Sarcouncil Journal of Medical Sciences

ISSN(Online): 2945-3526

Volume- 05| Issue- 03| 2026

Research Article

Received: 20-02-2026 | Accepted: 15-03-2026 | Published: 30-03-2026

Iron Overload Arthropathy in Hemochromatosis: Hematologic and Rheumatic Rehabilitation Approaches

Dr. Ahmed Mezaal Hussein Alhussein[1], Dr. Amjad Sabeeh Sayel[2] and Dr. Ehab Sabri Maseer[3]

[1]M.B.CH.B., F.I.B.M.S. \ (Rheum & Med Rehab), Iraqi Ministry of Health, Thi-Qar Health Directorate, Al-Nasiriyah Teaching Hospital, Thi-Qar, Iraq.

[2]M.B.CH.B., F.I.B.M.S. \ (Adult Clinical Hematology), Iraqi Ministry of Health, Thi-Qar Health Directorate, Al-Nasiriyah Teaching Hospital, Thi-Qar, Iraq.

[3]M.B.CH.B., F.I.B.M.S. \ (Rheum & Med Rehab), Iraqi Ministry of Health, Thi-Qar Health Directorate, Al-Nasiriyah Teaching Hospital, Thi-Qar, Iraq.

Abstract: Background: Hereditary hemochromatosis (HH) is a systemic disease caused by iron overload, most frequently as iron overload arthropathy (IOA), a debilitating disease, which is marked by joint pains, stiffness, and structural damage. Although therapeutic phlebotomy is effective in the management of systemic toxicity, stable arthropathy frequently occurs without hematologic control that leaves a major gap in the management of patients. Purpose: The objective of this research was to describe haematological and rheumatic manifestations of iron overload arthropathy in a group of 112 patients with hereditary hemochromatosis of genetically confirmed pathology, determine independent predictors of acute joint disease and liver cirrhosis, and determine the functional outcomes of a multidisciplinary rehabilitation regimen. The patients were sampled among various hospitals of Iraq, and a retrospective-prospective observational study was carried out on 112 adult patients with HFE-related hemochromatosis and arthropathy as presented in the clinic. The variables comprised demographic (data), Iron overload indicators (serum ferritin, transferrin saturation ratio, cumulative blood volume), and detailed rheumatic evaluation (data), such as joint distribution, visual analogue pain scale (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI), and radiographic classification. Descriptive statistics, Pearson correlation matrices, and multivariate logistic regression were employed in order to establish predictive indices of acute hip osteoarthritis and advanced liver cirrhosis. A part of the patients included in the study was subjected to a 12-week standardised multidisciplinary rehabilitation intervention (physical therapy, occupational therapy, and pain management) as allowed, and the functional measures were compared before and after intervention with the use of paired t-tests. A part of the patients included in the study was subjected to a 12-week standardised multidisciplinary rehabilitation intervention (physical therapy, occupational therapy, and pain management) as allowed, and the functional measures were compared before and after intervention with the use of paired t-tests. Findings: The patient group (75% male; mean age at diagnosis 52.4 ± 11.2 years) exhibited a usual distribution of joint involvement, with 69.6% of patients having the second and third metacarpophalangeal joints being affected and 25% having hip arthropathy. The median serum ferritin concentration was 1850±1240 µg/L. There were significant positive correlations between serum ferritin levels and the severity of the injury visible on radiographs ($r=0.56$, $p<0.001$), and between the indexes of iron accumulation and impairment of functions (HAQ-DI: $r=0.41$, $p<0.001$). The logistic regression analysis indicated that serum ferritin level above 1000 -1 (odds ratio 3.45, 95% confidence interval 1.52 7.82) and the homozygous C282Y genotype (odds ratio 3.00, 95% confidence interval 1.15 7.85) are independent variables that predict severe hip osteoarthritis. It is remarkable that the presence of osteoarthritis was a good predictor of severe liver cirrhosis (odds ratio 4.26, 95% confidence interval 1.859.80). The patients reported statistically significant changes in pain scores (the visual analogue pain scale decreased by 6.2 to 3.8, $p < 0.001$), functional disability (the Health Disability Assessment Index decreased by 1.4 to 0.9, $p < 0.001$) and mobility (the six-minute walking distance increased by 70 metres, $p < 0.001$) but there was no change in radiographic damage after receiving rehabilitation intervention. The mobility of the patients (six-minute walking distance improved by 70 metres, $p < 0.001$) did improve, but they did not see any improvement in radiographic damage. Conclusion: Iron overload of hemochromatosis is a prevalent and disabling disease that is closely linked with iron overload, and it is regarded as a primary sign of progressive liver cirrhosis. Although normalisation of blood counts through phlebotomy is imperative in the prevention of visceral complications, it is not adequate in the reversal of stable arthropathy. The outcomes of these studies highlight the necessity to incorporate specific rheumatic rehabilitation into the regular clinical procedures. An interdisciplinary strategy to treat iron deficiency and functional reclamation can greatly enhance quality of life and physical capacity and demand a paradigm shift to a model of comprehensive management of hemochromatosis, putting musculoskeletal health in the forefront and metabolic regulation in the background.

Keywords: Iron, Hemochromatosis, Hematologic, Rheumatic, Rehabilitation, Patients, HAQ-DI, radiographic.

INTRODUCTION

Hereditary hemochromatosis (HH) is the most prevalent autosomal recessive inherited disorder in Northern European populations whose major pathogenesis is the impaired intestinal iron absorption resulting in the systemic iron loading where Iron overload arthropathy (IOA) is a unique rheumatic disease that occurs as a result of the excess infiltration of iron in the synovium and articular cartilage which initiate a cascade of oxidative stress, chondrocyte toxicity, [Adams, P. C., & Agnew, S. 1996; Alvi, A. T. *et al*., 2023; Bacon, B. R. 2012] and secondary crystal deposition. Although therapeutic phlebotomy is effective in reversing the damage of the visceral

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

*Corresponding Author: Dr. Ahmed Mezaal Hussein Alhussein

DOI- https://doi.org/10.5281/zenodo.19328614

organs and restoring normal levels of survival, IOA tends to progress without hematologic control, leading to chronic pain and severe functional disability, as well as a marked decrease in the quality of life of the affected patients. The surplus of non-transferrin-binding iron is in the cells of the synovial lining and chondrocytes and triggers the production of reactive oxygen species through the Fenton reaction [Bardou-Jacquet, E. *et al*., 2020] where At the same time, iron overload alters the metabolism of pyrophosphate, which preconditions the formation of calcium pyrophosphate dihydrate (CPPD) crystals, which is called chondrocalcinosis (or pseudogout)Nevertheless, the disease similarly displays a tendency to large weight-bearing joints, especially the knees and hips, in which it may appear to resemble either rapid-onset osteoarthritis or avascular necrosis. In extreme situations, total joint arthroplasty is required in the hip, which is a critical cross-border between hematologic management and orthopedic intervention [Bassett, M. L. *et al*., 2011; Brissot, P. *et al*., 2018; Camaschella, C. *et al*., 2020].

The epidemiological evidence indicates that arthropathy occurs in about 50 to 70 percent of symptomatic patients of HH, and it commonly manifests itself in the fourth or fifth decade of life. A groundbreaking cohort study of 112 patients who were confirmed as having HH showed the severity of this complication, indicating that hip arthropathy was evident in a quarter of the group and that the duration of untreated iron overload was strongly linked to it. Most importantly, more recent studies show that the presence of arthropathy is not only a localized problem of joints but also an effective predictor of more intense hepatic fibrosis, implying that musculoskeletal symptoms could be an indicative of a cumulative body burden of increased iron extravagance and more severe systemic disease [Feder, J. N. *et al*., 2003; Fleming, R. E., & Ponka, P. 2012; Fletcher, L. M. *et al*., 2002; Ganz, T., & Nemeth, E. 2012]. The treatment of IOA is a complicated clinical issue despite the obvious biological processes and extremely high occurrence rates. The gold standard of reducing total body iron, therapeutic phlebotomy, is effective in preventing iron buildup and preventing the formation of progressive visceral complications formation. But it has always been shown that once joint damage has set in, it is severely irreversible after iron is lost. Progressive joint destruction and debilitating pain is often felt by patients long after the serum ferritin levels are normal and transferrin saturation has been addressed. Such an association between hematologic remission and rheumatic progression poses a therapeutic gap which cannot be filled only with phlebotomy. As a result, a necessity to include specialized rheumatic rehabilitation measures into the normal care routine of HH patients is one of the urgent issues [Girelli, D. *et al*., 2022; Golfeyz, S. *et al*., 2018; Harrison-Findik, D. D. 2007].

The biomechanical and inflammatory peculiarities of the disease should be addressed by rehabilitation strategies of the IOA. There is a need to have physical therapy interventions aimed at reducing the functional limitations on the MCP stiffness and hip/knee degeneration to address the problem of MCP stiffness. Occupational therapy is important to modify activities of daily living (ADL) to maintain autonomy, especially for the severely involved patient of the hand, thereby increasing their grip strength and dexterity [Harrison-Findik, D. D. *et al*., 2006; Jacobi, N., & Herich, L. 2016] Moreover, the pain management methods, such as pharmacologic treatment of the CPPD flares, and non-pharmacologic approaches, such as hydrotherapy, are crucial elements of the overall care plan. However, there is scant literature on organized rehabilitation regimes that are specifically designed to suit the hemochromatosis population. The available research is mostly concerned with the genetic and hematologic basis of the disease, and there is a lack of information on the effectiveness of a combined hematologic and rehabilitative approach [Kew, M. C. 2014].

This research aims to fill this gap in knowledge by integrating the data on the relationship between hematologic markers and rheumatic outcomes of 112 patients with hereditary hemochromatosis. The study will evaluate the demographic distributions, parameters of iron loads, specific frequencies, and statistical associations between ferritin levels and disability scores to define the unique rehabilitation needs of such a population. By the use of logistic regression models, we will determine independent predictors of severe arthropathy and determine the possibility of early intervention to modify the course of the disease.

MATERIAL AND METHOD

We used a retrospective-prospective observational cohort design in order to define the clinical, hematologic, and functional characteristics of iron overload arthropathy (IOA) of hereditary

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

hemochromatosis (HH) patients with a molecular diagnosis. Data collection was done at a tertiary referral center that deals with metabolic liver disease and rheumatology in the period between January 2022 and December 2025. The Institutional Review Board approved the study protocol, and it was conducted in compliance with the Declaration of Helsinki; prior to enrolling in the study, each participant signed a written informed consent.

One hundred and twenty successive adults of 18 years of age or older carried by a definitive arthropathy were used. The measurement of arthropathy was made as the chronic joint pain, lasting over three months, and that was supported by radiographic evidence of joint space loss, the development of osteophytes, or chondrocalcinosis in plain film or ultrasonography. The information was abstracted using electronic health records, structured patient interviews, as well as standardized clinical assessments and divided into four major domains. The demographic and clinical factors included age, sex, ethnicity, body mass index (BMI), smoking habits, alcohol use, presence of comorbid conditions including diabetes mellitus and cardiovascular disease and family history of HH and Rheumatologic assessment recorded joint involvement based on the anatomical location (MCP joints, wrists, hips, knees, shoulders, ankles), and pain severity on a 10-point Visual Analog Scale (VAS), functional disability on a Health Assessment Questionnaire (HAQ-DI), radiographic severity on a modified Kellgren-Lawrence scale (0-4) of the affected joint, and the presence of chondrocalcinosis defined by using radiography or dual energy CT. Rehabilitation and functional outcomes measured included referrals into physical therapy, occupational therapy, pain management programs, and use of assistive devices, and objective measures of grip strength (kg, as measured using a Jamar dynamometer), hip range of motion (degrees of goniometric measurement), and performance on the 6MWT.

The secondary outcomes were identification of factors that predict severe hip arthropathy requiring surgical intervention, the relationship between hematologic parameters and the functional disability (HAQ-DI), and the assessment of the effectiveness of the integrated rehabilitation (physical and occupational therapy) in terms of functional outcome following the intervention.

The SPSS Statistics v28.0 were performed to conduct a statistical analysis (IBM). Continuous variables were summarized using mean and standard deviation as descriptive statistics, and as the frequency (percentage) as a descriptive statistic in categorical variables (see Table 1-3). Normal tests were done through the Shapiro-Wilk test. The bivariate associations were investigated through the Pearson correlation coefficient (r) in a correlation matrix (Table 4) with a significance set at $p < 0.05$. Multivariate logistic regression models were built to determine the independent predictors of dichotomous outcomes (severe hip arthropathy (Kellgren Lawrence grade 3 or higher or previous hip arthroplasty) and advanced hepatic fibrosis (F3-F4 on biopsy or transient elastography) and included the candidates (p=0.10 or less) on the univariate analysis, and the results were presented as Odds Ratios (OR) with Confidence Interval (CI) (Tables 5-6 The Hosmer Lemeshow goodness- of-fit was used to determine the model fit. In the rehabilitation sub -analysis, the pre- and post-intervention functional scores were compared with paired t-tests or Wilcoxon signed-rank tests, with the two-tailed p-value being set to statistically significant (2-tailed, 0.05).

Referred patients were taken to the rheumatic rehabilitation, where a 12-week period of multidisciplinary assessment was done. Physical therapy was based on low-impact aerobic conditioning, joint-specific strengthening, and flexibility training, occupational therapy on joint protection measures, training on adaptive equipment, and energy saving, and pain management incorporated pharmacologic optimization, such as colchicine of calcium-pyrophosphate dihydrate (CPPD) for flare-ups, prudent use of NSAIDs, and non-pharmacologic treatment, including thermotherapy and transcutaneous electrical nerve stimulation. Re-evaluation of outcomes was carried out at the end of the intervention program.

RESULTS

Table 1: Describe primary results according to Demographic and Clinical Characteristics (N=112)

Variable	Category / Unit	Frequency (n)	Percentage (%)	Mean	SD
Gender	Male	84	75.0%	-	-
	Female	28	25.0%	-	-

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

Age at Diagnosis	Years	-	-	52.4	11.2
Age at Arthropathy Onset	Years	-	-	46.8	9.5
Duration of Symptoms	Years	-	-	8.6	6.4
Joint Pain Severity	VAS (0-10)	-	-	6.2	2.1
Functional Limitation	HAQ Score (0-3)	-	-	1.4	0.8

Table 2: Representing mean and SD of Hematologic and Iron Overload Parameters

Parameter	Unit	Total Cohort (N=112) Mean	SD	Range
Serum Ferritin	µg/L	1,850	1,240	300 – 6,500
Transferrin Saturation	%	78.5	14.2	45 – 100
Hemoglobin	g/dL	14.8	1.6	11.0 – 17.5
Mean Corpuscular Volume (MCV)	fL	94.2	8.5	82 – 110
Liver Iron Concentration	µmol/g dry weight	385	195	150 – 900
Phlebotomy Volume (Lifetime)	Liters	45.6	22.1	10 – 120

Table 3: Assessment findings according to Distribution of Arthropathy by Joint Site

Joint Site	Affected Patients (n)	Frequency (%)	Bilateral Involvement (%)
Second/Third MCP Joints	78	69.6%	85.0%
Wrists	54	48.2%	60.0%
Hips	28	25.0%	70.0%
Knees	35	31.2%	55.0%
Shoulders	22	19.6%	45.0%
Ankles	18	16.1%	50.0%
Chondrocalcinosis (Any)	32	28.6%	-

Table 4: Describe results according to Correlation Matrix: Iron Load vs. Clinical Outcomes

Variable	Serum Ferritin	Transferrin Saturation	Phlebotomy Volume	Age	HAQ Score
Serum Ferritin	1.00				
Transferrin Saturation	0.68*	1.00			
Phlebotomy Volume	0.72*	0.55*	1.00		
Age	0.34*	0.21	0.45*	1.00	
HAQ Score (Disability)	0.41*	0.38*	0.49*	0.52*	1.00
Radiographic Score	0.56*	0.44*	0.61*	0.48*	0.75*

**p < 0.05. Strong correlations between iron load (ferritin/phlebotomy volume) and joint damage are well-documented.*

Table 5: Assessment outcomes according to Logistic Regression: Predictors of Severe Hip Arthropathy

Predictor Variable	Beta Coefficient	Odds Ratio (OR)	95% CI	P-value
Serum Ferritin (>1000 µg/L)	1.24	3.45	1.52 – 7.82	0.003
Male Gender	0.88	2.41	1.05 – 5.54	0.038
Age (>50 years)	0.65	1.92	0.88 – 4.18	0.099
C282Y Homozygosity	1.10	3.00	1.15 – 7.85	0.025
Duration of Untreated IO	0.04	1.04	1.01 – 1.07	0.012
Presence of Chondrocalcinosis	0.92	2.51	1.10 – 5.73	0.029

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

Table 6: Logistic Regression to assessment risk factor with Predictors of Advanced Hepatic Fibrosis

Predictor Variable	Beta Coefficient	Odds Ratio (OR)	95% CI	P-value
Presence of Arthritis	1.45	4.26	1.85 – 9.80	<0.001
Serum Ferritin (>1000)	1.12	3.06	1.35 – 6.95	0.007
AST/ALT Ratio	0.78	2.18	1.02 – 4.65	0.044
Platelet Count (<150k)	0.95	2.58	1.15 – 5.80	0.021
Alcohol Consumption	0.55	1.73	0.75 – 4.00	0.198

Table 7: Frequency of required Rehabilitation Needs and Functional Status

Rehabilitation Domain	Intervention Required (n)	Frequency (%)	Mean Sessions Needed	SD
Physical Therapy (Mobility)	88	78.6%	24.5	12.0
Occupational Therapy (ADL)	65	58.0%	18.2	8.5
Assistive Devices (Cane/Walker)	42	37.5%	-	-
Joint Replacement Surgery	30	26.8%	-	-
Pain Management Program	55	49.1%	15.0	6.0
Hydrotherapy Participation	38	33.9%	30.0	15.0

interventions and mean functional scores.

Table 8: Comparison of means Outcomes Post-Rehabilitation and Hematologic Control

Outcome Measure	Baseline Mean	Baseline SD	Post-Treatment Mean	Post-Treatment SD	P-value
VAS Pain Score	6.2	2.1	3.8	1.9	<0.001
HAQ Disability Index	1.4	0.8	0.9	0.6	<0.001
Range of Motion (Hip Flexion)	85°	15°	105°	12°	0.002
Grip Strength (kg)	22.5	8.0	26.8	7.5	0.015
6-Minute Walk Test (meters)	380	95	450	85	<0.001
Serum Ferritin (µg/L)	1850	1240	150	80	

Comparison of means before and after integrated management (Phlebotomy + Rehab).

DISCUSSION

These results, on one hand, can be deemed to be strong proof of the complex interdependence of the systemic iron burden and the musculoskeletal pathology, and, on the other hand, clearly indicate the importance of complex rehabilitation approaches that are not limited only to standard hematologic treatment. We support and extend prior studies that have identified a unique clinical phenotype of hemochromatosis-related arthropathy and indicate that the joint involvement is not only a secondary complication but also a primary manifestation that has a profound effect on the course of the disease, functional outcomes, and overall quality of life. The prevalence of second and third metacarpophalangeal joint involvement, which is almost 70% of∴ our cohort, supports the diagnostic value of such a pattern in the clinical presentation of iron overload arthropathy in comparison with primary osteoarthritis and other inflammatory arthritides [Marrero, J. A. *et al*., 2018; Muckenthaler, M. U. *et al*., 2017]. This observation is consistent with the classic studies of Axford and collaborators who initially defined MCP joint propensity in hemochromatosis and more recent imaging studies that have used ultrasonography and MRI to describe the exact patterns of iron deposition on the synovia and the cartilage erosion of these joints [Nemeth, E., & Ganz, T. 2021] Nevertheless, our research contributes to the existing literature a valuable level of specificity in the fact that though MCP involvement is very common, it is the large joint arthropathy (mostly of the hips and knees) that is correlated with the highest degree of functional disability and rehabilitation requirements, thus posing a balancing act between diagnostic specificity and functional impact that clinicians must strike when prioritising therapeutic interventions [Pinyopornpanish, K. *et al*., 2023].

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

The strong relationships found between the levels of serum ferritin, transferrin saturation, and radiographic severity of joint destruction offer additional mechanistic understanding of the pathophysiology of iron overload arthropathy. The Pearson correlation coefficient of 0.56 between serum ferritin and radiographic score shows a moderate-to-strong linear relationship, which supports the hypothesis that a cumulative, rather than acute, variation of iron is the cause of the oxidative damage to articular structures [Reeder, S. B. *et al*., 2023]. This observation agrees with experimental models showing that the use of iron-catalysed generation of reactive oxygen species through the Fenton reaction leads to chondrocyte apoptosis, interference with extracellular matrix homeostasis, and stimulation of the expression of matrix metalloproteinases that degrade cartilage collagen and proteoglycans. Moreover, there was a strong association between transferrin saturation and functional disability scores (HAQ-DI), which may indicate that, despite the control of age and duration of disease, the extent of iron overload plays an independent role in patient-reported outcomes. Such an association between the biochemical regulation and clinical rheumatologic outcome implies that when the sequence of oxidative damage and structural joint change is triggered, it may become self-perpetuating, regardless of continuing iron deposition. This means that rehabilitation approaches should be aimed at preventing the development of further iron-mediated damage and at the treatment of the existing mechanical and inflammatory joint pathology [Sadasivam, N. *et al*., 2022; Schaefer, B. *et al*., 2024].

The logistic regression results provided in this paper can provide useful predictive information that can be used in risk stratification and focused intervention. The determination of serum ferritin levels more than 1000 μg/L as an independent predictor of severe hip arthropathy with an odds ratio of 3.45 can be used as a measurable level which can be used by clinicians to identify patients who are at risk of severe large joint disease. Likewise, hip-related C282Y homozygosity and C282Y homozygosity strongly correlates with the severity of the disease, which indicates that more intensive monitoring and rheumatologic referral may be beneficial to patients with this genotype. [Singh, P. *et al*., 2012] The most clinically important, perhaps, is that the presence of arthropathy itself was a strong predictor of advanced hepatic fibrosis with an odds ratio of 4.26. This finding questions the classical organ-specific approach to the management of hemochromatosis and suggests a more holistic method to the analysis of the patient's rheumatic manifestation in the form of an in-depth evaluation of the involvement of visceral organs. Practically, it implies that when a patient comes to the medical facility with unexplained MCP joint pain or early hip osteoarthritis, rheumatologic evaluation should be combined with liver function and iron tests, and possibly, elastography and biopsy to consider the presence of concurrent hepatic fibrosis. This type of combined diagnostic tool may enable a faster intervention at any stage of multiple organ systems, which may have a positive impact on the overall morbidity of untreated iron overload.

The rehabilitation statistics of our cohort indicate the high cost of functional deficiency and the possible advantages of the multidisciplinary intervention. The large proportion of physical therapy referrals (78.6ʿ) and occupational therapy engagement (58.0□) is indicative of the awareness that treating clinicians possess regarding the fact that pharmacologic and haemodynamic management cannot eliminate the functional impairment caused by iron overload arthropathy. The major enhancements associated with a decrease in pain scores, HAQ-DI, the range of movement, and six-minute walk distance after a standardised 12-week rehabilitation programme give preliminary support to the effectiveness of the structured intervention. The results are of special interest because radiographic joint damage is irreversible in this group; the ability of functional outcomes to improve in the presence of anatomical structural abnormalities indicates that the rehabilitation techniques aimed at muscle strength, joint range, and movement patterns can be used to overcome the deficit of anatomy and reestablish normal function. Particular attention should be paid to the fact that hydrotherapy was included into rehabilitation approach of a third of patients since the buoyancy and resistance characteristics of water can provide patients with weight-bearing joint pain with unique opportunities to perform exercises with minimal mechanical stress. The inconsistency in rehabilitation attendance and results of our cohort, however, also points to the necessity of individualised strategies taking into consideration such individual factors of the patient that include age, comorbidities, socioeconomic status, and personal preferences. Future studies ought to investigate the ideal time, intensity, and length of rehabilitation interventions and the

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

possible synergistic impact of co-administering physical therapy with pharmacologic treatment of chondrocalcinosis (colchicine) or of inflammatory elements of the disease (disease-modifying antipheumatic drugs). There are various weaknesses of this study that should be taken into serious consideration when analysing the outcomes that have been reported. To begin with, the observational design does not allow making conclusive causal conclusions about the attributes of the parameters of iron overload and the severity of arthropathy; although tendencies are noted, confounding factors that are immeasured, including genetic modifiers, environmental exposures, or lifestyles, may have an impact on iron metabolism and on the severity of arthropathy. Second, the retrospective nature of the data gathering process will create the risk of selection bias and incomplete record keeping, specifically in the context of rehabilitation interventions that might have taken place beyond the tertiary care centre. Third, the ethnic makeup of our cohort was rather homogenous; the majority of its members were of Northern European descent, which might not be applicable to other populations, or even to those in which HFE mutation prevalence varies. Fourth, radiographic severity was measured using plain radiography, and this method can miss subtle cartilage damage in comparison with more sensitive imaging methods like MRI or quantitative ultrasonography; future research in this area that embraces this modality is likely to provide more sensitive markers of disease progression and treatment response. Lastly, the rehabilitation results were measured only at one time point after the intervention, which eliminated the potential of assessing long-term sustainability of the functional improvements; longitudinal follow-up would be useful in determining the degree to which the benefits are maintained, reduce, or that they necessitate continuous maintenance therapy. Second, arthropathy predicts advanced hepatic fibrosis, which implies that joint symptoms in patients should be followed by a thorough assessment of liver status, which may reveal those patients who would respond to more aggressive iron depletion or antifibrotic treatments. Third, the fact that functional improvement after rehabilitation occurred demonstrates the importance of incorporating physical and occupational therapy into the mainstream of care pathways of hemochromatosis, beyond a hematologic model of care as well as the high-risk subgroups (patients having ferritin >1000 /L or C282Y homozygosity) allow identifying high-risk subgroups, which is an opportunity to implement specific monitoring and prevention measures, which can reduce the degree of joint damage in the most at-risk patients.

As a researcher, a number of opportunities arise out of this research. Longitudinal studies are also necessary to determine how iron depletion, damage progression, and functional outcomes are related over time, and this may help to determine the critical periods to intervene. Higher-level evidence would be provided with randomised controlled trials comparing particular rehabilitation protocols, such as the evidence of various exercise modalities, frequencies, and durations, which would be useful in informing clinical practise. Future molecular studies of the dissociation of iron normalisation with progression of joint disease can help discover new therapeutic agents, including antioxidants, chondroprotective factors, or iron-induced inflammatory mediators.

CONCLUSION

the practical gains seen after multidisciplinary rehabilitation underscore the possibility of interventions, which can be applied to increase the quality of life, even in the environment of irreversible structural joint damage as well as These data support the paradigm shift in the management of hereditary hemochromatosis which should no longer be based on single approach to the iron depletion but should be elucidated by the inter-disciplinary approach to patients with an arthropathy burden by iron-overload which includes the rheumatologic assessment, functional rehabilitation, and patient-centred outcomes as the means to improve the long-term outcomes of a population with this debilitating disease.

REFERENCES

1. Adams, P. C., & Agnew, S. "Alcoholism in hereditary hemochromatosis revisited: prevalence and clinical consequences among homozygous siblings." *Hepatology* 23.4 (1996): 724-727.
2. Alvi, A. T., Santiago, L. E., Nadeem, Z., & Chaudhry, A. "Fulminant Hepatic Failure With Minimal Alcohol Consumption in a 25-Year-Old Female With Hereditary Hemochromatosis: A Rare Case." *Cureus* 15.9 (2023).
3. Bacon, B. R. "Hemochromatosis: discovery of the HFE gene." *Missouri medicine* 109.2 (2012): 133.

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

4. Bardou-Jacquet, E., Morandeau, E., Anderson, G. J., Ramm, G. A., Ramm, L. E., Morcet, J., & Deugnier, Y. M. "Regression of fibrosis stage with treatment reduces long-term risk of liver cancer in patients with hemochromatosis caused by mutation in HFE." *Clinical Gastroenterology and Hepatology* 18.8 (2020): 1851-1857.
5. Bassett, M. L., Hickman, P. E., & Dahlstrom, J. E. "The changing role of liver biopsy in diagnosis and management of haemochromatosis." *Pathology* 43.5 (2011): 433-439.
6. Brissot, P., Cavey, T., Ropert, M., Gaboriau, F., & Loréal, O. "Hemochromatosis: a model of metal-related human toxicosis." *Environmental Science and Pollution Research* 25.3 (2018): 2007-2013.
7. Camaschella, C., Nai, A., & Silvestri, L. "Iron metabolism and iron disorders revisited in the hepcidin era." *Haematologica* 105.2 (2020): 260.
8. Feder, J. N., Gnirke, A., Thomas, W., Tsuchihashi, Z., Ruddy, D. A., & Basava, A. "The discovery of the new haemochromatosis gene. 1996." *Journal of Hepatology* 38.6 (2003): 704-709.
9. Fleming, R. E., & Ponka, P. "Iron overload in human disease." *New England Journal of Medicine* 366.4 (2012): 348-359.
10. Fletcher, L. M., Dixon, J. L., Purdie, D. M., Powell, L. W., & Crawford, D. H. "Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis." *Gastroenterology* 122.2 (2002): 281-289.
11. Ganz, T., & Nemeth, E. "Hepcidin and iron homeostasis." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1823.9 (2012): 1434-1443.
12. Girelli, D., Busti, F., Brissot, P., Cabantchik, I., Muckenthaler, M. U., Porto, G., & Nomenclature Committee of the International Society for the Study of Iron in Biology, "Hemochromatosis classification: update and recommendations by the BIOIRON Society." *Blood* 139.20 (2022): 3018-3029.
13. Golfeyz, S., Lewis, S., & Weisberg, I. S. "Hemochromatosis: pathophysiology, evaluation, and management of hepatic iron overload with a focus on MRI." *Expert review of gastroenterology & hepatology* 12.8 (2018): 767-778.
14. Harrison-Findik, D. D. "Role of alcohol in the regulation of iron metabolism." *World journal of gastroenterology: WJG* 13.37 (2007): 4925.
15. Harrison-Findik, D. D., Schafer, D., Klein, E., Timchenko, N. A., Kulaksiz, H., Clemens, D., & Gollan, J. "Alcohol metabolism-mediated oxidative stress down-regulates hepcidin transcription and leads to increased duodenal iron transporter expression." *Journal of Biological Chemistry* 281.32 (2006): 22974-22982.
16. Jacobi, N., & Herich, L. "Measurement of liver iron concentration by superconducting quantum interference device biomagnetic liver susceptometry validates serum ferritin as prognostic parameter for allogeneic stem cell transplantation." *European journal of haematology* 97.4 (2016): 336-341.
17. Kew, M. C. "Hepatic iron overload and hepatocellular carcinoma." *Liver cancer* 3.1 (2014): 31-40.
18. Marrero, J. A., Kulik, L. M., Sirlin, C. B., Zhu, A. X., Finn, R. S., Abecassis, M. M., & Heimbach, J. K. "Diagnosis, S taging, and M anagement of H epatocellular C arcinoma: 2018 P ractice G uidance by the A merican A ssociation for the S tudy of L iver D iseases." *Hepatology* 68.2 (2018): 723-750.
19. Muckenthaler, M. U., Rivella, S., Hentze, M. W., & Galy, B. "A red carpet for iron metabolism." *Cell* 168.3 (2017): 344-361.
20. Nemeth, E., & Ganz, T. "Hepcidin-ferroportin interaction controls systemic iron homeostasis." *International journal of molecular sciences* 22.12 (2021): 6493.
21. Pinyopornpanish, K., Tantiworawit, A., Leerapun, A., Soontornpun, A., & Thongsawat, S. "Secondary iron overload and the liver: a comprehensive review." *Journal of Clinical and Translational Hepatology* 11.4 (2023): 932.
22. Reeder, S. B., Yokoo, T., França, M., Hernando, D., Alberich-Bayarri, Á., Alústiza, J. M., & Martí-Bonmatí, L. "Quantification of liver iron overload with MRI: review and guidelines from the ESGAR and SAR." *Radiology* 307.1 (2023): e221856.
23. Sadasivam, N., Kim, Y. J., Radhakrishnan, K., & Kim, D. K. "Oxidative stress, genomic integrity, and liver diseases." *Molecules* 27.10 (2022): 3159.
24. Schaefer, B., Pammer, L. M., Pfeifer, B., Neururer, S., Troppmair, M. R., Panzer, M., & Zoller, H. "Penetrance, cancer incidence and survival in HFE haemochromatosis—A

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher

population-based cohort study." *Liver International* 44.3 (2024): 838-847.
25. Singh, P., Kaur, H., Lerner, R. G., Patel, R., Rafiyath, S. M., & Singh Lamba, G. "Hepatocellular carcinoma in non-cirrhotic liver without evidence of iron overload in a patient with primary hemochromatosis. Review." *Journal of gastrointestinal cancer* 43.1 (2012): 36-39.

Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Alhussein, A. M. H., Sayel, A. S. & Maseer, E. S. "Iron Overload Arthropathy in Hemochromatosis: Hematologic and Rheumatic Rehabilitation Approaches." *Sarcouncil journal of Medical sciences* 5.3 (2026): pp 36-44.

Copyright © 2022 The Author(s): This work is licensed under a Creative Commons Attribution- NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0) International License

Publisher: SARC Publisher