Disease progression and cardiovascular risk into adulthood in juvenile idiopathic arthritis

Thesis for the degree of philosophiae doctor (Ph.D.)

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List of papers

I. Hanne A Aulie MD, Anne M Selvaag MD PhD, Anne Gunther MD, Vibke Lilleby MD Phd, Øyvind Molberg MD PhD, Anders Hartmann MD PhD, Hallvard Holdaas MD Phd, Berit Flatø MD PhD. Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis. Ann Rheum Disease Published online first [2.april 2014] doi:10.1136/ard-2013-204804.

II. Hanne A Aulie, Mette-Elise Estensen, Anne Marit Selvaag, Vibke Lilleby, Klaus Murbraech, Berit Flatø, Svend Aakhus. Cardiac function in adult patients with juvenile idiopathic arthritis. *In press*

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Abbreviations

ACR = American College of Rheumatology

AIx = Augmentation Index

ANA = Antinuclear antibodies

AUC = Area under the curve

BMI = Body mass index

BP = Blood pressure

CRP = C-reactive protein

CT = Computed tomography

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

DMARD = Diseases-modifying anti-rheumatic drug

DT = Deceleration time

E = Early diastolic flow velocities

E´ = Mitral annular velocity in diastole

E/A ratio = Peak early-to-late ratio mitral flow velocity

ECG = Electrocardiography

EF = Ejection fraction

ESR = Erythrocyte sedimentation rate

EULAR = European League Against Rheumatism

FPS = Frames per second

HAQ = Health Assessment Questionnaire

HBA1c = Glycated haemoglobin

HDL = High-density lipoprotein

HF = Heart failure

HLA = Human leukocyte antigen

HOMA-IR = Homeostasis model assessment for insulin resistance

HRQoL = Health-related quality of life

hs-CRP = High-sensitivity C-reactive protein

IHD = Ischaemic heart disease

IL = Interleukine

ILAR = International League of associations for Rheumatology

IQR = Interquartile range

IVRT = Isovolumic relaxation time

JADAS = Juvenile Arthritis Disease Activity Score

JCA = Juvenile chronic arthritis

JIA = Juvenile idiopathic arthritis

JRA = Juvenile rheumatoid arthritis

LA = Left atrium

LDL = Low-density lipoprotein

LROM = Limited range of motion

LV = Left ventricle

NSAID = Non-steroidal Anti-Inflammatory Drug

OUH = Oslo University hospital

PWV = Pulse wave velocity

QTc = Corrected QT

RA = Rheumatoid Arthritis

RF = Rheumatoid factor

S´ = Mitral annular velocity in systole

SBP = Systolic blood pressure

SD = Standard deviation

SF-36 = Short Form-36 health survey

SPSS = Statistical Package for the Social Sciences

TNF = Tumor necrosis factor

VAS = Visual analogue scale

1. INTRODUCTION

Juvenile idiopathic Arthritis (JIA) is the most common inflammatory rheumatic disease in childhood. The disease is heterogeneous, divided into seven categories, with a disease activity that varies from affecting only a few joints for a limited period of time to long-lasting active disease until adulthood.[1] The medical treatment for JIA has gone through great improvements during the last decades and today includes numerous options with proved efficacy.[2] When we started our study, few long-term follow-up studies had evaluated the level of disease activity and long-term outcome in JIA patients.

A strong link between atherosclerosis and inflammation has been established,[3] and sustained inflammation is believed to accelerate atherosclerosis in patients with adult arthritis such as rheumatoid arthritis (RA).[4] Given the overlap in pathogenesis between RA and JIA, interest has increased concerning cardiovascular risk in JIA. At the time our study was started, the cardiovascular risk in adults with long-standing JIA had not previously been evaluated.

Because of the Norwegian population register, it is possible to trace patients still living in Norway who no longer are in the system of the Oslo University Hospital (OUH), providing excellent conditions for carrying out a long-term follow-up study. Inspired by our research group´s previous follow-up studies of JIA patients and concurrent work by Dr. Provan at Diakonhjemmet Hospital on cardiovascular risk in RA patients, we decided to carry out a long-term follow-up study in adult JIA patients with a focus on disease progression and cardiovascular risk.

2. BACKGROUND

JIA

Definition and classification

JIA is a heterogeneous disease defined by synovial inflammation of the joints that persists for at least 6 weeks in patients younger than 16 years, with other causes of arthritis excluded. It is categorised according to number and location of joints affected, involvement of other organ systems, patient characteristics, and presence of the autoantibody rheumatoid factor (RF). The International League of Associations for Rheumatology (ILAR) has developed the most recent classification criteria for JIA, the ILAR criteria.[1] These criteria comprise seven categories: systemic arthritis, RF-negative polyarthritis, RF-positive polyarthritis, oligoarthritis, enthesitis related arthritis, psoriatic arthritis, and undifferentiated arthritis (Table 1). Earlier, two classification criteria were used: the criteria for juvenile rheumatoid arthritis (JRA) that excluded childhood arthritis associated with axial disease or psoriasis,[5] and the criteria for juvenile chronic arthritis (JCA) that included these categories in addition to arthritis related to inflammatory bowel disease, thus comprising a more heterogeneous patient group.[6]

Uveitis is an important feature of JIA most often seen in patients with early onset of arthritis and antinuclear antibody (ANA) positivity.[7;8]

Table 1. The ILAR criteria for the classification of JIA

Systemic arthritis	Arthritis and quotidian fever for at least 2 weeks + at least one of the following: - Non-fixed erythematous rash - Generalised lymph node enlargement - Hepatomegaly and/or splenomegaly - Serositis *Exclusions: a – d*
RF-negative polyarthritis	Arthritis affecting 5 or more joints during the first 6 months. RF-negative. *Exclusions: a - e*
RF-positive polyarthritis	Arthritis affecting 5 or more joints during the first 6 months. RF-positive. *Exclusions: a, b, c, e*
Oligoarthritis	Arthritis affecting 1-4 joints during the first 6 months of the disease course. Two subcategories: - Persistent oligoarthritis: arthritis affecting 1-4 joints throughout the disease course - Extended oligoarthritis: arthritis affecting 1-4 joints during the first 6 months, but affecting a total of more than 4 joints after 6 months *Exclusions: a - e*
Enthesitis related arthritis	Arthritis and/or enthesitis + at least 2 of the following: - Sacroiliac joint tenderness - HLA-B27 positivity - Male onset age >6 years - Anterior uveitis - HLA-B27 related disease in first-degree relative *Exclusions a, d, e*
Psoriatic arthritis	Arthritis and psoriasis, or arthritis + at least 2 of the following: - Dactylitis - Nail pitting or oncholysis - Psoriasis in a first-degree relative *Exclusions: b - e*
Undifferentiated arthritis	Arthritis that does not fulfil criteria in any category or in 2 or more of the above categories.

JIA = juvenile idiopathic arthritis, ILAR = International League of Associations for Rheumatology, RF = rheumatoid factor

Exclusions:
a. Presence of psoriasis or psoriasis in a first-degree relative
b. HLA-B27 positive male >6 years old
c. Presence of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter´s syndrome, or acute anterior uveitis in patient or first-degree relative
d. RF-positivity
e. Presence of systemic arthritis

Epidemiology

JIA is the most common rheumatic disease in childhood. The disease has a female predominance (60-70%),[9-12] except for an equal to male predominance seen in enthesitis related arthritis.[13;14] Average age at onset is found to be 7 years,[9;10] and a tendency to bimodal age distribution with a slightly elevated incidence in the age groups 1-3 and 8-9 years is reported in Nordic studies.[9;15]

The annual incidence of JIA is approximately 15 per 100,000 children up to age 16 years, ranging from 11-23 in the Nordic countries to 6.6-10 in Germany and the United Kingdom.[9;10;15-18] The worldwide prevalence is 16-150/100000, including studies from the Nordic countries that have reported a prevalence rate of 86-148/100 000.[10;14;18]

Aetiology and pathogenesis

The aetiology of JIA is mainly unknown but most likely it is multifactorial. It may be triggered by an interaction between a particular complex polygenic predisposition, autoimmunity and various unknown environmental factors.[11] The human leukocyte antigen (HLA) gene is the best documented genetic predisposition found to determine development of JIA, and the haplotype HLA-DR8 has been identified to associate with most RF-negative JIA subtypes.[19-21] Additionally, non HLA-related immune genes including cytokine genes and other immune genes, also play a role in the susceptibility for JIA.[22;23] Infections, vaccinations, and trauma have been investigated as possible triggers of the disease, but a clear association has so far not been found.[11;24;25]

The process of synovial inflammation in JIA is characterised by infiltration of T-cells, B-cells, macrophages, plasma cells, and dendritic cells, leading to hypertrophy of the synovia.[26] Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin (IL) -1 and IL-6 are identified in the synovial tissue and fluid of children with

JIA and believed to play a central role in the inflammatory process.[27-29] JIA shares pathogenic features with adult RA concerning the process of synovial inflammation,[30] but the genetic markers identified in JIA differ greatly from those presented in RA.

RF antibody is seen in a small subset of JIA patients with a polyarthritis that resembles adult RF-positive RA.[31] ANA is mainly present in girls with early onset of oligoarthritis or polyarthritis with late onset,[32] and its presence is associated with an increased risk of uveitis.[7;8]

JIA disease course and outcome

The disease course and outcome in JIA are heterogeneous. Some patients experience affection of a few joints only and disease remission after a few years without any sequelae. Others have persistently active disease also in adulthood or experience different degrees of active disease varying with periods of remission. Numerous outcome studies following juvenile arthritis patients for 10-20 years have been presented since the year 2000 (Table 2), but the remission rates reported vary from 33 to 63%.[13;33-41] Studies have been difficult to compare because of differences in classification and criteria for remission used. The Wallace criteria for remission and the ILAR classification criteria for JIA developed in 2004 will hopefully lead to less variability among studies in the future.[1;42] Patients with RF-positivity and/or in the polyarticular and extended pauciarticular disease categories have been found to be less likely to experience remission while the greatest remission rates have been identified in the persistent oligoarticular and systemic disease categories.[34;35;38;39;41]

Table 2. Follow-up studies for 10 years or more after 2000

Author, year	Disease duration (mean/ median, yrs)	Pts (no.)	Remission criteria	Remission (%)	Classification criteria	Presence of each JIA category (%)
Zak et al. 2000	26 (SD 6)	65	No symptoms or objective signs of active JCA and normal ESR >2 years without any anti-rheumatic treatment	63	JCA/EULAR	Systemic art.: 8 Polyart.: 26 Pauciart. pers.: 32 Pauciart. ext.: 34
Packham et al. 2002	28 (range 8-73)	246	The absence of clinical inflammation determined with the Thompson-Kirwan scale,[43] and normal inflammatory markers (CRP and ESR)	Clinically: 57 Laboratory: 46	JIA/ILAR	Systemic art.: 21 Polyart. RF-: 17 Polyart. RF+: 15 Oligoart. pers.: 6 Oligoart. ext.: 22 Enthesitis art.: 13 Psoriatic art.: 5
Oen et al. 2002	11 (range 5-23)	392	Absence of active arthritis while off all anti-rheumatic medications for at least 2 years	39	JRA/ACR	Systemic art.: 12 Polyart. RF-: 20 Polyart. RF+: 10 Pauciart. pers.: 46 Pauciart. ext.: 11
Minden et al. 2002	17 (range 10-30)	215	At least 5 of; no joint pain, tenderness or swelling, no morning stiffness or fatigue and normal ESR, and not received anti-rheumatic drugs for 2 or more months (ACR criteria for remission in RA).[44] Plus no inflammatory spinal pain or active uveitis	40	JIA/ILAR	Systemic art.: 14 Polyart. RF-: 1 Polyart. RF+: 13 Oligoart.: 40 Enthesitis art.: 15 Psoriatic art.: 1 Other art.: 16
Fantini et al. 2003	10 (SD 7)	683	No signs of disease activity in the absence of anti-rheumatic therapy for at least 6 months	33	JCA/EULAR	Systemic art.: 13 Polyart. RF-: 12 Polyart. RF+: 3 Oligoart. pers.: 47 Oligoart. ext.: 15 Psoriatic art.: 3 Ankylosing spondylitis: 1 Art. associated with IBD: 0.4 Undifferented spondyloarthropathies: 5

Foster et al. 2003	21 (range 3-61)	82	Physician´s global assessment scale of disease activity = 0	61	JIA/ILAR	Systemic art.: 15 Polyart. RF-: 24 Polyart. RF+: 15 Oligoart. pers.: 16 Oligoart. ext.: 10 Enthesitis art.: 12 Psoriatic art.: 9
Flatø et al. 2003	15 (range 12-25)	268	At least 5 of no joint pain, tenderness or swelling, no morning stiffness or fatigue and normal ESR (ACR criteria for remission in RA) [44] had to be fulfilled for at least 2 years. Off anti-rheumatic medication during the last 2 years	50	JRA /ACR	Systemic art.: 6 Pauciart.: 40 Polyart.: 54
Flatø et al. 2006	15 (range 12-22)	55	The ILAR criteria for clinical remission in JIA*	44	Enthesitis related arthritis only	Enthesitis related art.: 100
Arkela-Kautiainen et al. 2005	16 (range 6-24)	123	ESR ≤20 mm/h, morning stiffness ≤15 minutes, no tender or swollen joints, off anti-rheumatic drugs or glucocorticoids for at least the past 2 years	35	JIA/ILAR	Systemic art.: 2 Polyart. RF-: 19 Polyart. RF+: 3 Oligoart. pers.: 63 Oligoart. ext.: 12 Psoriasis art.: 1
Flatø et al. 2009	15 (SD 2)		The ILAR criteria for clinical remission in JIA*	55 (Psoriasis art.) 54 (Oligoart.) 43 (Polyart	ILAR	Psoriasis art.: 13 Oligoart.: 58 Polyart.: 29

*Inactive disease is defined as having no active arthritis, fever, serositis, rash, splenomegaly, or generalised lymphadenopathy attributable to JIA, no active uveitis, normal CRP or ESR, and a physician's global assessment of disease activity rated as the best possible score for the instrument used. Clinical remission on medication is defined as minimum 6 continuous months of inactive disease on medication. Clinical remission off medication is defined as minimum 12 months of inactive disease off all anti-arthritic and anti-uveitis medication.[42]

SD = standard deviation, JCA = juvenile chronic arthritis, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, CRP = C-reactive protein, JIA = juvenile idiopathic arthritis, ILAR = International League of Associations for Rheumatology, RF = rheumatoid factor, JRA = juvenile rheumatoid arthritis, IQR = interquartile range, ACR = American College of Rheumatology, RA = rheumatoid arthritis, IBD = inflammatory bowel disease.

Medical treatment of JIA

The medical treatment of JIA has evolved considerably in recent decades, from involving only a few treatment options with uncertain effect toward an early aggressive treatment approach that includes numerous options.

Glucocorticoid joint injections of affected joints in active oligo- or polyarthritis are recommended as first-line therapy or in combination with the below mentioned treatments. A clinical improvement for at least 6 months after an injection have been found in 69% of the joints injected.[45]

Monotherapy with non-steroidal anti-inflammatory drug (NSAID) for 1-2 months is used as treatment for patients with newly diagnosed oligoarticular JIA.[2] If NSAID response is insufficient, or there is an initially high disease activity or polyarthritis, then disease-modifying anti-rheumatic drugs (DMARD) are recommended. The most widely used DMARD, methotrexate, is a folic acid analogue that interferes with DNA production. Methotrexate has been used to reduce disease activity in JIA patients since the early 1980s.[46;47] The emergence of biologic therapy in 1999 resulted in a great enhancement of JIA treatment efficacy.[48-50] TNF inhibitors are recommended as second- or third-line therapy after 3 months of insufficient outcome with treatment with methotrexate in oligo- or polyarticular JIA, but might also, in cases with active sacroiliitis, be chosen as second line therapy if insufficient response of NSAID.[2]

The treatment of systemic JIA differs from the other subtypes. Monotherapy with NSAID is rarely sufficient in these patients, but systemic glucocorticoids and anti-IL-1 or anti-IL-6 agens are often needed.[2]

Prognostic factors

The evaluation and measurement of active disease is an essential feature in JIA because

persistently active disease may cause joint damage and a reduction in physical function. When we started our study, only two publications reported investigations into the factors that might predict long-term active disease. In a study from 2000, Zak et al. reported that a longer disease duration was a predictor of unfavorable disease outcome in patients with persistent JCA 26 years after disease onset.[41] In 2003, Flatø et al. found that a long duration of elevated erythrocyte sedimentation rate (ESR), young age at onset, DRB1*08, RF-positivity, and a large number of affected joints within the first 6 months were risk factors for persistently active disease after 15 years.[35]

Patient-reported health status

As defined by the World Health Organization, health is a *"state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"*.[51] Because JIA is a chronic disease from childhood, physical, mental, and social well-being are important aspects of the disease course. The Health Assessment Questionnaire (HAQ) was developed in the 1980s with the goal of measuring long-term health outcomes and function in patients with arthritis [52] and has been used in numerous long-term follow-up studies of juvenile arthritis patients. Most studies report that approximately 40% of patients have some limitation of their physical function after more than 10 years of disease duration as measured by HAQ>0, but severe limitations were found in a small group (around 10%) of the patients.[35;38;53-55]

Health related quality of life (HRQoL) has been a focus for several studies of juvenile arthritis patients with long-term disease duration reporting a poorer HRQoL in young adults with juvenile arthritis compared to matched controls from the general population.[33;35;37;54]

Evaluation of active disease

In adult rheumatology, scores like Disease Activity Score 28 are developed by pooling

disease activity measures into one composite score.[56] Interest has increased in recent years in developing a standardised measure for the evaluation of JIA disease activity resulting in the Juvenile Arthritis Disease Activity Score (JADAS), a composite disease activity score for JIA that was developed in 2009.[57] JADAS is found to enable monitoring of the JIA disease course over time and comparisons of disease activity across groups.[57]

A longitudinal follow-up study of JIA patients for 30 years has not previously been performed. Additionally, long-term follow-up studies using the recently developed criteria for remission and the JADAS for evaluation of disease activity are lacking.

Cardiovascular disease (CVD)

Definition and epidemiology

Ischaemic heart disease (IHD) including angina pectoris, myocardial infarction, and ischeamic heart failure (HF), is most commonly caused by atherosclerosis. CVD, especially myocardial infarction and stroke, is the cause of death for approximately 17 million people annually, and thus is the most important cause of death by non-communicable diseases worldwide.[58] The well-defined risk factors for IHD; smoking, diabetes, hypertension, abdominal obesity, dyslipidemia, psychosocial factors, low consumption of fruit and vegetables, high levels of alcohol consumption, and physical inactivity together account for 90% of the risk for myocardial infarction worldwide.[59] Different tools have been developed for calculating individual cardiovascular risk in patients based on these established risk factors. Such tools are the US Framingham general CVD risk score,[60] the European SCORE (Systematic COronary Risk Evaluation) for CVD,[61] and the Norwegian NORRISK cardiovascular risk score.[62]

Pathogenesis of atherosclerosis

An initial event of the atherosclerotic process is endothelial dysfunction, which induces expression of adhesion molecules that enables T-lymphocytes and monocytes to migrate into the intima, the inner layer of the arterial wall, and accumulate. In the presence of oxidised low-density lipoprotein (LDL), monocytes mature into activated macrophages that internalise lipoproteins and turn into foam cells.[63] The accumulation of foam cells together with T-cells, mast cells, and dendritic cells initiates the formation of the atherosclerotic lesion, and the secretion of pro-inflammatory cytokines promotes local inflammation and plaque growth.[64] Further accumulation of smooth muscle cells, connective tissue, T-lymphocytes, and lipids contributes to the expansion and development of the atherosclerotic lesions.[63] These lesions may gradually be covered by a fibrous cap, intrude into the arterial wall, and change the blood flow.[65] Ulceration of an atherosclerotic plaque may lead to thrombosis, which may trigger myocardial infarction and ischaemic stroke.

Autopsies of the aorta and coronary arteries of children and young adults dying from various causes have revealed that the atherosclerotic process in some cases, begins already in childhood and youth.[66;67] In fact, evidence suggests that fatty streak formation may begin in utero.[68]

Inflammation and atherosclerosis/IHD

A strong link between atherosclerosis and inflammation has been established.[3] Inflammatory processes may cause endothelial dysfunction through oxidative stress and inhibited NO-mediated vasodilatation,[69] and elevated levels of C-reactive protein (CRP) has been shown to suppress the production of NO and its bioactivity.[70] Mediated through endothelial dysfunction, inflammation may promote changes in the extracellular matrix as a result of smooth muscle cell proliferation and increased collagen stiffening, leading to stiffening of the large arteries.[71] Increased levels of immune cells, adhesion molecules, and cytokines are identified in

hypertension,[72] but an exact pathology is not yet established. HF and left ventricular (LV) diastolic dysfunction are also found to be associated with cardiac inflammation.[73-75]

Markers of subclinical CVD

Early detection is crucial for the prevention of IHD. Novel non-invasive methods allow assessment of arterial properties, subclinical atherosclerosis, and cardiac function. Arterial pulse wave velocity (PWV) is a marker of large arterial stiffness, and the augmentation index (AIx) reflects arterial stiffness by a combination of pulse wave reflection, LV ejection, and heart rate.[76] Coronary artery calcification is a marker of coronary atherosclerosis and may be determined by computed tomography (CT).[77] These markers are proved to be associated with subsequent CVD and all-cause mortality in various populations.[78-81] Cardiac ultrasound, i.e. echocardiography provides detailed information on cardiac morphology, systolic and diastolic function, and general haemodynamics such as cardiac output and filling parameters, and is an important tool for diagnosis of HF in clinical cardiology.

Inflammatory arthritis and cardiovascular risk

Adult onset inflammatory arthritides are associated with an increased risk of cardiovascular mortality and morbidity,[82-85] independent of the presence of traditional cardiovascular risk factors.[86] Extensive research on subclinical CVD has demonstrated increased arterial stiffness, coronary atherosclerosis, and carotid atherosclerotic plaques in RA patients.[87-90] Evidence also points to a higher prevalence of diastolic dysfunction and an increased risk of HF in RA patients.[91;92] Sharing pathogenic similarities such as T-cell activation, production of pro-inflammatory cytokines, and increased expression of adhesion molecules, systemic inflammation is believed to play an important role in the accelerated atherosclerotic process

seen in RA.[4] In light of an overlap in pathogenesis between JIA and RA, interest has increased concerning cardiovascular risk in JIA.

The prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidaemia, and a sedentary lifestyle has scarcely been investigated in children with JIA. Two studies have showed increased levels of blood pressure (BP) in children with juvenile arthritis [93;94] while analysis of serum cholesterol levels in children with juvenile arthritis has yielded contradictory results.[95-97] Furthermore, lower levels of physical activity [98] and physical fitness as measured by $V0_{2peak}$ [99;100] are found in JIA patients when compared to healthy children. The use of anti-rheumatic drugs may also be a possible risk factor for developing early atherosclerosis in JIA. Methotrexate increases the level of homocysteine by the inhibition of folic acid, which again is associated with accelerated atherosclerosis.[101] The use of corticosteroids has been linked to an increased risk of myocardial infarction and hypertension in RA patients.[102;103] Additionally, a link has been established between NSAID use and increased BP in healthy individuals,[104;105] and both high-dose regimens of ibuprofen and diclofenac have been associated with a moderately increased risk of vascular events.[106] On the other side, anti-rheumatic drugs may act cardio-protective by reducing inflammation.

Only a few studies have reported the prevalence of subclinical CVD in JIA patients. In one study, PWV, as measured by magnetic resonance imaging, was higher in 31 JIA patients with a mean age of 14 years compared to matched controls.[107] Additionally, cardiac function was evaluated in two small studies, with results suggesting impaired diastolic function in children with juvenile arthritis when compared to controls.[93;94]

To the best of our knowledge, traditional cardiovascular risk factors, arterial properties, and cardiac function have not yet been studied in adult JIA patients.

3. AIMS OF STUDY

Main aim

To describe long-term disease activity and cardiovascular risk in a cohort of well-characterised adult JIA patients.

Specific aims

- To describe arterial stiffness and BP in JIA patients with active disease for at least 15 years compared to that of age- and gender-matched controls and to assess the level of coronary artery calcification in adults with JIA (paper I).
- To evaluate and compare LV systolic and diastolic function in JIA patients with active disease for at least 15 years to that in age- and gender-matched controls (paper II).
- To assess the level of traditional cardiovascular risk factors in JIA patients with long-term active disease compared to that in controls (papers I,II).
- To determine a possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics, coronary artery calcification and cardiac function (papers I,II).
- To longitudinally assess the disease activity and health status in JIA patients during 30 years of disease duration and investigate possible predictors of long-term active disease (paper III).

4. PATIENTS AND METHODS

Study design

Our study is a longitudinal, partly retrospective study of a cohort of JIA patients. Papers I and II have a case-control design, while paper III is an observational study. For papers I and II, only patients with active disease for at least 15 years were included. The patient:control ratios were 1:1 in paper I and 2:1 in paper II. In paper III, both patients with active disease and patients with disease in remission were included.

The 87/85 patients included in papers I and II were examined after a median of 29.2 years, and altogether the 176 included patients (paper III) were examined after 29.6 years. The follow-up is therefore referred to as the 30-year follow-up throughout this thesis.

Patients and controls

Patients

The patients invited to the study were selected from a cohort of 260 JIA patients who were referred for the first time to OUH from 1980 through September 1985 and later examined clinically after a median 15 years of disease duration (15-year follow-up), and by mailed questionnaires after a median 23 years (23-year follow-up). These patients have been described in detail in previous publications.[13;35;36] Of the 260 patients, 6 had died, thus, 254 patients were invited to participate in the present study.

After a median 30 years of disease duration, the 127 patients in the original cohort who still had active disease at the 15-year and 23-year follow-up were invited to participate in a clinical examination while the 127 patients who did not have active disease at the 15- and 23-year follow-up received a mailed questionnaire. To capture possible patients with a relapse of disease activity after 30 years, questions elicited data on received anti-rheumatic or anti-uveitis medication, history of joint injections, and the presence of uveitis during the last year.

To capture possible patients with a relapse of disease activity at the 23-year follow-up, the patients were asked if they used anti-rheumatic medication and if they recently had visited a rheumatologist. Of the patients expected to be in remission, 96 returned the questionnaire (30-year follow-up). Ten of these patients had disease relapse and were invited to participate in the clinical examination, by which 7 accepted. Together, 90 JIA patients with persistently active disease consented and enrolled in an extended clinical examination at OUH between May 2011 and March 2012 (30-year follow-up). All of the patients received one written reminder if they did not answer the first invitation. In all, 176 patients participated in the study.

Three patients were excluded from studies I and II because of pregnancy, which may influence arterial haemodynamics and cardiac function. Two patients were additionally excluded from study II because of technical complications with the ultrasound scanner (n=1) or severe heart disease without relation to JIA (n=1).

The patients were initially classified according to the ACR criteria for the classification of JRA [5] and reclassified according to the ILAR criteria based on clinical examination at the 15-year follow-up and retrospective chart reviews.

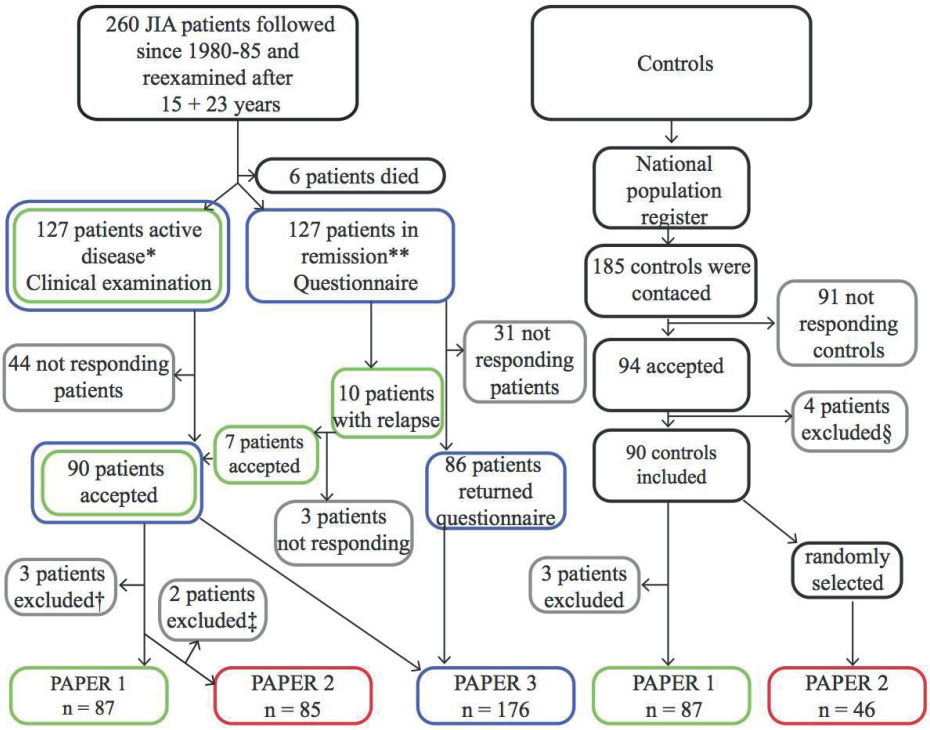
Non-participating patients

Sixty-seven patients did not respond to the invitation, and 11 chose not to participate. The 176 participants were comparable to the 84 non-participants (including the 6 deceased patients) with regard to gender, disease category, and disease duration, as well as physician's global assessment of disease activity, number of active joints, remission rate, the level of HAQ, and Short Form-36 health survey (SF-36) after 15 years, but the non-participants were slightly but statistically significant younger at onset than the participant group. When analysing the 47

eligible but not participating patients with active disease at the 15-year follow-up and the 87 included patients for paper I, the same trend was found.

Controls

In the first study (paper I), controls were matched one to one by age, gender, and living in a rural or not rural area. Patients living in the county of Oslo were matched with controls living in Oslo while patients living in the rest of Norway were matched with controls living in the county of Akershus. A company called Ergo Group AS, licensed to do searches in the National Population Register of Norway, made a random selection of 10 controls per patient. Controls were invited to participate in the study by one mailed letter, and no reminders were sent. If a response to the invitation was not received within 3 weeks, an invitation was sent to the next control on the list. Because the patient group consisted of only Caucasians, non-European controls were not invited. All responders were contacted and interviewed briefly by telephone before inclusion. Exclusion criteria for participating in the study were the presence of inflammatory arthritis, diabetes mellitus, or previous cardiovascular events. One potential control was excluded because of diabetes mellitus, and 3 potential controls were excluded because of the presence of inflammatory arthritis including JIA, ankylosing spondylitis, or gout. A letter of invitation to participate in a one-day examination was sent to 185 controls. Half of the controls were randomly chosen to participate in examinations for paper II (echocardiography) after accepting the invitation.



* Signs of active disease and/or on anti-rheumatic medication and/or off medication less than 2 years at 15- and/or 23-year follow-up.
** No sign of active disease and no use of anti-rheumatic or anti-uveitis medication for at least 2 years at 15- and/or 23-year follow-up.
† Excluded because of pregnancy.
‡ Excluded because of technical complications with the ultrasound scanner (n=1) or severe heart disease without relation to JIA (n=1).
§ Excluded because of the presence of diabetes mellitus or inflammatory arthritis .

Traditional cardiovascular risk factors

Traditional cardiovascular risk factors were measured in the 87 patients with long-term active disease and controls. Body mass index (BMI) and waist circumference were assessed. Information about smoking habits and physical activity was collected by a self-reported questionnaire. The validated Norwegian short International Physical Activity Questionnaire was used to assess the total physical activity of work and leisure time, separated into moderate and vigorous intensity.[108;109] Patients and controls were interviewed about family history of

premature CVD, defined as CVD in a first-degree relative before the age of 55 in men and 65 in women.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 minutes of rest in a supine position, and three measurements with a variance of <5 mmHg were averaged. The BP was assessed by use of oscillometric technique with Dinamap ProCare 300-Monitor (Criticon, GE Medical System, USA). The presence of arterial hypertension was defined as SBP/DBP >140/90 mmHg or use of antihypertensive medication.

Laboratory data

Blood screening was carried out in the morning after an overnight fast. LDL, high-density lipoprotein (HDL), and total cholesterol, triglycerides, high-sensitivity CRP (hs-CRP), glucose, glycated haemoglobin (HBA1c), insulin, and prohormone of brain natriuretic peptide were measured. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated from the product of fasting glucose (mmol/L) and insulin (pmol/L) divided by the constant 22.5.[110;111] One JIA patient had diabetes type 2 and was therefore excluded from analyses concerning HbA1c, glucose, and insulin. ESR and platelets were additionally assessed in the patients. ESR and platelet areas under the curve (AUCs) were calculated from parameters measured at disease onset and at the 15-year and 30-year follow-up. CRP AUC was calculated from the parameters assessed at the 15-year and 30-year follow-up.

Arterial stiffness

A Sphygmocor apparatus (Atcor Medical, Sidney, Australia) was used to assess PWV and AIx in patients and controls for paper I. The author of the thesis performed all measurements. The participants did not eat, drink (except water), or smoke for at least 3 hours before the examination.

To measure PWV, sequential recordings of pulse wave forms from the right common carotid artery and the left femoral artery were obtained and gated to an electrocardiogram for the assessment of transit time (Figure 1). The PWV was estimated as the surface distance between the two recording sites divided by the time delay between the feet of the two waveforms.[76] The surface distance was assessed as the distance from the suprasternal notch to the umbilicus plus 10 cm. Measurements fulfilled the automatic quality control (specified by the Sphygmocor apparatus) in 78 patients and 84 controls, and the mean of two measurements with a variance of <0.5 m/s was used in the statistical analysis.

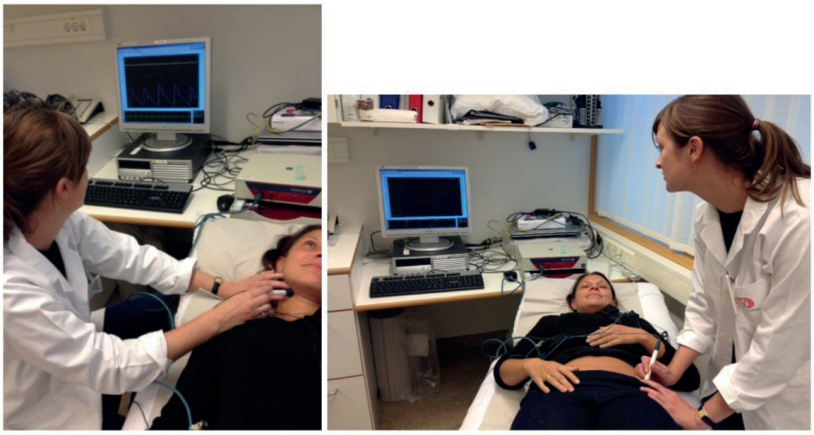


Figure 1: Measurements of PWV by use of the Sphygmocor apparatus. Left: recordings of pulse wave forms from the right common carotid artery, right: recordings of pulse wave forms from the left femoral artery.

AIx was defined as the change in pressure between the second and first systolic peaks of the central pressure waveform, expressed as a percentage of the pulse pressure and standardised to a heart rate of 75 beats/minute.[76] The aortic pressure waveform and AIx were generated from recordings of the radial artery waveform by use of an integrated transfer

system.[112] The average of three AIx measurements, all having a quality index score >85%, was used for analysis. Measurements of sufficient quality were obtained in 79 patients and 87 controls.

PWV and AIx are markers expressing somewhat different aspects of arterial stiffness recommended to be coupled for the measurement of arterial function. PWV is the speed by which the pressure wave moves down the aorta and is thus a direct measure of large arterial stiffness. AIx is more of an indirect measure of arterial stiffness that quantifies the combination of the forward pressure from LV contraction, the amplitude from the reflected peripheral wave, and the heart rate.[76] PWV has a well-documented ability to predict CVD and is regarded as the "gold standard" for the assessment of arterial stiffness.[76;79] AIx is proved to have predictive value for CVD in selected diseases.[80]

Coronary artery calcification

Coronary artery calcification was quantified by use of a 320-detector row CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) for paper I and calculated as an Agatston score (figure 2).[77;113] A dedicated workstation (Vitrea fX, Vital Images, Minnetonka, Minnesota, USA) with a computerised program (Coronary Artery Calcium Scoring) with a threshold of 130 HU was used to estimate the amount of coronary calcification as an Agatston score.[77;113] A total of 84 patients underwent coronary calcification scoring. Because of a small potential risk associated with radiation, controls were not included.

The presence of coronary artery calcification is demonstrated as a predictor of cardiovascular events,[78] and survival rates are found to be closely associated with the total amount of coronary calcification.[114] Furthermore, the coronary artery calcification score may provide additional and independent predictive information about cardiovascular events and

all-cause mortality beyond the traditional risk factor models such as the Framingham risk model.[114;115]

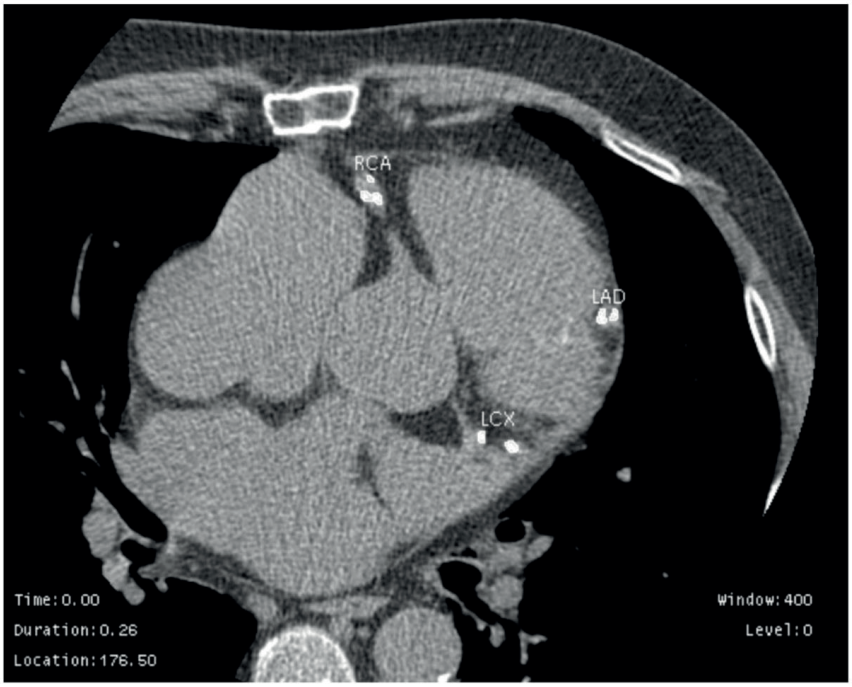


Figure 2: Coronary artery calcification as measured by coronary CT.

Echocardiography

Standard transthoracic echocardiographic examination was performed using a Vivid 7 or E9 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) with the participants in standard parasternal (short- and long-axis) and apical (four-chamber, two-chamber, and long-axis) projections (paper II).[116] All recordings were measured after at least 5 minutes of rest, and 3 consecutive heart cycles were stored for offline analyses using dedicated software (BT 12, EchoPAC, GE Vingmed Ultrasound). Frame rate was >100 frames per second (FPS) at the time of tissue Doppler recordings, and >40 FPS during 2D imaging.

LV end-diastolic volume and ejection fraction (EF) were measured by Simpson´s modified biplane rule using endocardial contours in the four- and two-chamber views.[117] LV dimensions were assessed per convention from parasternal M-mode registrations. Left atrial (LA) area was measured in the four-chamber view.

Pulsed-wave Doppler signal with the sample volume at the tip of the mitral leaflets (apical position) was used to record LV early (E) and late (A) diastolic flow velocities, deceleration time (DT), and isovolumic relaxation time (IVRT).[118] LV mitral annular velocities in systole (LV s´) and early diastole (LV e´), were measured in the septal and lateral mitral annulus by colour tissue Doppler imaging (Figure 3). The E/e´ ratio was calculated.[119]

Global longitudinal strain was measured to obtain regional and global myocardial function by use of speckle tracking echocardiography (2D strain method, EchoPac, GE Vingmed, BT 11/12) in an 18-segment model.[120]

All echocardiographic recordings and analyses were carried out by one investigator (HAA). Offline data reanalyses were blinded for patient/control identity and clinical information. All parameters were averaged from three heart cycles, except for the global longitudinal strain, which was obtained from analyses of single beat recordings of 3 apical image projections.

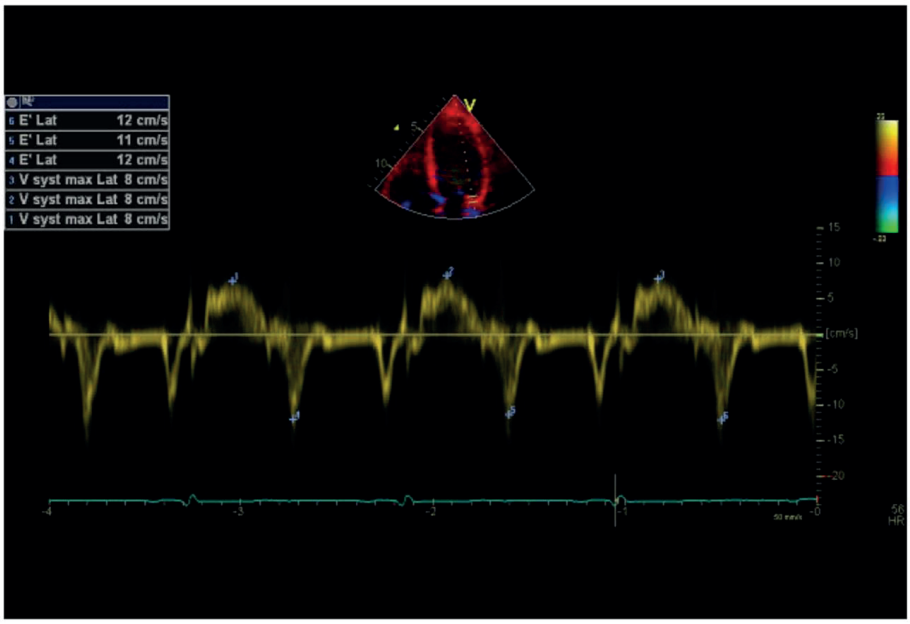


Figure 3: Pulsed tissue Doppler recordings on the lateral mitral annulus.

Echocardiography is an effective method for the evaluation of *systolic* and *diastolic* cardiac function and has evolved as a widely used tool in the clinical practice of cardiology and research.

Systolic dysfunction is characterised by a decrease in ventricular myocardial contractility followed by a reduction in EF. Several echocardiographic methods provide information about ventricular systolic function such as EF, and fractional shortening. s´ and longitudinal peak-systolic global strain are newly developed echocardiographic modalities that provide additional information on regional and global systolic myocardial function and contractility.[120-122]

Diastolic dysfunction is mainly dependent on myocardial relaxation, compliance, and LV load and may initially present as cardiac dysfunction with preserved EF.[123] *Impaired relaxation* of the LV is characterised by prolonged transmitral IVRT and DT and decreased peak early-to-late ratio mitral flow velocity (E/A ratio). To compensate for the impaired relaxation, LV filling pressure will increase to maintain the SV, resulting in a *pseudonormal* filling pattern with early and late mitral inflow velocities of similar magnitudes. A further rise in LA pressure will result in a *restrictive filling pattern,* which is characterised by an increased E/A ratio, shortening of the IVRT and DT, and increased E/e´.[118] E/e´ ratio is shown to be a non-invasive parameter of LV filling pressure.[119;124] An E/e´ >15 can be categorised as an elevated LV filling pressure, while E/e´ <8 indicates a normal LV filling pressure.[119] For values between 8 and 15, additional echocardiographic diastolic parameters are needed to evaluate if the filling pressure is abnormal.

Electrocardiography (ECG)

A standard 12-channel ECG recording was performed in patients and controls for paper II. The ECG recordings were reviewed for abnormalities such as corrected QT (QTc) prolongation, T wave abnormalities, bundle branch blockage, and chamber enlargement by a researcher blinded to clinical information and patient/control identity. Abnormal ECG recordings were classified as pathologic ECG or borderline pathologic ECG. The rhythm, PR-interval, QRS duration, and QTc interval were measured.

Clinical JIA data

A clinical examination was performed in the patients with long-term active disease by one of three senior physicians (BF, AMS, VL) experienced in paediatric rheumatology. The clinical examination included general organ status, registration of the use of medication since last

follow-up, registration of number of joints (71 joint count) with swelling, tenderness, and limited range of motion (LROM), number of active joints (swelling or both tenderness and LROM), and a physician´s global assessment of disease activity (on a 10-cm visual analogue scale (VAS), where 0 means no disease activity and 10 means severe disease activity, and on a 5-point Likert scale where 1 means inactive and 5 very severe disease activity.)

Disease onset was defined as the date that arthritis was documented by a physician. Medical records were retrospectively reviewed at the 15-year follow-up for variables concerning onset of the disease.[13;35;36]

The controls underwent a general clinical examination by a doctor (HAA).

Remission

Inactive disease was defined according to the criteria for clinical remission in JIA; as having no active arthritis, fever, serositis, rash, splenomegaly, or generalised lymphadenopathy attributable to JIA, no active uveitis, normal CRP or ESR, and a physician's global assessment of disease activity rated as the best possible score for the instrument used, for all the patients at the 15-year follow-up, and for patients clinically examined at the 30-year follow-up.[42] For patients not examined at the 30-year follow-up, i.e. in remission off medication for at least 12 months at the 15-year follow-up, inactive disease at the 30-year follow-up was defined as no history of flare after 23 and 30 years. Clinical remission on medication was defined as a minimum of 6 continuous months of inactive disease on medication. Clinical remission off medication was defined as a minimum of 12 months of inactive disease off all anti-arthritic and anti-uveitis medication.

Measures of health status

For the assessment of health status, questionnaires on physical function including the HAQ

and SF-36 were used. The HAQ includes 8 areas of daily activities; dressing, arising, eating, walking, hygiene, reach, grip, and activities, and a subjective estimate of pain and mental functioning, and only the patients completed it.[52] Each area was scored from 0 to 3, and a HAQ disability index of 0 was the best possible score, indicating no functional limitation.

SF-36 is a generic measure of HRQoL, by which the Norwegian version 1.0 was used in this study.[125] The SF-36 consists of 36 items divided into eight scales aggregated into a Physical Component Summary score and a Mental Component Summary Score. Both scores are reported to have a mean of 50 based on the 1998 US general population. The HAQ and SF-36 were used in paper III to compare health status and HRQoL in JIA patients between the 15- and 30-year follow-up.

JADAS

Disease activity was also measured by JADAS, a composite score calculated on the basis of four JIA disease activity measurements including number of joints with active disease, the physician's global assessment of disease activity measured on a 10-cm VAS where 0 means no activity and 10 means maximum activity, patient's global assessment of well-being measured on a 10-cm VAS where 0 means doing very well and 10 means doing very poorly, and standardised ESR.[57] Recently, a JADAS3 was created and evaluated to calculate a score without ESR.[126] We used the JADAS3 version (paper III) for the purpose of also including the patients who were in remission. Missing data for the physician's global assessment of patients without signs of disease activity or off anti-rheumatic medication were replaced by 0, in accordance with the median score for the patients we had examined who were in remission. A JADAS below 4.5 has been found to correlate as a cut-off value for an acceptable symptom state for children with JIA.[127] Consequently, we chose JADAS3 >4.5 as a level of a high symptom state.

Statistics

Comparisons between JIA patients and matched controls (papers I and II) or between the two patient groups (papers II and III) were made using the two-tailed paired sample t test (paper I) and independent sample t test (papers II and III) for continuous normally distributed variables, the Wilcoxon rank-sum test (paper I) and Mann-Whitney U test (paper II) for continuous non-normally distributed values, and McNemar´s test (paper I) and the χ^2 test (papers II and III) for categorical variables. The Wilcoxon rank-sum test was also used for comparisons of continuous non-normally distributed data from the 15- and 30-year follow-up, and Friedman's two-way analysis of variance was utilized for comparisons at more than two time points (paper III).

The Kruskal-Wallis test was used to analyse differences between more than two groups regarding non-normally distributed continuous variables (the JADAS3 across the JIA categories). Spearman's correlation was used to measure the association among cumulative inflammatory burden, years on prednisolone, and LV diastolic function (paper II), and between the JADAS3 and categories of disease activity (paper III).

To explore associations between traditional cardiovascular risk factors and disease variables and arterial haemodynamics, age- and gender-adjusted linear regression analyses were applied. Multivariate analyses with backward deletion of possible determinants based on the previously performed age- and gender-adjusted linear regression analyses/Spearman´s correlation were used to identify determinants of arterial stiffness and LV diastolic function (papers I and II). Age- and gender-adjusted logistic regression analyses were used to explore associations with traditional cardiovascular risk factors as well as disease variables and coronary artery calcification (paper I). Logistic regression analyses were also used to assess predictors of active disease at 30 years from baseline/15-year follow-up (paper III).

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) Versions 18 and 20 (SPSS, Chicago, IL, USA). For all analyses, p values <0.05 (2 tailed tests) were considered statistically significant.

Ethics

The study was approved by the Regional Ethics Committee for Medical Research (regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst (No.2011/982)), and all participants gave written informed consent according to the Declaration of Helsinki (2008).

5. SUMMARY OF RESULTS

PAPER I

The aims of paper I were to identify the level of arterial haemodynamics and traditional cardiovascular risk factors in adult JIA patients with long-term disease activity as compared to controls, and to assess coronary artery calcification in JIA patients. Furthermore, we wanted to investigate the possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics and coronary artery calcification.

This study included 87 patients with well-characterised JIA and a median disease duration of 29.2 (range 28.2-30.6) years and 87 randomly selected age- and gender-matched controls. The markers for arterial stiffness, PWV and AIx, blood pressure, and traditional cardiovascular risk factors were measured in patients and controls. Coronary artery calcification was measured in patients.

The findings were as follows:

- Mean PWV was higher in JIA patients than controls (7.2 m/s versus 6.9 m/s, p=0.035). AIx also tended to be higher in patients than controls, but no statistically significant difference was found (p=0.154). The SBP and DBP were higher in patients than controls (p=0.050 and p=0.029). A total of 7% of 84 JIA patients had a coronary artery calcification score above 10, and 19% had a score from 1 to 10.
- A higher frequency of the JIA patients than the controls were daily smokers (25% versus 13%, p=0.043). Arterial hypertension was present in 11% of patients and 2% of controls (p=0.039). The levels of HOMA-IR and hs-CRP were higher in patients than controls (p=0.034 and p=0.001). The JIA patients reported performing more physical activity of moderate intensity than the controls (p=0.001).
- DBP was the only determinant of PWV in multivariate analyses. Concerning AIx, markers identified as determinants were age, female gender, DBP, daily smoking, less

vigorous physical activity, platelets AUC, number of joints with LROM, and years on prednisolone. A coronary calcification score >0 in the JIA patients was associated with SBP, years on prednisolone, blood glucose, waist circumference, and BMI.

Our results demonstrate altered arterial haemodynamics in JIA patients with long-term active disease as compared to controls. Arterial stiffness as measured by PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease activity and treatment variables.

Paper II

The aims of paper II were to compare the cardiac function in adult JIA patients with long-term active disease to that of age- and gender-matched controls and to assess whether a larger inflammatory burden, more severe disease, or the use of anti-rheumatic medication had an adverse effect on cardiac function.

This study included 85 patients with well-characterised JIA and a median disease duration of 29.2 (range 28.2-30.6) years and 46 randomly selected age- and gender-matched controls. Cardiac function was measured by echocardiography and ECG in patients and controls.

The findings were as follows:

- The parameters of systolic function were comparable between JIA patients and the controls. Interventricular septum thickness was thicker in patients than controls (p=0.036). Echocardiographic parameters of diastolic function were within normal range for patients, but when compared to controls, transmitral DT was lower (p=0.029), and lateral E/e´ and LA area were higher (p=0.036, p=0.015, respectively).
- E/e´ measured at the 30-year follow-up was higher in the JIA patients with hs-CRP ≥2, a polyarticular disease course, and/or ≥3 joints with LROM compared to those with

less severe disease (p=0.004, p=0.050, and p=0.016, respectively). Cumulative markers of disease activity such as longer duration of active disease, ESR AUC, CRP AUC, and years on daily prednisolone correlated positively with higher lateral E/e´ (p=0.023, p=0.042, p=0.033, and p=0.021, respectively). Age (p=0.010) and duration of active disease (p=0.046) were identified as determinants of higher lateral E/e´ at the 30-year follow-up.

- The QTc interval was comparable between patients and controls (p=0.409), but the heart rate as measured by ECG was higher in patients (p=0.001).

These results show that JIA patients with long-term active disease had altered LV morphology and diastolic function compared to controls. Higher LV filling pressure was correlated with large inflammatory burden, severe disease, and prolonged daily prednisolone use.

Paper III

The aims of paper III were to longitudinally assess disease activity and health status in JIA patients during 30 years of disease duration and investigate possible predictors of long-term active disease.

This study included 176 patients (median age 38.8 years) previously examined after 15 and 23 years. Patients were assessed by questionnaires after a median of 29.6 years (range 20.6-39.9) of disease duration. Ninety patients were also clinically examined. JADAS was used to measure disease activity, and health status was assessed by HAQ and SF-36.

The findings were as follows:

- A total of 41% of the patients had active disease or were in remission on medication, and 59% were in clinical remission off medication at the 30-year follow-up. A total of 87% of patients in remission off medication at the 15-year follow-up were still in remission at the 30-year follow-up, and 64% of the patients with active disease at the

15-year follow-up had active disease at the 30-year follow-up. Altogether, 70% of the patients had an unchanged category of disease activity from the 15- to 30-year follow-up. The remission rates were highest in patients with persistent oligoarticular and systemic JIA (80% and 83%, respectively) and lowest in those with polyarticular RF-positive and enthesitis related juvenile arthritis (17% and 37%, respectively, p=0.001).

- At 30-year follow-up 56% of the patients who were not in remission off medication used DMARDs and/or prednisolone, 12% used NSAIDs, and 32% used no medication.
- The JADAS3 median value was 1.9 (range 0.2-23.1) for the total study group. Patients with systemic JIA or persistent oligoarthritis had lower values for JADAS3 than those with polyarticular RF-positive JIA. The JADAS3 had a strong correlation with disease activity categories (active disease, remission on/off medication) with a Spearman's correlation coefficient of 0.73 ($p<0.001$). A total of 41% of the patients had JADAS3 $\leq$1.0, 13% had JADAS3 between 1.1 and 2.0, 18% had JADAS3 between 2.1 and 4.5, and 28% had JADAS3 >4.5. All patients with a JADAS3 $\leq$1.0 were in remission. Of the patients with a JADAS3 >4.5, 80% had active disease, and 20% were in remission.
- There were significant improvements in the physician's global assessment of disease activity, number of active joints, ESR, and CRP (all $p<0.05$) from the 15- to 30-year follow-up, but no difference in number of joints with LROM, patient's global assessment, HAQ, and SF-36 in patients with long-term active disease.
- Predictors of active disease or being on anti-rheumatic medication after 30 years were: HLA-DRB1*01 positivity, physician's global assessment of disease activity at the 15-year follow-up, and a short duration of total time in remission at the 15-year follow-up. A higher physician's global assessment of disease activity at the 15-year follow-up was a predictor of a high symptom state (JADAS3 >4.5) at the 30-year follow-up.

6. DISCUSSION

The first part of the discussion will address the strengths and limitations of the methodology used in the papers included in this thesis. The second part will be a discussion of the main results.

Methods, strengths and limitations

Study design

The major strength of this study is the long-term follow-up of a well-characterised cohort of JIA patients with a median disease duration of 30 years. The same doctor who included the patients at disease onset, Dr Berit Flatø, has been the head of the project during the whole observational period.

Our study has several limitations concerning study design. All participants were assessed by questionnaires at 30-year follow-up, but an invitation to a 1-2 day clinical examination was sent to the JIA patients with long-term *active* disease only for two reasons, as follows:

- Previous studies in adult RA patients have shown that patients with disease in remission had a comparable cardiovascular risk to controls,[88] and we wanted to assess patients with long-term inflammation from childhood.
- It is challenging economically and practically to clinically examine a high number of patients who have gone into early remission.

As explained in the methods chapter of this thesis, the questionnaires screened for relapse of disease activity. However, we cannot exclude that some of the patients who were expected to be in remission had disease activity that had been discovered by a clinical examination, but went undetected with the questionnaire.

Ideally, the patients should have been examined more often during the disease course than at the median 15-, 25-, and 30-year follow-up, but because the patients were included from the whole country, more frequent follow-ups would have been too challenging economically and practically.

Patients

The participation rate for the patients in this study was 69%, and because 31% of patients were lost to follow-up, the remission rate reported in paper III may not be completely correct. The non-participants were younger but otherwise comparable to participants in regard to gender, disease category, disease duration, and disease activity at the 15-year follow-up.

The patients were all referred to the hospital, which usually indicates inclusion of patients with more severe disease than population based cohorts like in the study by Bertilsson et al.[128] The access to specialist care for patients with chronic diseases is good in Scandinavia, and all JIA patients are usually referred to a specialist at least for diagnosis. However, our hospital is a secondary or tertiary referral center for patients outside the Oslo area, indicating that patients with mild disease may not have been referred. On the other hand, the patient characteristics such as gender distribution and age at disease onset in our cohort were comparable to those in epidemiological studies in Scandinavia.[9;128] Furthermore, the representation of JIA disease categories resembles the distribution in a German cohort followed for 16.5 years by Minden et al.,[38] but consists of more patients with oligoarticular and fewer with polyarticular JIA compared to a cohort from UK followed for 21 years by Foster et al. (Table 2).[37] JIA patients followed routinely by adult rheumatologists will include patients with more long-term active disease than a cohort including all first referrals from a given period, indicating less bias toward patients with severe disease in our total cohort (paper III).

Controls

The controls were matched one-to-one to the patients by age, gender, and urban versus non-urban regions (paper I), and 51% of the invited controls agreed to join the study. A weakness of this study is the relatively large number of non-participating controls, which may have caused a selection bias. By investigating CVD, the study might have attracted individuals concerned about their health because of an increased cardiovascular risk. On the other side, the study also might have attracted very healthy and physically active individuals interested in their cardiovascular status. Patients living in Oslo were matched to controls living in Oslo while patients living in the rest of Norway were matched with controls living in the county of Akershus, a more rural county situated next to the county of Oslo. Ideally, controls should have been recruited from the county where the patients were situated, but because Norway is such a big country, doing so was not possible for practical and economic reasons.

Assessment of cardiovascular status

Different methods can be used for the detecting of subclinical CVD. By choosing markers for arterial stiffness, coronary atherosclerosis, and cardiac function, we tried to capture the different stages of subclinical CVD.

Blood pressure and arterial stiffness show a diurnal variation, and these markers should therefore be measured at the same time of day in all participants when comparing two groups.[129;130] Additionally, abstention from smoking, food, and alcohol for 3 hours prior to the examination is recommended for the assessment of arterial stiffness.[76] These guidelines were followed in our study. For the estimation of the surface distance travelled by the PWV, we chose to assess the distance from the suprasternal notch to the umbilicus plus 10 cm as recommended by the manufacturer. The procedures measuring the PWV travel distance varies among studies and comparisons of PWV values between studies may therefore be

difficult. Nonetheless, the same method was used for patients and controls in our study.

The determination of aortic AIx from peripheral recorded pulse pressure waveforms has been controversial. The proximal arteries exhibit greater elastic properties than the distal arteries in young and healthy individuals while the elasticity of the proximal arteries diminishes in older people and in the presence of CVD.[131] However, the method used in our study is found to correspond with aortic pressure assessed invasively and is widely accepted.[112;132;133]

Coronary artery calcium score is an established marker of future CVD, and a coronary calcium score of 0 in asymptomatic individuals indicates a low risk for severe coronary atherosclerosis.[134] Nevertheless, cardiac CT without contrast is limited by a low sensitivity for identifying soft plaques without calcification.[135] A weakness of this study is that we could not compare the amount of coronary calcium found in the JIA patients with matched controls. Because cardiac CT scanning involves small radiation doses, controls were not scanned for ethical reasons.

The author of this thesis was trained at the "echo laboratory" at the Department of Cardiology, OUH, to establish an adequate technique for recording and analysis of echocardiographic data. A more experienced staff member was available to help if imaging was difficult. Several limitations are associated with the echocardiographic technique. Global strain depends on a high image quality in all three apical projections. Small changes in probe and heart position may influence the assessments of velocities and deformation with the tissue Doppler method. All measurements were controlled by experienced cardiologists (ME, SA), and suboptimal images were excluded. For all parameters except for global strain, images from fewer than 7 individuals were excluded. Global strain included 57 of 87 patients and 41 of 46 controls.

Considerations of methods measuring JIA disease activity

Patients were examined by three senior physicians experienced in paediatric rheumatology (AMS, BF, and VL) at the 30-year follow-up, and by four paediatric rheumatologists (including BF) at the 15-year follow-up.[35] At the 15-year follow-up, inter-rater variability was tested, and at the 30-year follow-up, a consensus meeting was held before the study started. Nevertheless, the comparisons of the physician´s global assessment between the 15- and 30-year follow-up may have been influenced by observer variability and the long time gap between the examinations. A strength of our study is that joint status was also assessed by ultrasound at standardised locations in all patients who were examined after 30 years, indicating more reliable assessments of the number of active joints than by the use of clinical examinations only.[136;137]

JADAS is a relatively new instrument for JIA patients evaluated for children. A limitation of our study is that we used this instrument in adult JIA patients by which not have been evaluated. We found that JADAS3 correlated strongly with categories of disease activity suggesting a good construct validity of this instrument also in adults. On the other hand we discovered that JADAS3 also captured other aspects of the burden of disease, such as damage and overall well-being in adult JIA patients, as some patients in remission had high symptom states (JADAS3 >4.5).

When calculating JADAS, we replaced missing data for the physician´s global assessment of patients without signs of disease activity (the patients who received the questionnaire and were not clinically examined at the 30-year follow-up) with 0 in accordance with the median score for the patients we had examined who were in remission. This replacement is a limitation of our study. Furthermore, a weakness of our study is that we used the cut-off values for acceptable symptom state defined according to JADAS but used the JADAS3 version to measure disease activity in the patients because ESR was missing in

patients not examined clinically. A JADAS score would have been slightly higher than a JADAS3 score in those patients with elevated ESR.

Statistical limitations

In papers I and II, multiple comparisons were performed between patients and controls (paper II) and to assess the association between disease variables and markers of subclinical CVD within the patient group (papers I and II). When performing multiple comparisons, there is an inherent risk for type I statistical error, which is a limitation of this study.

Discussion of main findings

Subclinical CVD in JIA patients (papers I and II)

We found a slightly increased PWV, DBP, and SBP in JIA patients with at least 15 years of active disease compared to controls, and AIx was numerically but not statistically significantly higher in the JIA patients. In addition to the study of Argyropoulou et al., who found increased PWV as assessed by magnetic resonance imaging in 31 children with JIA,[107] two additional studies have investigated arterial properties in JIA patients since we began our work, but the results are conflicting. Vlahos et al. found no difference in PWV in 30 children and adolescents (age range 7-18 years) with JIA compared to controls,[138] while Satija et al. found reduced arterial compliance in 31 children (mean age 10 years) with JIA as compared to controls.[139] Analyses of the blood pressure level in children with juvenile arthritis have also showed conflicting results.[93;138;140;141]

The patients of our study underwent cardiac CT scanning, which showed that the level of coronary artery calcification was not different from the levels reported in a large study including healthy asymptomatic individuals of comparable age.[142]

With echocardiographic examination, we found that systolic function was comparable between patients and controls. These results are in contrast with Oguz et al. and Bharti et al. who reported an impairment of systolic LV function as reflected by decreased EF in children and adolescents with juvenile arthritis.[93;94] Furthermore, we found a slightly larger interventricular septum thickness in the JIA patients compared to the controls. Concerning diastolic function, a lower mitral deceleration time, a higher E/e´, and a larger LA area were identified in our JIA patients as compared to the controls. Additionally LV e´ tended to be higher in the JIA patients. These results indicate a slightly impaired diastolic function in adult JIA patients. Previous echocardiographic evaluation of cardiac function in 30-50 juvenile arthritis patients with a mean age of 9-15 years suggested diastolic dysfunction, as measured by decreased transmitral E/A ratio, and higher IVRT as compared to controls.[93;94;140;143;144] In our study, these markers of diastolic function were comparable between patients and controls. However, in line with our study, Lianza et al. and Koca et al. found decreased LV e´ in children with JIA compared to controls,[144;145] and a higher E/e´ was reported in JIA patients by Koca et al.

Clinical implications of subclinical CVD

What is the clinical implication of a slightly higher level of subclinical CVD in adult JIA patients? The mean PWV in the patients was 7.2 m/s, below the value (10 m/s) classified as asymptomatic target organ damage by the European Society of Hypertension and European Society of Cardiology hypertension guidelines.[146] However, our patients were 25 years younger than the general population that this threshold represents.[147] The clinical implication of a PWV that is 0.3 m/s higher in JIA patients than controls is unclear. Vlachopoulos et al. found in their meta-analysis that a 1 m/s increase in PWV corresponded to a 15% increased risk in cardiovascular and all-cause mortality after adjusting for age and sex.[79] In a more

recent meta-analysis, Ben-Shlomo et al. found that after full adjustment for cardiovascular risk factors (smoking, diabetes, anti-hypertensive medication, DBP, and cholesterol) a 1 m/s increase in PWV correlated with a 7% increased risk of cardiovascular events for a 60 year old man.[148] However, PWV was reported to more strongly predict future cardiovascular events in younger versus older people in the study by Ben-Shlomo et al. The difference in PWV between patients and controls in our study was no longer statistically significant when adjusted for DBP, demonstrating that the higher DBP in the patient group contributed to the increased PWV.

The JIA patients had 3.7 mmHg higher SBP and 3 mmHg higher DBP than controls, but the mean levels were within normal limits. In a large meta-analysis including almost 1 million people without previous stroke or heart disease, a lowering of 20 mmHg usual (i.e.: long-term average) SBP and 10 mmHg usual DBP down to at least 115/75 mmHg were identified as correlating with approximately a doubling of stroke and IHD death rates at ages 40-69 years.[149] According to their calculations, a decrease in usual SBP of 2 mmHg would be associated with approximately 10% lower stroke mortality and 7% decreased mortality from IHD, indicating that the findings of our study are of clinical significance.

Our finding of a slightly larger interventricular septum thickness in the JIA patients compared to the controls is in accord with the higher BP measured.[150] The finding of a lower transmitral DT, higher E/e´ ratio, and larger LA area in the patients in this study indicates a higher LV filling pressure in the JIA patients compared to the controls.[119;151;152] An increased LV filling pressure correlates with diastolic dysfunction and HF,[153;154] but the parameters of diastolic function were all within normal levels in our study, suggesting a subclinical increased LV filling pressure in our JIA patients. The clinical implication of a 0.5 higher E/e´ is uncertain, but the deviation from control values concerning
several diastolic parameters indicate a marginal but definite impairment of diastolic LV

function in the JIA patients.

Interestingly, the patients had a higher resting heart rate (68 versus 60 beats/minute) than controls as measured by ECG. In a study from 2010 including 28 000 individuals without CVD, a 15 beats/minute increase in resting heart rate corresponded to a hazard ratio for CVD mortality of 1.24 in men and 1.32 in women after adjusting for age, gender, total cholesterol, physical activity, SBP, BMI, and HDL.[155]

One might speculate whether the higher frequency of daily smokers influenced the slightly higher level of subclinical CVD measured in the patients in our study.[156] Smoking was tested as a possible confounder for PWV and AIx in multiple linear regression analysis in paper I, but a statistical association was found with AIx only, together with several other CVD risk factors and JIA disease variables.

Based on the evidence presented, we believe that the higher PWV, BP, LV filling pressure, and resting heart rate found in the JIA patients compared to matched controls corresponds to a slightly higher risk of future CVD.

Traditional cardiovascular risk factors in JIA patients

Concerning traditional cardiovascular risk factors in JIA patients with at least 15 years of disease activity, we found a higher frequency of daily smokers and arterial hypertension and higher levels of HOMA-IR and hs-CRP as compared to controls.

To our knowledge, only one study has previously investigated smoking habits in juvenile arthritis patients, finding a lower frequency of daily smoking among adolescents with juvenile arthritis than that reported in a survey of the general adolescent population of the same area (the Northwest Ohio Youth Tobacco Survey).[157] The contrasting finding of a higher frequency of daily smokers in our study may be explained by the differences in age and variations geographically between the two cohorts. Further studies are needed on this

topic.

HOMA-IR is a method for assessing insulin resistance, and higher levels may be associated with an increased susceptibility of developing diabetes.[111] Despite the higher HOMA-IR in the JIA patients, both fasting HbA1c and glucose, diagnostic markers of diabetes mellitus used in clinical practice, were similar to the values found in the controls. No studies have previously looked at the prevalence of insulin resistance in JIA patients.

Interestingly, the JIA patients had lipid profiles that were comparable to the controls. Studies analysing serum cholesterol levels in children with juvenile arthritis have shown contradictory results.[95-97;141;158] In contrast to our findings, the only previous study looking at cholesterol levels in adult JIA patients reported dyslipidemia in the patient group (mean age 22) compared to controls.[159]

Hs-CRP concentration is found to have a strong continuous correlation with cardiovascular risk,[160] and the American Heart Association and Centers for Disease Control suggested in 2003 that hs-CRP levels of <1 mg/L represented low risk, values from 1-3 mg/L average risk, and values >3 represented high vascular risk.[161] The median hs-CRP value in the patients in our study was double that of controls (1.8 versus 0.9 mg/L) and may suggest a slightly increased cardiovascular risk.

A sedentary lifestyle is a well-known risk factor for CVD, and lower levels of physical activity [98;162] and physical fitness as measured by $V0_{2peak}$ [99;100] have been reported in children with JIA when compared to healthy children. Interestingly our results were not in agreement with previous reports, as our patients performed more physical activity of moderate intensity than controls, and the average number of hours per week spent on physical activity of vigorous intensity was similar between the groups. Since the 1990s, a "change of advice" has been adopted by the physical therapists and clinicians at the OUH, who started to encourage JIA patients to perform as much physical activity as possible. Our results may reflect a new

"trend" of JIA patients not having a sedentary lifestyle. However, because physical activity was assessed by a questionnaire only, our results should be interpreted with caution.

Association of JIA disease variables and subclinical CVD

In papers I and II, comprehensive analyses were performed to investigate the associations between JIA disease variables and subclinical CVD in JIA patients. The JIA disease variables were mainly selected based on ¨JIA core set outcome variables".[163] We found that parameters reflecting (cumulative) inflammatory burden such as higher platelets-, ESR-, and CRP AUC, and a longer duration of active disease were associated with higher levels of arterial stiffness, DBP, and LV filling pressure. Parameters reflecting disease severity such as several joints with LROM and a polyarticular disease course correlated with higher arterial stiffness and LV filling pressure, and prolonged prednisolone use was associated with higher levels of arterial stiffness, BP, coronary artery calcification, and LV filling pressure.

Similar results have been reported by Provan et al. who found that elevated baseline CRP predicted higher AIx and PWV after 15 years of disease duration in RA patients.[164] Higher CRP has also been identified as correlating with deterioration of myocardial function in individuals without CVD.[165] Elevated levels of the parameter of number of joints with LROM reflects disease damage but may also, together with polyarticular disease course, reflect a high inflammatory burden over many years. Prolonged daily prednisolone use was associated with most markers of subclinical CVD in our study, which corresponds with the reported association between corticosteroids and a higher risk of developing hypertension and cardiovascular events in RA patients.[102;103;166] The use of systemic corticosteroids has greatly decreased with the introduction of biologic therapy and Methotrexate [167] and may not be as important a cardiovascular risk factor for patients diagnosed with JIA today. Yet, in addition to cumulative corticosteroid use, this parameter probably also reflects a high inflammatory

burden in our patients. The identified association between a high inflammatory burden and increased subclinical CVD in adult JIA patients suggests a need for an enhanced awareness of cardiovascular symptoms in patients with severe JIA.

Disease activity and remission in JIA patients after 30 years (paper III)

A frequently asked question from newly diagnosed JIA patients and their parents is if JIA is a lifelong disease and what the prognosis is. This question is also central when following JIA patients through the years because disease activity may fluctuate and flares can appear after years of remission.

We found that 59% of JIA patients were in remission (off medication) after 30 years. As discussed earlier, previously reported remission rates have varied greatly between studies (Table 2). Since we started our study, Bertilsson et al. have published an epidemiologic study of 86 JCA patients followed for 17 years, reporting a remission rate lower than ours, at 40%.[128] With an epidemiologic study, one would expect the remission rate to be higher and not lower compared to what we found in our referral-based study. This unexpected outcome may be explained by a low rate of patients who received early treatment with DMARDs in the study by Bertilsson et al., i.e.: 16% of the patients had received DMARDs within the first 2 years, and 15% were on DMARDs at the 5-year follow-up around 1990. In 1997 at the 15-year follow-up of some of the same patients as those included in the present study, 76% had received one or more DMARD.[35] The remission rate in our study was in concordance with that of most long-term studies of juvenile arthritis patients with a disease duration of 21-28 years, reported at around 57-63%.[37;40;41] However, this is the first long-term follow-up study using the newly developed remission criteria for JIA.[42] We also found that 46% of the patients had a considerably high symptom state as measured by JADAS >2.1. Our results indicate that JIA lasts into adulthood for about half of the patients.

This study confirmed what was previously known: disease category is of great importance for future remission rates and the severity of the disease. A total of 80% of patients with persistent oligoarticular JIA were in remission in our study. In contrast, 50% of those with extended oligoarthritis or RF-negative polyarthritis at 15 years were in remission at the 30-year follow-up. When diagnosing a child with oligoarthritis, it is difficult to predict the course of the disease. Studies have shown that 30-50% of patients with initial oligoarthritis develop extended oligoarthritis.[38;168;169] Only one of the patients with polyarticular RF-positive JIA was in remission after median 30 years, confirming that this category is a long-lasting disease similar to that of RA in adults.[31] Surprisingly, 83% of the 12 patients with systemic JIA were in remission. This category consists of few patients in Scandinavia. The disease course is often severe at diagnosis including fever, rash, arthritis, and involvement of inner organs and may in some cases be difficult to treat.[170] However, similar remission rates (75-83%) for systemic juvenile arthritis have recently been reported in other Nordic studies.[128;169] The same pattern according to differences between JIA categories was seen in the levels of JADAS3: patients with systemic JIA or persistent oligoarthritis had lower levels of JADAS3 than those with polyarticular JIA.

An important finding of our study is that 70% of patients were in the same category of disease activity at 15 and 30 years, and 87% of patients in remission off medication after 15 years were still in remission at the 30-year follow-up. This stability of remission is in contrast with the study by Bertilsson et al., who reported a remission rate of 61% after 17 years among those in remission after a 5-year follow-up.[128] Other previous studies have reported that disease activity alternates greatly in the first years after diagnosis.[171-173] Our study suggests a higher probability of reaching a state of stable remission in the long-term perspective.

Predictors of long-term active disease

HLA-DRB1*01, physician's global assessment of disease activity, and a short duration in remission at the 15-year follow-up predicted active disease after 30 years of disease duration in our study. In line with these findings, disease activity measured as a long duration of elevated ESR and a large number of affected joints within the first 6 months were identified as risk factors for persistently active disease in the same cohort at the 15-year follow-up.[35] DR1 has previously been correlated with markers of severe disease course such as joint erosions and polyarticular course type in patients with oligoarticular onset and with RF-positive polyarticular juvenile arthritis.[21;35;174] Few studies have looked at early predictors of long-term active disease, but Bertilsson et al. found that remission at the 5-year follow-up was the most important predictor of remission at 17-year follow-up.[128]

Changes in disease activity and health status from 15- to 30-year follow-up

We found that physician reported data on disease activity and inflammatory markers improved from 15 to 30 years in the patients with persistently active disease, but patient reported health status was stable. This is in contrast with Zak et al. that reported an increase in disability in 63 JCA patients between the 10-year follow-up in 1979/1980 and 26-year follow-up in 1996/1997.[41] Older studies have also showed an increase of disability in patients with juvenile arthritis during the years.[12;175] An improvement in disease activity and health status but not in pain has previously been reported after 3 years of follow-up in Norwegian children with juvenile arthritis.[176] Corresponding to our study, the HAQ values given at the 5-year follow-up (median children HAQ 0.1, range 0.0-1.9) were similar to the values at the 17-year follow-up (median HAQ 0.0, range 0.0-1.5) in the study by Bertilsson et al.[128] Our findings of longitudinally improved markers of disease activity and stability in patient reported health status most probably reflect that the patients are more effectively treated now than 15 years

ago. Overall well-being, disability, damage, and psychosocial effects of the disease may, in addition to disease activity, be integrated into the patient's global assessment and SF-36. Previous reports have described a poorer HRQoL as measured by SF-36 in young adults with juvenile arthritis compared to matched controls from the general population.[33;35;37;54] The lack of improvement in the patient reported measures may be caused by permanent damage to the joints. Preliminary analyses of the radiographs taken of ankles, knees, and wrists gave the impression that joint damage and arthrosis were present in a considerable large part of the patients. This needs to be investigated more thoroughly and will be the focus of future work.

Medication at 30-year follow-up

After 30 years, only 56% of the 73 patients with active disease were on DMARDs, prednisolone, and/or anti-TNF treatment, indicating that a relatively large portion of the patients were not satisfactorily treated. This finding was surprising but is in accordance with the study by Bertilsson et al. reporting that only 44% of 36 juvenile arthritis patients who were not in remission after 17 years used DMARDs, biologics, or prednisolone.[128] Transition from a department of paediatric to adult rheumatology may have influenced the treatment that the JIA patients received. In a Canadian study of 100 JIA patients, a high rate of unsuccessful transfers from paediatric to adult care was found at a 2-year assessment, despite a coordinated transfer process.[177] Patients with less active disease at the time of transfer were identified as most likely to be lost to follow-up. Furthermore, a German study including 654 patients showed that health status deteriorated after discharge from paediatric care in patients with long-standing JIA.[178] This issue is an important one that needs to be further addressed.

7. MAIN CONCLUSIONS

- Arterial stiffness and blood pressure were slightly higher in adult JIA patients with long-term active disease compared to controls. A total of 26% of patients had detectable coronary artery calcification, and 7% of these had coronary calcification scores above 10, a frequency no higher than that reported in asymptomatic individuals of comparable age.
- The adult JIA patients with long-term active disease had comparable systolic function but differed from controls in having a thicker interventricular septum and altered diastolic parameters indicating a higher LV filling pressure. Additionally, a higher heart rate as measured by ECG was found in the patients.
- Some traditional cardiovascular risk factors were more prevalent in the adult JIA patients with long-term active disease than in controls, including a higher frequency of daily smoking and arterial hypertension, and higher levels of HOMA-IR and hs-CRP, but the lipid profile was comparable between patients and controls.
- A high inflammatory burden, severe disease, and prolonged daily prednisolone use were associated with higher levels of arterial stiffness, DBP, coronary artery calcification, and LV filling pressure in adult JIA patients with long-term active disease.
- A total of 41% of JIA patients were not in remission off medication after 30 years of disease duration, and 28% had a high symptom state (JADAS3 >4.5).
- The overall remission rates after 15 years were comparable to the rates after 30 years of disease duration. Physician's assessment of disease activity and inflammatory markers were improved, but patient reported health status was not. DR1, elevated CRP, high physician's global assessment of disease activity, and a short total time in remission at the 15-year follow-up predicted disease activity at the 30-year follow-up.

Concluding remarks and future perspective

Two issues are important to keep in mind when reading the discussion and the conclusion of this thesis. This study is the first to follow JIA patients for 30 years of disease duration. Our results tell us a lot about the disease outcome after 30 years at this point of time, but in 10-20 years, the story may be different because of the big changes in the medical treatment of JIA today compared to the early 1980s. Nevertheless, none of the medications used today cure JIA, they only attenuate the inflammation.

Second, concerning cardiovascular risk, we may have performed this study too early. The patients had a median age of 39 years, and CVD rarely affects individuals at such young ages. In fact, the European (SCORE) and Norwegian (NORRISK) CVD risk scores do not include in the risk calculators parameters for individuals younger than age 40 years.[61;62] With this in mind, it is tempting to suggest that our study group will see these patients again in 10-15 years. Follow-up plans concerning cardiovascular risk in this cohort have not yet been made, but without doubt, it would be very interesting to investigate the later clinical implications of the slightly higher subclinical CVD found in JIA patients with active disease for at least 15 years after disease onset.

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