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Evaluating before and after effect of oral iron supplementation on serum hepcidin level in Oral Submucous Fibrosis: A clinical study

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Abstract

Background

Oral submucous fibrosis (OSMF) is a chronic, progressive condition of the oral cavity characterized by inflammation and fibrosis of the submucosal tissues. Iron deficiency is a common finding in OSMF patients, which may contribute to the pathogenesis of the disease. Hepcidin, a key regulator of iron homeostasis, has been implicated in various fibrotic conditions. This study aimed to evaluate the effect of oral iron supplementation on serum hepcidin levels in OSMF patients.

Materials and Methods

A total of 60 patients diagnosed with OSMF were enrolled in this clinical trial. Participants were randomly assigned into two groups: the intervention group received oral iron supplementation (100 mg of elemental iron daily) for 12 weeks, while the control group received a placebo. Serum hepcidin levels were measured using enzyme-linked immunosorbent assay (ELISA) at baseline and at the end of the intervention. Clinical parameters, including mouth opening and burning sensation, were also assessed.

Results

At baseline, the mean serum hepcidin levels were 15.4 ± 3.2 ng/mL in the intervention group and 14.8 ± 2.9 ng/mL in the control group. After 12 weeks, the intervention group showed a significant increase in mean serum hepcidin levels to 23.6 ± 4.1 ng/mL ($p < 0.01$), whereas the control group showed no significant change (15.0 ± 3.1 ng/mL). Additionally, the intervention group exhibited significant improvements in clinical parameters, with a mean increase in mouth opening by 5.3 ± 1.2 mm and a reduction in burning sensation by 3.1 ± 0.9 points on a visual analog scale ($p < 0.05$).

Conclusion

Oral iron supplementation significantly increases serum hepcidin levels in patients with OSMF and is associated with improvements in clinical symptoms. These findings suggest that iron supplementation may play a therapeutic role in the management of OSMF.

Keywords

Oral submucous fibrosis, iron supplementation, hepcidin, clinical trial, fibrosis, oral health.

Introduction

Oral submucous fibrosis (OSMF) is a chronic, progressive, scarring disease affecting the oral cavity and sometimes the pharynx. It is characterized by inflammation and progressive fibrosis of the submucosal tissues, leading to restricted mouth opening, burning sensation, and increased risk of malignancy (1). The etiology of OSMF is multifactorial, with areca nut chewing being the most significant risk factor (2). However, nutritional deficiencies, particularly iron deficiency, have also been implicated in the pathogenesis of OSMF (3).

Iron plays a crucial role in various physiological processes, including oxygen transport, DNA synthesis, and cellular respiration. It is also essential for the maintenance of epithelial integrity and immune function (4). Hepcidin, a liver-derived peptide hormone, is a key regulator of iron homeostasis in the body. It controls iron absorption and distribution by binding to the iron export protein ferroportin, leading to its degradation and subsequent reduction in iron efflux from enterocytes, macrophages, and hepatocytes (5).

Recent studies have suggested that hepcidin may have a role in the fibrotic process. Elevated hepcidin levels have been observed in various fibrotic conditions, including liver fibrosis and systemic sclerosis (6,7). However, there is limited information on the role of hepcidin in OSMF. Given the association between iron deficiency and OSMF, it is plausible that dysregulated hepcidin levels may contribute to the disease pathology.

The aim of this clinical trial was to evaluate the effect of oral iron supplementation on serum hepcidin levels in patients with OSMF. We hypothesized that iron supplementation would increase serum hepcidin levels and potentially improve clinical symptoms in OSMF patients. This study provides insights into the potential therapeutic role of iron supplementation in the management of OSMF and the underlying mechanisms involving hepcidin.

Materials and Methods

Study Design

This clinical trial was designed as a randomized, double-blind, placebo-controlled study to evaluate the effect of oral iron supplementation on serum hepcidin levels in patients with oral submucous fibrosis (OSMF).

Participants

A total of 60 patients diagnosed with OSMF, aged between 18 and 60 years, were enrolled in the study. Inclusion criteria included clinically diagnosed OSMF with symptoms such as restricted mouth opening and burning sensation in the oral cavity. Exclusion criteria included patients with systemic diseases, history of iron supplementation in the past six months, pregnancy, and those with a known allergy to iron supplements. The study was approved by

the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Randomization and Blinding

Participants were randomly assigned into two groups using a computer-generated randomization schedule: the intervention group (n=30) and the control group (n=30). The intervention group received oral iron supplementation (100 mg of elemental iron daily) for 12 weeks, while the control group received a placebo. Both the participants and the investigators were blinded to the group assignments.

Intervention

The intervention group received ferrous sulfate tablets, providing 100 mg of elemental iron daily, for 12 weeks. The control group received placebo tablets identical in appearance to the iron tablets. Compliance with the supplementation was monitored by counting the remaining tablets at each follow-up visit.

Outcome Measures

The primary outcome measure was the change in serum hepcidin levels from baseline to the end of the 12-week intervention. Secondary outcome measures included changes in clinical parameters such as mouth opening and burning sensation.

Serum Hepcidin Measurement

Fasting blood samples were collected from all participants at baseline and at the end of the 12week intervention. Serum was separated by centrifugation and stored at -80°C until analysis. Serum hepcidin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit

Clinical Assessment

Mouth opening was measured using a Vernier caliper from the mesioincisal edge of the upper central incisor to the mesioincisal edge of the lower central incisor. The burning sensation was assessed using a visual analog scale (VAS) ranging from 0 (no burning) to 10 (severe burning).

Statistical Analysis

Data were analyzed using SPSS software (version 23). Descriptive statistics were used to summarize the baseline characteristics of the participants. Paired t-tests were used to compare the changes in serum hepcidin levels and clinical parameters within each group, while independent t-tests were used to compare the differences between the groups. A p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of the study participants are summarized in Table 1. There were no significant differences between the intervention and control groups in terms of age, gender, duration of OSMF, or baseline serum hepcidin levels.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Intervention Group (n=30)	Control Group (n=30)	pvalue
Age (years)	35.2 ± 8.1	34.8 ± 7.9	0.82
Gender (M/F)	18/12	17/13	0.80
Duration of OSMF (years)	3.6 ± 1.2	3.7 ± 1.1	0.76
Baseline Serum Hepcidin (ng/mL)	15.4 ± 3.2	14.8 ± 2.9	0.62

Changes in Serum Hepcidin Levels

After 12 weeks of intervention, the intervention group showed a significant increase in serum hepcidin levels compared to the baseline ($p < 0.01$). The control group showed no significant change in serum hepcidin levels ($p > 0.05$). The changes in serum hepcidin levels are presented in Table 2.

Table 2: Changes in Serum Hepcidin Levels

Group	Baseline (ng/mL)	12 Weeks (ng/mL)	Change (ng/mL)	p-value
Intervention Group	15.4 ± 3.2	23.6 ± 4.1	8.2 ± 2.1	< 0.01
Control Group	14.8 ± 2.9	15.0 ± 3.1	0.2 ± 0.3	0.68

Clinical Parameters

The intervention group showed significant improvements in clinical parameters after 12 weeks of iron supplementation. There was a significant increase in mouth opening and a reduction in the burning sensation compared to the baseline ($p < 0.05$). The control group did not show significant changes in these clinical parameters. The results are detailed in Table 3.

Table 3: Changes in Clinical Parameters

Parameter	Group	Baseline	12 Weeks	Change	pvalue
Mouth Opening (mm)	Intervention Group	25.6 ± 4.2	30.9 ± 5.1	5.3 ± 1.2	< 0.05
	Control Group	26.0 ± 4.0	26.2 ± 4.3	0.2 ± 0.3	0.60
Burning Sensation (VAS)	Intervention Group	7.8 ± 1.5	4.7 ± 1.3	-3.1 ± 0.9	< 0.05
	Control Group	7.6 ± 1.4	7.5 ± 1.5	-0.1 ± 0.2	0.72

Oral iron supplementation resulted in a significant increase in serum hepcidin levels and improvement in clinical symptoms of OSMF patients. The control group did not show any significant changes in serum hepcidin levels or clinical parameters, indicating the specific effect of iron supplementation in the intervention group.

Discussion

The results of this clinical trial demonstrate that oral iron supplementation significantly increases serum hepcidin levels in patients with oral submucous fibrosis (OSMF) and is associated with notable improvements in clinical symptoms such as mouth opening and burning sensation. These findings suggest a potential therapeutic role for iron supplementation in the management of OSMF, which warrants further exploration.

Hepcidin, a key regulator of iron homeostasis, plays a crucial role in iron absorption and distribution in the body (1). It has been implicated in various fibrotic conditions, and its dysregulation may contribute to the pathogenesis of OSMF (2,3). In our study, the significant increase in serum hepcidin levels following iron supplementation indicates that iron homeostasis is indeed disrupted in OSMF patients and that correcting iron deficiency can restore hepcidin levels. This finding is consistent with previous studies that have shown elevated hepcidin levels in response to iron supplementation in conditions associated with iron deficiency (4,5).

The clinical improvements observed in our study, such as increased mouth opening and reduced burning sensation, further support the role of iron in the pathophysiology of OSMF. Iron is essential for maintaining epithelial integrity and immune function, both of which are compromised in OSMF (6). By restoring iron levels, iron supplementation may help in repairing damaged epithelial tissues and reducing inflammation, thereby alleviating symptoms of OSMF.

Our findings align with those of previous studies that have highlighted the association between nutritional deficiencies and OSMF. For instance, studies have reported that iron deficiency is common in OSMF patients and that nutritional supplementation can improve clinical outcomes (7-10). However, our study is one of the few that specifically investigates the impact of iron supplementation on serum hepcidin levels and its correlation with clinical improvement in OSMF.

There are several strengths to our study, including the randomized, double-blind, placebocontrolled design, which minimizes bias and enhances the validity of our findings. Additionally, the use of serum hepcidin as a biomarker provides a mechanistic insight into the effects of iron supplementation in OSMF.

However, our study also has limitations. The sample size was relatively small, and the duration of the intervention was limited to 12 weeks. Larger studies with longer follow-up periods are needed to confirm our findings and to determine the long-term benefits and safety of iron supplementation in OSMF patients. Furthermore, our study did not investigate other potential mechanisms through which iron supplementation may exert its effects, such as changes in oxidative stress or inflammatory markers, which could be explored in future research.

Conclusion

In conclusion, our study provides evidence that oral iron supplementation significantly increases serum hepcidin levels and improves clinical symptoms in OSMF patients. These findings suggest that iron supplementation could be a valuable therapeutic strategy in the

management of OSMF, particularly in patients with iron deficiency. Further research is needed to validate these findings and to explore the underlying mechanisms in greater detail.

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