) noted that non-participant RA patients were already older and had more severe diseases than participants (20), which may explain the more favourable prognosis among participant RA patients. To minimize selection bias, we also compared the mortality and causes of death in the total RA population to the general population. As seen, the degree of increased mortality varies considerably, depending on the study cohort and comparison material (2.64 versus 1.71).

It is generally accepted that RA patients die more often of infections than subjects in the general population (5, 2–6, 9, 12, 13, 16). Our study also showed that the mortality due to infections was increased in RA patients. In mortality studies, causes of death are usually classified according to the ICD. In this classification, for example, deaths due to respiratory infections are classified under the heading of respiratory diseases. Only systemic infections and contagious or epidemic diseases are classified as infectious diseases. It is thus no simple matter to evaluate the real risk of mortality due to infections. We found an increased mortality attributable to respiratory diseases. This excess was associated mainly with such infections as pneumonia and bronchitis. Moreover, the cause of death is usually classified according to the underlying cause of death. If immediate causes of death are considered, the frequency of infections would be greater.

It has been suggested that haematopoietic malignancies, such as leukaemia, lymphoma, and multiple myeloma, occurred frequently among RA patients, but results have been contradictory (1, 3, 4, 6, 11, 12, 21, 23). In 1993 Gridley and associates (23) observed that RA patients were at decreased risk of colorectal malignancies, but increased risk of lymphomas. They surmised that the use of non-steroidal anti-inflammatory drugs may protect from colorectal cancer. In our study, the incidence of deaths due to malignancies was higher among RA patients than in the general population or controls, and there was a moderate increase of haematopoietic cancers among RA patients. We observed no significant differences in the incidence of tumours of other sites or type.

An increased incidence of death due to cardiovascular diseases (CVD) has been reported in some studies (4, 5), but not in all (1, 12). Our analyses showed an increased risk of CVD among RA patients, but the risk was lower than other disease categories. The risk of CVD was comparable to those in other Scandinavian studies. It has been suggested that the use of aspirin protects from cardiovascular death in these patients (25). An increased mortality due to vascular diseases may be explained by variations in the use of corticosteroids (26) or disease-modifying antirheumatic drugs (DMARDs) (26), or possibly in smoking habits (22). Recently, it has been reported that untreated RA patients have different lipid profiles from controls, and the inflammatory condition of RA may affect the metabolism of high-density lipoprotein cholesterol and apoA1 (27). Systemic inflammation associated with RA may also play an important role here (28). These differences may possibly expose RA patients to a higher risk of atherosclerosis.

Deaths due to renal diseases have been reported to make a significant contribution to the increased mortality in RA (2, 4, 29, 30). Renal amyloidosis has been considered the main cause. In 1986, Laakso et al (29) reported that 6% of men and 12% of women died of renal amyloidosis. At the same time, Boers et al reported that amyloidosis was found in 14 (11%)

of 132 necropsied patients (30). Later, Myllykangas-Luosujärvi et al (31) reported that 15% of excess mortality was caused by amyloidosis. In the original cross-sectional prospective study of 604 RA patients, amyloidosis was found in 13 (20). In the present study, we found that amyloidosis was mentioned on 28 (7.3%) death certificates, in 12 cases as an underlying cause, in nine as an immediate cause, and in seven as a contributory cause of death. Twenty-one RA patients had died of end-stage renal amyloidosis, and one as a result of urinary bladder perforation due to amyloidosis. Thus, 6% of deaths in RA patients could be explained by amyloidosis.

The treatment of RA until 1988, when the original cross-sectional study was performed, was fairly conservative compared to present practice. Most patients were treated with single DMARD therapy, and only a small proportion with cytotoxic drugs, such as azathioprine or methotrexate. The poor prognosis of RA patients in this study may reflect the efficiency of the treatment of RA in the 1970s and 1980s. Long-term follow-up studies will show if the outcome of RA patients treated with modern treatments, such as combination therapies and biological preparations, will be better in the future.

In conclusion, we observed that RA patients had an increased mortality compared to age- and sex-matched controls, or to the general Finnish population. Over 40% of deaths were due to cardiovascular diseases in all study groups. RA patients had an increased risk of dying of respiratory, gastrointestinal, cardiovascular, and urogenital diseases, as well as infections and haematopoietic malignancies, compared to controls or the general population.

Acknowledgements

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ERRATUM

The authors apologise for an error that appeared in the article by Sihvonen et al. in the October/November issue 2004 of the Scandinavian Journal of Rheumatology (Scand J Rheumatol. 2004;33:221–7), entitled 'Death rates and causes of death in patients with rheumatoid arthritis: a population-based study'. The error relates to the standardised mortality rates (SMR), comparing death rates of patients with that of the general population or controls were partly miscalculated by producing SMRs that were 50 to 100% in excess of the correct ones. The wrong figures neither changes the end results nor the message of the study. The correct Table 2, which shows the main result, and the correct SMRs, is published in full below.

Table 2. SMR in RA populations and controls compared to the general population or matched controls.

ICD code		Total RA population General population		Participant RA patients Matched controls		Controls/ General population	
		n=1042		n=604		n=457	
		SMR	95% CI	SMR	95% CI	SMR	95% CI
A00-A99	Infections	**4.12**	**1.78–8.13**				
C00-C97	Cancers	**1.20**	**1.02–1.52**	1.61	1.48–1.76	**0.61**	**0.34–1.00**
E00-E90	Endocrine						
F00-F98	Mental			1.11	0.95–1.28		
I00-I99	Cardiovascular	**1.23**	**1.05–1.43**	1.75	1.65–1.85	**0.66**	**0.45–0.93**
J00-J99	Respiratory	**1.16**	**1.01–1.76**	5.00	4.35–5.72	**0.23**	**0.03–0.84**
K00-K93	Gastrointestinal	**2.12**	**1.26–3.35**	1.91	1.52–2.37	**0.67**	**0.08–2.43**
N00-N98	Urogenital	**3.50**	**1.98–6.35**				
S00-T98	Injuries	**0.16**	**0.01–0.56**	0.75	0.58–0.96	**0.50**	**0.02–0.68**
A00-T98	All categories	**1.37**	**1.23–1.51**	1.71	1.64–1.77	**0.68**	**0.53–0.86**

SMR=Observed mortality of RA patients and controls in relation to expected mortality in the general population or controls; CI=Confidence intervals.

Original Paper

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Clinical Practice

Renal Disease as a Predictor of Increased Mortality among Patients with Rheumatoid Arthritis

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Abstract

Aims and Methods: Mortality among RA patients and controls was analyzed with special attention to renal disease in population-based material (originally screened in 1988) of 604 patients with RA (470 females, 134 males) and 457 age- and sex-matched controls (352 females, 105 males). In the original RA population, isolated hematuria (HU) was observed in 54, isolated proteinuria (PU) in 27, combined hematuria and proteinuria (HUPU) in 7, chronic renal failure (CRFtot) in 36 and isolated chronic renal failure without HU or PU (CRFisol) in 15 patients. Among the controls, HU was observed in 39, PU in 11, CRFtot in 32 and CRFisol in 16 subjects. HUPU was not observed in any of the controls. Microalbuminuria (20–200 μg/min) was observed in 34 RA patients and in 27 controls. Histologically confirmed amyloidosis was found in 13 RA patients and mesangial glomerulonephritis (MesGN) in 17 patients. The mortality was evaluated in 1999 from data of the Statistical Office of Finland. Statistical analysis was performed by Cox regression analysis. ***Results:*** Mortality was significantly increased in the RA population as compared to controls: hazard ratio (HR) 1.78 (95% CI 1.34–2.31) for all RA patients; HR 2.12 (1.52–2.94) for females; HR 1.15 (0.75–1.77) for males. In the RA material, increased mortality was detected in patients with HUPU (HR 4.45; 1.54–12.84), PU (HR 3.54; 1.88–6.65), CRFtot (HR 3.74; 2.55–5.56) or microalbuminuria (HR 2.77; 1.64–4.69) when compared to those with normal clinical renal findings, whereas HU (HR 1.49; 0.88–2.52), CRFisol (HR 1.71; 0.82–3.54), bacteriuria (HR 0.96; 0.35–2.59) or pyuria (HR 0.65; 0.09–4.65) did not predict mortality. Renal amyloidosis was associated with an over twofold mortality rate (HR 2.31; 1.03–5.15), whereas mortality was within expected limits in RA patients with MesGN (HR 1.61; 0.49–5.24). ***Conclusion:*** Our results show that nephropathy presenting with combined hematuria and proteinuria, proteinuria, microalbuminuria or histologically confirmed amyloidosis is associated with increased mortality in RA patients, whereas mortality is within expected limits in those with isolated hematuria or mesangial glomerulonephritis.

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Introduction

Life expectancy in patients with rheumatoid arthritis (RA) is markedly shortened as compared with that of subjects without RA [1–11]. Most studies have demonstrated increased mortality due to infections [1, 2, 4–7, 9–12], cardiovascular [1, 4, 6], gastrointestinal [7, 8, 10–15] and renal diseases [1, 2, 4–9, 12–16], and a few studies also due to cancers [8, 10, 17].

Epidemiological studies have unquestionably demonstrated increased mortality attributable to renal diseases in RA. However, recent studies show that this excess is only slight when amyloidosis is excluded [7, 8, 15]. Investigators report few deaths related to urinary tract infections and urosepsis [7, 8, 16], chronic nephritis [8, 16] or renal calculi [8], whereas renal deaths due to analgesic nephropathy are markedly less common or even absent in more recent studies [15].

Death from renal disease has thus been explained mainly by amyloidosis, while the role of other renal diseases such as mesangial glomerulonephritis has not been established. The aim of this study was to estimate mortality among RA patients with special attention to clinical renal findings and histologically confirmed renal diseases in a population-based material of RA patients and age- and sex-matched controls.

Patients and Methods

Study Population

The original cross-sectional study concerned persons living in the city of Tampere (170,511 inhabitants in 1987, 3.5% of the population of Finland). According to the register of the Social Insurance Institute of Finland (March, 1987), 1,385 persons had been admitted to the 90% refund category for antirheumatic drug therapy for RA. In 1987–1988, re-evaluation of the original physicians' certificates, and supplemented where necessary with clinical examination and patient histories, 1,051 persons (834 females, 217 males) could be confirmed as suffering from definite or classic RA according to the diagnostic criteria of the American Rheumatism Association [18]. In 1988, these subjects were invited to participate in a prospective study of renal and urinary tract diseases in patients with RA [19]; 604 (470 females, 134 males) were enlisted. Age- and sex-matched controls were invited for those RA patients who participated in the study in 1988. Each patient was assigned two controls from the remaining population of Tampere, and if the first of these did not participate, the second person was invited. A total of 457 controls (352 females, 105 males) were studied prospectively. The mean age of patients with RA was 59 ± 13 years, of controls 58 ± 12 years. The mean duration of RA was 15 ± 10 years. In the prospective study [19], the general state of health, functional capacity (HAQ), renal and urinary tract diseases, treatments, extra-articular manifestations and severity of RA were carefully recorded.

Methods in the Prospective Study of Renal and Urinary Tract Diseases in Patients with RA

Instructions for fasting, urine collections and blood samples were given by the same specially trained nurse. The renal and urinary tract diseases were screened by first morning urine sample, 8-hour urine collection (from 10 p.m. to 6 a.m.), and blood sample at the end of urine collection. First morning urine samples were studied with a dipstick (Nephur-7-Test RL, Boehringer Mannheim, Germany) and if positive, by microscopic examination of the sediment. Other screening methods included serum creatinine by an Auto Analyzer based on the Jaffe reaction form, urine albumin excretion by immunoassay and urine bacterial culture.

Hematuria was defined as a positive dipstick result in two consecutive urine samples. Proteinuria was screened by dipstick and if urine albumin excretion was 15 mg/8 h or more, 24-hour urinary protein excretion was measured. Proteinuria was defined as urine protein excretion 150 mg/24 h or more. Reduced renal function was defined as serum creatinine 100 μmol/l or more in females and 115 μmol/l or more in males, microalbuminuria as a urine albumin excretion rate (UAER) of 20–200 μg/min and pyuria as presence of more than four white blood cells per high-power field on a centrifuged urine specimen. Bacteriuria was defined as bacterial growth equal or greater than 10^5 colony-forming units/ml without symptoms of urinary tract infection or pyuria.

Patients with hematuria, proteinuria or reduced renal function were further studied by clinical examination and renal imaging (ultrasound and nephrography or alternatively intravenous urography). Hematuria was studied by urine cytology, urethrocystoscopy and evaluation of the bleeding diathesis. Renal needle biopsy was considered indicated if (1) hematuria was constant and no urological lesions could be found, or (2) proteinuria was 500 mg/24 h or more and there was no contraindication for biopsy. Renal biopsy specimens were examined by light and immunofluorescence microscopy.

Renal Findings in the Original Cross-Sectional Study

In the original cross-sectional study of 604 RA patients, isolated hematuria (HU) was observed in 54 (8.9%), isolated proteinuria (PU) in 27 (4.5%), combined hematuria and proteinuria (HUPU) in 7 (1.2%), chronic renal failure (CRFtot) in 36 (5.9%) and isolated chronic renal failure without HU or PU (CRFisol) in 15 (2.5%) patients. Among the same patients bacteriuria was observed in 15 (2.5%) and pyuria in 6 (0.9%), microalbuminuria was observed in 34 (5.6%) patients. Histologically confirmed renal amyloidosis was found in 13 (2.2%) patients and mesangial glomerulonephritis (MesGN) in 17 (2.8%). In the original material of 457 controls, HU was observed in 39 (8.5%), PU in 11 (2.4%), CRFtot in 32 (7.0%) and CRFisol in 16 (3.5%); bacteriuria was detected in 12 (2.6%) and pyuria in 14 (3.1%). HUPU was not observed in any but, microalbuminuria was observed in 27 (5.9%) controls.

Establishment of Mortality and Causes of Death

Information on vital status on August 31st 1999 and times of death were evaluated from data from the Official Statistics of Finland. The causes of death were taken from the official death certificates, autopsy reports and hospital records. Death certificates were available in 98% of cases among RA patients and 99% of controls. The underlying, immediate and contributory causes of death were recorded. Causes were classified according to the rules of the World Health Organization (WHO) using the 9th Revision of the International Classification of Diseases (ICD-9). The risk of death was esti-

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Pasternack

Table 1. Number of deaths among RA patients and controls with clinical renal findings or histologically confirmed renal diseases

	RA patients (n = 604)			Controls (n = 457)		
	patients in original material	deaths during follow-up		patients in original material	deaths during follow-up	
		n	%		n	%
Clinical findings						
Isolated hematuria (HU)	54	20	37	39	7	18
Chronic renal failure (CRFtot)	36	20	56	32	16	50
Microalbuminuria (MICALB)	34	16	47	27	3	11
Isolated proteinuria (PU)	27	14	52	11	3	27
Isolated chronic renal failure (CRFisol)	15	8	53	16	9	56
Bacteriuria	15	4	27	12	2	17
Combined hematuria and proteinuria (HUPU)	7	4	57			
Pyuria	6	1	17	14	4	28
Histology findings						
Mesangial glomerulonephritis (MESGN)	17	4	24			
Amyloidosis (AMYL)	13	8	62			

Original material was screened in 1988. Follow-up was until 1999.

mated by univariate Cox proportional hazards survival analysis, and expressed as Hazard ratio (HR) with 95% confidence intervals (95% CI). The multivariate Cox proportional hazards model quantifies the predictive values of each variable when all variables are considered together. We used the forward selection method performed in a step-wise manner. Differences were considered significant at p value less than or equal 0.05. The data were recorded and statistical calculations performed using the SPSS/Win (Version 9.0) software. Ethical approval was obtained from the Finnish Ministry of Social Affairs and Health.

Results

Mortality among RA Patients

During the follow-up a total of 160 (26%) RA patients had died – 109 (23%) females and 51 (38%) males. Mortality was significantly increased in the RA population as compared to controls (p < 0.05). Age-adjusted HR were 1.78 (95%CI 1.34–2.31) for all RA patients, 2.12 (1.52–2.94) for females and 1.15 (0.75–1.77) for males as compared to the controls.

Clinical Findings

Altogether 20 (37%) RA patients with isolated hematuria (HU), 14 (52%) patients with isolated proteinuria (PU), 4 (57%) patients with combined hematuria and proteinuria (HUPU), 20 (56%) with chronic renal failure (CRFtot) and 8 (53%) with isolated chronic renal failure (CRFisol) had died (table 1). Sixteen patients (47%) with microalbuminuria, 4 (27%) with bacteriuria and 1 (17%) with pyuria had also died (table 1).

Table 2 shows results of univariate Cox regression analysis. The mortality was increased in RA patients with HUPU, with PU, or with microalbuminuria when compared to patients with normal renal findings, whereas in those with HU, CRFisol, bacteriuria or pyuria, the mortality was within expected limits. However, taking all patients with reduced renal function (serum creatinine 100 µmol/l or more in females and 115 µmol/l or more in males), including those with other abnormal renal findings such as HU, PU or HUPU, reduced renal function (CRFtot) also predicted increased mortality.

Similar predictive effects were also noted in the multivariate model, which included age, sex, duration of RA, other diseases (diabetes, hypertension, coronary artery disease and heart failure), functional capacity measured by Heath Assessment Questionnaire (HAQ), incidence of rheumatoid nodules and clinical renal findings, as forced into the model one by one (table 3). If RA patients with amyloidosis were excluded from the model, then PU, CRFtot and microalbuminuria, but not HUPU predicted increased mortality. Two RA patients with HUPU had histology-confirmed amyloidosis, this comprising almost 30% of all patients with HUPU.

Table 2. Parameters predicting mortality: results of univariate Cox regression analysis with follow-up time in RA patients and controls

Variables	RA patients (n = 604)			Controls (n = 457)		
	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.08	1.06–1.11	<0.001	1.11	1.07–1.13	<0.001
Sex (M/F)	2.51	1.72–3.65	<0.001	2.04	1.17–3.45	0.006
RA severity						
Duration of RA (years)	0.99	0.97–1.00	0.172			
HAQ	1.63	1.25–2.12	<0.001			
RA nodules	1.77	1.24–2.51	0.001			
Other diseases						
Diabetes	1.33	0.81–2.17	0.249	1.71	0.75–3.27	0.147
Hypertension	1.48	1.05–2.08	0.021	1.05	0.59–1.71	0.830
Coronary artery disease	0.92	0.61–1.41	0.727	1.54	0.78–2.78	0.179
Heart failure	1.98	1.34–2.92	<0.001	0.93	0.37–4.82	0.841
Renal diseases						
Isolated proteinuria (PU)	3.54	1.88–6.65	<0.001	1.31	0.41–5.38	0.678
Isolated hematuria (HU)	1.49	0.88–2.52	0.132	1.61	0.70–3.50	0.237
Combined proteinuria and hematuria (HUPU)	4.45	1.54–12.84	0.005			
Chronic renal failure (CRFtot)	3.74	2.55–5.56	<0.001	3.33	1.84–5.99	<0.001
Isolated chronic renal failure (CRFisol)	1.71	0.82–3.54	0.147	4.47	2.07–10.05	<0.001
Microalbuminuria (MICALB)	2.77	1.64–4.69	0.002	0.69	0.21–2.25	0.453
Renal amyloidosis (AMYL)	2.31	1.03–5.15	0.040			
Mesangial glomerulonephritis (MESGN)	1.61	0.49–5.24	0.426			

RA = Rheumatoid arthritis; hazard ratio (HR) = relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only; 95% CI = confidence interval.

Histological Findings

Eight (62%) RA patients with histologically confirmed renal amyloidosis and 4 (24%) with mesangial glomerulonephritis (MesGN) had died (table 1). Renal amyloidosis was associated with over 2-fold mortality, whereas mortality was within expected limits in RA patients with MesGN (table 2). In the multivariate model, as described above, the results were similar (table 4).

Mortality among Controls

During the follow-up, a total of 71 (16%) deaths occurred in the control group, 47 (13%) females and 24 (23%) males.

Clinical Findings

Altogether seven (18%) subjects with HU, 3 (27%) with PU, 16 (50%) with CRFtot and 9 (56%) with CRFisol had died (table 1), as also 3 (11%) subjects with microalbuminuria, 2 (17%) with bacteriuria and 4 (29%) with pyuria (table 1). Among the control group, CRFtot was the only clinical renal finding related to increased

mortality in both the univariate and the multivariate model when compared with controls with normal renal and urinary tract findings (tables 2, 3).

Causes of Death among RA Patients

Table 5 shows that most deaths among RA patients with abnormal renal findings were due to cardiovascular diseases. In other disease categories there were no marked differences between RA patients with or without abnormal renal findings. Three RA patients with PU and 1 with HU had died of renal amyloidosis. RA was recorded as an underlying cause of death in three death certificates among patients with HUPU. Two of these had died due to renal amyloidosis. Amyloidosis was recorded only as a contributory cause of death in three death certificates among cases with microalbuminuria.

Amyloidosis was recorded in four and RA in two death certificates as an underlying cause of death in RA patients with histology-confirmed amyloidosis. In two death certificates cardiovascular diseases were recorded as an underlying cause of death and there was no mention of amy-

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Table 3. Clinical renal findings as a predictor of increased mortality

Variables	RA patients (n = 604)			Controls (n = 457)		
	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.09	1.06–1.11	<0.001	1.11	1.08–1.14	<0.001
Sex (M/F)	2.50	1.71–3.65	<0.001	1.96	1.17–3.25	0.009
RA severity						
HAQ	1.35	1.02–1.78	0.013			
RA nodules	1.78	1.25–2.53	0.001			
Other diseases						
Hypertension	1.53	1.09–2.13	0.012			
Heart failure	1.87	1.29–2.73	0.001			
Renal diseases						
Isolated proteinuria (PU)	3.84	2.10–6.99	<0.001			
Combined proteinuria and hematuria (HUPU)	3.92	1.36–11.21	0.011			
Chronic renal failure (CRFtot)	2.73	1.64–4.53	<0.001	3.48	1.95–6.20	<0.001
Isolated chronic renal failure (CRFisol)				4.53	2.19–9.36	<0.001
Microalbuminuria (MICALB)	2.08	1.21–3.58	0.007			

Final results of stepwise multivariant Cox regression analysis with follow-up time in RA patients and controls, including age, sex, RA duration, HAQ, incidence of nodules, other diseases (diabetes, hypertension, coronary artery disease, heart failure) and clinical renal findings.

RA = Rheumatoid arthritis; hazard ratio (HR) = relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only; 95% CI = confidence interval.

loidosis. Three RA patients with histologically confirmed MesGN had died of cardiovascular diseases and 1 patient due to sepsis.

Causes of Death among Controls

Table 6 shows that most deaths among controls with abnormal renal findings were due to cardiovascular diseases. The most common causes of death in control subjects with HU were cancers (one renal).

Discussion

A high mortality attributable to renal disease in RA patients has been demonstrated in many earlier reports [1, 2, 4–9, 13–15]. The increased mortality may be due to RA itself, to the mode of treatment, to concomitant or associated diseases or a combination of these. Renal disease in the form of papillary necrosis is no longer a problem in the treatment of RA since the withdrawal of phenacetin [20, 21], but chronic renal failure due to amyloidosis is still a potential cause of death [16, 22].

We found that RA patients with HUPU or PU were liable to increased mortality compared to RA patients

Table 4. Histologically confirmed renal disease as a predictor of mortality

	RA patients (n = 604)		
	HR	95% CI	p value
Age, years	1.08	1.06–1.10	<0.001
Sex (M/F)	2.69	1.85–3.90	<0.001
RA severity			
HAQ	1.50	1.15–1.96	0.002
RA nodules	1.70	1.20–2.41	0.002
Other diseases			
Hypertension	1.56	1.12–2.18	0.007
Heart failure	1.76	1.22–2.54	0.002
Renal diseases			
Renal amyloidosis (AMYL)	3.49	1.16–5.00	0.003

Final results of stepwise multivariant cox regression analysis with follow-up time in RA patients

RA = Rheumatoid arthritis; hazard ratio (HR) = relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only; 95% CI= confidence interval.

Table 5. Underlying causes of death among RA patients with abnormal renal findings

ICD code		Clinical renal findings						Histological findings	
		PU (n = 27)	HU (n = 54)	HUPU (n = 7)	CRFisol (n = 15)	CRFtot (n = 36)	MICALB (n = 34)	MESGN (n = 17)	AMYL (n = 13)
A00–A99	Infections		1 (1.8%)					1 (5.9%)	
C00–C97	Cancers		3 (5.5%)		1 (6.7%)	1 (5%)	2 (5.9%)		
E00–E90	Endocrine								
F00–F98	Mental				1 (6.7%)	1 (5%)			
I00–I99	Cardiovascular	8 (30%)	12 (22%)	1 (14%)	5 (33%)	10 (50%)	10 (29%)	3 (18%)	2 (15%)
J00–J99	Respiratory	1 (3.7%)							
K00–K93	Gastrointestinal	1 (3.7%)	1 (1.8%)		1 (6.7%)	3 (15%)	2 (5.9%)		
M00–M99	Musculoskeletal			2 (29%)		2 (10%)			2 (15%)
N00–N98	Urogenital	3 (11%)	1 (1.8%)	1 (14%)		3 (15%)			4 (31%)
Q00–Q99	Other								
V01–Y98	Injuries	1 (3.7%)	2 (3.7%)				1 (2.9%)		
	unknown						1 (2.9%)		
A00–Y98	All categories	14 (52%)	20 (37%)	4 (57%)	8 (53%)	20 (53%)	16 (47%)	4 (24%)	8 (62%)

PU = Isolated proteinuria; HU = isolated hematuria; HUPU = combined hematuria and proteinuria; CRFtot= chronic renal failure; CRFisol = isolated chronic renal failure without HU or PU; AMYL = renal amyloidosis; MESGN = mesangial glomerulonephritis; MICALB = microalbuminuria.

Table 6. Underlying causes of death among controls with abnormal renal findings

ICD code		PU (n = 11)		HU (n = 39)		CRFisol (n = 16)		CRFtot (n = 32)		MICALB (n = 27)	
		n	%	n	%	n	%	n	%	n	%
A00–A99	Infections										
C00–C97	Cancers			5	13	3	19	3	19	1	3
E00–E90	Endocrine										
F00–F98	Mental	1	9								
I00–I99	Cardiovascular	2	18	1	2.5	4	25	10	62	2	7
J00–J99	Respiratory										
K00–K93	Gastrointestinal			1	2.5	1	6	2	13		
M00–M99	Musculoskeletal										
N00–N98	Urogenital										
Q00–Q99	Other										
V01–Y98	Injuries							1	6	1	6
A00–Y98	All categories	3	27	7	18	9	56	16	50	3	11

PU = Isolated proteinuria; HU = isolated hematuria; HUPU = combined hematuria and proteinuria; CRFisol = isolated chronic renal failure; MICALB = microalbuminuria.

with normal clinical renal findings. Renal amyloidosis may explain these findings, in that persistent PU is the most common clinical manifestation in patients with amyloidosis [19, 23] and HUPU is also frequently a consequence of amyloidosis [19]. HU, which is a common clinical manifestation in patients with MesGN [19, 23], was not associated with increased mortality. Isolated chronic renal failure(CRFisol) did not predict increased mortality, but reduced renal function with other abnormal renal finding such as PU, HU or HUPU (CRFtot)

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was associated with a higher death rate. This finding supports the previous conclusion that proteinuria is more sensitive in the detection of renal damage in RA compared to measurement of serum creatinine [24, 25]. Besides, in the original study in 1988 [19] isolated renal failure (CRFisol) was associated with ageing and hypertension and was milder than in RA patients with CRFtot.

Many studies have shown that severely affected RA patients are at greater risk of developing and dying of renal amyloidosis. Here renal abnormalities such as PU, HUPU or histology-confirmed amyloidosis predicted increased mortality, although the severity of RA was standardized in the multivariate model. In the original study in 1988 [19] isolated proteinuria (PU) was observed in 27 and combined hematuria and proteinuria (HUPU) in 7 RA patients. Histologically confirmed renal amyloidosis was observed in 13 patients, 9 of these included in the PU group and 2 in the HUPU group. So, almost 30% of patients in the HUPU group had amyloidosis. When the patients with amyloidosis were excluded from the multivariate mode, HUPU did not independently predict increased mortality. This finding could be a consequence of a small size of the subgroup.

Although AA amyloidosis is one of the most prominent complications of RA, it has been mentioned on the death certificates in only a few percent of cases in earlier mortality studies. In a hospital-based series reported by Cobb et al. [1], including 583 RA patients, 12 (13%) RA had died of renal failure, 4 (3%) of them due to amyloidosis. Dutchie et al. [2] report that out of the 307 RA patients, 13 (17%) died of renal disease, but the proportion of amyloidosis was not reported. In the hospital-based series of 1,000 RA patients (176 patients died), a group of Koota et al. [5] report amyloidosis as the cause of death in 8% of cases (50 subjects) coming to autopsy. Boers et al. [26] have reported on a material of 132 necropsied RA patients, where 11% of patients had died of renal amyloidosis. Myllykangas-Luosujärvi et al. [22] have reported on a nationwide series of 1,666 RA patients deceased in 1989 and of whom 5.8% died of amyloidosis.

In the original cross-sectional prospective study of 604 RA patients amyloidosis was found in 13 [29, 30]. In the present study, amyloidosis was mentioned in 12 (7.5%) death certificates, in 5 cases as an underlying cause, in 4 as an immediate cause and in 3 as a contributory cause of death. Eleven RA patients had died of end-stage renal amyloidosis and 1 patient of urinary bladder perforation due to amyloidosis. Thus, less than 8% of all deaths among RA patients could be explained by amyloidosis.

MesGN among RA patients has been described in a number of renal biopsy materials during the past 30 years [27–31]. In these series MesGN has usually been detected in patients with hematuria, but Helin et al. [31] found that it was also frequent in proteinuric patients. Korpela et al. [32] noted that isolated hematuria in RA patients with MesGN was a favorable clinical sign, whereas proteinuria predicted a poorer prognosis. However, relatively little attention has hitherto been paid to the long-term prognosis of RA patients with MesGN.

Microalbuminuria has been associated with increased cardiovascular mortality in patients with hypertension [33, 34], and in elderly patients in general [35]. Little attention has been paid to microalbuminuria among RA patients, although it is generally known that proteinuria may be the first clinical sign in many renal disorders, like for example AA amyloidosis, MesGN and gold and penicillamine-induced nephropathies [20, 31]. In the present study, microalbuminuria predicted increased mortality in RA patients, whereas it was not associated with higher rate in the controls. The most common causes of death in RA patients with microalbuminuria were cardiovascular diseases (63%); amyloidosis was recorded only as a contributory cause of death in three cases. Whether microalbuminuria in some patients is an early sign of RA-related disorders such as AA amyloidosis or MesGN remains to be evaluated.

Among the control group only chronic renal failure (CRF) predicted increased mortality. Subjects with CRF were older and suffered more frequently from hypertension and diabetes than other controls. These facts may explain the increased mortality among subjects with CRF.

In conclusion, this cross-sectional, population-based study showed that nephropathy presenting with combined hematuria and proteinuria, proteinuria, microalbuminuria or histologically confirmed amyloidosis is associated with increased mortality among RA patients, whereas mortality was within expected limits among RA patients with isolated hematuria or mesangial glomerulonephritis.

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The Predictive Value of Rheumatoid Factor Isotypes, Anti-Cyclic Citrullinated Peptide Antibodies, and Antineutrophil Cytoplasmic Antibodies for Mortality in Patients with Rheumatoid Arthritis

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ABSTRACT. *Objective.* To evaluate the significance of rheumatoid factor (RF) and its isotypes (IgA RF, IgG RF, and IgM RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and antineutrophil cytoplasmic antibodies (ANCA) in predicting mortality in patients with rheumatoid arthritis (RA).
Methods. The study population comprised 604 patients with RA participating in a cross-sectional study in 1987. Presence of RF (n = 604), RF isotypes (n = 206), anti-CCP (n = 184), and ANCA (n = 200) were determined in these patients from available baseline sera. Vital status was assessed in 1999 and multivariate Cox regression analysis used to compare mortality in RA patients with or without different antibodies.
Results. Of the 604 patients with RA, 55% were positive for RF, 66% for anti-CCP, and 14.5% for perinuclear ANCA. Twelve patients (19%) with RF were anti-CCP-negative and 34 (40%) without RF were anti-CCP-positive. Of the total 604 patients, 160 had died by 1999. Positive RF and high IgA and IgM RF levels predicted increased mortality, while positive anti-CCP or ANCA did not. However, high anti-CCP levels were related to an increased mortality risk.
Conclusion. Patients with RA with positive RF, especially IgA and IgM isotypes, carry a risk of dying earlier than patients without these serological findings. (J Rheumatol 2005;32:2089-94)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES   MORTALITY   RHEUMATOID FACTOR

The diagnosis of rheumatoid arthritis (RA) depends primarily on clinical manifestations of the disease. Up to 80% of patients with RA are rheumatoid factor (RF) seropositive[1], but these antibodies are also present in relatively high percentages in other autoimmune diseases and infections and even in healthy persons, particularly elderly individuals[2,3].

Since the discovery of RF, more specific autoantibodies have been found in the sera of patients with RA. However, many have been either less sensitive or technically inconvenient for routine use. Antibodies against cyclic citrullinated peptide (anti-CCP) were first reported in 1998[4] and were found to have very high specificity[5]. Commercial test kits were soon available and after few years' development of the CCP antigen, test sensitivity rose to a high level. Anti-CCP can be detected at an early stage, even before onset of clinical symptoms of RA[6].

Among serological markers, RF has been recognized as an important predictor of more severe disease, including extraarticular manifestations or bone erosion[7-9] and increased mortality[7,10-14]. Anti-CCP and antineutrophil cytoplasmic antibodies (ANCA) have been reported to be associated with disease severity and bone erosions[8,9,15-18]. This is the first study to evaluate anti-CCP and ANCA with respect to mortality in patients with RA.

MATERIALS AND METHODS

Study population. In 1987 in the city of Tampere (170,511 inhabitants in that year, 3.5% of the population of Finland) 1051 persons (834 women, 217 men) had confirmed definite or classic RA[19] according to diagnostic criteria of the 1958 American Rheumatism Association[20]. In 1988, 604 of these patients (470 women, 134 men) participated in a study of renal and urinary tract diseases in patients with RA, where general state of health, renal and urinary tract diseases, treatments, and severity of RA (using for example the Health Assessment Questionnaire, HAQ) were carefully recorded and RF determined[19]. At the time of the original study the mean age of 604 RA patients was 59 ± 13 years and the mean duration of RA 15 ± 10 years.

Altogether, 103 RA patients had clinical signs or symptoms of renal dis-

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ease in the original study in 1988[19]. Paired controls (matched for age, sex, and duration of RA) were selected for this nephropathy group from the remaining RA patients with normal serum creatinine and urinalysis[19]. RF isotypes (IgA, IgG, and IgM), anti-CCP, and ANCA in patients in the nephropathy group and their paired controls were determined from baseline serum stored at –20°C[18,19]. Serum was available for RF isotype analyses in 206 cases, for anti-CCP in 184, and for ANCA in 200. The study protocol was approved by the Ethics Committee of Tampere University Hospital.

IgA, IgG, and IgM RF determinations by enzyme immunoassays. RF was determined by quantitative immunoturbidic assay (FS-RF, positive if ≥ 30 U/ml) and by Waaler-Rose test (WaRo, positive if ≥ 64). A patient was considered RF-positive if a positive result was obtained in any assay used. RF isotype specificity (IgA, IgG, IgM) was determined by enzyme immunoassay (EIA)[21,22] using swine IgG as antigen source.

Anti-CCP antibody determination by EIA. Second-generation ELISA kits for detection of IgG anti-CCP antibodies were purchased from Euro-Diagnostica (Immunoscan RA, Mark 2, Malmo, Sweden). The assay was performed according to manufacturer's instructions. Quantitative antibody levels (in arbitrary units, U) were obtained from the standard curve defined by the manufacturer. Results were considered positive when the antibody level exceeded 25 U. Sera with absorbances over the highest standard (1600 U) were diluted and reanalyzed.

ANCA determinations by indirect immunofluorescence. Indirect immuno-fluorescence employing ethanol and formalin-fixed human granulocytes was used to detect ANCA[23]. Different staining patterns of ANCA, i.e., cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA), were identified. Positive sera were titrated to endpoint. Dilutions of 1:20, 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000, and 1:4000 were used for titration and titers ≥ 50 were considered positive. In all pANCA-positive patients, antinuclear antibodies (ANA) were also determined on cryostat sections of rat liver and kidney. If positive for ANA, the patient was considered to be pANCA-positive only if the pANCA titer was more than 2 dilution factors higher than that of ANA[24].

Evaluation of mortality. Information on vital status on August 31, 1999, and time of death was evaluated from data of the Official Statistics of Finland as described[25,26].

Statistical analysis. SPSS software version 11.5 was used for statistical analysis. Risk of death was estimated by using Cox proportional hazard survival analysis with followup time (from the original study to death) as response variable, and is expressed as hazard ratio (HR) with 95% confidence intervals (CI). The multivariate model quantifies the predictive value of each variable in the model when all variables are analyzed together. We used the forward selection method performed in a stepwise manner. The multivariate model included age and disease duration at study entry, sex, and different serum antibodies (RF isotypes, anti-CCP, and ANCA) as independent variables. Subgroups of RA patients with and without antibodies were compared using Student's t test, Kruskal-Wallis test (for continuous variables), and the chi-square test (for categorical variables). P values less than 0.05 were considered significant. Kaplan-Meier curves were generated for the patients with or without antibodies comparing survival for each year of followup.

RESULTS

Baseline descriptive data in the original study. Baseline data on patients with RA with and without antibodies studied are presented in Table 1. The sex ratio of patients with different antibodies did not differ from those without, but patients with RF and anti-CCP were older. More severe RA was associated with positive RF, anti-CCP, and pANCA. Patients without anti-CCP determination (n = 22) did not differ from those with the determination (data not shown). Occurrence of other diseases such as diabetes, hypertension, coronary disease, and heart failure was similar in every patient group (data not shown).

Altogether, 330 (55%) patients with RA were positive for RF using WaRo or FS-RF analyses (Table 1). EIA analyses showed IgA RF in 97 (48%), IgG RF in 60 (29%), and IgM RF in 123 (60%) patients. The proportion of RF-positive patients was 59% if all 5 determinations were taken into account. Altogether, 122 (66%) had anti-CCP antibodies; 34 (40%) of the RF-negative patients were anti-CCP-positive and 12 (19%) of RF-positive patients were anti-CCP-negative. One hundred thirty-four (73%) patients had RF and/or anti-CCP antibodies and 50 (27%) were negative for these antibodies. We found pANCA in 29 (15%) and atypical cANCA in 2 (1%) (Table 1).

Mortality and RF, anti-CCP, and pANCA. Out of the 604 patients with RA, 160 (26%) had died by 1999. The mean age at death was 75.9 ± 9.6 years. Survival probability curves in RA patients with or without different antibodies are presented in Figure 1.

Altogether, 104 (32%) of the RF-positive and 56 (21%) of the RF-negative patients had died by the time of evaluation of vital status in 1999 (Figure 1a; p = 0.003). In univariate Cox regression analysis positive RF predicted increased mortality in the total RA population (Table 2). The same was also observed in a multivariate model including age, sex, disease duration, nephropathy data, and RF as independent variables (Table 2). The risk ratio (hazard ratio, HR) varied slightly depending on the definition of RF positivity used (HR 1.32–1.80, Table 2). If HAQ or subcutaneous nodules were added to the model, positive RF did not predict increased mortality. Nor did positive RF predict mortality if the model included only RA patients with anti-CCP antibody determination (n = 184). In that cohort high FS-WaRo titer (HR 1.001, p = 0.018), but neither positivity of RF isotypes nor their levels, predicted increased mortality.

By 1999, 38 (39%) IgA RF-positive and 36 (33%) IgA RF-negative patients (p = 0.445), 26 (43%) IgG RF-positive and 48 (33%) IgG RF-negative (p = 0.131), 50 (40%) IgM RF-positive and 24 (30%) IgM RF-negative patients (p = 0.171) had died. High IgA RF and IgM RF levels predicted increased mortality in the multivariate model including age, sex, disease duration, and RF status as independent variables (HR = 1.003, p = 0.003 for IgA RF; HR = 1.002, p = 0.006 for IgM RF; Table 2), whereas a high level of IgG RF did not. If HAQ or subcutaneous nodules were added to the model, the IgA RF level still predicted increased mortality (HR 1.003, p = 0.05), but IgM RF did not.

Fifty (41%) of the anti-CCP-positive and 19 (31%) anti-CCP-negative RA patients had died by 1999 (Figure 1b; p = 0.171). Positive anti-CCP (≥ 25 U) did not predict mortality (Table 2). However, high levels of anti-CCP (over median value of population ≥ 174 U) predicted increased mortal-

Table 1. Characteristics of RA patients with or without different antibodies in the original study in 1988. Results are expressed as medians unless otherwise defined. Comparison between patients with and without different antibodies was made using Student's t test, Mann-Whitney test (for continuous variables) and the chi-square test (for categorical variables). P values less than 0.05 were considered significant. RF was considered positive if quantitative immunoturbidic assay was ≥ 30 U/ml or Waaler-Rose-test titers ≥ 64.

	RF (n = 604)			Anti-CCP (n = 184)			pANCA (n = 198)		
	Pos n = 330	Neg n = 274	p	Pos n = 122	Neg n = 62	p	Pos n = 29	Neg n = 169	p
Age, yrs	59.7	57.3	0.021	63.9	58.7	0.005	59.9	62.3	0.301
Male, %	24	20	0.161	26	26	0.915	14	28	0.111
Disease duration, yrs	14.2	14.7	0.594	15.7	16.3	0.715	19.3	15.4	0.054
ESR, mm/h	33	25	< 0.001	36.8	30.27	0.083	46	32	0.002
Hb, g/l	128	130	< 0.001	126	130	0.065	122	129	0.018
HAQ, 1–3	0.71	0.43	< 0.001	0.88	0.54	0.001	1.11	0.68	0.003
Subcutaneous nodules, %	46	30	< 0.001	45	22	0.005	52	39	0.179
Nephropathy, %	17.3	16.7	0.673	52.5	54.8	0.943	72	45	0.005
Positive RF, %				72*	19*	0.001	59*	56*	0.809
Positive anti-CCP, %	88*	40*	< 0.001				66*	56*	0.105

RF: Rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; pANCA: perinuclear antineutrophil cytoplasmic antibodies; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; Hb: hemoglobin. * Percentages were calculated only for patients with both antibody determinations.

ity in the univariate model (HR = 1.68, p = 0.034; Table 2). In the age, sex, and disease duration adjusted multivariate model, the tendency was the same (HR = 1.60, p = 0.057; Table 2). If HAQ or subcutaneous nodules were added into the model, high anti-CCP level did not predict mortality. A total of 53 (40%) patients with RF and/or anti-CCP antibodies and 16 (32%) patients without these antibodies had died by 1999. Mortality was not significantly different in these groups (Figure 1c; p = 0.347) and positivity for RF and/or anti-CCP did not predict mortality in the univariate or multivariate model (Table 2).

Twelve (41%) of the pANCA-positive and 64 (38%) of the pANCA-negative RA patients had died by 1999 (Figure 1d; p = 0.720). Neither positivity for pANCA nor high ANCA titers predicted mortality in the univariate or multivariate model (Table 2).

DISCUSSION

Our objective was to analyze whether RF, anti-CCP, and ANCA have an association with mortality as they have with severe disease. All 5 RF detection methods were evaluated either alone or in combination, and this is the first study to assess the predictive value of anti-CCP and ANCA in respect to mortality in patients with RA.

In previous studies, positive RF has predicted increased mortality[10-14], but the risk related to positive RF has varied considerably (OR 1.93–11.9)[12,13]. High levels of RF have also been reported to be associated with increasing mortality risk[10,11]. However, only IgM RF and not other RF isotypes have usually been measured[11-13]. In our study, positive RF (WaRo or FS-RF positive) predicted increased mortality when all patients with RA were included in the statistical analyses. The same result was obtained when any one of the 5 RF methods was taken into account. The risk of death var-

ied from 1.32 to 1.80 depending on the definition of RF positivity used, slightly lower than in previous studies[12,13]. However, in a smaller subgroup (only patients with anti-CCP antibody determination) high FS-WaRo titers but not RF isotypes predicted increased mortality. If the HAQ or RA nodules were added to the multivariate model, positive RF did not predict increased mortality. This might be due to HAQ and positive RF being highly correlated variables and in fact measuring the same aspect: disease severity. Both IgA RF and IgM RF levels predicted increased mortality in the multivariate model including age, sex, and disease duration. Even if HAQ or subcutaneous nodules were added in the model, IgA RF level still predicted increased mortality.

The proportion of RF-positive patients in the original study was 55% (59% if all tests were taken into account), which was lower than generally regarded. The total RA population (n = 604) was population-based, which might partly explain this discrepancy. On the other hand, 70% of RA patients with nephropathy and 69% of RA patients without nephropathy (paired controls) were RF positive. So patients with RF isotypes, anti-CCP, and pANCA determinations were more likely to be RF-positive and the proportion was similar to earlier reports. The cutoff level of FS-RF (≥ 30 IU/ml) was higher than generally used. If the cutoff value for FS-RF was ≥ 15 IU/ml or ≥ 20 IU/ml, the proportion of RF positive patients rose to 67% or 64%, respectively.

B cell activation and production of RF is an indicator of severe disease in RA[27]. RF has an immune complex processing capacity to activate the complement cascade contributing to target organ involvement[28]. High RF levels have been associated with subcutaneous nodules[29] and extraarticular manifestations such as rheumatoid vasculitis[30], which have themselves been reported to correlate with increased mortality in RA[31]. Although the difference in prognosis

A Survival probability and RF

B Survival probability and anti-CCP

C Survival probability and RF and/or anti-CCP

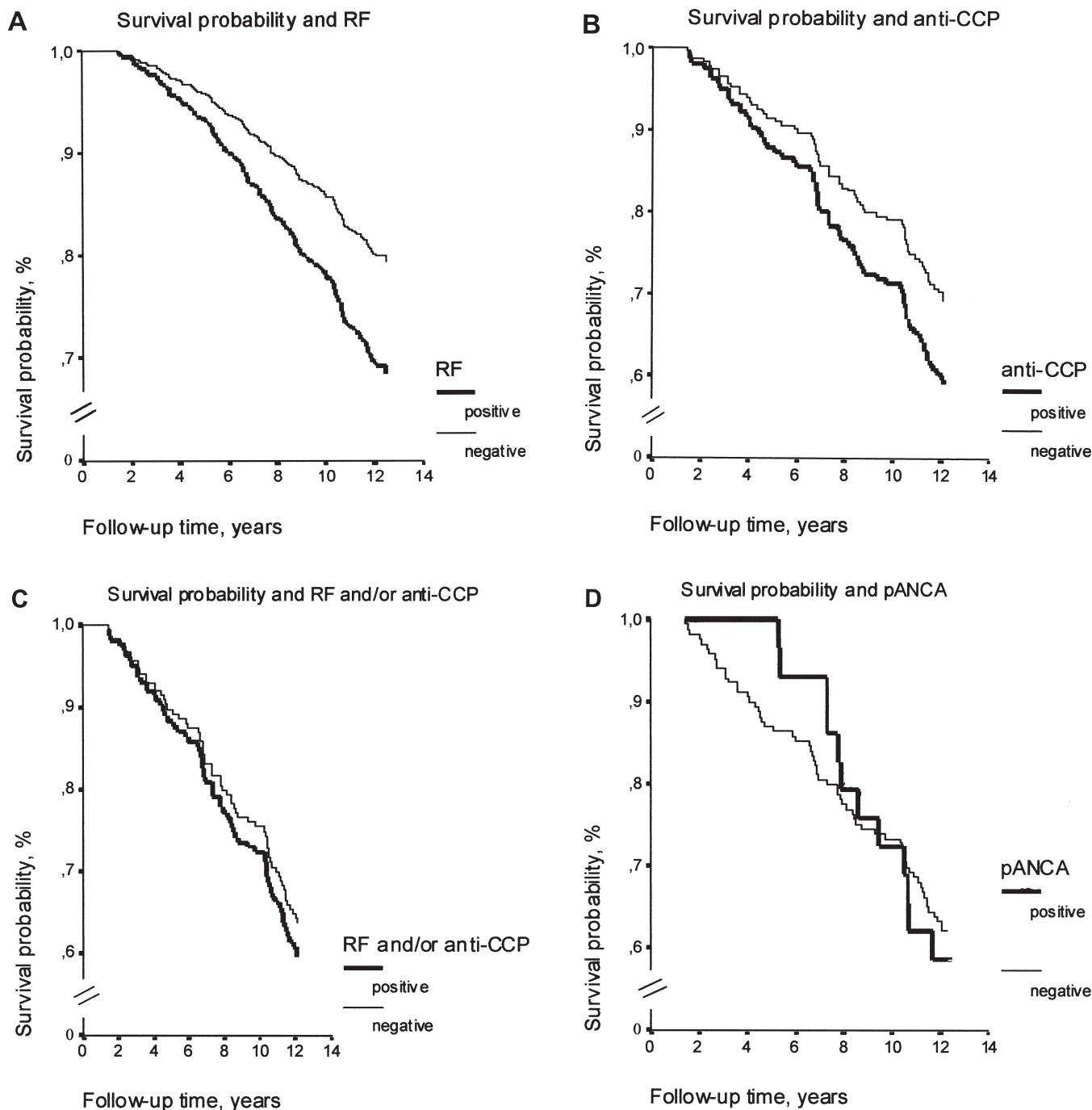**D** Survival probability and pANCA

Figure 1. Kaplan-Meier plots for mortality according to the presence or absence of (A) rheumatoid factor (RF); (B) anti-citrullinated peptide antibodies (anti-CCP); (C) RF and/or anti-CCP; and (D) perinuclear antineutrophil cytoplasmic antibodies (pANCA).

between RF-positive and RF-negative RA patients is quite obvious, the role of RF is not clear.

In our cohort, 66% of patients had anti-CCP antibodies, a slightly higher occurrence than found in previous studies[6,9]. Nineteen percent of patients with RF were anti-CCP-negative and 40% without RF had anti-CCP. The proportion of RF-negative patients with anti-CCP is similar to that previ-ously described[8,32,33]. Presence of anti-CCP did not predict mortality when a cutoff value of 25 U was used. However, high anti-CCP levels were associated with increased mortal-ity risk. Patients with RF or anti-CCP antibodies appeared to be subject to higher mortality than those without these anti-bodies (40% vs 32%), but the difference was not statistical-ly significant. This might be a consequence of the small size

Table 2. Immunological features as predictors of mortality in patients with RA. Results of the Cox univariate analyses and age, sex, and disease duration adjusted multivariate model when each immunological test was at a time in the model. Anti-CCP levels were divided in 2 categories by using median level of the population (174 U) as cutoff value. High anti-CCP level included mean values over 174 U.

Variable	N	Univariate Model			Multivariate Model		
		HR	95% CI	p	HR	95% CI	p
Age, yrs	604	1.09	1.07–1.11	0.001	1.09	1.04–1.09	0.001
Gender, male	604	2.29	1.63–3.20	0.001	2.19	1.56–3.07	0.001
Disease duration, yrs	604	0.96	0.94–0.98	0.001			
HAQ, 0–3	604	1.80	1.42–2.28	0.001	2.03	1.63–2.53	0.001
Subcutaneous nodules	604	1.53	1.09–2.15	0.013	2.04	1.49–2.79	0.001
RF (any of the 5 RF tests positive)	604	1.80	1.28–2.53	0.001	1.55	1.10–2.19	0.011
RF (WaRo and/or FS-RF positive)	604	1.64	1.18–2.27	0.002	1.49	1.07–2.06	0.017
RF WaRo	604	1.32	0.95–1.82	0.089	1.57	1.13–2.19	0.007
FS-RF	604	1.63	1.18–2.24	0.003	1.41	1.01–1.95	0.038
RF WaRo, titer	604	1.001	1.000–1.001	0.004	1.001	1.001–1.002	< 0.001
FS-RF, level	604	1.001	1.001–1.02	< 0.001	1.001	1.001–1.001	< 0.001
RF IgA, level	206	1.005	1.002–1.008	0.001	1.003	1.002–1.008	0.003
RF IgG, level	206	1.008	1.001–1.015	0.049			
RF IgM, level	206	1.002	1.000–1.003	0.024	1.002	1.001–1.003	0.006
Anti-CCP	184	1.44	0.85–2.44	0.176			
Anti-CCP, level	184	1.000	1.000–1.000	0.010	1.000	1.000–1.000	0.044
High anti-CCP level	184	1.68	1.04–2.72	0.034	1.60	0.98–2.68	0.057
RF and/or anti-CCP	184	1.51	0.84–2.71	0.126			
pANCA	200	1.05	0.56–1.95	0.868			
pANCA, titer	200	1.000	0.999–1.001	0.769			

HR: hazard ratio, relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only. 95% CI: 95% confidence interval; N = number of patients with antibody determination; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; WaRo: Waaler-Rose test positive if titer ≥ 64; FS-RF: quantitative immunoturbidic assay of RF positive if ≥ 30 U/ml; anti-CCP: anti-cyclic citrullinated peptide antibodies positive if > 25U; pANCA: perinuclear antineutrophil cytoplasmic antibodies positive if titer ≥ 50.

of these subgroups. Positive pANCA was found in 14.5% of patients, which is slightly lower than in other reports[34,35]. Neither ANCA positivity nor high ANCA titers were related to mortality in the univariate or multivariate model in this cohort, a circumstance for which we can offer no good explanation.

The limitation of this study is that the cohort was not population-based as was the original study of 604 patients. Part of the immunological determination was done in RA patients with nephropathy and their paired controls without nephropathy. In addition, the study population here consisted of RA patients with long disease duration. Although these factors might have a confounding effect, our results seem to indicate that patients with RA with high immunological activity appear to carry an increased risk of death. It would be desirable to measure this activity at disease onset and focus the most effective treatment on these patients. Moreover, it would also be beneficial to assess the predictive value of anti-CCP for mortality in RA patients from antibodies already determined in early RA.

In summary, the presence of RF, particularly high IgA RF and IgM RF levels, predicted increased mortality in patients with RA. Positive anti-CCP or ANCA were not associated with mortality risk, but high anti-CCP levels predicted increased mortality.

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Mortality in Patients with Rheumatoid Arthritis Treated with Low-Dose Oral Glucocorticoids. A Population-Based Cohort Study

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ABSTRACT. *Objective.* To evaluate mortality and causes of death in patients with rheumatoid arthritis (RA) treated with low-dose oral glucocorticoids.

Methods. Mortality was analyzed in population-based data of 604 patients with RA. In the original study in 1988, state of general health, severity of RA, and treatment including the use of oral glucocorticoids were recorded. In 1999 vital status and causes of death were evaluated. Mortality in patients with RA who had not received glucocorticoids (Group A, n = 209) was compared to that in patients treated with glucocorticoids for less than 10 years (Group B, n = 276) or for more than 10 years (Group C, n = 119).

Results. From onset of RA to 1999, 395 (65%) patients had been treated with oral glucocorticoids. In 1999 a total of 160 (26%) patients had died, 23% of patients in Group A, 21% in Group B, and 45% in Group C. In multivariate Cox regression analysis, male sex (hazard ratio 2.50; 95% CI 1.74–3.59), impaired functional capacity by Health Assessment Questionnaire (HR 2.11; 95% CI 1.65–2.96), heart failure (HR 1.96; 95% CI 1.36–2.84), and diabetes (HR 1.87; 95% CI 1.17–3.01) predicted increased mortality. In the same analysis glucocorticoid treatment for 1 year increased the mortality risk by 14% (HR 1.14; 95% CI 0.98–1.27, p = 0.057) and treatment over 10 years by 69% (HR 1.69; 95% CI 1.12–2.56, p = 0.011) compared to RA patients without treatment. The major cause of death was cardiovascular disease in all groups, but infections and intestinal perforations due to amyloidosis were more frequent in patients with long-lasting glucocorticoid therapy. Lymphomas were more frequent in all patients treated with glucocorticoids (Groups B and C) than in those not receiving glucocorticoids.

Conclusion. Patients with RA treated with low-dose oral glucocorticoids for more than 10 years had increased mortality compared to those who did not receive glucocorticoids or whose duration of treatment was less than 10 years. The increased mortality was related mainly to infections and complications caused by systemic amyloidosis. (J Rheumatol First Release Aug 1 2006)

Key Indexing Terms:

RHEUMATOID ARTHRITIS   MORTALITY   GLUCOCORTICOIDS

Many studies have established increased mortality among patients with rheumatoid arthritis (RA)[1-7], but some recent reports show that mortality is fairly similar to that in the general population[8-10]. In many studies the major cause of death has been cardiovascular diseases[1-4,6,7]. Some observational studies suggest that the increased mortality may be associated with glucocorticoid (GC) therapy, and several large retrospective studies indicate that longterm low-dose GC therapy is a significant independent predictor of numerous, potentially serious adverse events[11]. The potential toxicity of GC is well documented[12]. The risk for GC-induced side effects increases with dose and duration of use[13]. There is also individual variability for development of side effects depending on age and sex of the patient, and on other, less well defined factors[14]. One confounding factor is that GC may be prescribed in severe cases of RA[2], and such patients may be expected to have a higher mortality rate regardless of cause of death[2]. We investigated whether longterm GC treatment is associated with mortality in a population-based study of patients with RA.

MATERIALS AND METHODS

Study population. In 1987 in the city of Tampere (1987 population 170,511, 3.5% of the population of Finland) 1051 persons (834 women, 217 men) were confirmed to have definite or classic RA according to the diagnostic criteria of the American Rheumatism Association[15]. In 1988, they were invited to participate in a study of renal and urinary tract diseases in RA; altogether, 604 persons (470 women, 134 men) were studied prospectively. The rest were

studied retrospectively by evaluating medical records[16]. In the original study, general state of health, other diseases, and severity and treatments of RA were carefully recorded.

In 1988, the current and previous oral glucocorticoid therapy was carefully recorded, including the generic drug and doses and length of treatment in months. Use of intraarticular GC injections was not recorded. Data on oral GC treatment during the years 1988 to 1999 or at time of death were collected retrospectively from hospital records as accurately as possible (n = 556). We were unable to gather any information about GC treatment of 48 RA patients during the years 1988-99.

Evaluation of mortality and causes of death. Information on the vital status in 1999 and the underlying and immediate causes of death were evaluated as described[3]. Mortality in RA patients who did not receive GC therapy (Group A) was compared to that in patients treated with GC (Groups B and C). In the non-GC group (Group A) patients were treated with oral GC for < 1 month, while in the GC group the treatment had been continued for at least 1 month, but < 10 years in Group B or > 10 years in Group C. Patients with no data on GC treatment from the years 1988-99 (n = 48) were included in Group B. Some of them had been treated with GC for longer than 1 month but < 10 years before 1988. The rest had never received GC before 1988, but data on GC treatment were not available after that. The results did not change when those 48 patients were excluded from the model. Cause of death was not known for 2 patients in the GC Groups B and C and for one patient in Group A, as death certificates were not available. Autopsy was performed in 20 (38%) of the RA patients in Group A, in 17 (37%) in Group B, and in 16 (29%) in Group C.

Ethical approval for the study was obtained from the Finnish Ministry of Social Affairs and Health and from the Ethical Committee of Tampere University Hospital.

Statistical analyses. Kaplan-Meier plots were generated for RA patients in Groups A, B, and C comparing survival for each year of followup. Risk of death was estimated by Cox proportional hazards survival analysis with followup time (time from original study to death) as the response variable, and is expressed as hazard ratio (HR) with 95% confidence intervals. The multivariate Cox proportional hazards model quantifies the predictive values of each variable in the model when all variables are considered together. We used the forward selection method performed in a stepwise manner. Standard statistical methods were employed including Student's paired t test, Kruskal-Wallis test, and chi-square test. Differences were considered significant at p value ≤ 0.05. Data were recorded and calculations performed using SPSS/Win (v 11) software.

RESULTS

Descriptive data in 1988. Descriptive data of patients with RA without GC therapy (Group A) and those treated with GC (Groups B and C) in the original study in 1988 are presented in Table 1. Altogether, 65% of RA patients (total 395: 311 women, 84 men) had been treated with oral GC until 1999, 276 of them for < 10 years (Group B) and 119 for > 10 years (Group C). Age and sex ratio of RA patients in the GC Groups B and C did not differ from those in Group A. However, patients in Groups B and C had more severe disease. Occurrence of other diseases was similar in all groups (Table 1).

Mortality. In 1999 a total of 160 (26%) participating patients with RA had died. Mortality was increased in RA patients treated with GC for more than 10 years (Group C) and they died at younger age than those in Groups A or B (p = 0.003). Forty-eight (23%) patients in Group A, 57 (21%) in Group B, and 53 (45%) in Group C had died (p = 0.001). The mean age at death was 78 ± 8 years in Group A (80 ± 7 for women, 71

± 8 for men), 77 ± 10 years in Group B (77 ± 7 for women, 75 ± 6 for men), and 73 ± 10 years (74 ± 9 for women, 71 ± 7 for men) in Group C. Figure 1 shows the cumulative survival rate in all groups.

The underlying causes of death noted in death certificates are shown in Table 2. The major cause of death was cardiovascular disease in all groups; mortality from cardiovascular diseases was not higher in the GC Groups B and C than in the non-GC Group A. Underlying causes of death were more frequently classified under the categories of musculoskeletal and urogenital disease in patients with long-lasting GC treatment. Increased mortality in these categories was found to be due to infections or intestinal perforations in all cases according to the immediate cause of death.

Causes of death in detail

Group A. One patient was reported to have died from septicemia and one from esophageal perforation. In 2 cases pneumonia was recorded as cause of death in the category of respiratory diseases. One patient died due to myeloma and 6 due to dementia (Table 2). Infections were quite frequent immediate causes of death, including 11 deaths from pneumonia and one from septicemia (Table 3). Neither RA nor amyloidosis was recorded in any death certificate in patients who had not had GC treatment.

Group B. There was no death due to septicemia, but in 2 cases pneumonia was recorded as cause of death. Altogether, 15 patients had died from malignancies; 3 of these died from lymphoma and one from polycythemia vera. Renal amyloidosis was given as underlying cause of death in 2 patients, and 4 patients died due to dementia (Table 2). Infections were frequent immediate causes of death, including 9 deaths from pneumonia, 2 septicemia, one erysipelas, and one bronchitis (Table 3).

Group C. Two patients had died due to septicemia and in 3 patients pneumonia was recorded as cause of death in the category of respiratory diseases. A total of 10 patients died from malignancies, including 3 from lymphoma (Table 2). There were 11 deaths from pneumonia, 3 septicemia, and one record of pyelonephritis as cause of death (Table 3). Four patients died after intestinal perforation, and 3 of these had histologically confirmed amyloidosis. When RA was recorded as an underlying cause of death, immediate cause of death was renal amyloidosis, pneumonia, and intestinal perforation in 2 cases, respectively, and pyelonephritis in one. Altogether, RA was recorded in 7 and renal amyloidosis in 4 death certificates.

In examining immediate causes of death, RA patients in Group C died more frequently due to infections (p = 0.013; Table 3) and intestinal perforations due to amyloidosis (p < 0.001; Table 3) than patients in Groups A and B. Moreover, deaths due to lymphoma were noted only in patients with GC treatment (Groups B and C; p = 0.039). Only one patient had had cytotoxic treatment at the time of death; cause of death

Table 1. Characteristics of RA patients with or without glucocorticoid treatment at the time of the original study in 1988.

| | Glucocorticoid Groups | | | |
	Group A, n = 209	Group B, n = 276	Group C, n = 119	p
Age, yrs, median	58.9	57.7	60.7	0.186
Male, %	24	19	27	0.173
Disease duration, yrs, median	14.0	14.1	15.8	0.929
Severity of RA				
ESR, mm/h, median	23	28	45	< 0.001
Hb, mg/l, median	133	130	121	< 0.001
HAQ (1–3), median	0.38	0.54	1.05	< 0.001
Positive RF, %	43	56	73	< 0.001
Subcutaneous nodules, %	33	36	57	< 0.001
Other diseases, %				
Diabetes	5	7	7	0.661
Coronary artery disease	15	11	15	0.286
Heart failure	12	14	19	0.182
Hypertension	22	20	22	0.809

Group A: no glucocorticoid treatment, Group B: glucocorticoid treatment less than 10 years, Group C: glucocorticoid treatment for more than 10 years. Comparisons between different groups by Kruskal-Wallis test (for continuous variables) and chi-square test (for categorical variables). ESR: erythrocyte sedimentation rate, Hb: hemoglobin, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor.
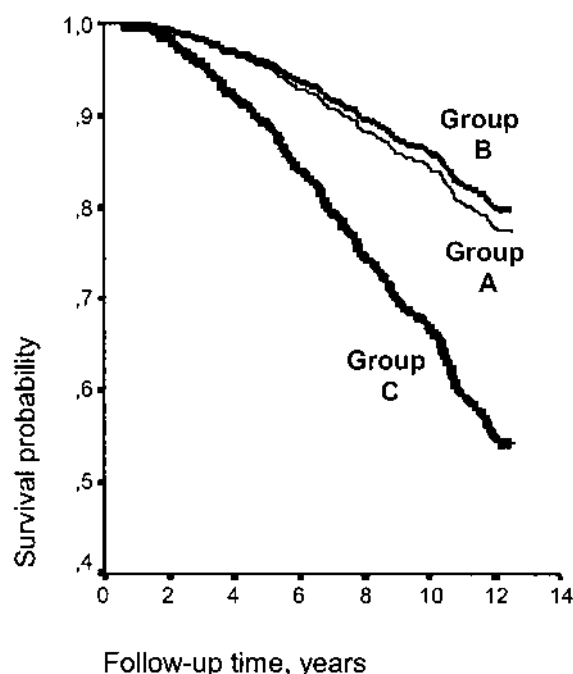

Figure 1. Kaplan-Meier curve illustrates the probability of death during followup time in patients with glucocorticoid treatment (Groups B and C) without treatment (Group A).

was septicemia. However, even if the results are statistically significant, the numbers of the patients with different diagnoses are small, and that must be taken into account when interpreting the causes of death.

Factors predicting mortality. Results of univariate and multi-variate Cox regression analysis are shown in Table 4. In the model that included age, sex, duration of RA, functional capacity [by Health Assessment Questionnaire (HAQ)], presence of subcutaneous nodules, other diseases (coronary artery disease, diabetes, heart failure and hypertension), therapy with disease modifying antirheumatic drugs (gold sodium thiomalate, hydroxychloroquine, penicillamine, sulfasalazine) and GC therapy, as forced into the model at the same time, male sex, impaired functional capacity by HAQ, heart failure, diabetes, and oral GC treatment were associated with increased mortality. GC treatment for 1 year increased the mortality risk by 17% (p = 0.002) in the univariate model and by 14% (p = 0.057) in the multivariate model (Table 4). In the multivariate model, patients who had had longterm GC treatment (> 10 years) increased the mortality risk by 69% (p = 0.011) compared to patients without GC treatment.

DISCUSSION

Life expectancy in patients with RA is markedly shortened compared with subjects without RA[1-4,6,7]. Most studies have described an increased mortality from infections and cardiovascular, gastrointestinal, and renal diseases, and in some studies from malignancies[3-5]. There is strong evidence that increased mortality is linked to severity of RA[17,18], but the role of glucocorticoid treatment is not clear. We sought to establish in a population-based investigation whether longterm low-dose GC treatment contributes to the increased mortality.

A limitation of our study is the rather low participation rate in the original study. Only participant patients with RA were included in the present study, because we did not have suffi-

Table 2. Underlying causes of death in death certificates of RA patients without glucocorticoid treatment (Group A) and patients treated with glucocorticoid less than 10 years (Group B) or for more than 10 years (Group C).

International Classification of Diseases Code	Glucocorticoid Groups						
	Group A, n = 209		Group B, n = 276		Group C, n = 119		
	n	%	n	%	n	%	p
A00-A99 Infections	1	0.5	0		2	2	0.094
Septicemia	1		0		2		
C00-C97 Malignancies	7	3	15	5	10	8	0.144
Lymphoma	0		3		3		
Others	7		12		7		
F00-F98 Mental	6	3	4	1	1	1	0.346
Dementia	6		4		1		
I00-I99 Cardiovascular	26	12	28	10	20	17	0.188
Coronary artery disease	16		18		13		
J00-J99 Respiratory	4	2	3	1	6	5	0.045
Pneumonia	2		2		4		
Pulmonary fibrosis	0		0		2		
Other	2		1		0		
K00-K93 Gastrointestinal	2	1	1	0.4	2	2	0.405
Intestinal perforation	1		0		0		
Other	1		1		2		
M00-M99 Musculoskeletal	0		0		7	6	< 0.001
Rheumatoid arthritis	0		0		7		
N00-N98 Urogenital	0		2	0.7	4	3	0.011
Renal amyloidosis	0		2		4		
V01-Y98 Injuries	1	0.5	3	1	0		0.433
Unknown	1	0.5	1	0.4	1	1	
All categories	48	23	57	21	53	45	< 0.001

n = number of patients in the group, % = number of deaths in the particular disease category/number of patients in the group. Comparisons between groups by chi-square tests.

Table 3. Infections and gastrointestinal perforations as immediate causes of death in RA patients without glucocorticoid treatment (Group A), with glucocorticoid treatment less than 10 years (Group B), or for more than 10 years (Group C).

	Glucocorticoid Groups						
	Group A, n = 209		Group B, n = 276		Group C, n = 119		
	n	%	n	%	n	%	p
Infections	12	6	13	5	15	13	0.013
Septicemia	1	0.4	2	0.7	3	3	
Pneumonia	11	5	9	0.3	11	9	
Other	0	0	2	0.7	1	0.8	
Gastrointestinal perforations due to amyloidosis	0	0	0	0	4	3	< 0.001

Comparisons between groups by chi-square tests.

ciently detailed data on GC treatment from disease onset to 1988 in the patients studied retrospectively (non-participants) as we had in participants. Non-participant patients were older (64 ± 15 vs 59 ± 13 yrs) and had longer disease duration than participant patients (17 ± 11 vs 15 ± 10 yrs) in 1988. Death rates and causes of death in all patients have been reported[3]. Non-participant RA patients had increased mortality compared with participants, but causes of death were fairly similar. The main causes of death were cardiovascular diseases (over 40%) and about 20% of patients died due to malignancies[3].

Allebeck, et al[19] and Mitchell, et al[17] found no significant differences in RA mortality rates associated with GC treatment. Pincus, et al[18] and Leigh, et al[20] reported increased mortality with prednisone use in patients with RA, but both studies conceded that prednisone use may simply have been a marker of increased disease activity. Scott, et al[21] noted 35% mortality by 20 years in the followup study of 112 RA patients assigned to a standard regimen that included prednisone. The investigators attributed at least some of these deaths to use of GC[21]. Wolfe, et al[5] showed that the use of prednisone was

Table 4. Indicators predicting mortality; results of univariate Cox regression analysis and multivariate model by forward stepwise method.

Variables	Univariate Model			Multivariate Model		
	HR	95% CI	p	HR	95% CI	p
Age (yrs)	1.09	1.07–1.11	< 0.001	1.08	1.06–1.10	< 0.001
Sex (male)	1.89	1.36–2.64	< 0.001	2.50	1.74–3.59	< 0.001
RA severity						
Duration of RA (yrs)	1.01	0.99–1.03	0.062	0.95	0.93–0.97	< 0.001
Subcutaneous nodules	2.15	1.56–2.94	< 0.001			NS
HAQ (1–3)	2.15	1.75–2.63	< 0.001	2.11	1.65–2.96	< 0.001
Other diseases						
Coronary artery disease	2.29	1.57–3.34	< 0.001			NS
Diabetes	3.81	2.46–5.88	< 0.001	1.87	1.17–3.01	0.009
Heart failure	4.61	3.31–6.41	< 0.001	1.96	1.36–2.84	0.001
Hypertension	2.33	1.68–3.23	< 0.001			NS
Medication						
Gold sodium thiomalate (yes/no)	0.61	0.44–0.85	0.004			NS
Hydroxychloroquine (yes/no)	0.72	0.48–1.07	0.107			NS
Penicillamine (yes/no)	1.01	0.67–1.52	0.946			NS
Sulfasalazine (yes/no)	0.73	0.46–1.15	0.177			NS
Glucocorticoid (yrs)	1.17	1.06–1.31	0.002	1.14	0.98–1.27	0.057

HR: Hazard ratio, HAQ: Health Assessment Questionnaire score 1–3, NS: nonsignificant.

clearly a risk factor for higher mortality in RA regardless of age, sex, or disease severity. They also showed that cardiovascular diseases were the leading cause of death[5]. However, Wållberg-Johnsson, *et al*[22] found no relationship connecting mortality from cardiovascular diseases to the use of GC in their cohort of 606 patients with RA.

We observed that patients with RA treated with GC (Groups B and C) had a more severe disease than those in the non-GC Group A at the screening in 1988. However, in the multivariate model including medication and variables describing disease severity, longterm oral GC therapy still predicted an increased risk of death. In these patients' death certificates, RA and amyloidosis were recorded more often as underlying cause of death, and the immediate causes of death were infections or intestinal perforations due to amyloidosis in all cases.

We also noted increased mortality from infections in other disease categories, especially from pneumonia, in RA patients with GC treatment of more than 10 years. The propensity of GC to predispose to infections is controversial[23]. It has been suggested that the risk of infection is dependent on the dose and duration of GC therapy[13]. The use of low-dose GC does not seem to impair host resistance to infection. Several studies demonstrate that prednisone dosages < 10 mg/day do not suppress macrophage function sufficiently to allow opportunistic infection, and even large doses are required to inhibit other defence mechanisms such as neutrophil function[24,25]. The relative risk of infection across a number of clinical settings was roughly 2-fold compared to that in controls in a metaanalysis of 71 trials involving more than 2000 GC-treated patients[25]. The risk varied according to type of disease treated. Doran, *et al*[26] analyzed risk factors for infections in

609 patients with RA; they noted that the relative risk was 1.70 in RA patients compared to controls, with increasing age, extraarticular manifestations, leukopenia, and GC use as independent risk factors.

Some studies have suggested that GC treatment is associated with accelerated arteriosclerosis[27,28]. In a study of 647 patients with RA the investigators reported that GC exposure was associated with increased carotid plaques, independent of known cardiovascular risk factors[29]. Wållberg-Johnsson, *et al*[30] reported that GC increased mortality due to cardiovascular diseases if given early in RA, but not when given extensively during the course of the disease. They suggested that GC treatment early in disease may possibly indicate an active, aggressive RA, in agreement with high erythrocyte sedimentation rate, rather than indicating a risk of GC treatment per se. In the large prospective study by Solomon, *et al*[31], patients with RA had 2-fold higher risk for myocardial infarction than the general population even after adjusting for known and potential cardiovascular risk factors. Unfortunately they did not have detailed information about GC treatment or inflammatory markers. On the other hand, GC could also reduce the risk of atherosclerosis by controlling inflammation[32]. In our study RA patients treated with GC (Groups B and C) did not have increased mortality from cardiovascular diseases compared to those without GC therapy (Group A).

Peptic ulcers have long been considered a complication of GC therapy. A prospective study of 1400 patients receiving GC therapy showed an overall 2-fold higher risk of peptic ulcers[33]. However, multivariate analysis showed that concomitant use of nonsteroidal antiinflammatory drugs (NSAID) explained the increased risk of ulcers[33]. Myllykangas-Luosujärvi, *et al*[34] noted that nearly two-thirds of the putative treatment-related

deaths in their series were attributed to the use of NSAID, and a considerable proportion of deaths were due to perforation or bleeding of the lower small or large intestine. We found 4 deaths from intestinal perforation in RA patients treated with GC over 10 years compared to one among patients who did not receive GC. Three out of 4 patients who died from intestinal perforation used both GC and NSAID medications, and all of them also suffered from amyloidosis.

One interesting finding in our study was that 6 patients in the GC groups had died from lymphoma. Many studies have reported an association of RA with lymphoproliferative malignancies[35-37]. Cytotoxic drugs such as azathioprine and cyclophosphamide have been associated with increased incidence of lymphomas[38], but there is also evidence that the lymphoma risk is associated with the severity of RA[36,37] or immunologic alterations accompanying RA, such as chronic immune stimulation[36] or Epstein-Barr virus infection[38,39]. In our study patients who died from lymphoma had not received any cytotoxic drugs up to the screening in 1988 or after that, but they had more severe RA at study entry.

We found that patients with RA treated with low-dose oral glucocorticoids for more than 10 years had increased mortality compared to those who did not receive glucocorticoids or whose duration of treatment was less than 10 years. Increased mortality was related mainly to infections and complications caused by systemic amyloidosis.

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