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ORIGINAL RESEARCH

Altered Iron Regulation and the Role of Ferritin Heavy Chain in Dermatomyositis Patients

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Background: Dermatomyositis (DM) is an acquired autoimmune disease, the underlying mechanism of which remains unclear. Systemic and myocellular iron homeostasis are deeply connected to inflammation, hypoxia, mitochondrial dysfunction, and different forms of cell death, which are involved in the pathogenesis of DM. This study aimed to investigate changes in key iron regulators transferrin receptor 1 (TfR1), ferroportin (Fpn), ferritin heavy chain (FTH), and mitochondrial ferritin (FtMt) in DM and their possible roles.

Methods: We included 11 patients with DM, 9 patients with disease controls, and 7 patients as normal controls. Systemically, ELISA was performed to measure the serum hepcidin levels. We used qRT-PCR and Western blotting to quantitatively analyze transferrin receptor 1(TfR1), ferroportin (Fpn), ferritin heavy chain (FTH), and mitochondrial ferritin (FtMt) in the muscle biopsy samples obtained from patients. Immunohistochemical staining and immunofluorescence were performed to determine protein expression.

Results: Elevated serum hepcidin levels were observed in the patients with DM. In muscle tissues, the results showed increased mRNA levels of *TfR1, Fpn, FTH* and elevated protein levels of Fpn, FTH, and FtMt, but not TfR1, indicating an iron-scavenging state in myocytes of DM patients. Ultimately, we observed that FTH enhanced signal intensity was present, especially in perifascicular atrophic myofibers (PFA), but not in necrotic fibers, suggesting a possible role of FTH in PFA.

Conclusion: Iron regulators are altered in patients with DM, and the overexpression of FTH may contribute to the pathogenesis of perifascicular atrophy.

Keywords: dermatomyositis, iron regulation, ferritin heavy chain, perifascicular atrophy, idiopathic inflammatory myopathy

Introduction

Dermatomyositis (DM) is an autoimmune disease characterized by skin lesions and muscle weakness.[1] Unlike immune-mediated necrotizing myositis (IMNM), which predominantly affects skeletal muscle, DM is a multiorgan disease that often affects the skin, lungs, and joints. However, the mechanisms underlying this autoimmunity remain unclear. The pathological characteristics of DM include perifascicular atrophy (PFA), focal loss of capillaries,[2] and overexpressionof IFN-inducible genes.[3]

Iron is a vital element that participates in a wide variety of biological processes in the body, especially in cells with high mitochondrial activity, such as skeletal muscle myocytes, which require iron not only for electron transport but also for myoglobin production. Iron regulation is tightly regulated. Systemic iron is controlled by the hepcidin-ferroportin (Fpn) axis. And cellular iron homeostasis is regulated by IRPs of iron regulatory proteins (binding with IREs), which can regulate the expression of iron metabolism related genes by Iron responsive element (IREs).[4] Intracellularly, iron is involved in ROS formation, mitochondrial dysfunction, programmed cell death, and oxygen regulation.[5] The cellular iron-regulatory IRP/IRE system responds to cellular iron levels, hypoxia and ROS.[3] In dermatomyositis, mitochondrial abnormalities and increased ROS levels have been observed,[6,7] and the increased staining of apoptosis- and pyroptosis-related proteins has

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been proven.[8–10] Iron regulation also involves crosstalk with oxygen regulation. Researchers has been detected over-expressed HIF-1α in perifascicular atrophy fibers.[11]

Systemically, it is well known that iron plays important roles in host defense and inflammation.[12] Serum ferritin is important in the pathogenesis of various inflammatory and autoimmune diseases.[13,14] In dermatomyositis patients, hyperferritinemia was reported, especially in those with rapidly progressive interstitial lung disease.[15,16] This indicates that iron regulation is involved in DM. Hepcidin is a central systemic iron-regulatory hormone that is produced by hepatic cells and inhibits plasma iron concentration by degrading ferroportin in the duodenum to reduce dietary absorption, and in macrophages and hepatocytes to limit iron release.[17] Hepcidin expression is regulated by iron signaling, erythropoiesis, oxygen tension, and inflammation. In systemic inflammatory diseases, hepcidin synthesis is mainly upregulated through the IL-6/STAT-3 pathway by stimulating *HAMP* transcription and other factors such as IFNs, activin B, and IL-1β. Elevated levels of IL-6 have been reported to be related to hyperferremia in myositis,[18] and IFN-β levels have been shown to be increased in both serum and myocytes in dermatomyositis.[6] However, hepcidin levels have not been determined.

The direct links between systemic and intracellular iron metabolism, inflammation, mitochondrial dysfunction, and hypoxia make iron regulation a potential participant in the pathogenesis of dermatomyositis. Thus, this study aimed to investigate the iron regulatory status of DM and its potential role. Currently, there is no widely accepted animal model of DM that recapitulates the classic pathological features of human disease. We compared the levels of key iron regulators in serum and muscle biopsy samples of patients with DM and healthy controls. The results reveal the iron metabolism status in dermatomyositis and provide clues for further studies on the molecular mechanisms of perifascicular atrophy. An increased understanding of the role of iron regulation will open new therapeutic avenues for patients with DM.

Materials and Methods

Patients and Samples

According to 2004 European Neuromuscular Center criteria,[19] we retrospectively enrolled 11 early untreated dermatomyositis patients, 5 IMNM patients and 4 dystrophin patients as disease controls, 7 patients without pathological findings as normal controls. These patients were admitted in the the first affiliated hospital of Soochow University between Nov 2018 and Nov 2022 with muscle biopsy results. Patients who received immunosuppressant/intravenous corticosteroid treatment or combined treatment with other autoimmune diseases/tumors were excluded from this study. All muscle biopsies were performed for diagnostic purposes, as indicated by muscle weakness or increased creatine kinase level. In parallel, blood samples were collected from the above patients muscle biopsy results, including 8 dermatomyositis patients, 6 non-DM myositis patients, and 3 control patients at the time of muscle biopsy.

Ethical Statements

The Clinical Research Ethical Committee of the First Affiliated Hospital of Soochow University approved this retrospective observational study protocol. The protocols were in accordance with the Declaration of Helsinki. Written informed consents were acquired from all participants or their legal guardians.

Elisa

Serum Hepcidin levels were measured using an ELISA kit purchased from PC-Biotech (PC-Biotech, China, PCDBH0207) according to the manufacturer's instructions. All samples were measured in duplicate.

Real-Time Quantitative Polymerase Chain Reaction

Total RNA was extracted from muscle tissues using a tissue RNA purification kit plus (ES science, Ltd., China, ES-RN002plus), and cDNA was synthesized from 0.2 μg of total RNA using a reverse transcription kit (ES science, Ltd., China, ES-RT001). RT-qPCR was performed with the 7500 FAST Real-Time PCR system (Roche, Basel, Switzerland) using SYBR Green Master Mix (Thermo Fisher, A25742) in a 20-μL volume. The comparative CT method ($2^{-\Delta\Delta CT}$) was used to analyze the relative gene expression. The primers used are listed below.

GAPDH: 5'-CATGTTCGTCATGGGTGTGAACCA-3'(Forward)
5'- AGTGATGGCATGGACTGTGGTCAT-3'(Reverse);
FTH1 (FTH): 5'-AGCTCTACGCCTCCTACGTT-3'(Forward)
5'-AAGGAAGATTCGGCCACCTC-3'(Reverse);
FtMt: 5'-CATGCCATGGAGTGTGCTCT-3'(Forward)
5'-AATCGCACAAATGGGGGTCA-3'(Reverse);
SLC40A1 (Fpn): 5'-TGAGCCTCCCAAACCGCTTCCATA-3'(Forward)
5'-GGGCAAAAAGACTACAACGACGACTT-3'(Reverse);
TFRC (TfR1): 5'-GGCTGTATTCTGCTCGTGGA-3'(Forward)
5'-CCCCAGAAGACATGTCGGAAA-3'(Reverse).

Western Blotting

Western blotting was performed on the muscle homogenates using a BCA assay kit (ES science Ltd., China, ES6002) to determine the protein concentration. Ten micrograms of protein were loaded on a 7.5%-12.5% SDS-polyacrylamide gel, depending on the MW for electrophoresis. The primary antibodies anti-FtMt (Abcam, ab66111), anti-FTH (Cell Signaling Technology, 4393s), anti-Fpn (NOVUS, 45356), anti-TfR1 (Proteintech 66180), anti-VDAC1 (Abcam, ab154856), and anti-GAPDH (Abcam, ab181602) were used at a dilution of 1:1000. Secondary antibodies were purchased from Cell Signaling Technology (#7076 for anti-mouse IgG and #7074 for anti-rabbit IgG) at 1:3000 dilution. Signals were detected by chemiluminescence using the Western blotting luminol reagent (Millipore, WBKLS0100).

Immunohistochemistry

All muscle biopsies were frozen in liquid nitrogenchilled isopentane. Eight-micrometer cryostat sections of muscle tissue were air-dried at room temperature for 30 min. Immunohistochemical analysis was performed on eight-micrometer cryostat muscle tissue using a PV-9000 polymer detection system (ZsBio Ltd., China). All slides were incubated overnight at 4 °C with the following primary antibodies (brand, number, and dilution): Anti-Ferritin heavy chain antibody (FTH) (Abcam, ab65080, 1:100), anti-ferroportin antibody (Fpn) (Proteintech 26601, 1:50), anti-transferrin receptor-1 antibody (TfR1) (Abcam, ab8598, 1:10), anti-mitochondrial ferritin antibody (FtMt) (Abcam, ab66111, 1:50); Anti-CD68 antibody (ZsBio, TA802952). After washing with phosphate-buffered saline (PBS), the sections were incubated with a polymer helper for 30 min, followed by polymerized-horseradish-peroxidase-conjugated anti-mouse/rabbit immunoglobulin G (IgG) for 30 min at 37 °C. Peroxidase activity was determined using diaminobenzidine.

Immunofluorescence Staining

Immunofluorescence labeling was used to colocalize CD68 with FTH. The following antibodies were used: anti-CD68 (Servicebio, GB113150, 1:3000 dilution), and anti-FTH (Abcam, ab65080, 1:200). Each primary antibody was applied to the slices at 4 °C overnight, followed by application of goat anti-rabbit or anti-mouse HRP-conjugated IgG as a secondary antibody (Servicebio, GB113150, 1:500 dilution). All the slides used DAPI for nuclear staining. The slides were digitized using an automated microscopic scanner (Panoramic Digital MIDI, 3DHISTECH, Hungary).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 9.2 (GraphPad Software, San Diego, CA, USA). The Mann–Whitney Comparison was used to compare variables between the groups was made by Mann–Whitney *U*-test. Results are expressed as means ± S.E.M.S, and statistical significance was set at $p<0.05$.

Result

Clinical and Pathological Characteristics of DM Patients

Muscle tissues were obtained from 11 DM patients, 5 with IMNM patients, 4 with dystrophin patients and 7 patients without histological myopathy. In the DM group, 7 patients showed histological evidence of perifascicular atrophy

(PFA). The basic profiles are presented in Table 1. 5 IMNM patients were included in this study, in which 3 of them conducted the MSA test (one was anti-HMGCR antibody-positive and two were anti-SRP antibody-positive). We chose patients with IMNM as myositis controls first, because the pathological features of IMNM are distinguishable from those of other IIMs, making the diagnosis undoubtable Second, unlike antisynthetase antibody syndrome, which shares similar systemic symptoms with DM, IMNM mainly affects the muscle tissue. 4 patients diagnosed with muscular dystrophy based on clinical, pathological, and genetic results were included as non-myositis disease controls who showed necrotic fibers and inflammatory infiltrates. 4 patients were diagnosed with facioscapulohumeral muscular dystrophy (FSHD), LAMA2-related muscular dystrophy, limb-girdle muscular dystrophy type 2A (LGMD 2A), and Becker muscular dystrophy (BMD). Patient information is presented in Table 1.

Elevated Serum Hepcidin Levels in DM Patients

We obtained serum samples from 14 patients with idiopathic inflammatory myopathy (IIM), 8 of which were classified as having DM and 6 as having other myositis, and 3 normal control patients. All of these patients had both pathological and myositis specific antibody (MSA) results. Serum hepcidin levels were significantly increased in DM patients (5349±1449 pg/mL) compared with normal controls (3258±156.6 pg/mL, p=0.0121), while no significant difference was found between DM and other-IIM patients (p=0.0593) (Figure 1).

Altered Iron Regulation in Dermatomyositis

We first focused on changes in four key iron regulatory genes in the muscle tissue of patients by measuring the mRNA levels of transferrin receptor 1 (TfR1) for iron intake, ferroportin (Fpn) for iron export, ferritin heavy chain (FTH), and mitochondrial ferritin (FtMt) for iron storage with ferroxidase activity. As shown in Figure 2A, TfR1, Fpn, and FTH levels were significantly different from those in normal controls (p=0.0019, p<0.0001, p=0.0002, respectively). Further comparison with disease controls showed that the gene expression of FTH (p=0.0087 vs IMNM group) was indicating an increasing trend.

Immunoblotting was used to determine the protein levels of the four iron regulators. To eliminate the influence of mitochondrial mass, we adjusted FtMt expression with VDAC1 (voltage-dependent anion channel 1).[20] As shown in Figure 2B, we found elevated levels of Fpn, FTH, and FtMt, but not TfR1, in patients with DM compared to normal controls (p<0.0001 for Fpn, FTH, and FtMt; p=0.0028 for FtMt adjusted with VDAC1). Enhanced iron storage and export, but not import, indicated an iron-scavenging state of myofibers. We then compared the disease controls and found significant increases in Fpn (p=0.0059 vs dys; p=0.0192 vs IMNM) and FTH (p=0.0015 vs dys; p=0.0192 vs IMNM). FtMt only exhibited differences in patients with dystrophy but not patients with IMNM.

Table 1 Dermatomyositis Patients' Profile

No.	Gender	Age (Years)	Disease Duration	Skin Rash	MSA	Serum Hepcidin (pg/mL)	PFA
1	Female	42	3 months	N	NXP2 (+)	5165.44	Y
2	Female	52	5 months	Y	TIF1 (+)	-	Y
3	Female	81	3 months	Y	TIF1 (+)	5405.91	Y
4	Female	64	8 months	Y	(−)	6342.87	Y
5	Male	80	1 year	Y	TIF1 (+)	-	Y
6	Male	24	1.5 year	Y	MDA5 (+)	3707.46	Y
7	Female	24	1 year	Y	MDA5 (+)	8327.55	Y
8	Female	51	2 years	Y	MDA5 (+)	4857.80	N
9	Male	57	1 week	Y	(−)	-	N
10	Male	54	1 month	Y	NXP2 (+)	4942.49	N
11	Male	52	1 month	Y	MDA5 (+)	4043.84	N

Abbreviations: MSA, myositis-specific autoantibody; PFA, perifascicular atrophy; Y, yes; N, No; (−), negative; -, no result.

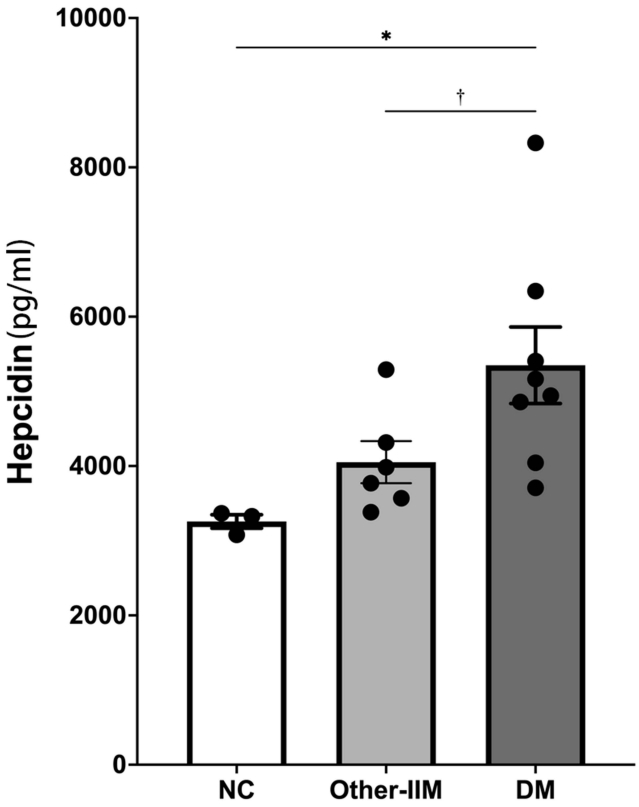

Figure 1 Level of serum hepcidin in dermatomyositis patients (pg/mL). *p<0.05 vs NC, †p=0.0593 vs other-IIM patients.
Abbreviations: NC, normal control (n=3); other-IIM, non-dermatomyositis idiopathic inflammatory myopathy (disease control, n=6); DM, dermatomyositis (n=8).

In conclusion, Fpn and FTH are overexpressed transcriptionally and post-transcriptionally in patients with DM comparing to normal and disease controls. We infer that it was a myocellular iron-scavenging form to protect cells from the toxic effects of increased levels of iron.

Overexpressionof FTH – A Possible Mechanism for Perifascicular Atrophy

Furthermore, we determined the expression of TfR1, Fpn, FTH, and FtMt in the IHC-Fr cells. Consistent with the WB results, TfR1 was only expressed in some inflammatory infiltrates but not in myofibers. Fpn showed increased expression in atrophic myofibers in DM and necrotic myofibers in IMNM. Interestingly, enhanced signal intensity of FTH was observed in the perifascicular atrophy cells of patients with DM, but not in the necrotic fibers of patients with IMNM. FtMt demonstrated widespread expression and was not restricted to atrophic or necrotic fibers. We also observed IHC-Fr results in patients with DM without PFA, and no specific myofibers were affected (Results showed in Figure 3).

Finally, we confirmed the typical FTH expression using IF. As shown in Figure 4, FTH was overexpressed in the perifascicular atrophy fibers of DM patients, whereas it showed increased expression in macrophage-infiltrating sites in IMNM patients. Thus, we conclude that FTH is especially overexpressed in the perifascicular atrophy regions, which may contribute to the formation of PFA.

Discussion

To date, the pathogenesis of dermatomyositis remains obscure; however, both adaptive and innate immune systems and non-immune mechanisms are involved.[21,22] Iron metabolism can participate in all aspects, including affecting immune cell function, interacting with oxygen regulation, and leading to mitochondrial dysfunction.[23,24] Diminished iron regulation has been reported in autoimmune diseases such as systemic lupus erythematosus (SLE).[25,26] In this study, our findings suggested that iron regulation is closely associated with DM. Systemically, serum hepcidin levels increase in

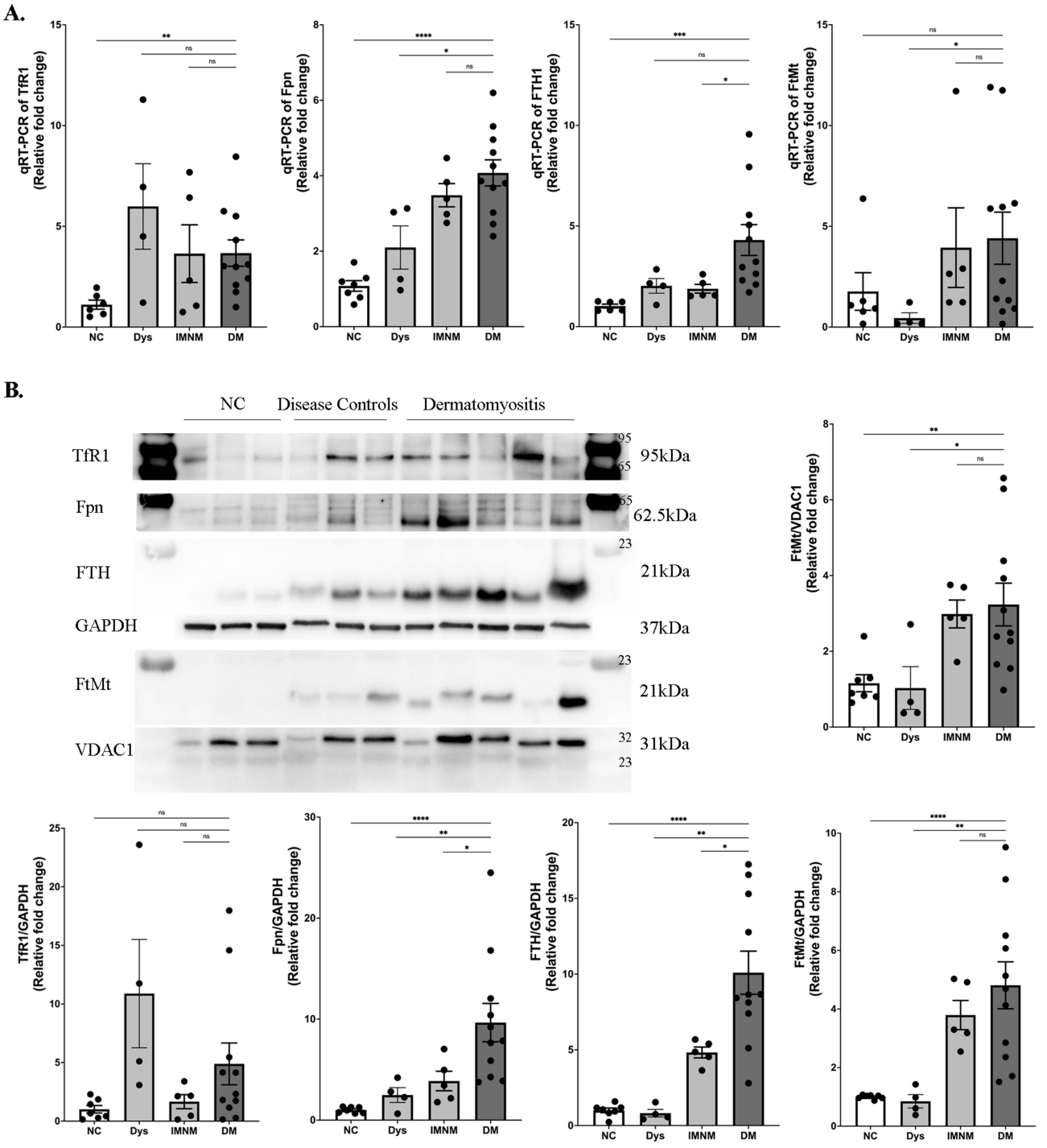

Figure 2 qRT-PCR and Western blot results of TfR1, Fpn, FTH, FtMt expression in DM muscles specimens. (**A**) The mRNA expressions of TfR1, Fpn, FTH, FtMt in DM muscle specimens, compared with NC, Dys, IMNM. (**B**) The protein expressions of TfR1, Fpn, FTH and FtMt in DM muscle samples compared with controls.
Notes: **p*<0.05; ***p*<0.002; ****p*<0.0002; *****p*<0.0001.
Abbreviations: NC, normal control (n=7); Dys, dystrophin patients (disease control, n=4); IMNM, immune-mediated necrotic myopathy patients (disease control, n=5); DM, dermatomyositis (n=11).

patients with DM. Cellularly, key iron regulators were adjusted at both transcriptional and post-transcriptional levels, with myocytes demonstrating an iron-scavenging state. In particular, elevated FTH levels indicate its role in perifascicular atrophy in patients with DM.Hepcidin, the master regulator of systemic iron metabolism, regarding systemic iron metabolism via the hepcidin-FPN (ferroportin) axis, followed by absorption through the Tf-Tfr1 complex endocytosis

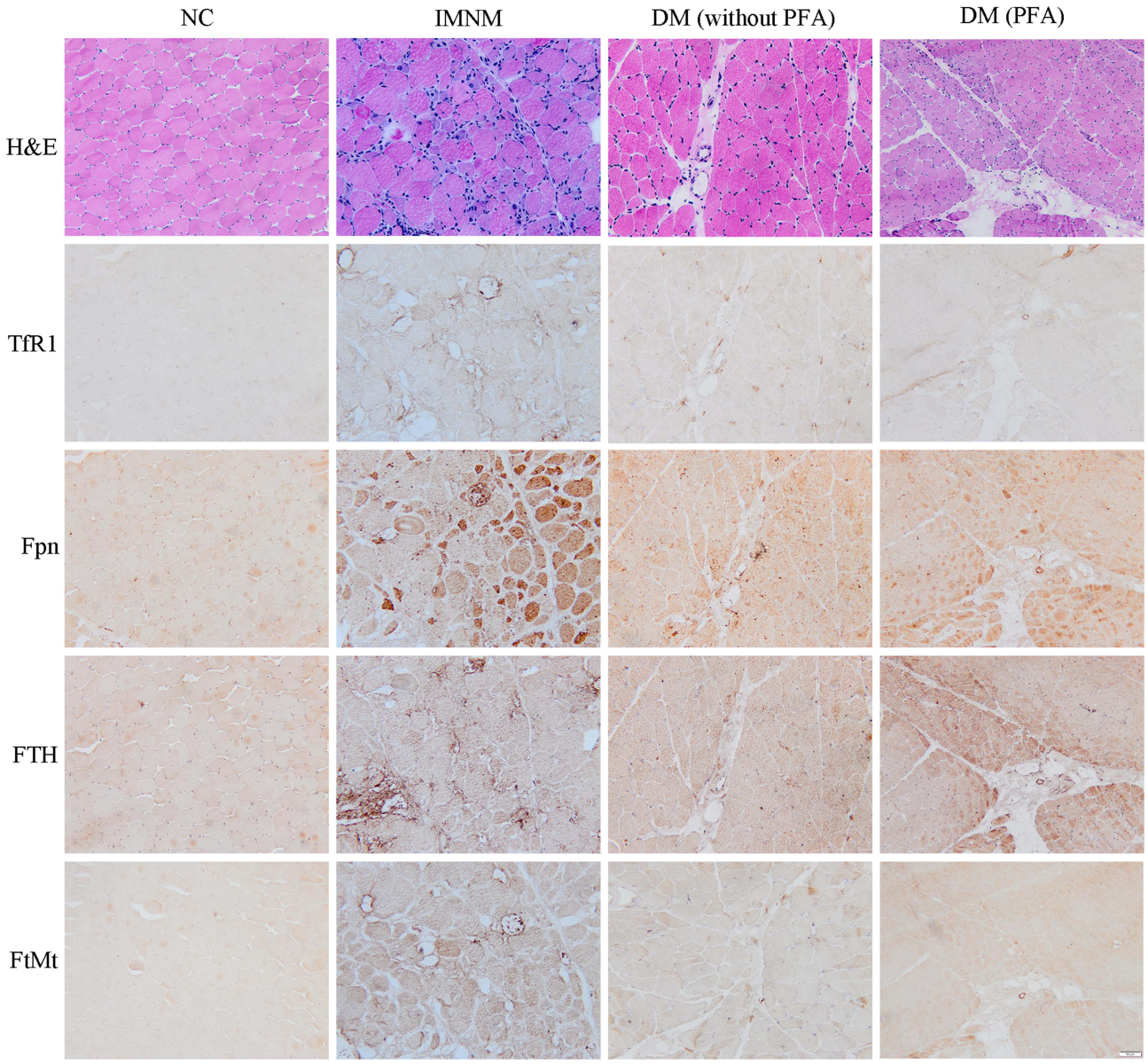

Figure 3 IHC-Fr results of TfR1, Fpn, FTH, FtMt expression in DM myofibers. Immunohistochemistry staining showed no specific type of TfR1 and FtMt expression in DM patients. Enhanced signal intensity of Fpn was demonstrated in necrotic fibers of IMNM and perifascicular atrophic fibers (PFA) of DM patients. Increased level of FTH was showed in PFA of DM patients, but not in IMNM patients. (x200; Bar: 50μm).
Abbreviations: NC, normal control; IMNM, immune-mediated necrotic myopathy; DM, dermatomyositis; PFA, perifascicular atrophy.

process, is induced by inflammation, particularly by IL-6.[27] Myositis is an autoimmune disease characterized by elevated levels of IL-6 and IFNs,[11,18] and it is not surprising to find elevated hepcidin levels in the serum samples of dermatomyositis patients, which indicates a systemic iron scavenging state.The transcriptional regulation of iron at the cellular level is regulated by various factors and specifically interacts with hypoxia. TfR1, ferritin, and Fpn are controlled by hypoxia-inducible factor (HIF) protein[28] binding to the hypoxia-response element (HRE) of target genes to promote expression. Loss of intramuscular capillaries is considered a hallmark of DM pathological features, and overexpression of HIF-1α and HIF-2α in muscle fibers has been identified in muscle biopsy samples from patients with DM.[11,29] Thus, as HIF-targeted genes, the crosstalk between hypoxia and iron regulation may explain the elevated transcriptional levels of TfR1, Fpn, and FTH in patients with DM. Functional binding sites for HIF-1α have been identified in the promoter regions of human FTMT. Its ability to prevent hypoxia-induced tissue damage has been demonstrated both in vitro and in vivo models.[30] In our study, an increased transcriptional level of FtMt was observed, but the difference was not

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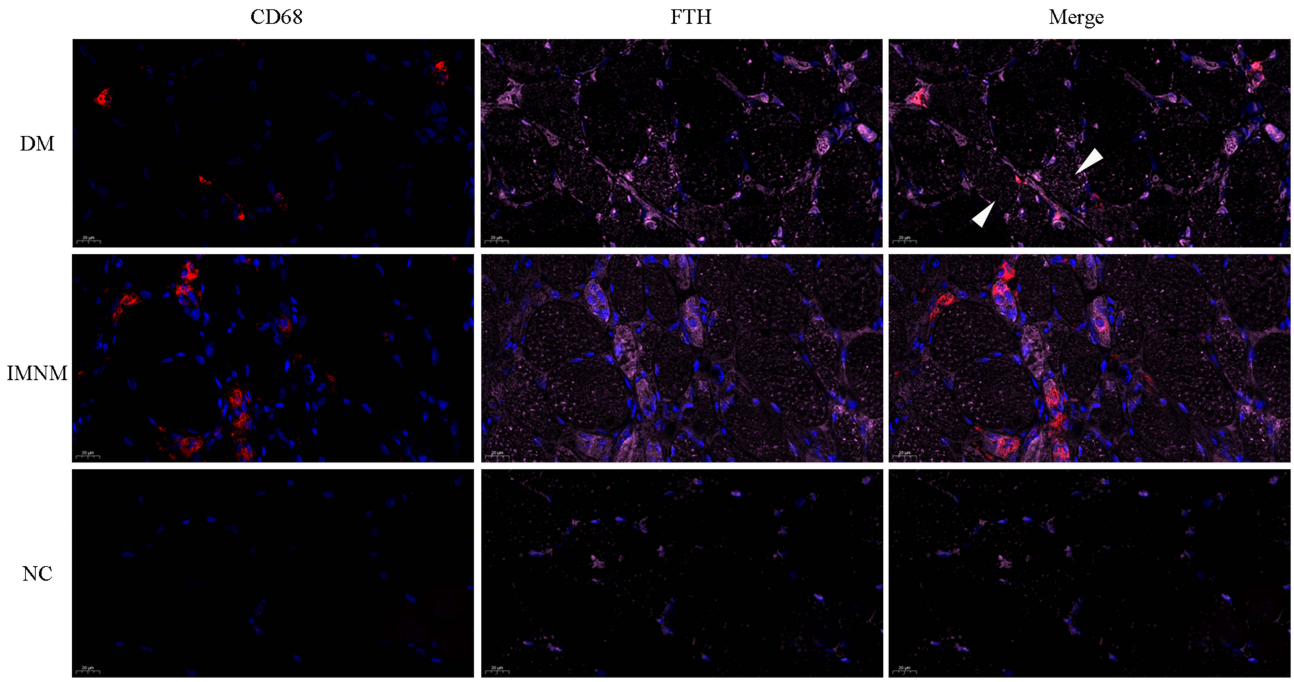

Figure 4 Immunofluorescence staining of FTH in DM myofibers. IF results showed positive FTH staining in the atrophic cells in DM (white triangles), on the contrary, posive FTH was only found in macrophage infiltrates sites in IMNM. (Bar: 20μm).
Abbreviations: NC, normal control; IMNM, immune-mediated necrotic myopathy; DM, dermatomyositis.

statistically significant. The expression of FTH mRNAs is also regulated via the activation of nuclear factor kappa B (NF-κB)[31] and NF-E2-related factor 2 (Nrf2). NF-κB is robustly overexpressed in myositis patients,[32,33] which explains the overexpression of FTH. Compared to normal controls and disease controls, increased mRNA levels of key iron regulatory genes were found in patients with DM which suggested an interaction between oxygen and iron metabolism in the pathogenesis of dermatomyositis.

Cellular iron is post-transcriptionally regulated by IRPs binding to mRNA IREs at the 3' untranslated regions (3'-UTRs) of TfR1, leading to its stabilization, and at the 5'-UTRs of FTH and Fpn to prevent their translation. IRPs are influenced by the iron status, ROS levels, and hypoxia, which protect cells from excess iron damage.[3] Under DM conditions, increased protein levels of Fpn and FTH, but not TfR1, corresponded to how the cells reacted to high iron/ROS levels. The level of FtMt also increases, which protects mitochondria from iron-induced ROS damage, but is not regulated by iron content.[30] Thus, our findings suggested a protective form of iron sequestration in DM patients' myocytes.

Elevated levels of FTH in dermatomyositis compared to normal controls, dystrophy patients, and other myositis patients suggest its special role in DM, not just secondary to inflammation. Excessive iron can generate a large amount of reactive oxygen species (ROS) through the Fenton reaction, which can cause cellular RNA, DNA damage, protein conformational changes, and lipid peroxidation, ultimately leading to cell damage.[34] By comparing FTH with FtMt, which is activated by high ROS levels, as well as between FTH and Fpn, which are both regulated by the IRE/IRP system, we inferred that FTH expression is associated with PFA to the pathogenesis of dermatomyositis, especially the formation of perifascicular atrophy, which is not just secondary to hypoxia, high intracellular ROS levels, or iron overload. However, the underlying mechanisms require further investigation. Previous in vitro experiments have shown that skeletal myocytes cultured under low-oxygen conditions exhibit increased *FTH* expression.[35] In iron-deficient conditions, significant increases in *Atrogin-1* and *MuRF1* expression and morphological abnormalities have been observed.[36] Based on our previous findings, iron deficiency may be secondary to the significantly high expression of FTH and Fpn in patients with DM. Thus, a possible mechanism for perifascicular atrophy may involve a combination of hypoxia and iron-scavenging. In addition, FTH functions by regulating MHC-I and CXCR4 expression.[37,38]

Conclusion

This study provides new insights into the potential role to DM pathogenesis – iron regulation in DM pathogenesis. In conclusion, our study showed 1) elevated serum hepcidin levels, 2) transcriptionally and post-transcriptionally altered iron regulation in the muscle tissue of patients with DM, and 3) a possible role of FTH in perifascicular atrophy in DM. These data reflect the tight relationship between iron and oxygen regulation, which requires further in vitro and in vivo experiments. Our study is the first to our knowledge to reveal the iron regulation status in myositis and provides a new insight for further study, including ferroptosis.

Of course, this study has limitations: small sample sizes (particularly controls), cross-sectional design, observational data and lack of validation in a large number of clinical samples,as well as in vitro models to validate the theory.

Abbreviations

IIM, idiopathic inflammatory myopathy; DM, dermatomyositis; IMNM, immune-mediated necrotic myopathy; PFA, perifascicular atrophy; TfR1, transferrin receptor 1; Fpn, ferroportin; FTH, ferritin heavy chain; FtMt, mitochondrial ferritin; IRE, iron-responsive element; IRP, iron regulatory protein; IHC-Fr, immunohistochemistry (frozen); IF, immunofluorescence.

Ethical Publication Statement

The authors confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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