Musculoskeletal Manifestations and Rheumatic Symptoms in Patients with Cystic Fibrosis (CF) — No Observations of CF-specific Arthropathy

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ABSTRACT. ***Objective.*** To determine the character and frequency of musculoskeletal manifestations and rheumatic symptoms in patients with cystic fibrosis (CF).

Methods. Rheumatic symptoms and signs of 70 patients with CF (age 6 to 61 yrs) were determined by interview and clinical assessment. Age and sex-matched healthy volunteers served as a control group. In CF patients, laboratory measures and bone mineral density (BMD) were investigated. The data were correlated with the CF phenotype [Shwachman Score (ShS), Chrispin-Norman Score (ChNS), and pulmonary function tests (PFT)].

Results. The prevalence of joint pain in the CF patients was 12.9%, with a mean duration of 7 days. Swollen joints were found in 4 patients. None fulfilled the criteria for rheumatoid arthritis or connective tissue disease. Adult CF patients complained more often about noninflammatory back pain and myalgia, and demonstrated reduced spine mobility and impaired everyday life functions compared with the controls. Symptomatic CF patients had elevated erythrocyte sedimentation rate and C-reactive protein levels and performed worse on the ShS, ChNS, and PFT than asymptomatic patients. Antibodies against exotoxin A of *Pseudomonas aeruginosa* and recombinant *Aspergillus fumigatus* allergen f4 were found more frequently in CF patients with arthralgia. BMD was decreased in adult patients with more severe CF.

Conclusion. In CF patients, the prevalence of rheumatic symptoms increases with age and CF severity. Our data suggest an association of infections with *P. aeruginosa* and *A. fumigatus* with the occurrence of rheumatic symptoms. However, no association of CF with definite inflammatory joint or connective tissue diseases was observed, and no CF-specific pattern of musculoskeletal symptoms was seen. (First Release Aug 1 2008; J Rheumatol 2008;35:1882–91)

Key Indexing Terms:
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ARTHROPATHY

Cystic fibrosis (CF) is the most common autosomal recessive inherited metabolic disorder of the western Caucasian population. Its hallmark is the production of highly viscous mucus by the exocrine glands followed by obstructive and inflammatory changes in the respiratory, digestive, and reproductive systems[1,2]. CF occurs in about 1 in 2500 to 3300 live births[2,3]. About 1 in 20 to 25 Caucasian Americans and Europeans is an unaffected carrier.

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Patients with CF are homozygous for CF gene mutations located on the long arm of chromosome 7, which codes for the CF transmembrane conductance regulatory protein (CFTR)[1,2]. More than 1400 gene mutations have been identified[1]. ΔF508 is the most common mutation worldwide[2]. CFTR is expressed in epithelial cells of the sweat gland ducts, respiratory tract, pancreatic and biliary ducts, and vas deferens. It functions as a regulated chloride channel, which itself regulates sodium and other channels[4]. CF epithelial cells are unable to secrete chloride ions. This leads to secretions of increased viscosity that impair the mucociliary clearance.

CF is a multisystem disease involving lungs, pancreas, liver, biliary system, intestine, reproductive system, and sweat glands. There is no clear association between genotype and phenotype in CF[1]. The pulmonary disease represents the main cause for morbidity and mortality[2] and is often combined with gastrointestinal manifestations.

In 1960, German patients with CF survived no longer than a median of 10 years. Advances in therapy have resulted in an increased life expectancy of about 45 to 50 years[5].

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In North America the current median survival age has risen to about 37 years[6]. Therefore, more rare and later complications like musculoskeletal manifestations now occur, imposing new challenges on the care of adult CF patients.

A number of rheumatic symptoms and signs are described in CF (Table 1, modified from Merkel[7]). Diminished bone mineralization[8,9] and joint symptoms[7,10-14] represent the most important complications. Their prevalence and their relation to pulmonary function, gastrointestinal disease, or infection are not clear.

CF arthropathy (CFA) can be seen in 2% to 9% of patients[7,10-13]. However, there is no formal definition of this entity. Merkel described CFA as a unique form of polyarthritis in CF patients consisting of a distinct compilation of symptoms not classifiable as any of the other rheumatic diseases and characterized by recurrent, often painful bouts of mono- or polyarthritis[7]. Bresnihan described transient self-limiting episodes of acute incapacitating joint pain and swelling involving single or multiple large or small joints in patients who were not necessarily undergoing an infective exacerbation[15]. Botton, *et al* reported CFA as recurrent monoarthritis or infrequent polyarthritis, often with pain, lasting one day to several weeks (mean 5 to 7 days)[10]. Flares are either self-limiting or may progress to chronic synovitis[3,7,10]. Onset of CFA is at a mean age of 16 years[11,12,16]. Knee joints are most often affected[10,17]. The term CFA may also comprise soft tissue swelling and periarticular erythema similar to erythema nodosum[11,12,14,18]. In addition to the joint symptoms, low-grade fever[3] or a variety of skin manifestations[7] such as purpura[12,19] and Raynaud's phenomenon[11] can occur.

Pulmonary hypertrophic osteoarthropathy (PHOA) is a non-CF-specific syndrome. It is characterized by abnormal proliferation of skin and periostal tissue of the distal parts of long bones and is associated with digital clubbing, worsening of pulmonary function, and painful periostitis[7,11,17,20].

A coincidence of rheumatoid arthritis (RA) and CF has been observed in a few patients[10,21,22]. Cases of cutaneous and systemic vasculitis including some with joint symptoms or myalgia have occurred[10,23]. The acquisition of bone mass in CF is reduced compared with age and sex-matched controls[8,9].

Back pain seems to correlate with severity of CF[10,24], impairing respiratory, vertebral, and postural function[25] and predisposing to musculoskeletal deformities like kyphosis[3,9,25-27].

Currently, there are few data on the character and frequency of rheumatic manifestations in CF. In addition, their pathogenic mechanisms are poorly understood. The aim of our study was to thoroughly characterize rheumatic symptoms and signs in CF, to identify possible associations between CF and definite rheumatic disorders, and to identify CF characteristics that predispose to rheumatic symptoms.

Table 1. Musculoskeletal manifestations in CF (modified from Merkel[7]).

Structure	Manifestations
Joints	Episodic arthritis/CF arthropathy (CFA)
	Pulmonary hypertrophic osteoarthropathy (PHOA)
	Antibiotics-associated arthralgia (fluoroquinolone, ciprofloxacin)
	Coincidences with other systemic disorders, e.g., RA, JIA, psoriatic arthritis, or sarcoidosis
	Arthropathy related to inflammatory bowel disease
Bones	Osteopenia and osteoporosis
Blood vessels	Vasculitis (cutaneous or systemic)
	Musculoskeletal strains, injuries, postural abnormalities

MATERIALS AND METHODS

Patients and controls. Rheumatic symptoms and signs of 70 pediatric (age 6–18 yrs) and adult CF patients (maximum age 61 yrs) were determined by standardized interview and physical examination. After recruiting the CF patients, control subjects (pupils and students) were chosen to match each patient by age and sex. The visual analog scale (VAS) for pain intensity and the German version of the Health Assessment Questionnaire (HAQ) were recorded. Reduced mobility of the spine was assessed by measuring finger-to-floor distance and the lumbar flexion test (Schober's sign).

For characterization of severity of CF, indicators such as CFTR mutation, body mass index (BMI), Chrispin-Norman Score (ChNS)[28], Shwachman Score (ShS)[29], pulmonary function tests (PFT), oxygen saturation, immunoglobulin G concentration, microbiological findings, therapeutic factors, and complications were recorded.

The ChNS is calculated by scoring not present (0 point), present but not marked (1 point), or marked features on thoracic radiographs (0 to 30 points). The ShS is calculated by scoring patient's general activity, physical examination, nutritional status, and radiographic findings using a scale of 0 to 25 points for each category (0 to 100 points) and grading "severe" ($\leq$ 40 points), "moderate" (41–55), "mild" (56–70), "good" (71–85), and "excellent" (86–100).

The study was approved by the Ethics Committee of Martin-Luther University Halle-Wittenberg. All patients and controls gave written informed consent. Patients were recruited from the CF units of the Departments of Paediatrics and Internal Medicine. To define a particular rheumatic disorder, e.g., RA, the usual validated classification criteria were used. Characteristics of substudy subjects are given in Table 2.

Ultrasound. Symptomatic joints were examined by ultrasonography using a 7.5–10 MHz linear transducer (Toshiba Eccocee).

Laboratory testing. In CF patients, we determined laboratory measures such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibodies (ANA and ANA profile), anti-cyclic citrullinated peptide antibodies (anti-CCP; Immunoscan RA, Euro Diagnostica AB, Malmö, Sweden), and antibodies against Pseudomonas and Aspergillus species (Pharmacia CAP System, Freiburg, Germany).

Cytokine detection. Samples were obtained from a group of 25 randomly selected, asymptomatic (n = 4) and symptomatic CF patients (history of arthralgia, n = 18; back pain, n = 13; nonspecific pain without allocation to an anatomical structure, n = 1). This group was matched one to one for age and sex to patients with inflammatory arthritis including juvenile idiopathic arthritis (JIA; n = 16), RA (n = 7), and reactive arthritis (n = 2). The sera were analyzed by cytometric bead array (Human Inflammation Kit, BD Biosciences Pharmigen, San Diego, CA, USA) in order to quantitatively measure interleukin 8 (IL-8), IL-1ß, IL-6, IL-10, tumor necrosis factor (TNF), and IL-12-p70. Fluorescence-activated cell sorter (FACS) analysis

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Table 2. Characteristics of substudy subjects.

Study	No. of Subjects	Mean Age, yrs (SD)	Male	Female	BMI, kg/m^2	Active Symptoms	Symptoms in History	No Symptoms
Total								
History and clinical examination	CF group: 70	21.6 (9.6)	34	36	19.5	10	43	17
	Controls: 70	22.1 (9.2)	34	36	22.0	4	39	26
Substudy								
Cytokine detection (CBA)	CF group: 25	21.3 (6.4)	15	10	19.9	4	18	3
	Inflammatory arthritis: 25	21.8 (14.1)	15	10	ND	25	ND	0
Densitometry								
DEXA lumbar spine	33 (CF)	26.2 (8.4)	17	6	20.7	7	21	5
DEXA femoral neck	27 (CF)	27.9 (8.4)	12	15	20.6	7	17	3

BMI: body mass index; CF: cystic fibrosis; CBA: cytometric bead array analysis; DEXA: dual-energy X-ray absorptiometry; ND: Not determined.

was performed by FACSCalibur (BD Biosciences). All procedures were performed according to the manufacturer's recommendations.

Densitometry. In adult CF patients, BMD (g/cm^2) was measured by dual-energy X-ray absorptiometry (DEXA; Lunar®) at the lumbar spine L1 to L4 (n = 33) and at the femoral neck (n = 27), and the Z-score and BMD in percentages adjusted to age were evaluated.

Statistical analysis. The presence of rheumatic symptoms was correlated with data describing the phenotype and extent of CF such as the ShS, ChNS, and PFT. Analyses were performed using SPSS 12.0 (SPSS, Chicago, IL, USA). Level of significance was defined as $\alpha = 0.05$. All cross tables were tested using chi-square and Fisher's exact test. For between-group comparisons nonparametric tests including Mann-Whitney U test, Kruskal-Wallis test, and Fisher's exact test (2-sided) were applied. Correlations were determined by Spearman coefficient. Binary logistic regression was performed to investigate the influence of CF characteristics on joint pain or back pain.

RESULTS

Characteristics of the study population. Baseline characteristics of patients and controls are shown in Table 3. Ninety percent of CF patients carried at least one ΔF508 allele; 55.7% were homozygous and 34.3% heterozygous. Body height ($p = 0.005$), weight ($p < 0.001$), and BMI ($p < 0.001$) were lower in the CF group compared with controls. Oxygen saturation of adult CF patients was slightly, but significantly lower than in CF children ($p = 0.049$). Forced vital capacity (FVC) ($p = 0.044$), forced expiratory volume in 1 second (FEV_1) ($p = 0.003$), and maximum expiratory flow at 25% of remaining FVC (MEF_{25}) ($p < 0.001$) were lower in adult CF patients compared to CF children. Correspondingly, the ShS ($p = 0.010$) and ChNS ($p < 0.001$) were worse in CF adults. ShS and ChNS levels of CF children and adults with or without joint pain and back pain, respectively, are shown in Figure 1.

Rheumatic symptoms and clinical findings. In general, adult CF patients complained about rheumatic symptoms more frequently than controls ($p = 0.013$). CF patients with musculoskeletal symptoms performed significantly worse with respect to the ShS ($p = 0.010$), ChNS ($p < 0.001$), FEV_1

Table 3. Demographic characteristics of 70 patients with CF and 70 age and sex-matched healthy controls.

Variables	CF Patients, n = 70	Controls, n = 70
Children (< 18 yrs)	25 (mean age 12.7 yrs, SD 3.3)	25 (mean age 13.0 yrs, SD 3.3)
Prepubertal	12 (mean age 9.7 yrs, SD 2.1)	ND
Pubertal	13 (mean age 15.4 yrs, SD 1.5)	ND
Adults (> 18 yrs)	45	45
Mean age, yrs	21.6	22.1
Female/male	36/34	36/34
Mean height, cm	161.3	168.5
Mean weight, kg	51.8	63.3
BMI, kg/m^2	19.5	22
ShS, mean value (SD)	61.7 (9.9)	ND
ChNS, mean value (SD)	11.8 (6.4)	ND
FVC, % of rated value (SD)	78.4 (24.4)	ND
FEV_1, % of rated value (SD)	70.8 (26.3)	ND
MEF_{25} % of rated value (SD)	39.5 (26.5)	ND

BMI: body mass index; ShS: Shwachman Score; ChNS: Chrispin-Norman Score; FVC: forced vital capacity; FEV_1: forced expiratory volume, 1s; MEF_{25}: maximum expiratory flow at 25% of remaining FVC; ND: not determined.

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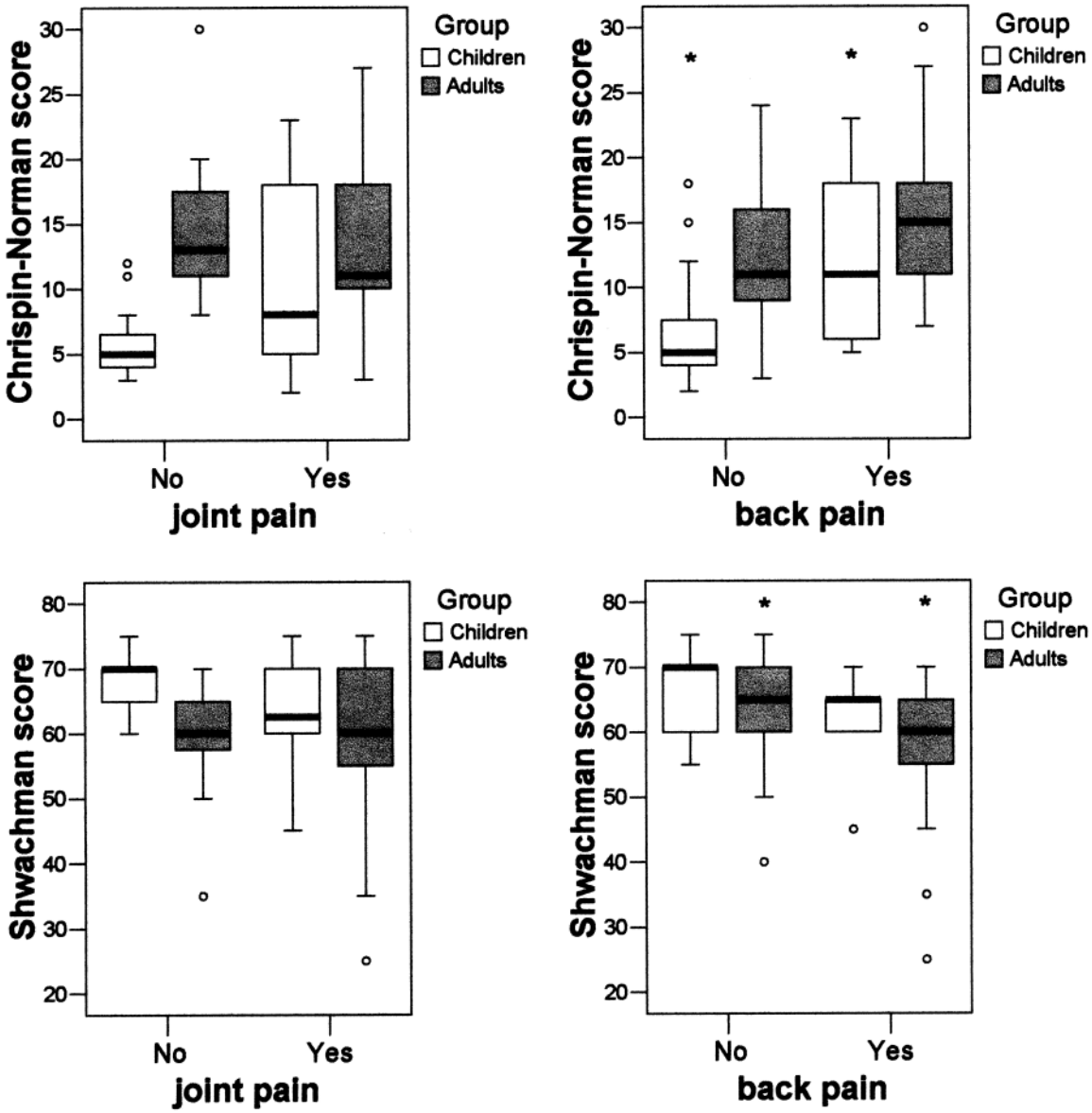

Figure 1. Chrispin-Norman Scores and Shwachman Scores describe the severity of CF in children and adults with or without joint pain and back pain. *Significant difference.

(p = 0.002), and MEF_{25} (p = 0.004) than asymptomatic patients.

Joints (p = 0.024) and the spine (p = 0.006) were more often symptomatic in the CF group than in controls, whereas there was no significant difference with regard to musculature or tendons, respectively. The prevalence of joint pain in the CF population was 12.9% versus 5.7% in controls. Joint pain (p = 0.024) and loss of motion (p < 0.001) were found more frequently in CF patients, whereas there was no significant difference concerning objective inflammatory signs such as joint swelling or warming (Figure 2). The duration of the joint pain episodes was longer in the CF patients, a median of 7 days versus a median of 1 day in the control group (p = 0.001). Swollen joints were found in 4 CF patients, mostly affecting the knee joint. However, the criteria for RA or other distinct inflammatory rheumatic disease were not fulfilled by any CF patient. Digital clubbing (p = 0.047) was present more frequently in adult CF patients than in CF children and could not be found in the control group. CF patients complained more frequently about acute (p < 0.001) as well as recurrent (p = 0.001) joint symptoms than the controls. We found no significant difference between prepubertal and pubertal CF subjects concerning the frequency of joint (p = 0.144) and back pain (p = 0.541).

Yearly chest radiographs were performed in all CF patients routinely for determination of the ChNS. Only a single 32-year-old female patient reported thoracic pain in which radiograph revealed scoliosis, spondylosis, and inter-

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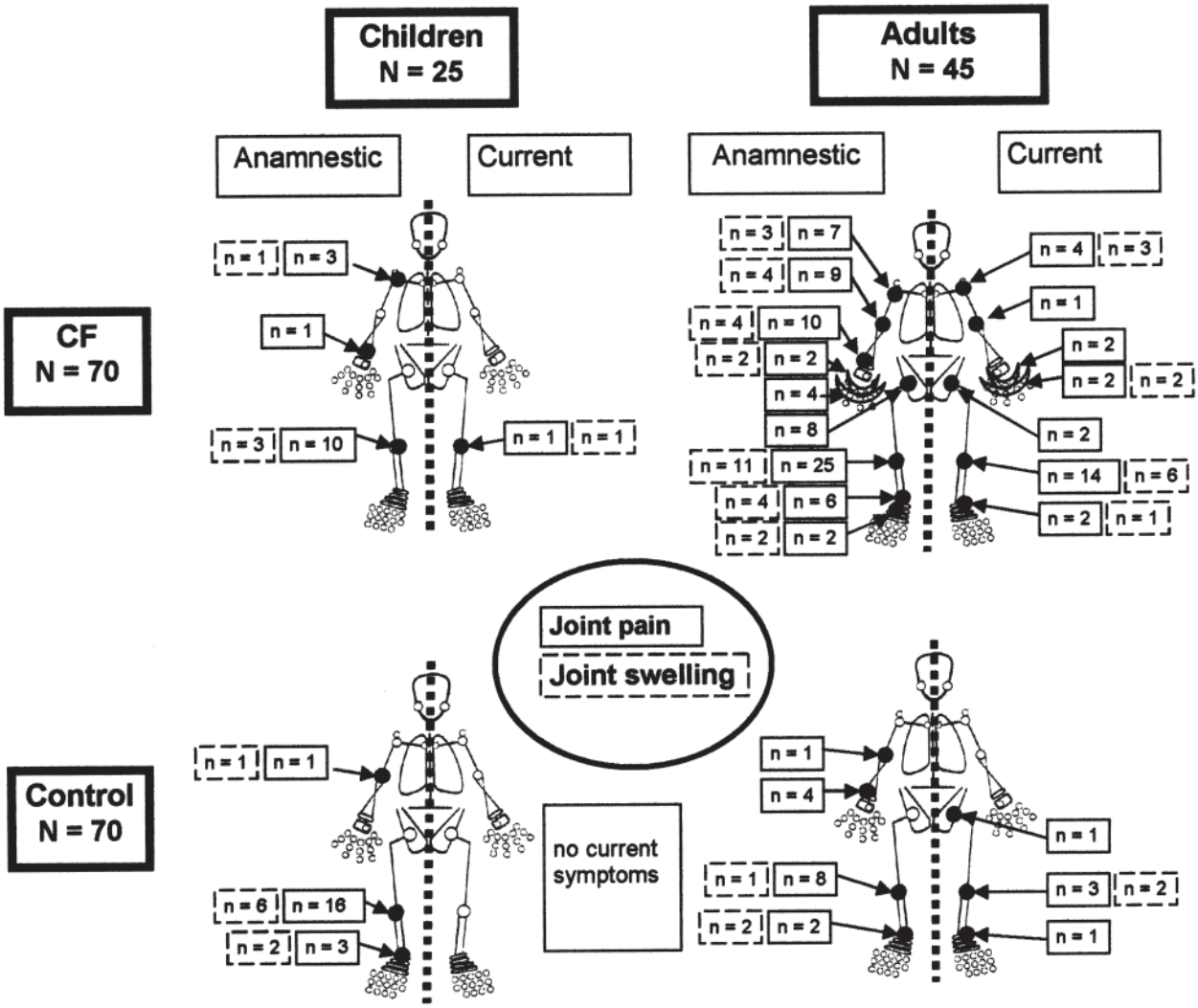

Figure 2. Absolute frequency of joint pain and swelling differentiating between anamnestic and current symptoms in children and adults with CF and healthy controls.

vertebral osteochondrosis of the thoracic spine without fracture signs. Since most patients had no current back pain and no strong clinical evidence for fractures, we did not obtain additional radiographs.

Adult CF patients reported more noninflammatory back pain ($p = 0.054$) and nonspecific pain without allocation to an anatomical structure ($p = 0.009$). CF patients with back pain performed significantly worse on ShS ($p < 0.001$), ChNS ($p < 0.001$), FVC ($p = 0.003$), FEV_1 ($p < 0.001$), and MEF_{25} ($p < 0.001$) than asymptomatic patients. Further, CF patients with nonspecific pain had significantly diminished values of the ShS ($p = 0.007$), FVC ($p = 0.040$), and FEV_1 ($p = 0.022$). CF patients taking systemic corticosteroids more frequently showed nonspecific pain not attributable to an anatomical structure than CF patients without this medication ($p = 0.012$).

Adult CF patients displayed a reduced mobility of the spine. CF patients reported a higher intensity of VAS pain ($p < 0.001$) and more marked impairment of everyday life functions in the HAQ ($p < 0.001$; Figure 3).

Ultrasonography. Ten CF patients with current joint symptoms underwent ultrasonography. In 2 cases, inflammatory signs such as a hypoechoic structure and effusion were identified. All other patients revealed nonspecific findings only.

Laboratory testing. Median values of ESR ($n = 70$, $p = 0.013$, Fisher's exact test (2-sided)) and CRP ($n = 70$, $p = 0.010$) were significantly elevated in CF patients with musculoskeletal symptoms in comparison with CF patients who were asymptomatic. In 2 CF patients a slightly elevated RF was detected ($n = 65$). One female adult CF patient had positive anti-CCP without signs of inflammatory arthritis ($n = 67$). In 67.2% of the CF patients tested ($n = 64$), ANA of varied titers and different patterns were identified. ANA from titer 1:40 upwards were detected more frequently in adult CF patients than in children ($p < 0.001$). Further analysis of ANA profiles revealed nonspecific findings only. An associ-

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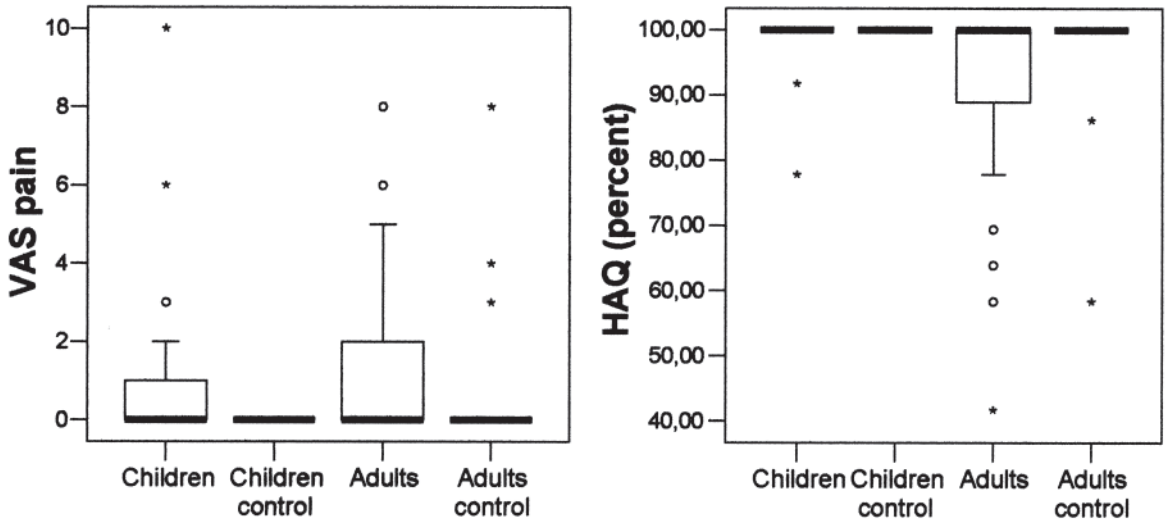

Figure 3. Visual analog scale (VAS) results for pain intensity (0 to 10) and for everyday life functions in the German version of the Health Assessment Questionnaire (HAQ) in children and adults with CF and healthy controls. The everyday functions of the control children were not impaired (100%).

ation between ANA and symptoms typical for connective tissue diseases could not be found.

Adult CF patients were more often colonized with *Pseudomonas aeruginosa* than children (p = 0.003). Positive titers against exotoxin A of *P. aeruginosa* were detected more frequently in CF patients with musculoskeletal symptoms (p = 0.027) and with arthralgia (p = 0.037) than in asymptomatic patients. Moreover, positive antibodies against recombinant *Aspergillus fumigatus* allergen f4 were found more often in CF patients with arthralgias compared with asymptomatic patients (p = 0.037).

Flow cytometric analysis of cytokines by cytometric bead array. There were no significant differences in the serum levels of IL-8, IL-1ß, IL-6, IL-10, TNF, and IL-12-p70 between the CF patients and the group of patients with inflammatory arthritis. No associations of cytokine concentrations and the occurrence of musculoskeletal symptoms were observed.

Bone densitometry using DEXA. BMD was decreased in adult CF patients compared with age-matched controls and, in patients older than 26 years, compared with the peak bone mass (Table 4). We identified a significant correlation between weight and BMD, whereas height correlated only with BMD at the femoral site in CF patients older than 26 years. The Z-score correlated directly with the ShS at both sites of measurement (lumbar spine: Spearman coefficient 0.479, p = 0.004; femoral neck: Spearman coefficient 0.407, p = 0.025), and indirectly with the ChNS at the lumbar spine (Spearman coefficient –0.379, p = 0.025), indicating an association of CF severity and reduction of BMD.

Binary logistic regression. Simple and multiple binary logistic regression procedures were performed to identify variables connected with the occurrence of joint pain and back pain. The results are given in Table 5.

DISCUSSION

Patients with CF can develop various musculoskeletal symptoms[15]. These occur mostly in juvenile and adult patients, but can be present in children, too[17]. As in other publications[10,11,16,17], we found the frequency of joint and vertebral symptoms was higher in CF patients than in controls. The prevalence of musculoskeletal symptoms and signs increased with age and was associated with worsening clinical status and pulmonary function in our study, in accord with Massie, *et al*[20].

Whereas 40% of CF children complained about current and anamnestic joint pain, 60% of the adult CF patients did so. It can only be speculated whether the higher prevalence of joint symptoms in adulthood is merely coincidental, or whether chronic infections, early osteoarthritis, or postural abnormalities of adult patients contribute to these findings. Of interest, Epker, *et al* found no significant relationship between age and report of pain or pain-related impairment in adult patients with CF[30]. Koh, *et al* also found no effect of age concerning pain in children with CF aged 8 to 17 years[31].

However, we found no coincidence of CF and definite rheumatic disorders. Laboratory and imaging findings were mostly nonspecific.

Several different types of musculoskeletal manifestations were described in CF, such as CFA or episodic arthritis, PHOA, and others like coexisting RA or medication-related symptoms. In addition, osteoporosis, with a higher risk for fractures and spinal deformities, is a well established complication of CF.

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Table 4. Results of osteodensitometry by dual-energy x-ray absorptiometry (DEXA) in the adult CF patients.

DEXA Results	N	Mean (SD)	Median	Minimum	Maximum
Lumbar spine (L1-L4)					
BMD (g/cm^2)	33	1.1 (0.1)	1.0	0.8	1.4
Z-score	33	–0.6 (1.0)	–0.8	–2.7	1.5
Age-adapted (%)	33	93.6 (9.9)	92.0	79	116
Femoral neck					
BMD (g/cm^2)	27	0.9 (0.1)	0.9	0.6	1.2
Z-score	27	–0.7 (0.7)	–0.7	–2.5	0.6
Age-adapted (%)	27	92.1 (9.3)	91.0	68	108

BMD: bone mineral density.

Table 5. Significant results of simple and multiple binary logistic regression models to identify explanatory variables of the 2 categorical response variables investigated, joint pain and back pain.

Analysis	Response Variables	Explanatory Variables	Total Percentage of Correctly Predicted	Regression Coefficient	p
Simple	Joint pain	Body height	62.9	0.044	0.017
		Elevated ESR	61.4	1.107	0.033
	Back pain	Age	75.7	0.146	< 0.001
		Body height	62.9	0.038	0.038
		Chrispin-Norman score	70.0	0.169	0.001
		Shwachman score	65.7	–0.105	0.003
		FVC, % of rated value	67.1	–0.032	0.007
		FEV_1, % of rated value	72.9	–0.052	< 0.001
		MEF_{25}, % of rated value	77.1	–0.052	< 0.001
		Elevated ESR	71.4	1.833	0.001
		CRP	67.1	0.041	0.075
Multiple	Joint pain	Body height	62.9	0.044	0.017
	Back pain	Age	77.1	0.100	0.018
		FEV_1, % of rated value		–0.042	0.003

CF arthropathy (CFA) is a constellation of several syndromes[32] and remains a vaguely characterized term[13,17]. The prevalence of joint symptoms and pain in our study was 12.9% in CF patients versus 5.7% in the controls, whereas published data assumed 5% to 10% prevalence[16].

The character and duration of these symptoms were comparable to those of other studies. Joint symptoms were first described by Newman and Ansell in 5 children with recurrent mono- and polyarticular arthralgia mostly of large joints, accompanied by swelling and loss of motion[18]. The medium duration of joint pain of 7 days was significantly longer than in our control group, corresponding to other reports[7]. The pathogenesis and etiology of CFA are unknown. Different theories have been proposed[7]: CFA as reactive arthritis reacting to bacteria such as *P. aeruginosa*, HLA-associated arthritis, CFA associated with a specific CF genotype, and CFA as a special form of enteropathic arthritis.

We have presumed the following causes of swollen joints in the 4 CF patients: noninflammatory effusion (after excessive exercise), nonclassifiable inflammatory joint effusion, and osteoarthritis. However, only 2 of these joints presented with pathologic findings on ultrasound, since ultrasound was performed 2 days later and after antiinflammatory therapy. As the CF patients with swollen joints had only marginal effusions, arthrocentesis was not performed. Slightly elevated anti-CCP antibodies were found in a single patient without inflammatory arthritis. As the RF was negative, these anti-CCP antibodies were considered nonspecific.

We found that CF patients with musculoskeletal symptoms in general demonstrated significantly worse CF outcome measures. However, joint related symptoms were evenly distributed in CF patients, independent of CF severity. The latter finding corresponds with the results of others[12,14]. Whereas some studies had found a coincidence of joint symptoms[10,33] and pulmonary infections, others did not[11,12,20]. Most of our patients did not undergo radiographic analysis of joints. According to other investigators, radiographic results of affected joints were mostly negative[7].

Although digital clubbing in patients with progressing CF is frequent, full-blown PHOA is rather rare, occurring in 2% to 7% of patients[7,12], mostly in older individuals[12]. Correspondingly, we found digital clubbing more often in

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CF adults than in children. None of our patients had PHOA. Cases of arthritis linked to hyperuricemia, bowel resection, sepsis, psoriasis, or pancreatitis have been published. In a few CF patients, seropositive RA[7,11,19,21,22] and arthritis due to sarcoidosis[34], vasculitis[23], or secondary amyloidosis have been found. In contrast, we could not identify any of these entities in our cohort. The connection of CF and inflammatory joint diseases postulated by several investigators relies mostly on single case reports or smaller cohorts. In contrast, we systematically screened a larger patient group for signs and symptoms of these disorders; therefore, we are confident that our observations are valid. Nevertheless, the advances of therapy in recent years might have altered the natural course of CF.

Two of our CF patients complained of arthralgia in association with ciprofloxacin intake. This type of arthropathy, which has no radiological correlate, was found in 36 of 1113 CF patients[35].

Most authors have found a diminished BMD by DEXA in CF patients[36-39]. Haworth, *et al* observed a mean BMD Z-score of –1.21 standard deviations (SD) at the proximal femur of juvenile and adult CF patients[8]. Bhudhikanok, *et al*[40] reported Z-scores of –1.7 SD at the lumbar site and –1.9 SD at the femoral neck. This was comparable to the BMD levels of our patients. In contrast, Hardin, *et al*[41] described normal BMD in 41 CF patients compared to a control group matched for lean tissue mass, height, age, and sex, whereas BMD of their CF cohort was significantly lower than in another control group matched for age and sex only.

Further, we detected a statistically significant association between the Z-score and the ShS at both measuring sites and ChNS at the lumbar site. Thus, we conclude that the clinical and radiological extent of CF influences BMD. Conway, *et al* discovered a correlation of the BMD at lumbar and femoral sites with ShS[39]. A low BMI in CF patients has been associated with decreased BMD[3,26,37,38], a finding that agrees with our data. The possible causes of low BMD are manifold[3,7,9,10] and include deficiencies in nutrition and fat-soluble vitamins, intestinal malabsorption of calcium and vitamin D, glucocorticoid therapy, impaired production of sexual hormones with delayed puberty and skeletal maturation, and ΔF508 genotype[42]. In CF patients under age 19 years, BMD may appear normal, but the bone mineral content may be decreased due to short and narrow bones[43]. From age 20 years onward, a significant loss of bone substance starts[38]. Of interest, this cannot be compensated for by relatively high doses of calcium and vitamin D[8,9,37]. There is no clear evidence of an impaired metabolism of calcium, phosphate, or vitamin D in the literature[7,8]. However, delayed bone age was frequently observed[8]. Osteopenia, fracture, kyphosis, and pain are interrelated in CF patients[3,7].

Back pain is present in up to 94% of CF patients[3], whereas 46% of our CF patients reported back pain. Those patients had significantly worse levels in the ChNS, ShS, and PFT than patients without back pain. Postural abnormalities are frequent in adult patients with CF and increase with age. Thoracic pain similar to costochondritis is common, probably caused by chronic cough[7]. Kyphosis was detected in 5 of 16 CF patients, in whom 4 patients had a diminished BMD[7,38]. Progressing vertebral deformities, fractures, and severe kyphosis[7] accompany the worsening of lung function. Increased work of breathing leads to diminished airway clearance, increasing amounts of sputum, and chronic cough. The latter contributes to an impaired posture, muscular imbalances, and back pain[25,27], and a progressing vertebral flexion to relieve breathing[3]. We found impaired posture in 49% of CF patients and kyphotic changes in 8% of the children and in 17.8% of the adults.

Decreased muscle strength and function have been reported in CF[44]. The use of corticosteroids adversely affects muscle function in CF[45]. Correspondingly, CF patients of our cohort taking systemic corticosteroids complained significantly more frequently about nonspecific pain than patients without this medication.

We found that patients with symptomatic CF had significantly elevated inflammatory indicators, especially ESR. Correspondingly, it is known that patients with JIA had a generally diminished pain threshold compared with healthy controls, correlating with disease activity and VAS[46]. Pain and inflammation are linked through the action of various mechanisms. Interestingly, joint nerves become sensitized during inflammation[47]. Moreover, the antinociceptive capacity of endomorphin-1 decreases during chronic arthritis due to a reduced expression of μ-opioid receptor in the joint[47].

We detected a slightly positive RF in 2 cases. The American College of Rheumatology (ACR) criteria for RA were not fulfilled in the respective patients. RF is negative in most patients with CF[7,11,12,14,18,48,49]. CF patients with arthralgia more often have positive RF of various types[10,48], which might be associated with exacerbation of infection[33,48]. Seropositive RA in CF was described in single cases[7,11,15,19,21,22]. Neither our results nor reports from the literature support the idea of an association between CF and RA[33].

Autoantibodies reacting with cyclical citrullinated peptides (CCP) are specific for RA sera, having a specificity of about 97% and sensitivity of about 60%[50]. To our knowledge, the presence of CCP antibodies has not been investigated in CF to date. We detected positive CCP antibodies in one symptomatic female CF patient, who did not fulfill the ACR criteria for RA. Interestingly, ΔF508 occurs more frequently in RA patients without CF than in the healthy population. There is a higher incidence of bronchiectasis, probably as a result of CFTR mutation[51]. This association has lead to speculation about episodic arthritis in CF being a mild form of RA, progressing to definite RA after years of

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antigen stimulation[10]. ANA are negative or nonspecific in the majority of patients with CF[7,12]. We identified ANA of different titers and patterns in 43 of our 64 CF patients tested. There was no relationship between presence of ANA and symptoms typical for connective tissue disease.

P. aeruginosa is the most important pathogen in CF[2]. Progression of the pulmonary disease determines the clinical prognosis of most patients with CF. *P. aeruginosa* is capable of penetrating into the hypoxic airway regions. The bacteria form biofilm-like macrocolonies[52,53] that evade eradication despite high antibody titers, promoting chronic infection with airway destruction and worsening lung function. As expected, our adult CF patients were significantly more frequently colonized with *P. aeruginosa* than the children. In addition, antibodies against bacterial elastase were found more often in the adults with CF.

Symptomatic CF patients with arthralgia more often had elevated titers against *P. aeruginosa* exotoxin A compared with asymptomatic patients. The pathogenic mechanism that links *P. aeruginosa* infections to symptoms is poorly understood. There were no signs of septic arthritis by *P. aeruginosa* in our patients. Single cases of osteomyelitis and arthritis due to puncture wounds[54] and of septic arthritis in a diabetic patient[55] have been reported. It is more likely, however, that noninfectious phenomena similar to those seen in reactive arthritis are responsible for the arthralgias in our patients. *P. aeruginosa* infections have been reported to cause reactive arthritis after chronic tonsillitis[56] and to trigger vasculitic purpura[57].

A. fumigatus belongs among the ubiquitous fungi detectable in about 50% of CF airway surface fluid[2,58]. Similar to *P. aeruginosa*, *A. fumigatus* frequently persists in the lungs. The interaction between *A. fumigatus* and its host organism ranges from simple colonization to allergic bronchopulmonary aspergillosis, which represents a mixed type-1 and type-3 immune response characterized by production of antibodies of IgE, IgG, and IgA type[59]. Despite our relatively small sample group of 50 patients, we identified a significant relationship between specific IgE antibodies against the specific Aspergillus antigen rAsp f4 and arthralgia in CF patients, as well as significant associations between positive IgA antibodies against *A. fumigatus* and back pain, especially thoracic spine pain, and arthralgia, respectively.

Arthritis and osteomyelitis by *A. fumigatus* are mostly seen in immune compromised[60], transplanted[61], leukemic[60], or neutropenic[62] patients and after trauma or surgery. To our knowledge, there are no reports of *A. fumigatus* arthritis or osteomyelitis in CF. Our clinical findings were not suspicious for a direct colonization of joints, bones, or spinal structures by Aspergillus species in any case. Thus, noninfectious mechanisms analogous to those of Pseudomonas infection might explain our observation.

For further studies, patients with other chronic diseases such as insulin-dependent diabetes mellitus or bronchial asthma should be involved as a positive control.

The prevalence of rheumatic symptoms increases with age and CF severity. Rheumatic symptoms and signs in CF are variable and nonspecific, but they are found more frequently than in healthy control subjects. The main determinants are CF severity (ShS, ChNS) including dystrophy and pulmonary impairment (PFT), low BMD, and infections with *P. aeruginosa* and *A. fumigatus*. We did not observe a coincidence of CF and definite rheumatic disorders, providing no support for the idea of triggering of autoimmune diseases in CF. According to our results CF arthropathy does not represent a specific entity and cannot be defined by certain laboratory or imaging findings.

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