ARTHRITIS & RHEUMATISM
Vol. 62, No. 12, December 2010, pp 3792–3798
DOI 10.1002/art.27712

Musculoskeletal Disease Burden of Hereditary Hemochromatosis

Enijad Sahinbegovic,[1] Tomáš Dallos,[2] Elmar Aigner,[3] Roland Axmann,[1] Bernhard Manger,[1] Matthias Englbrecht,[1] Maximilian Schöniger-Hekele,[4] Thomas Karonitsch,[4] Tanja Stamm,[4] Martin Farkas,[5] Thomas Karger,[6] Ulrich Stölzel,[7] Gernot Keysser,[8] Christian Datz,[3] Georg Schett,[1] and Jochen Zwerina[1]

Objective. **To determine the prevalence, clinical picture, and disease burden of arthritis in patients with hereditary hemochromatosis.**

Methods. **In this cross-sectional observational study of 199 patients with hemochromatosis and iron overload, demographic and disease-specific variables, genotype, and organ involvement were recorded. The prevalence, intensity, and localization of joint pain were assessed, and a complete rheumatologic investigation was performed. Radiographs of the hands, knees, and ankles were scored for joint space narrowing, erosions, osteophytes, and chondrocalcinosis. In addition, the number and type of joint replacement surgeries were recorded.**

Results. **Joint pain was reported by 72.4% of the patients. Their mean ± SD age at the time of the initial joint symptoms was 45.8 ± 13.2 years. If joint pain was present, it preceded the diagnosis of hemochromatosis by a mean ± SD of 9.0 ± 10.7 years. Bony enlargement was observed in 65.8% of the patients, whereas synovitis was less common (13.6%). Joint space narrowing and osteophytes as well as chondrocalcinosis of the wrist and knee joints were frequent radiographic features of hemochromatosis. Joint replacement surgery was common, with 32 patients (16.1%) undergoing total joint replacement surgery due to severe OA. The mean ± SD age of these patients was 58.3 ± 10.4 years at time of joint replacement surgery. Female sex, metacarpophalangeal joint involvement, and the presence of chondrocalcinosis were associated with a higher risk of early joint failure (i.e., the need for joint replacement surgery).**

Conclusion. **Arthritis is a frequent, early, and severe symptom of hemochromatosis. Disease is not confined to involvement of the metacarpophalangeal joints and often leads to severe damage requiring the replacement of joints.**

Hereditary hemochromatosis is an inherited disease characterized by progressive iron overload limited to specific organ systems. Liver fibrosis progressing to cirrhosis and hepatocellular carcinoma as well as cardiomyopathy are potentially fatal conditions (1). Skin hyperpigmentation, hypogonadism, and diabetes mellitus are well-known disease manifestations in these patients (2). Early detection of hereditary hemochromatosis and

Supported by the DFG Focus Programme SPP 1468 "Osteoimmunology–IMMUNOBONE: A program to unravel the mutual interactions between the immune system and bone" and by grants from the German Ministry for Education and Research ANCYLOSS project (to Dr. Schett), the Spondyloarthritis Immunology Research Alliance (to Dr. Schett), European Union projects Masterswitch, Kinacept, and Adipoa (to Dr. Schett), the German Society of Rheumatology (to Dr. Zwerina), and the Interdisciplinary Centre for Clinical Research at the University of Erlangen–Nuremberg (to Drs. Schett and Zwerina). Dr. Dallos is recipient of an Articulum Fellowship.

[1]Enijad Sahinbegovic, MD, Roland Axmann, MD, Bernhard Manger, MD, Matthias Englbrecht, Dipl-Psych Univ, Georg Schett, MD, Jochen Zwerina, MD: University of Erlangen–Nuremberg, Erlangen, Germany; [2]Tomáš Dallos, MD, PhD: University of Erlangen–Nuremberg, Erlangen, Germany and Comenius University in Bratislava, Bratislava, Slovakia; [3]Elmar Aigner, MD, Christian Datz, MD: Hospital Oberndorf, Oberndorf, Austria; [4]Maximilian Schöniger-Hekele, MD, Thomas Karonitsch, MD, Tanja Stamm, PhD: Medical University of Vienna, Vienna, Austria; [5]Martin Farkas, MD: Hospital Wiener Neustadt, Wiener Neustadt, Austria; [6]Thomas Karger, MD: Rheumapraxis Cologne, Cologne, Germany; [7]Ulrich Stölzel, MD: Hospital Chemnitz, Chemnitz, Germany; [8]Gernot Keysser, MD: Martin Luther University Halle-Wittenberg, Halle/Saale, Germany.

Drs. Sahinbegovic, Dallos, and Aigner contributed equally to this work.

Address correspondence and reprint requests to Jochen Zwerina, MD, Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen–Nuremberg, Krankenhausstrasse 12, 91054 Erlangen, Germany. E-mail: jochen.zwerina@uk-erlangen.de.

Submitted for publication January 24, 2010; accepted in revised form August 10, 2010.

treatment with phlebotomy therapy can prevent excess morbidity and mortality (1). Most patients with clinically overt hereditary hemochromatosis show the C282Y homozygous mutation in *HFE* and have elevated serum ferritin levels at the time of diagnosis (3).

C282Y homozygous gene mutations are common in persons of northern European descent, with an estimated prevalence of ~0.5% (4). Despite this fact, the clinical penetrance of the C282Y homozygous mutation seems to be low (5). Additional modifiers such as alcohol intake or chronic viral hepatitis infection determine the phenotype of persons with *HFE* mutations (6,7). Several studies failed to show strong evidence for a specific clinical presentation of persons with C282Y homozygosity on a population-based level (8). Thus, regular screening for hemochromatosis is currently not routinely applied (9).

Arthritis is a common clinical symptom in patients with hereditary hemochromatosis. Schumacher first described a specific arthropathy in patients with hemochromatosis in 1964 (10). Although joint pain is rather common in the general population, a clinically distinct arthropathy can develop in patients with hemochromatosis, which presents as arthritis of the second and third metacarpophalangeal (MCP) joints and has a clinical picture resembling that of osteoarthritis (OA) and rarely resembling that of rheumatoid arthritis (11–13). However, the involvement of other joints and a presentation that often is nonspecific lead to the late diagnosis of hemochromatosis (14,15). Population-based studies even question the specificity of hemochromatosis to cause arthritis, because joint pain is a fairly common finding in the general population (8).

Thus, the clinical course and impact of arthritis in patients with hereditary hemochromatosis are still uncertain, despite the fact that arthritis is often the initial clinical manifestation leading to the diagnosis of hereditary hemochromatosis. We therefore assessed a cohort of patients with hereditary hemochromatosis and iron overload for manifestations of degenerative and inflammatory arthritis.

PATIENTS AND METHODS

Study population. Within a 3-year period (2005–2008), patients with hereditary hemochromatosis were recruited in 7 participating centers to participate in a cross-sectional prospective study on the clinical phenotype of patients with hemochromatosis and iron overload. To meet the inclusion criteria, patients had to have serologic signs of iron overload (serum ferritin level >300 ng/ml for men and postmenopausal women, >200 ng/ml for premenopausal women) with increased transferrin saturation (>55% for men, >45% for women), independent of the presence of clinical symptoms related to iron overload, at the time of the diagnosis of hereditary hemochromatosis. Using patient databases from each center, we identified eligible subjects. Potential study subjects (n = 350) received a letter of invitation to participate. A total of 219 patients volunteered and were screened, and 205 of them fulfilled the inclusion criteria. Data were incomplete for 6 patients, resulting in the inclusion of 199 patients. Patients were recruited from the gastroenterology (n = 107), hematology (n = 25), and rheumatology (n = 67) departments. All subjects gave written informed consent to participate in the study, which was approved by the local ethics committees of the participating institutions.

Clinical history and assessment. All participants completed a detailed questionnaire that included demographic data. Information on *HFE* genotype, initial serum ferritin values, and transferrin saturation as well as the number of phlebotomies performed was retrieved, and blood samples for confirmatory *HFE* genotyping were drawn. The disease manifestations of hereditary hemochromatosis, including liver disease, diabetes mellitus, and heart disease, were assessed. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Smoking status and alcohol consumption were recorded as detailed previously (16). A clinical history for joint pain, duration of symptoms, morning stiffness, and response to treatment was obtained. A structured clinical and rheumatologic examination including a 44-joint count for swollen, tender, and bony swollen joints was performed by a single rheumatologist (ES). Hand, hip, and knee pain, fatigue, hand function, disease activity, and fatigue as assessed by the patient and global health as assessed by the examining rheumatologist were recorded on a visual analog scale. The number and type of joint replacement surgeries were recorded. Joint replacement surgery due to fractures was not included in this analysis.

Radiographic assessment. Standard radiographs of hand, knee, and ankle joints were obtained for the assessment of characteristic radiographic changes in 170 patients (85.4%), and a full set of radiographs (required for the assessment of chondrocalcinosis in all joints) was available for 168 patients (84.4%). A validated dichotomous radiographic scoring system assessing the presence of 4 radiographic features (joint space narrowing, erosions, osteophytes, and chondrocalcinosis) (17) was used for the evaluation of all radiographs. According to this scoring system, 1 point is given for the presence of each of the 4 features; the presence of osteophytes and erosive changes is scored separately at the proximal and distal portions of the assessed joint, thus yielding a total of 6 points if all features are present. All radiographs were assessed by a single reader experienced in radiograph assessment (BM). A cumulative score (MCP2/MCP3 score; maximum 24 points) incorporating the presence of radiographic changes in the second and third MCP joints was used for further analysis. A 4-grade scale was applied to quantify the severity of radiographic changes in the MCP, wrist, and ankle joints.

Statistical analysis. For descriptive statistics of cohort characteristics, the mean values for age, BMI, laboratory parameters, and clinical assessment scores were calculated and expressed as the mean ± SD. Prevalence was estimated as the observed proportions and was expressed as the percent of the

total number of patients. The significance of differences between compared groups was calculated using the chi-square test or Fisher's exact test (for sex, genotype, and presence of chondrocalcinosis and iron overload–related disease), and the *t*-test was used for data with a normal distribution. *P* values less than or equal to 0.05 were considered significant. Analysis of the descriptive statistics was performed using GraphPad Prism 5.02 software.

A logistic regression model was used to predict the presence or absence of total joint replacement among patients with hereditary hemochromatosis. Predictors were tested for inclusion in the model by following a stepwise forward approach with Wald's chi-square test cutoff at $P \leq 0.05$ as an inclusion criterion. Odds ratios (ORs) for all included predictors and the corresponding 95% confidence intervals (95% CIs) were also obtained. Each step of predictor inclusion was evaluated by an omnibus chi-square test for verifying the significant regression components in view of their individual additional benefit. The predictive quality of the regression model was evaluated by assessing the percentage of correctly predicted cases involving the presence or absence of total joint replacement. Nagelkerke's R^2 statistic following the ordinary least squares approach was calculated for an estimation of variance in joint replacements accounted for in the model. Finally, we tested the complete logistic regression model against a constant-only model to assess the common use of included predictors. All reported *P* values are 2-sided. Logistic regression was performed using PASW software version 17.0.2 (SPSS).

RESULTS

General characteristics. This cohort comprised 199 patients with hereditary hemochromatosis (134 men [67.3%] and 65 women [32.7%]). The mean ± SD age of the patients at the time of study inclusion was 55.9 ± 12.2 years (range 25–79 years). Hereditary hemochromatosis had been diagnosed at a mean ± SD age of 49.6 ± 11.9 years. The mean ± SD serum ferritin level at the time of diagnosis was 2,090 ± 2,173 ng/ml. The *HFE* genotype was determined in all patients, and the majority of patients (88.4%) were homozygous for C282Y (Table 1).

Patient-reported musculoskeletal symptoms. We first analyzed the self-reported musculoskeletal symptoms in this cohort (Table 2). Joint pain in any region was present in 106 patients (53.3%) at the time of the diagnosis of hemochromatosis and was present in 144 patients (72.4%) at the time of study inclusion, with a mean ± SD duration of symptoms of 12.2 ± 11.4 years. The onset of joint pain occurred early (at a mean ± SD age of 45.8 ± 13.2 years) and, if joint pain was present at the time of the diagnosis of hemochromatosis, it preceded the diagnosis by a mean ± SD of 9.0 ± 10.7 years. We also assessed the response of the musculoskeletal symptoms to iron-depleting therapy. Among the 132 patients who experienced joint symptoms and, at the same time, underwent iron-depleting phlebotomy therapy, only 18 patients (13.6%) reported improvement of joint pain upon treatment, while 87 patients (65.9%) experienced no significant change, and 27 patients (20.5%) experienced worsening of their symptoms despite iron-depleting therapy.

Table 1. Clinical characteristics of the patients*

Demographic variables	
No. of patients	199
Men/women	134 (67.3)/65 (32.7)
Age at inclusion, mean ± SD (range) years	55.9 ± 12.2 (25–79)
Body mass index, mean ± SD kg/m^2	26.6 ± 3.9
Smoking	105 (52.8)
Alcohol intake	128 (64.3)
Disease-specific variables	
Age at hemochromatosis diagnosis, mean ± SD years	49.6 ± 11.9
Highest ferritin level, mean ± SD (median [range]) ng/ml	2,090 ± 2,173 (1,218 [261–14,080])
Phlebotomy therapy	182 (91.5)
Age at start of phlebotomy therapy, mean ± SD years	49.7 ± 11.6
Duration of phlebotomy therapy, mean ± SD years	5.9 ± 6.8
Total number of phlebotomies, mean ± SD	51.4 ± 62.0
Genotype	
C282Y homozygous	176 (88.4)
Compound heterozygous	13 (6.5)
Other†	10 (5.0)
Organ involvement	
Elevated aminotransferase level	81 (41.5)
Liver fibrosis/cirrhosis	36 (18.1)
Diabetes mellitus	27 (13.6)
Cardiomyopathy	22 (11.1)

* Except where indicated otherwise, values are the number (%) of patients.
† C282Y heterozygous, n = 4 (2.0%); H63D homozygous, n = 2 (1.0%); H63D heterozygous, n = 1 (0.5%); juvenile hemochromatosis, n = 1 (0.5%); t+IVS2+4T/C+IVS2+4T/C, n = 1 (0.5%); R226W/C282Y, n = 1 (0.5%).

Physician's assessment of musculoskeletal symptoms. An experienced rheumatologist performed a standard rheumatologic examination of all patients. No patient had evidence of concomitant inflammatory rheumatic disease such as rheumatoid arthritis, as judged by clinical, radiographic, and serologic studies. Ninety-five patients (47.7%) had at least 1 tender joint (mean ± SD

Table 2. Rheumatic disease signs and symptoms in the patients (n = 199)*

Self-reported symptoms	
Joint pain at time of study inclusion	144 (72.4)
Age at initial joint symptoms, mean ± SD years	45.8 ± 13.2
Duration of joint symptoms, mean ± SD years	12.2 ± 11.4
Joint pain at time of hemochromatosis diagnosis	106 (53.3)
Morning stiffness	58 (37.1)
Morning stiffness duration, mean ± SD minutes	35.2 ± 29.1
Joint involvement, at hemochromatosis diagnosis/at study inclusion	
Spine	8 (5.6)/17 (11.9)
Hip	14 (9.8)/38 (26.6)
Knee	59 (41.3)/85 (59.4)
Ankle	17 (11.9)/47 (32.9)
Foot	6 (4.2)/31 (21.7)
Shoulder	3 (2.1)/21 (14.7)
Elbow	0 (0.0)/7 (4.9)
Wrist	1 (0.7)/17 (11.9)
Fingers	32 (22.4)/74 (51.7)
Data not available	3 (2.1)/3 (2.1)
Hand function score, mean ± SD (0–100 VAS)	35.5 ± 27.9
Hand pain score, mean ± SD (0–100 VAS)	25.7 ± 25.2
Hip pain score, mean ± SD (0–100 VAS)	16.3 ± 23.8
Knee pain score, mean ± SD (0–100 VAS)	23.4 ± 23.4
Disease activity score, mean ± SD (0–100 VAS)	32.2 ± 25.0
Fatigue score, mean ± SD (0–100 VAS)	37.0 ± 28.8
Physician's assessment	
Physician's global assessment score, mean ± SD (0–100 VAS)	19.6 ± 23.4
Tender joint count ≥1	95 (47.7)
Tender joint count, mean ± SD	4.5 ± 4.3
Bony enlargement joint count ≥1	131 (65.8)
Bony enlargement joint count, mean ± SD	11.0 ± 8.6
Swollen joint count ≥1	27 (13.6)
Swollen joint count, mean ± SD	3.2 ± 2.8

* Except where indicated otherwise, values are the number (%). VAS = visual analog scale.

4.5 ± 4.3 joints, range 1–23), while 27 patients (13.6%) had at least 1 swollen joint (mean ± SD 3.2 ± 2.8 joints, range 1–11). Bony enlargement was by far the most common sign and was present in 131 patients (65.8%) (mean ± SD 11.0 ± 8.6 joints, range 1–34) (Table 2).

Tender second and third MCP joints were documented in only 25 patients (14.7%; mean ± SD 2.4 ± 1.3 joints), and swelling of the respective joints was even less frequent (18 patients [10.6%]; mean ± SD swollen joint count 2.5 ± 1.0). In contrast, bony enlargement of 1 second or third MCP joint was present in 102 patients (60.0%; mean ± SD 3.2 ± 1.1 joints).

Radiographic features. To determine radiographic involvement in patients with hemochromatosis, we used a previously defined radiography scoring system (17). Joint space narrowing was common in all joints assessed (18.0% in ankle joints, 47.6% in third MCP joints). Similarly, osteophyte formation was frequent and was observed at the proximal and distal sites of >40% of second and third MCP joints and in 39.4% of ankle joints (proximal bone). In general, proximal osteophytes were slightly more frequent than distal osteophytes, with the difference being most prominent in the ankle joints (39.4% versus 18.0%). Chondrocalcinosis in at least 1 joint was identified in 57 patients (33.5%). Although chondrocalcinosis was observed in all joints assessed, it occurred most frequently in the wrist (14.8%) and knee (19.6%) joints (Table 3).

To determine the pattern of MCP joint involvement irrespective of its severity, the presence of at least 1 radiographic feature in MCP joints was considered in a separate analysis. At least 1 radiographic feature in any MCP joint was present in 115 patients (69.5%). Interestingly, although only the second and third MCP joints were involved in 37 patients (32.2%), and all 4 assessed MCP joints were involved in 77 patients (67.0%), isolated fourth and fifth MCP joint involvement was observed in only 1 patient.

Regarding the severity of involvement, second and third MCP joints were significantly more severely affected than fourth and fifth MCP joints (mean ± SD

Table 3. Prevalence of radiographic features of hemochromatosis-related arthropathy*

Joint	MCP2	MCP3	MCP4	MCP5	Wrist	Knee	Ankle
No. of patients	166	166	166	166	165	161	164
No. of joints	332	332	332	332	330	322	328
Joint space narrowing	43.1	47.6	20.2	16.6	37.0	-	18.0
Erosion/cyst proximally	26.5	27.7	10.5	4.8	9.7	-	10.4
Erosion/cyst distally	7.5	6.9	3.6	0.6	17.0	-	6.7
Osteophyte proximally	43.4	45.8	26.2	16.3	13.9	-	39.4
Osteophyte distally	41.0	41.6	20.5	11.1	10.3	-	18.0
Chondrocalcinosis	3.0	3.9	1.5	1.2	14.8	19.6	6.1

* Except where indicated otherwise, values are the percent of joints. MCP2 = second metacarpophalangeal joint.

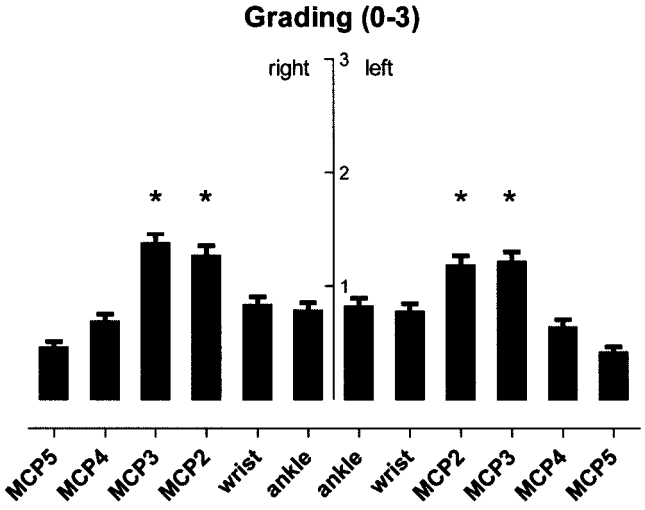

Figure 1. Severity of articular changes as assessed by a 4-grade scale. The left and right second through fifth metacarpophalangeal (MCP2–MCP5), wrist, and ankle joints of the patients were scored for the presence of osteoarthritis lesions. Values are the mean and SD. * = $P < 0.0001$ versus MCP4 and MCP5.

grade 1.25 ± 0.05 versus 0.54 ± 0.04; $P < 0.0001$) (Figure 1). The severity of wrist and ankle involvement did not differ significantly from the severity of MCP joint involvement overall (for MCP joints, mean ± SD grade 0.89 ± 1.14; for wrist joints, mean ± SD grade 0.80 ± 1.05; for ankle joints, mean ± SD grade 0.80 ± 1.05; $P > 0.05$ for all comparisons).

Prevalence of and risk factors for joint replacement surgery. In light of the high prevalence of clinical and radiographic signs of arthropathy in our cohort of patients with hereditary hemochromatosis, we next analyzed the prevalence of joint failure. Thirty-two patients (16.1%) underwent total joint replacement surgery due to severe OA. The mean ± SD age of these patients (18 men and 14 women) at the time of joint replacement surgery was 58.3 ± 10.4 years. Overall, a total of 52 joints were replaced. Fifteen patients (46.6%) had 1 joint replaced, 14 patients (43.8%) had 2 joints replaced, and 3 patients (9.4%) underwent 3 joint replacement surgeries. The most common regions for replacement were the hip joints (n = 44 joints), while knee joints (n = 6) and ankle joints (n = 2) were replaced much less frequently.

For calculating the importance of predictor variables for the presence or absence of total joint replacement, a logistic regression model following a stepwise forward technique was set up. Thirty-nine of the 199 patients had to be excluded from further regression analysis due to missing values for the predictor variables; therefore, 160 patients were included. Predictor variables for the constant-based regression model were the following: age, sex, BMI, alcohol consumption (units/year), smoking (pack-years), manual activity (hours/week), age at the time of diagnosis of hemochromatosis, genotype, MCP2/MCP3 radiograph score, MCP2/MCP3 tender joint count, MCP2/MCP3 swollen joint count, MCP2/MCP3 bony enlargement joint count, diabetes mellitus, structural liver disease (cirrhosis or fibrosis), and highest documented serum ferritin value.

As a result of the stepwise forward procedure and according to the Wald's test criterion, the MCP2/MCP3 radiograph score (χ^2 [1df] = 14.43, $P < 0.001$, OR 1.20, 95% CI 1.09–1.32), female sex (χ^2 [1df] = 5.84, $P = 0.16$, OR 4.44, 95% CI 1.33–14.83), and chondrocalcinosis (χ^2 [1df] = 4.09, $P = 0.43$, OR 2.38, 95% CI 1.02–5.49) remained significant predictors to distinguish between patients with hemochromatosis who did or did not undergo total joint replacement. The MCP2/MCP3 radiograph score emerged as the most predictive variable according to Wald's chi-square statistics. Omnibus chi-square tests at each step of predictor inclusion confirmed the findings of Wald's test by showing significant results for each added regression component, as follows: for the first step (inclusion of the MCP2/MCP3 radiograph score), χ^2 (1df) = 20.35, $P < 0.001$; for the second step (inclusion of sex), χ^2 (1df) = 5.48, $P = 0.19$; and for the third step (inclusion of chondrocalcinosis), χ^2 (1df) = 4.61, $P = 0.32$. The predictive classification of the model was good, with an overall success rate of 86%. The variance in total joint replacement status accounted for was small (Nagelkerke's $R^2 = 0.30$). However, the results of a test of the full model with all 3 predictors compared with a constant-only model were statistically significant (χ^2 [3df] = 30.45, $P < 0.001$), indicating that the MCP2/MCP3 radiograph score, sex, and chondrocalcinosis, as a set, reliably distinguished between patients with and those without total joint replacement.

DISCUSSION

When we applied previously used criteria related to tenderness of the second or third MCP joint (8), only 10.6% of patients with hemochromatosis and iron overload in our cohort fulfilled these criteria. In contrast, bony enlargement of the second and third MCP joints, indicating OA, was highly prevalent. Our clinical and radiography data supported the high frequency of arthritis of the second and third MCP joints in patients with hemochromatosis-associated arthropathy. More impor-

tantly, the severity of radiographic changes was distributed evenly throughout different joint compartments such as the MCP, wrist, and ankle joints. Hence, hemochromatosis-related arthropathy is not restricted to the second and third MCP joints.

Chondrocalcinosis is a common finding in hemochromatosis arthropathy and is present in one third of patients (11,18,19). However, we do not know whether crystal deposition in the joints of patients with hemochromatosis is a secondary phenomenon due to existent OA or vice versa. Interestingly, we frequently identified knee chondrocalcinosis in this cohort, while knee joint replacement was rare. The radiographic presence of chondrocalcinosis was, however, linked to MCP joint involvement and the need for joint replacement early in life (early joint failure) in our patients. Future studies should address these intriguing findings.

The clinical course of arthritis in patients with hemochromatosis remains unclear. Although liver damage (except end-stage liver disease) is reversible in many patients, musculoskeletal symptoms may not respond to iron-depleting therapy (20). This observation is supported by the results of our study, because only 13.6% of patients experienced relief from arthritis-related symptoms after initiation of iron-depleting therapy. The majority of patients either had no response to therapy or experienced progression of their musculoskeletal symptoms. Importantly, hemochromatosis with iron overload was associated with a considerable risk of joint failure, as evidenced by a high rate of joint replacement surgery. Thus, we observed that 16% of study patients underwent replacement of at least 1 joint. The hip joint was by far the joint most frequently replaced, further suggesting the involvement of a specific joint in patients with hemochromatosis (21,22). Importantly, we recently demonstrated a 9-fold increased risk of early joint failure in patients with hemochromatosis compared with the general population (23).

When searching for risk factors for joint replacement surgery, we made an unexpected observation: neither age nor BMI, which are established risk factors for primary OA (16), determined the risk of joint replacement surgery in patients with hemochromatosis. In contrast, sex, radiographic changes in the MCP joints, as well as chondrocalcinosis were strongly associated with joint replacement surgery, suggesting that OA in the context of hemochromatosis is distinct from idiopathic OA, which is strongly associated with older age and a higher BMI (24). Moreover, first joint replacement surgeries occurred early in life (in patients even younger than age 60 years), reemphasizing the high musculoskeletal disease burden of hemochromatosis. In support of this notion, a substantial proportion of patients with hemochromatosis in our study underwent multiple joint replacement surgeries.

Regarding the limitations of our study, we attempted to eliminate possible bias leading to the preferential inclusion of patients with hemochromatosis and arthropathy, by recruiting a significant proportion of patients in non-rheumatology centers (64.8% of all patients). The prevalence of clinical manifestations other than arthritis in the patients with hemochromatosis in our cohort is comparable with that in already-reported cohorts (25,26). Also, asymptomatic patients identified by an accidental finding of pathologic iron metabolism parameters and by the screening of relatives of affected patients were not excluded from our study. More importantly, the prevalence of joint replacement surgery as a significant end point was not different between patients originating from rheumatology and non-rheumatology centers (15.7% versus 16.3%; *P* not significant).

In conclusion, we observed that musculoskeletal disease in patients with hemochromatosis is not confined to MCP joint involvement but also reflects OA in multiple joints. Moreover, the musculoskeletal disease burden in hemochromatosis is high and associated with a substantial risk of undergoing joint replacement surgery. MCP joint involvement, chondrocalcinosis, and female sex, but not age and BMI, are predictors for joint failure in patients with hemochromatosis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Zwerina had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sahinbegovic, Dallos, Aigner, Axmann, Manger, Englbrecht, Schöniger-Hekele, Karonitsch, Stamm, Farkas, Karger, Stölzel, Keysser, Datz, Schett, Zwerina.

Acquisition of data. Sahinbegovic, Dallos, Aigner, Axmann, Manger, Schöniger-Hekele, Karonitsch, Stamm, Farkas, Karger, Stölzel, Keysser, Datz.

Analysis and interpretation of data. Sahinbegovic, Dallos, Englbrecht, Karger, Stölzel, Datz, Schett, Zwerina.

REFERENCES

1. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985;313:1256–62.
2. McNeil LW, McKee LC Jr, Lorber D, Rabin D. The endocrine manifestations of hemochromatosis. Am J Med Sci 1983;285:7–13.
3. Datz C, Lalloz MR, Vogel W, Graziadei I, Hackl F, Vautier G, et

al. Predominance of the HLA-H Cys282Tyr mutation in Austrian patients with genetic haemochromatosis. J Hepatol 1997;27:773–9.
4. Meier P, Schuff-Werner P, Steiner M. Hemochromatosis gene HFE Cys282Tyr mutation analysis in a cohort of Northeast German hospitalized patients supports assumption of a North to South allele frequency gradient throughout Germany. Clin Lab 2005;51:539–43.
5. Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. Best Pract Res Clin Haematol 2005; 18:203–20.
6. Scotet V, Merour MC, Mercier AY, Chanu B, Le Faou T, Raguenes O, et al. Hereditary hemochromatosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. Am J Epidemiol 2003;158: 129–34.
7. Diwakaran HH, Befeler AS, Britton RS, Brunt EM, Bacon BR. Accelerated hepatic fibrosis in patients with combined hereditary hemochromatosis and chronic hepatitis C infection. J Hepatol 2002;36:687–91.
8. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221–30.
9. Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2005;143:517–21.
10. Schumacher HR Jr. Hemochromatosis and arthritis. Arthritis Rheum 1964;7:41–50.
11. Adamson TC III, Resnik CS, Guerra J Jr, Vint VC, Weisman MH, Resnick D. Hand and wrist arthropathies of hemochromatosis and calcium pyrophosphate deposition disease: distinct radiographic features. Radiology 1983;147:377–81.
12. Hamilton EB, Bomford AB, Laws JW, Williams R. The natural history of arthritis in idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. Q J Med 1981;50:321–9.
13. Jager HJ, Mehring U, Gotz GF, Neise M, Erlemann R, Kapp HJ, et al. Radiological features of the visceral and skeletal involvement of hemochromatosis. Eur Radiol 1997;7:1199–206.
14. Rollot F, Wechsler B, du Boutin LT, De Gennes C, Amoura Z, Hachulla E, et al. Hemochromatosis and femoral head aseptic osteonecrosis: a nonfortuitous association? J Rheumatol 2005;32: 376–8.
15. Walker RJ, Dymock IW, Ansell ID, Hamilton EB, Williams R. Synovial biopsy in haemochromatosis arthropathy: histological findings and iron deposition in relation to total body iron overload. Ann Rheum Dis 1972;31:98–102.
16. Schett G, Kiechl S, Bonora E, Zwerina J, Mayr A, Axmann R, et al. Vascular cell adhesion molecule 1 as a predictor of severe osteoarthritis of the hip and knee joints. Arthritis Rheum 2009; 60:2381–9.
17. Dallos T, Sahinbegovic E, Aigner E, Axmann R, Schoeniger-Hekele M, Karonitsch T, et al. Validation of a radiographic scoring system for haemochromatosis arthropathy. Ann Rheum Dis 2010. E-pub ahead of print.
18. Atkins CJ, McIvor J, Smith PM, Hamilton E, Williams R. Chondrocalcinosis and arthropathy: studies in haemochromatosis and in idiopathic chondrocalcinosis. Q J Med 1970;39:71–82.
19. Zwerina J, Dallos T. Osteoarthritis in hereditary metabolic diseases. Z Rheumatol 2010;69:227–35. In German.
20. McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. Am J Med 1999;106:619–24.
21. Axford JS, Bomford A, Revell P, Watt I, Williams R, Hamilton EB. Hip arthropathy in genetic hemochromatosis: radiographic and histologic features. Arthritis Rheum 1991;34:357–61.
22. Montgomery KD, Williams JR, Sculco TP, DiCarlo E. Clinical and pathologic findings in hemochromatosis hip arthropathy. Clin Orthop Relat Res 1998:179–87.
23. Sahinbegovic E, Dallos T, Aigner E, Axmann R, Englbrecht M, Schoeniger-Hekele M, et al. Hereditary hemochromatosis as a risk factor for joint replacement surgery. Am J Med 2010;123:659–62.
24. Engstrom G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis: a population-based cohort study. Osteoarthritis Cartilage 2009;17:168–73.
25. Milman N, Pedersen P, a Steig T, Byg KE, Graudal N, Fenger K. Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. Ann Hematol 2001;80:737–44.
26. Valenti L, Fracanzani AL, Rossi V, Rampini C, Pulixi E, Varenna M, et al. The hand arthropathy of hereditary hemochromatosis is strongly associated with iron overload. J Rheumatol 2008;35: 153–8.