Journal of Dental Sciences 20 (2025) 995–1001

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Original Article

Hepcidin-regulated iron metabolism disorders in patients with stage III/IV periodontitis

Ye Han [1], Yuzhe Sun [1], Chang Shu, Zhaoguo Yue, Xiaochi Chang, Cheng Lin, Jie Zhang, Kaining Liu, Jianxia Hou*

Department of Periodontology, National Center of Stomatology & National Clinical Research Center for Oral Diseases, National Engineering Laboratory for Digital and Material Technology of Stomatology, Peking University School and Hospital of Stomatology, Beijing, China

Received 21 October 2024; Final revision received 26 October 2024
Available online 12 November 2024

KEYWORDS
Periodontitis;
Inflammation;
Iron metabolism;
Hepcidin

Abstract *Background: /purpose*The disorders of iron metabolism in periodontal diseases have been reported, however, there is still lack of comprehensive and thorough analyses about the association between periodontitis and iron metabolism disorders. This study aimed to examine the association between periodontitis and iron metabolism disorders, and to analyze the characteristic changes of iron metabolism in periodontitis patients.
Materials and methods: 79 Stage III/IV periodontitis patients and 79 healthy controls were enrolled in this study. Periodontal clinical parameters, system inflammation markers, iron metabolism parameters and hematological parameters were collected and compared at baseline and 3 months after non-surgical periodontal therapy.
Results: Stage III/IV periodontitis patients exhibited higher levels of systemic inflammatory markers including white blood cell (WBC) counts and high-sensitivity C-reactive protein (hs-CRP). Serum hepcidin and ferritin were significantly increased in the periodontitis group, meanwhile serum iron and transferrin were significantly decreased. Periodontal therapy attenuated the higher levels of hepcidin and ferritin, and the lower levels of Fe and transferrin in periodontitis patients at 3 months after therapy. Probing depth (PD), bleeding index (BI) and clinical attachment loss (CAL) were positively correlated with hepcidin and ferritin, and negatively correlated with Fe and transferrin respectively. Hepcidin was significantly negatively correlated with Fe and positively correlated with ferritin in periodontitis patients.

* Corresponding author. Department of Periodontology, Peking University School and Hospital of Stomatology, No. 22, Zhongguancun South Avenue, Haidian District, Beijing, 100081, China.
E-mail address: jxhou@163.com (J. Hou).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.jds.2024.10.028

Conclusion: Our findings suggest the association between periodontitis and iron metabolism disorders and indicate that periodontitis-activated host responses may increase the risk of iron metabolism disorders, while meaningfully provide new insights into the systemic effects of periodontitis.

Introduction

Periodontitis is a chronic inflammatory disease that affects tooth-supporting tissues, and it is also the main cause of tooth loss in adults.[1] Moreover, periodontitis is related to system inflammation[2] and linked epidemiologically with various chronic disorders, such as cardiovascular diseases,[3] type 2 diabetes mellitus,[4] rheumatoid arthritis,[5] et al. Our recent studies demonstrated a tendency of anemia of inflammation in periodontitis patients,[6,7] for which iron metabolism disorder is the major pathogenic factor.[8] Moreover, we also detected higher hepcidin, higher ferritin and lower serum Fe, which were key iron metabolism parameters, with periodontitis patients in a small sample size study.[7]

Iron is an essential element required for growth and survival and both iron deficiency and iron overload cause cellular and organ dysfunction. In the last decades, evidences confirmed that iron metabolism plays a key role in host defense.[9] Systemic iron metabolism involves intestinal iron absorption, utilization of iron for erythropoiesis, efficient recycling of iron from effete erythrocytes, and controlled storage of iron by hepatocytes and macrophages.[10] Plasma iron, bound to the transport protein transferrin, is mostly destined for iron delivery to marrow erythroblasts that consume iron to synthesize hemoglobin, meanwhile, ferritin stores iron and contributes to intracellular iron bioavailability.[11] Iron lies at the center of a battle for nutritional resource between host and their microbial which affects the availability of iron for microbes.[9]

Iron homeostasis is maintained by the tight regulation of the systemic iron-regulatory hormone, hepcidin, which is known as the key regulator of iron metabolism.[12] Hepcidin regulates intestinal iron absorption, serum iron concentrations, and tissue iron storage of ferritin and iron usage for hemoglobin synthesis. Hepcidin could induce by inflammatory signals including interleukin-6, which is important in the pathogenesis of iron metabolism disorders and host defense mechanism against infection.[13] Our previous study found higher serum hepcidin concentrations in periodontitis patients,[6] however, there is still unknown whether hepcidin is correlated to periodontitis severities and whether hepcidin plays key regulator role in iron metabolism disorders for periodontitis patients.

The disorders of iron metabolism in periodontal diseases have been reported in some clinical studies. Guo et al. reported serum hepcidin levels in chronic periodontitis groups were higher.[14] A few studies reported that lower serum iron[15] and transferrin levels in periodontitis patients.[16] Study found that higher concentrations of serum ferritin and a positive correlation between serum ferritin levels and the number of sites with PD $\geq$ 6 mm.[17] However, these studies only analyzed the change of some of these iron metabolism parameters in periodontitis patients, however the general changes of iron metabolism disorders in periodontitis patients is unknown until now. Additionally, previous studies didn't apply the new 2017 classification for periodontitis diagnosis, which defined different periodontitis severities as Stage I: initial periodontitis; Stage II: moderate periodontitis; Stage III/IV: severe periodontitis.[18] Consider that other studies have reported Stage I/II periodontitis showed no difference in inflammatory biomarkers and any glucose and lipid metabolism indexes,[19,20] we recruited Stage III/IV periodontitis patients in this current study. Given the above, there is still lack of comprehensive and thorough analyses about the characteristic changes of iron metabolism in periodontitis patients, and the association between periodontitis and iron metabolism disorders, as well as the regulator function of hepcidin in periodontitis patients are unknown as well.

Therefore, the aim of this study was to illuminate the characteristic disorders of iron metabolism in periodontitis patients, to further examine the correlations between periodontitis and iron metabolism disorders, and to explore the regulator function of hepcidin. The results will show convincing evidence on the association between periodontitis and iron metabolism disorders and enrich the understanding of the effect of periodontitis on general health.

Materials and methods

Study population and study procedure

This study was approved by the Ethics Committee of Peking University Health Science Center (Approval No. PKUSSIRB-202056090) and registered in the International Clinical Trials Registry Platform (ID: ChiCTR2000040451). The research had been carried out in accordance with the World Medical Association Declaration of Helsinki, and written informed consent was obtained from all subjects. The study focused on identifying participants with Stage III/IV periodontitis patients. The classification of periodontitis was based on the definitions provided by the 2017 World Workshop on Periodontal and Peri-Implant Disease and Conditions.[18] Healthy control subjects were selected with probing depth (PD) $\leq$ 3 mm, percentage of sites with bleeding on probing <10 %, and no attachment loss (AL). Individuals who were current or previous smokers, with systemic disease or pregnancy, history of taking iron or

other drugs to treat anemia, and history of periodontal therapy or antimicrobial therapy or usage of any medication within the previous 6 months were excluded.

After baseline examinations, all patients with periodontitis received non-surgical periodontal therapy, including oral hygiene instruction, supragingival scaling, subgingival scaling and root planing. Clinical re-evaluation and relevant tests were taken at 3 months after non-surgical periodontal therapy.

Clinical periodontal measurements

At baseline and 3 months after non-surgical periodontal therapy, the clinical periodontal status was assessed with probing depth (PD), bleeding index (BI) and clinical attachment loss (CAL). The measurements were done using the Williams periodontal probe on six points on each tooth. All examinations were performed by systematically trained and calibrated clinical periodontists.

Blood collection and laboratory measurements

Fasting blood samples were obtained from each subject between 08:00 and 11:00 local time by venipuncture using ethylenediamine-tetraacetic acid (EDTA) containing and coagulant containing tubes and were sent to testing laboratories within 30 min of collection. The technicians performed complete blood analysis by calibrated automated hematology analyzer (Sysmex, Kobe, Japan) and HITACHI 7170A biochemistry automatic analyzer (Hitachi, Tokyo, Japan). Biochemical analyses were conducted for white blood cell (WBC) counts, high-sensitivity C-reactive protein (hs-CRP), red blood cell (RBC) counts, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), serum Fe, serum ferritin, serum transferrin and serum transferrin saturation (TS). Serum concentrations of hepcidin were measured using enzyme-linked immunosorbent assay (ELISA) kits (#DHP250; R&D Systems, Minneapolis, Minnesota, USA) according to the manufacturers' instructions.

Statistical analysis

Variables are presented as mean ± standard deviation (SD; normal distribution). Statistical analyses were conducted using the Student's t test and Mann–Whitney U test for normal and abnormal distributed data, respectively; the chi-square test was used for categorical variables. Comparisons of clinical and blood parameters of patients with periodontitis between baseline and 3 months after periodontal therapy were performed using paired samples t-test or Wilcoxon Signed Ranks test. Correlation analysis was performed using Pearson or Spearman correlation analysis. All statistical analyses were performed using SPSS v20.0 software (SPSS v20.0; Chicago, IL, USA). A two-tailed P value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the study sample

In total, 79 Stage III/IV periodontitis patients (Stage III: n = 59, 74.68 %; Stage IV: n = 20, 25.32 %) and 79 healthy subjects were enrolled. In the periodontitis group, the mean values of PD, BI, and CAL were 5.17 ± 0.87 mm, 3.44 ± 0.58, and 4.83 ± 1.11 mm, respectively, all of which were significantly higher than in the control group ($P < 0.001$; Table 1).

The changes of system inflammation, iron metabolism and hematological parameters in periodontitis patients

Levels of systemic inflammatory markers, including WBC counts and hs-CRP were significantly increased in the periodontitis group ($P < 0.01$; Table 2).

For iron metabolism markers, mean serum hepcidin and ferritin were significantly increased in the periodontitis group ($P < 0.05$; Table 2). Meanwhile serum iron and transferrin were significantly decreased in periodontitis patients compared with healthy controls ($P < 0.05$; Table 2). There was no statistically significant difference of transferrin saturation.

Regarding hematological parameters, mean hemoglobin (HGB) was significantly lower in the periodontitis group ($P < 0.05$; Table 2). Erythropoietin (EPO) was increased in periodontitis patients ($P < 0.05$; Table 2). There was no statistically significant difference in red blood cell (RBC) counts, hematocrit (HCT) levels, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) or mean corpuscular hemoglobin (MCHC) between the two groups.

Table 1 Demographic features and clinical characteristics of the study subjects.

Variable	Control group (n = 79)	Periodontitis group (Stage III: n = 59; Stage IV: n = 20)	*P* value
Age	31.15 ± 6.97	34.32 ± 6.54	0.003*
Sex (male/Female)	36/43	39/40	0.799
PD (mm)	1.48 ± 0.53	5.17 ± 0.87	<0.001***
BI	1.21 ± 0.46	3.44 ± 0.58	<0.001***
CAL (mm)	0	4.83 ± 1.11	<0.001***

PD, probing depth; BI, bleeding index; CAL, clinical attachment loss. *$P < 0.05$, ***$P < 0.001$.

Table 2 Inflammation parameters, iron metabolism parameters and hematological parameters in Stage III/IV periodontitis patients and healthy controls.

Variable	Control group (n = 79)	Periodontitis patients (Stage III: n = 49; Stage IV: n = 30)	*P* value
System inflammatory markers			
WBC (109/L)	5.47 ± 1.15	6.42 ± 1.49	0.001**
Hs-CRP (mg/L)	0.36 ± 0.63	1.20 ± 1.63	0.002**
Iron metabolism markers			
Hepcidin (ng/ml)	28.38 ± 18.19	43.35 ± 29.40	0.004**
Fe (μmol/L)	16.54 ± 5.09	14.58 ± 3.22	0.037*
Ferritin (ng/ml)	96.65 ± 75.57	176.70 ± 110.00	<0.001***
Transferrin (mg/dL)	290.60 ± 53.46	252.90 ± 52.50	<0.001***
TS (%)	28.91 ± 11.51	27.80 ± 7.71	0.541
Hematological parameters			
RBC (1012/L)	4.58 ± 0.48	4.68 ± 0.50	0.440
HGB (g/L)	140.80 ± 14.75	131.50 ± 13.12	0.002**
HCT (L/L)	0.41 ± 0.03	0.40 ± 0.04	0.264
MCV(fL)	89.15 ± 3.88	88.14 ± 4.91	0.289
MCH (pg/cell)	30.58 ± 1.86	29.98 ± 2.25	0.123
MCHC (g/dL)	342.80 ± 11.62	338.70 ± 11.94	0.096
EPO (IU/L)	26.92 ± 12.65	38.65 ± 18.60	0.002**

WBC: white blood cell; hs-CRP, high-sensitivity C-reactive protein; TS, transferrin saturation; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; EPO, erythropoietin. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

The changes of system inflammation and iron metabolism 3 months after non-surgical periodontal therapy

There were significant reductions in WBC counts and hs-CRP at 3 months after periodontal therapy ($P < 0.05$; Table 3). Moreover, periodontal therapy attenuated the higher levels of hepcidin and ferritin, and the lower levels of Fe and transferrin in periodontitis patients ($P < 0.05$; Table 3). HGB and HCT levels were significantly increased in periodontitis patients at 3 months after periodontal therapy compared with baseline ($P < 0.001$; Table 3).

Table 3 Changes in parameters at 3 months after non-surgical periodontal therapy.

Variable	Baseline (n = 56)	After therapy (n = 56)	*P* value
Periodontal clinical parameters			
PD (mm)	5.17 ± 0.87	3.00 ± 0.46	<0.001***
BI	3.44 ± 0.58	1.76 ± 0.73	<0.001***
System inflammation markers			
WBC (109/L)	6.42 ± 1.49	5.69 ± 1.39	0.008**
Hs-CRP (mg/L)	1.20 ± 1.63	0.63 ± 0.56	0.048*
Iron metabolism markers			
Hepcidin (ng/ml)	43.35 ± 29.40	30.55 ± 20.00	0.032*
Fe (μmol/L)	14.58 ± 3.22	17.04 ± 4.35	0.007**
Ferritin (ng/ml)	176.70 ± 110.00	110.90 ± 80.87	<0.001***
Transferrin (mg/dL)	252.90 ± 52.50	273.20 ± 49.53	<0.001***
TS (%)	27.80 ± 7.71	30.12 ± 10.86	0.205
Hematological parameters			
RBC (1012/L)	4.68 ± 0.50	4.72 ± 0.53	0.636
HGB (g/L)	131.50 ± 13.12	142.50 ± 15.35	<0.001***
HCT (L/L)	0.40 ± 0.04	0.42 ± 0.04	0.261
MCV (fL)	88.14 ± 4.91	88.00 ± 5.45	0.876
MCH (pg/cell)	29.98 ± 2.25	29.62 ± 2.50	0.587
MCHC (g/L)	338.70 ± 11.94	336.5 ± 10.53	0.271
EPO (IU/L)	38.65 ± 18.60	22.91 ± 18.23	<0.001***

WBC: white blood cell; hs-CRP, high-sensitivity C-reactive protein; TS, transferrin saturation; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; EPO, erythropoietin. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Correlation between periodontal parameters and system inflammation parameters and iron metabolism parameters in periodontitis patients

The assessment of correlations between periodontal parameters and system inflammation parameters showed that WBC and hs-CRP was significantly positively correlated with PD (r = 0.289, r = 0.662, respectively; $P < 0.05$, Table 4), as well as positively correlated with BI (r = 0.224, r = 0.647, respectively; $P < 0.05$, Table 4) and CAL (r = 0.321, r = 0.634, respectively; $P < 0.001$, Table 4).

Additionally, there were significantly positive correlation between PD and hepcidin (r = 0.21), ferritin (r = 0.195) and negative correlation between PD and Fe (r = −0.476) and transferrin (r = −0.192). BI was also significantly positively correlated with hepcidin (r = 0.205) and ferritin (r = 0.228) and negatively correlated with Fe (r = −0.533). No correlation was found between BI and transferrin. CAL was significantly positively correlated with hepcidin (r = 0.293) and ferritin (r = 0.284), and negatively correlated with Fe (r = −0.498) and transferrin (r = −0.199) (Table 4).

Correlations between hepcidin and Fe, ferritin, transferrin in periodontitis patients

Hepcidin was significantly negatively correlated with Fe (r = −0.373) and positively correlated with ferritin (r = 0.480), however, no correlation was found between hepcidin and transferrin (Table 5).

Table 5 Correlations between hepcidin and Fe, ferritin, transferrin in periodontitis patients.

Variable	Basic value	Fe (μmol/L)	Ferritin (ng/ml)	Transferrin (mg/dL)
Hepcidin (ng/ml)	r	−0.373	0.480	0.156
	P	0.049*	<0.001***	0.205

*$P < 0.05$, ***$P < 0.001$.

Discussion

To the best of our knowledge, this is the first study to examine the association between periodontitis and iron metabolism disorders. Notably, our study manifested the disorders of iron metabolism as higher serum hepcidin concentration and higher ferritin levels, along with lower serum Fe and transferrin levels in Stage III/IV periodontitis patients. Additionally, this study further detected significant correlations between PD, BI, and CAL and hepcidin, Fe and ferritin. Specifically, significant correlations between hepcidin and Fe and ferritin indicated key regulator function of hepcidin in iron metabolism disorders for periodontitis patients. Moreover, non-surgical periodontal therapy ameliorated system inflammation and iron metabolism disorders. Overall, these findings suggested the association between periodontitis and iron metabolism disorders and indicated that periodontitis-activated host responses might increase the risk of iron metabolism disorders, while meaningfully provides new insights into the systemic effects of periodontitis.

Recent years, iron metabolism has been reported that played a key role in host defense.[21] Evidence have verified that periodontitis is also an inflammatory disease with the host immune activation,[22] therefore, we explored whether periodontitis is associated with ironmetabolism disorders. The results showed charasteristics changes of higher hepcidin and ferritin levels, and lower Fe and transferrin levels, meanwhile significant correlations between clinical periodontal parameters and iron metabolism parametes including hepcidin, Fe, ferritin, and transferrin. These all indicated that iron metabolism disorder participated in host immune-inflammatory responses evoked by periodontitis.

Serum iron concentrations markedly decrease in humans and animals during systemic infection or inflammation.[23] The hypoferremia is considered to result from a defense mechanism of the body to limit the availability of iron for extracellular pathogens, while on the other hand results in the limitation of iron supply to erythropoiesis. The lower levels of serum iron found in periodontitis patients implied that iron metabolism participated in the host defenses caused by periodontal pathogen.

Ferritin, the specialized cytoplasmic iron storage protein, plays an important role not only in iron metabolisms and in diseases characterized by inflammation, injury and repair.[24] Our previous studies showed ferritin is upregulated by the inflammation in periodontitis and may contribute to amplify the immune responses of periodontitis through the ERK/P38 MAPK pathways, which

Table 4 Correlations between periodontal parameters and inflammation parameters and iron metabolism parameters in periodontitis patients.

Variable	Basic value	WBC (10^9/L)	hs-CRP (mg/L)	Hepcidin (ng/ml)	Fe (μmol/L)	Ferritin (ng/ml)	Transferrin (mg/dL)
PD (mm)	r	0.289	0.662	0.21	−0.476	0.195	−0.192
	P	<0.001***	<0.001***	0.036*	<0.001***	0.029*	0.020*
BI	r	0.224	0.647	0.205	−0.533	0.228	−0.135
	P	*0.012**	<0.001***	0.042*	<0.001***	0.011*	0.106
CAL (mm)	r	0.321	0.623	0.293	−0.498	0.284	−0.199
	P	<0.001***	<0.001***	0.003**	<0.001***	0.001***	0.017*

PD, probing depth; BI, bleeding index; CAL, clinical attachment loss. *$P < 0.05$, ***$P < 0.001$.

demonstrated that ferritin play a pivotal role in the development of periodontal diseases.[25] Besides local periodontal tissue, the higher serum ferritin levels of system iron metabolism were also found in our current study.[26] In this stud, we further analyzed serum ferritin concentration in periodontitis patients, and we found higher ferritin level and positive correlations between PD, CAL and ferritin in periodontitis patients, which was the same tendency in other inflammatory diseases.[27]

Transferrin, the major plasma transport protein that carries iron to hemoglobin synthesis, is also an acute phase protein and decreased during infection.[9] In severe microbial invasions, the normal level of transferrin saturation of 25—35 % promptly can be depressed to as low as 5 %.[19] Study have reported that the decrease in serum transferrin levels with periodontal disease and serum transferrin levels increased after periodontal therapy.[16] The results of our study were consistent with previous study, transferrin serum level reversed after the recovery of periodontal inflammation, indicated an inverse relationship between transferrin serum levels and periodontitis.

Of the 30 or so essential micronutrients, iron is the only micronutrient known to have a regulatory hormone: hepcidin.[28] Hepcidin is regarded as the key mediator of iron metabolism, as well a bridge between innate immunity and iron metabolism.[29] The main mechanism of iron metabolism centers on the interaction between hepcidin and ferroportin, which is both the hepcidin receptor and the sole cellular iron exporter through which iron is transferred to blood plasma.[30] Inflammation induce hepcidin production, predominantly induced by IL-6, driving a decrease in serum iron by inhibiting the absorption of iron and promoting the sequestration of iron in ferritin.[31] Our previous study reported IL-6 could induce hepcidin production in periodontitis,[7] the results of this study further found the regulator function of hepcidin of up-regulated ferritin levels and down-regulated serum Fe levels. The underlying pathological mechanisms of periodontitis-related iron metabolism might be that periodontitis evokes immune-inflammatory responses, resulting in systemic inflammation, eventually inflammation-induced hepcidin leads to iron metabolism disorders.

Moreover, we further analyzed whether these abnormal parameters change after periodontal therapy. The results demonstrated that periodontal therapy attenuates the disorders of hepcidin, iron, ferritin, transferrin levels at 3 months after therapies. These findings highlighted the importance of effective periodontal therapies to reduce inflammation-activated immuno-inflammatory responses. Periodontal medicine has recently been developed and aims to treat systemic diseases associated with periodontal disease through the application of periodontal therapies.[32] It is recommended that periodontal treatments may have the most cost-effective beneficial effect not only on oral disease but also on systemic diseases.[33] Therefore, the importance of effective periodontitis management should be emphasized to prevent periodontitis progression, which could effectively reduce the risk of iron metabolism disorders and other systemic comorbidities. Accordingly, there is a need to improve education and awareness of periodontal treatment and preventive management to benefit the general health of periodontitis patients.

In summary, this study provided preliminary evidence that periodontitis was associated with iron metabolism disorders and highlights the importance of effective periodontal therapies to reduce the risk of periodontitis-related other systemic comorbidities. This study would provide new insights into the systemic effects of periodontitis.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This research was supported by research funds from the National Natural Science Foundation of China (Grant number 82071117), Beijing, China; the Natural Science Foundation of Beijing (Grant number 7212136), Beijing, China.

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