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Comparative Study of the Effects of Lactoferrin versus Oral Iron Therapy in Obese Children and Adolescents with Iron Deficiency Anemia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Greater prevalence of iron deficiency (ID) has been observed in overweight and obese children and adolescents. Hepcidin acts as a key regulator of iron metabolism. Hepcidin synthesis increases in response inflammatory cytokines especially Interleukin-6 (IL-6). Considering that obesity represents a low grade chronic inflammatory state, a high concentration of hepcidin has been found in obese children. Elevated hepcidin level in obese children is associated with diminished response to oral iron therapy. Lactoferrin is an iron-binding multifunctional glycoprotein and has strong capacity to modulate the inflammatory response by its capacity to reduce pro-inflammatory cytokine expression in vivo, including IL-6 and hepcidin.

Aim of the Work: To compare the efficacy of lactoferrin versus oral iron therapy in treatment of obese children and adolescents with iron deficiency anemia and the effect of therapy on serum hepcidin and interleukin 6 levels.

Methodology: This prospective randomized clinical trial was conducted on 40 obese children and adolescents aged between 6 –18 years suffering from iron deficiency anemia (IDA). They were

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equally randomized into one of 2 groups. Group A received regular oral lactoferrin in a dose of 100 mg/day. Group B received regular oral iron supplementation (Ferric hydroxide polymaltose) in a dose of 6 mg elemental iron/kg /day.Baseline investigations included complete blood count (CBC), iron profile (Serum ferritin, serum iron, total iron binding capacity (TIBC), transferrin saturation), serum Interleukin 6, and serum hepcidin. Reevaluation of CBC was done monthly while iron status parameters, serum IL-6 and serum hepcidin were reevaluated after 3 months of receiving regular therapy.

Results: Significant elevations in hemoglobin, MCV, MCH, Serum ferritin, serum iron and transferrin saturation with lactoferrin therapy compared to oral iron therapy. Significantly Lower TIBC after 3 months of lactoferrin therapy while the decrease in TIBC was insignificant in the iron therapy group.Lower serum hepcidin and IL6 after 3 months of lactoferrin therapy with no significant change in serum hepcidin and IL6 after iron therapy.

Conclusion: This study clearly demonstrated the superiority of lactoferrin over iron use as oral in the treatment of iron deficiency anemia in obese children not only for the better response of hematological and iron status parameters and less gastrointestinal side effects but also for its effect on decreasing inflammatory biomarkers as hepcidin and IL6.

Keywords: Lactoferrin; hepcidin; obesity; anemia.

1. INTRODUCTION

Childhood obesity is widely distributed in developed and developing countries. The prevalence of excess body weight has increased progressively in the past 30 years. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 [1]. One of the major causes of obesity is the rapid changes in lifestyles and dietary patterns, namely, from traditional to new diets with consumption of large amounts of fat, sugar and oil [2].

Obesity and iron deficiency are two of the most common nutritional disorders worldwide [3]. Several authors described a greater prevalence of iron deficiency (ID) in overweight and obese children and adolescents. Various hypotheses have been proposed for the association between obesity and iron deficiency. These include iron deficiency due to imbalanced nutrition in obese subjects, an increase in iron requirements due to increased blood volume, a decrease in myoglobin that binds iron in the muscles due to a decrease in physical activity, genetic predisposition [4].

Hepcidin, a 25 amino acid peptide, acts as a key regulator of iron metabolism [5]. It controls both iron entering to plasma from absorptive sites and iron released from stores. it reduces the absorption of iron from the small intestine, reduces the transfer of iron from macrophages to the plasma and/or prevents mobilization of stored iron reticuloendothelial system [4]. Hepcidin synthesis increases in response to increased circulating and tissue iron, inflammatory cytokines especially Interleukin-6 (IL-6) [6].

Considering that obesity represents a low grade chronic inflammatory state, a high concentration of hepcidin has been found in the obese despite iron deficiency [7]. This suggests that iron deficiency observed in the obese might arise from a hepcidin-related mechanism [3,8]. Moreover, elevated hepcidin level in obese children is associated with diminished response to oral iron therapy [9].

Lactoferrin, an iron-binding multifunctional cationic glycoprotein, is a key element of host defenses [10]. Its ability to bind ferric iron with high affinity and to retain it to low pH gives the protein bacteriostatic and antioxidant properties [11]. Lf exhibits other functions besides iron sequestration, such as a strong capacity to modulate the inflammatory response by its capacity to reduce pro-inflammatory cytokine expression in vivo, including IL-6 [12]. Oral lactoferrin administration was found to be helpful in reducing serum level of IL-6 and hepcidin in pregnant females suffering iron deficiency anemia [11].

This study was conducted to compare the efficacy of lactoferrin versus oral iron therapy in treatment of obese children and adolescents with iron deficiency anemia and the effect of therapy on serum hepcidin and interleukin 6 levels.

2. METHODOLOGY

This prospective randomized clinical trial was conducted on 40 obese children and adolescents

suffering from iron deficiency anemia (IDA) recruited from those attending the Pediatric Nutrition Outpatient Clinic of Gastroenterology and Nutrition Unit at Pediatric Department, Tanta university Hospitals.

2.1 Inclusion Criteria

The included children in this study aged between 6 to 18 years, had body mass index (BMI) ≥ the 95thpercentile for gender and age and diagnosed to have iron deficiency anemia based on the following criteria:

- Hemoglobin (Hb) concentration: Lower than 11.5 g/dl for children 5-11 years of age, Lower than 12 g/dl for those 12-15 years of age. For those older than 15years: hemoglobin lower than 12 g/dl in girls &lower than 13g/dl in boys.
- Ferritin lower than 30 µg/dl.
- Transferrin saturation below 16 %.

2.2 Exclusion Criteria

Children whose obesity due to syndromic problem (Prader Willi, Laurence-Moon Biedl syndrome, etc.),endocrinal causes (Cushing's syndrome or hypothyroidism) or obesity due to drug intake as corticosteroidsor antithyroid drugs. Children with: Systemic disease, Infection, inflammatory or collagen disease, Genetic causes of anemia as: thalassemia and sickle cell anemia were excluded from the study. In addition to children with higher risk of iron deficiency anemia e.g. (occult GIT blood loss, parasitic infestations and pubertal girls with heavy menstruation), children with Hemoglobin < 8gm/dl and who received iron therapy within the last 6 months before enrollment were also excluded.

All Patients were randomized into 2 groups:

- **Group A:** Twenty children and adolescents were given regular oral lactoferrin in a dose of 100 mg/day 15 minutes before meal mixed with either water, milk, or juice for 3 months.
- **Group B:** Twenty children and adolescents received regular oral iron supplementation (Ferric hydroxide polymaltose) in a dose of 6 mg elemental iron/kg /day 2hours after meals for 3 months.

All children and adolescents in the study were subjected to:

1) Full history taking with special emphasis on: Past history of systemic diseases, Maternal iron status during pregnancy, history of abnormal appetite (Pica), school performance in school-age patients, duration and type of previous iron therapy.
2) *Clinical examination:* Thorough clinical examination including Pallor, Nail's problems, Angular stomatitis, Glossitis, Pityriasis alba.
3) Anthropometric measures and Z-score calculation for (Weight, Height and Body mass index (BMI).
4) Laboratory investigations included: CBC, iron profile (Serum ferritin, serum iron, total iron binding capacity (TIBC), transferrin saturation), serum Interleukin 6, serum hepcidin at baseline. Reevaluation of CBC was done monthly. Iron status parameters, serum IL-6 and serum hepcidin were reevaluated after 3 months of receiving regular therapy.
5) Checking for patient compliance and asking for reported adverse effects as gastric irritation, abdominal pain, constipation, and dark stools.

2.3 Statistical Analysis

The collected data was coded, revised, tabulated, and analyzed through Statistical Package for Social Science (SPSS) version 20.0 software (Armonk, NY: IBM Corp). The descriptive statistics including percentages (%), arithmetic mean (X) and standard deviation (SD) were calculated for various qualitative and quantitative data to describe the study population.Significance of the obtained results was judged at the 5% level. The used tests were (Chi-square test, student t test, paired t test and Mann Whitney test).

3. RESULTS

There was no statistically significant difference between both groups as regard age, sex, residence, tanner staging and anthropometric measures (weight, height, BMI and their corresponding Z score) (Table1).

Table 2 shows insignificant difference in hemoglobin level between both groups at baseline and after 1 month of therapy. However, after 2 and 3 months of therapy, hemoglobin level was significantly higher in the lactoferrin group than the iron therapy group. Comparison

of hemoglobin level before therapy and on monthly follow up within each therapeutic group showed that in the lactoferrin therapy group hemoglobin was significantly higher after 1,2 and 3 months of therapy compared to before therapy. In the iron therapy group, no significant difference in Hb after 1month of iron therapy then significantly higher Hb was detected after 2 and 3 months of therapy.

As regard MCV, comparison of MCV before and on monthly follow up between lactoferrin and iron therapy groups revealed no significant difference between both groups at baseline. Significantly higher MCV was found in the lactoferrin therapy group than the iron therapy group at 1,2 and 3 months of therapy. Comparison of MCV before therapy and on monthly follow up within each therapeutic group revealed significantly higher MCV on each monthly follow up compared to before therapy in both therapeutic groups (Table 2).

As regard MCH, no significant difference was detected between both groups before therapy. Then significantly higher MCH was detected in the lactoferrin therapy group than the iron therapy group at all monthly follow ups. Comparison of MCH before therapy and on monthly follow up within each therapeutic group revealed significantly higher MCH on each monthly follow up compared to before therapy in both therapeutic groups (Table 2).

Table 1. Characteristics of the studied groups

	Groups					
	Group A Lactoferrin group (n=20)		**Group B Iron group (n=20)**		**Test of significance**	**P**
	No.	**%**	**No.**	**%**		
Age						
Min – Max	6 – 16		6 – 14		t = -0.586	0.281
Mean ± SD	9.57 ± 2.65		10.02 ± 2.29			
Sex						
Male	11	55.0	12	60.0	X^2= 0.102	0.749
Female	9	45.0	8	40.0		
Residence						
Urban	13	65.0	12	60.0	X^2= 0.107	0.744
Rural	7	35.0	8	40.0		
Tanner staging						
Prepubertal	14	70.0	11	55.0	X^2= 0.960	0.327
pubertal	6	30.0	9	45.0		
Weight (kg)						
Min – Max	39.0 – 94.5		35 – 86.5		t = -0.920	0.182
Mean ± SD	51.58 ± 15.16		55.72 ± 13.30			
Z score of weight						
IQR	1.52 – 2.85		1.97 – 2.63		Z = -0.270	0.787
Median	2.32		2.33			
Height (cm)						
Min – Max	116 – 167		115 – 161		t = -1.29	0.102
Mean ± SD	133.88 ± 13.18		138.9 ± 11.31			
Z score of height						
IQR	-0.530 – 0.115		-0.345 – 0.575		Z = -1.24	0.214
Median	-0.085		0.100			
BMI						
Min – Max	24.72 – 33.88		23.31 – 33.37		t = -0.323	0.374
Mean ± SD	28.15 ± 2.3		28.44 ± 3.14			
Z score of BMI						
IQR	2.0 – 3.7		2.34 – 3.42		Z = -0.663	0.509
Median	2.75		2.90			

X^2 for chi square test, t for t test, Z for Mann Whitney test

Table 2. Comparison of lactoferrin and iron therapy groups as regard hematological data

Hematological Data		Therapy Groups		Student t-test	
		Lactoferrin therapy group(n=20)	Iron therapy group (n=20)	t	P
Hemoglobin (gm/dl)	**Before therapy**				
	Mean ± SD	9.80 ± 0.49	9.9 ± 0.483	-0.773	0.222
	After 1 month				
	Mean ± SD	11.30 ± 0.38	11.07 ± 0.40	1.77	0.084
	After 2 months				
	Mean ± SD	11.74 ± 0.44	11.40 ± 0.48	2.39	0.029*
	After 3 months				
	Mean ± SD	12.48 ± 0.66	11.67 ± 0.33	4.95	<0.001*
	Paired t- test	P1<0.001*	P1<0.001*		
		P2<0.001*	P2 <0.001*		
		P3<0.001*	P3 <0.001*		
MCV (fl)	**Before therapy**				
	Mean ± SD	73.59 ± 5.24	70.75 ± 5.72	1.64	0.110
	After 1 month				
	Mean ± SD	77.12 ± 3.91	72.61 ± 5.79	2.89	0.006*
	After 2 months				
	Mean ± SD	78.15 ± 2.96	73.66 ± 5.73	3.11	0.004*
	After 3 months				
	Mean ± SD	80.01 ± 2.49	74.05 ± 5.58	4.36	<0.001*
	Paired t-test	P1<0.001*	P1=0.005*		
		P2<0.001*	P2 <0.001*		
		P3<0.001*	P3 <0.001*		
MCH (pg)	**Before therapy**				
	Mean ± SD	23.50 ± 2.09	23.29 ± 2.55	0.333	0.741
	After 1 month				
	Mean ± SD	25.33 ± 1.17	24.24 ± 1.99	2.09	0.042*
	After 2 months				
	Mean ± SD	26.45 ± 1.22	24.94 ± 1.83	3.07	0.004*
	After 3 months				
	Mean ± SD	27.54 ± 1.82	26.10 ± 1.41	2.80	0.008*
	Paired t-test	P1<0.001*	P1=0.001*		
		P2<0.001*	P2 <0.001*		
		P3<0.001*	P3 <0.001*		

t: for student t test

p: p value for comparing between the studied groups.

p1: p value for comparing between hematological data before therapy and after 1month.

p2: p value for comparing between hematological data before therapy and after 2months.

p3: p value for comparing between hematological data before therapy and after 3months.

Table 3 shows no significant difference in serum ferritin, serum iron, TIBC and transferrin saturation between the lactoferrin therapy group and oral iron therapy group before starting treatment. Significantly higher serum ferritin, serum iron and transferrin saturation in obese children receiving lactoferrin than obese children receiving iron therapy after 3 months of treatment. Significantly higher serum ferritin, serum iron and transferrin saturation after 3 months of therapy compared to before therapy in both therapy groups. On the other hand, significantly Lower TIBC was detected after 3 months of lactoferrin therapy while the decrease in TIBC was not significant in the iron therapy group. There was also insignificant difference in TIBC between both treatment groups after 3 months of therapy.

Table 4 shows insignificant difference as regard serum hepcidin between both lactoferrin and iron therapy groups before and after 3 months of therapy. However, significantly lower serum hepcidin was observed after 3 months of lactoferrin therapy with no significant change in serum hepcidin after 3 months of iron therapy.

No significant difference was also detected as regard serum IL6 between both lactoferrin and iron therapy groups at baseline with significantly lower serum IL6 in the lactoferrin therapy group than iron therapy after 3 months of therapy. Significant decrease in serum IL 6 after 3 months of lactoferrin therapy with no significant change in the serum IL6 level before and after iron therapy.

Fig. 1 shows statistically significant difference between the lactoferrin and iron therapy group as regard adverse effects of therapy. In the iron therapy group, 30% of the children had gastric irritation, 35% had nausea, 40% had abdominal pain, 55% had constipation and 75% experienced dark stools. On the other hand, children in the lactoferrin therapy group experienced fewer side effects. Only 5% had gastric irritation, 5% had nausea, 15% had constipation. No dark stools or abdominal pain were observed in the lactoferrin therapy group.

Table 3. Comparison of lactoferrin and iron therapy groups as regard iron profile

	Groups		t- test	
	Group A Lactoferrin group (n=20)	**Group B Iron group (n=20))**	**t**	**P**
Serum Ferritin (ng/ml)				
Before therapy:			-1.19	0.241
Min. – Max.	2.90 – 28.70	3.00 – 28.00		
Mean ± SD	16.88 ± 7.96	19.67 ± 6.81		
After 3 months:			2.468	0.018*
Min. – Max.	25.00 – 71.00	16.70 – 45.00		
Mean ± SD	38.33 ±12.65	29.95 ± 8.40		
Paired t test	P1 <0.001*	P2 <0.001*		
Serum Iron (µg/ml)				
Before therapy:			1.05	0.301
Min. – Max.	0.20 – 0.60	0.22 – 0.63		
Mean ± SD	0.46 ± 0.14	0.42 ± 0.14		
After 3 months:			2.52	0.016*
Min. – Max.	0.51 – 1.04	0.33 – 0.96		
Mean ± SD	0.72 ± 0.124	0.60 ± 0.171		
Paired t test	P1 <0.001*	P2 <0.001*		
TIBC (µg/ml)				
Before therapy:			1.676	0.101
Min. – Max.	3.50 – 4.71	3.25 – 4.80		
Mean ± SD	4.13 ± 0.458	3.90 ± 0.387		
After 3 months:			-1.147	0.259
Min. – Max.	2.80 – 4.20	3.30 – 4.20		
Mean ± SD	3.54 ± 0.435	3.68 ± 0.297		
Paired t test	P1 <0.001*	P2 = 0.248		
Transferrin saturation (%)				
Before therapy:			0.632	0.531
Min. – Max.	5.40 – 14.60	5.60 – 14.60		
Mean ± SD	11.15 ± 2.54	10.58 ± 3.08		
After 3 months:			2.938	0.006*
Min. – Max.	14.70 – 25.00	10.00 – 28.20		
Mean ± SD	20.32 ± 2.82	16.42 ± 5.23		
Paired t test	**P1 <0.001***	**P2 = 0.003***		

t: t for student t test, p1: p value for comparing between each parameter before therapy and after 3 months in the lactoferrin therapy group., p2: p value for comparing between each parameter before therapy and after 3 months in the oral iron therapy group

Table 4. Comparison of lactoferrin and iron therapy groups as regard serum hepcidin and IL6

	Therapy groups			
	Group A Lactoferrin group (n=20)	**Group B Iron group (n=20)**	**Z**	**P**
Serum hepcidin(ng/ml)				
Before			1.82	0.067
(IQR)	179.96 - 316.43	168.17 - 221.71		
Median	238.63	177.64		
After 3 months			0.635	0.522
(IQR)	119.49 - 220.39	109.94 - 209.23		
Median	179.74	170.19		
Wilcoxon Signed Ranks Test	P1 = 0.031*	P2= 0.262		
Serum IL6 (pg/ml)				
Before therapy			1.47	0.141
(IQR)	94.66 - 183.11 170.190	78.33 - 153.25		
Median		117.815		
After 3 months			-2.366	0.018*
(IQR)	61.87 - 37.21	181.58 - 48.31		
Median	55.28	91.42		
Wilcoxon Signed Ranks Test	P1 <0.001*	P 2= 0.885		

Z: Z for Mann Whitney's test
p1: p value for comparing between each parameter before therapy and after 3months in the lactoferrin therapy group
p2: p value for comparing between each parameter before therapy and after 3 months in the oral iron therapy group.

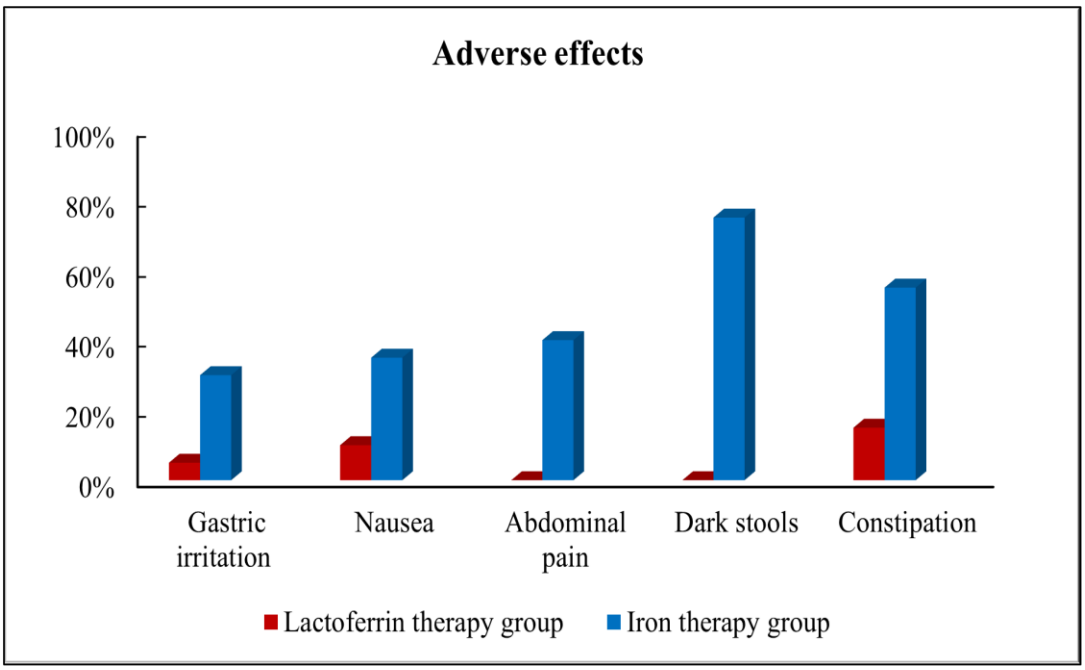

Fig. 1. Comparison of lactoferrin and iron therapy groups as regard adverse effects

4. DISCUSSION

It was found that increased hepcidin level in obese was associated with diminished response to oral iron therapy in childhood iron deficiency anemia [12]. Using lactoferrin has been described to counteract inflammatory disorders by down-regulating IL-6 and subsequently hepcidin transcription and by up-regulating ferroportin expression, to redistribute endogenous iron between tissue/secretions and blood [13].

To our knowledge, no study provided sufficient data about the role of lactoferrin in treating anemia in obese children. On comparing hemoglobin levels before starting therapy and on monthly follow up for 3 months, we found non-significant difference between both group before therapy *(P=0.222)*, then higher hemoglobin levels on 1, 2, 3 months follow up in the lactoferrin group compared to the iron therapy group. More increase in hemoglobin was noticed in the lactoferrin group versus oral iron group. This agrees with *El-Khawaga and Abdelmaksoud, (2019)* who assessed the efficacy of lactoferrin versus oral iron supplementation for treatment of IDA in primary schools' children and found higher hemoglobin in the lactoferrin group after 1month of therapy [14].

As regard MCV and MCH follow up, our study demonstrated no significant difference in MCV*(P=0.110)* and MCH *(P=0.741)* between both groups before therapy with significantly higher MCV and MCH in the lactoferrin group than the iron therapy group at the monthly follow up study. *El-Khawaga and Abdelmaksoud, (2019)* showed no significant difference between lactoferrin and iron therapy groups in MCV and MCH before and after therapy [14].

Serum ferritin in our study showed no significant difference between the lactoferrin therapy group and oral iron therapy group before starting treatment *(P=0.241)*. Significantly higher serum ferritin level in both groups after 3months of therapy *(P<0.001)* with higher ferritin level in obese anemic receiving lactoferrin than those receiving iron therapy *(P=0.018)*. These data are consistent with *Khawaga and Abdelmaksoud, (2019) study [14].*

Taruni et al, (2018) compared the efficacy of bovine lactoferrin versus ferrous sulphate in the treatment of iron deficiency anemia in non pregnant females. This study demonstrated insignificant decrease in ferritin with iron therapy while participants of lactoferrin therapy group demonstrated an increase in ferritin levels post-therapy which was also statistically insignificant [15].

In the present study,serum iron, TIBC, and transferrin saturation were evaluated before and after 3months of therapy with no significant difference observed between both therapy groups before starting treatment *(P=0.301), (P=0.101)*, *(P=0.531*) respectively. Then after 3months of therapy a significantly higher serum iron and Transferrin saturation was detected in lactoferrin therapy group than iron therapy group *(P=0.018), (P=0.006)* respectively. While on evaluating TIBC in our therapy groups, significantly Lower TIBC was found after 3 months of lactoferrin therapy *(P<0.001)* while the decrease in TIBC was not significant in the iron therapy group *(P=0.248)* which agrees with *Taruni et al, (2018*) [15].

Taruni et al, (2018) also showed significant increase in serum iron and transferrin saturation in non-pregnant young females received lactoferrin therapy with non-significant increase in the patients received ferrous sulfate [15].Meanwhile,*Khawaga and Abdelmaksoud, (2019)* study revealed significantly higher serum iron in school children with IDA treated with lactoferrin compared with those treated with iron with non-significant decrease in TIBC in both lactoferrin and iron therapy groups after 1 month of therapy [14].

On the other hand, a study by *Kamal et al, (2021*) included 150 children aged above 2 years suffering from iron deficiency anemia (divided into 3 therapy groups) the 1st group received lactoferrin100mg daily, while the 2nd group received lactoferrin 100mg combined with iron. The 3rd group received oral iron (ferric hydroxide polymaltose) for 3months.Hemoglobin (Hb), serum ferritin, serum iron, and TIBC among the three groups were significantly improved when compared with baseline levels after 1.5 and 3 months of treatment. The highest improvement was observed in the Lactoferrin 100mg combined with iron group followed by the oral iron group [16].

A specific lactoferrin receptor is present in the small intestine that can bind and internalize bovine lactoferrin. Microscopic examinations confirm that lactoferrin molecules bind to these receptors and penetrate the cells, subsequently

releasing the transported iron. The expression of intestinal lactoferrin receptors is regulated by the magnitude of cellular iron stores and increases with its deficit. Higher number of receptors corresponds to higher uptake of iron. This mechanism has been used to explain the high absorption of iron from human milk and this explain improvement in iron indices with lactoferrin therapy [17, 18].

In the present study, no significant difference was detected as regard serum hepcidin *(P=0.067)* and IL6 *(P=0.141)* between lactoferrin and iron therapy groups before therapy. After 3months of lactoferrin therapy a significant reduction in serum hepcidin *(P=0.031)* and IL6 *(P<0.001)* was detected. No significant difference in both the hepcidin *(P=0.262)* and IL6*(P=0.885)* after 3months of iron therapy. *Lepanto et al, 2018* showed significant decrease in hepcidin and IL6 in pregnant and non-pregnant women with inherited thrombophilia after 30 days of lactoferrin therapy with no decrease in hepcidin and IL6 after ferrous sulfate therapy [19].

Therefore, even if the mechanism by which bovine lactoferrin (bLf) exerts its anti-inflammatory activity is still under debate. There is strong evidence that bLf efficacy in treating iron deficiency anemia and anemia of inflammation is not linked to a direct iron supplementation, but to a more complex mechanism involving this protein in decreasing IL-6 and modulating hepcidin and Ferroportin, the most important iron homeostasis actors, both regulated by IL-6. This Promotes cellular iron efflux from tissues to the blood [20,21].

As regard adverse effects experienced by our patients in both therapeutic groups, statistically significant difference was detected between the lactoferrin and iron therapy group. More gastric irritation, nausea, and constipation in the iron therapy group. No dark stools or abdominal pain were observed in the lactoferrin group but were observed in the iron therapy group*. Rezk et al, (2016*) also reported that gastrointestinal adverse events occurred more frequently with ferrous sulphate than the lactoferrin group [22]. A meta-analysis by *Hashim et al, (2017)* reported fewer rates of epigastric discomfort, vomiting and constipation in patients treated with lactoferrin in comparison with those treated with ferrous sulphate. They reported that Abdominal colic and dark stools were predominate in the oral ferrous sulphate group [23].

The significant reduction in gastrointestinal adverse effects observed with oral lactoferrin can be due to absence of excess free iron available in the gastrointestinal tract. Thereby, it avoids mucosal irritation and disturbance of bowel motility. This is totally unlike treatment with oral ferrous salts of which only about 20-30% is absorbed, while the majority is carried through the gut lumen inducing free radical mediated damage to the gut mucosa and alteration of bowel motility [23]. These gastrointestinal side effects represent the main reason for low compliance with oral iron therapy [24, 25].

5. CONCLUSION

This comparative study clearly demonstrated the superiority of lactoferrin over iron use as oral in the treatment of iron deficiency anemia in obese children not only for the better response of hematological and iron status parameters and less gastrointestinal side effects but also for its effect on decreasing inflammatory biomarkers hepcidin and IL6.

CONSENT

Written informed consent was signed by the parents/caregivers.

ETHICAL APPROVAL

This study was approved by the local ethics committee of the Faculty of Medicine of Tanta University was obtained under registration number of 32591/09/18.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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