Pivotal role played by the consumption of a food supplement (composed of hydrolyzed sea fish cartilage, vitamin C, vitamin E, folic acid, zinc and copper) in the treatment of iron deficiency in a group of fertile female patients

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EFFECT OF TREATMENT WITH FOOD SUPPLEMENT (CONTAINING SELECTED SEA FISH CARTILAGE, VITAMIN C, VITAMIN E, FOLIC ACID, ZINC, COPPER) IN WOMEN WITH IRON DEFICIENCY: DOUBLE BLEND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL.

Aim. **The term iron deficiency is used to indicate a condition in which the content of iron (Fe) in the organism is low, even before the consequent reduction in erythropoiesis comes about.**
This clinical situation is very frequent in patients in fertile age. The therapy commonly used (Fe salts) is often poorly tolerated. The use of food supplement containing nutrients useful for improving the bioavailability of Fe and that is well tolerated can represent a valid alternative to iron therapy.
Methods. **The present study examines 49 fertile women with iron deficiency, of normal weight and not undergoing estroprogestin treatment. The patients underwent 3 assessments: basal, after 30 and after 60 days to determine their complete haemochrome, blood iron, blood ferritin, blood transferring, iron binding capacity, folates, TSH, FT3, and FT4. Following the basal assessment, patients were randomly assigned to 1 of 2 treatment groups: treatment A (25 patients): food supplement containing hydrolized sea fish cartilage, Vitamin C, vitamin E, folic acid, zinc, copper (Captafer); treatment B (24 patients): placebo.**
Results. **The patients were then subdivided into 2 groups according to the basal blood iron (<60 µg/dL) or blood ferritin (< 20 ng/mL) values. In the group presenting blood iron of <60 µg/dL only treatment A supplement produced a significant improvement in blood iron after 30 (P<0.001) and after (P<0.005) days of treatment. The group with basal blood ferritin of <20ng/mL presented blood iron levels of >60 µg/dL; in these patients after 60 days of treatment with the supplement, there was a significant increase in blood ferritin (P<0.05); the patients treated with placebo, on the other hand, did not show any significant difference compared to basal values.**
Conclusions. **This study has shown that, in patients with ion deficiency, the use of a food supplement, consisting of nutrients that improve the bioavailability of Fe, leads to a significant improvement in blood iron and blood ferritin levels.**
Key words: **Iron deficiency – Iron – Folic Acid – Vitamin C – Vitamin E – Sea Fish Cartilage.**

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Iron is a vital element within the human organism, albeit only in small quantities (the body contains 4 - 5 g), as it is an essential component of haemoglobin, myoglobin and iron-dependent enzymes [1]. The term 'iron deficiency is used to indicate a condition where the body's iron content is low, before the consequent reduction in erythropoiesis is determined [2]. There are, therefore, alterations in iron levels which are not accompanied by the classic haematological alterations, which appear in the phase following obvious anaemia and which can be defined as a reduction in the body's total haemoglobin content. This clinical scenario is frequently encountered in fertile female patients, [3, 4] due to iron loss resulting from changes in the rhythm, intensity or duration of menstrual periods, or due to a low intake of alimentary iron. This can occur in patients who do not eat meat products (for example, vegetarian women) or who do not consume adequate quantities of meat. From a symptomatological perspective, iron deficiency is characterized mainly by tiredness and a tendency to experience both physical and mental exhaustion easily, with no apparent cause [5, 12] and can therefore become a debilitating illness [13]. Iron salt supplements [14] are commonly used as a therapeutic treatment. However, this treatment is often poorly tolerated when used frequently, producing disturbing side effects on the gastrointestinal apparatus (nausea, digestive difficulties, abdominal heaviness and pain) [15]. Numerous studies have shown that certain nutrients, such as vitamin C [16-19], folic acid [20,21], vitamin E [22], zinc [23-25] and copper [26] are factors which facilitate the intestinal absorption of iron. Furthermore, recent *in vitro* studies have demonstrated the efficacy of hydrolyzed sea fish cartilage [27] in increasing the bioavailability of iron consumed in the diet. It is, however, possible to hypothesize that the use of a food supplement containing hydrolyzed sea fish cartilage, combined with the factors listed above, could be useful in improving iron absorption and enabling its correct usage by the organism, thereby representing a valid alternative to martial therapy in the treatment of iron deficiency. On the basis of these considerations, a study was carried out in a group of fertile patients diagnosed with iron deficiency in order to evaluate the efficacy of a food supplement composed of the nutrients listed above.

Apparatus and method

58 fertile female patients were enrolled following release of their informed consent (average age ± DS: 38 ± 9 years old). All patients were of normal weight (body mass index between 18 and 25; average ± DS: 23 ± 2), none was receiving estroprogestin therapy and all showed blood iron values lower than 60mg/dl or blood ferritin values lower than 20ng/ml; these are the haematochemical values used in the diagnosis of iron deficiency [28]. The patients were only admitted to the study following exclusion of all the main chronic pathologies which can cause iron deficiency (celiac disease, gastrointestinal tract haemorrhage, chronic inflammatory intestinal diseases, thyropathies). These were excluded by means of careful specialized internist visits and the appropriate haematochemical examinations. These patients underwent 3 evaluations (baseline visit, after 30 days and after 60 days of treatment) in order to determine complete haemochrome, blood iron, blood ferritin, blood transferrin, iron binding capacity, folates, TSH, FT3 and FT4. These haematochemical evaluations were carried out using standardized methods. In addition, the patients underwent evaluation of their emotional mood using the Beck Questionnaire [29], which was carried out at the baseline visit and then repeated after 60 days. After the baseline visit, which was carried out halfway through the menstrual cycle, the patients were assigned at random to one of two treatments:

- Treatment A: 30 patients took the food supplement (2 tablets per day) containing hydrolyzed sea fish cartilage, vitamin C, vitamin E, folic acid, zinc and copper

TABLE I - ***Nutritional information relating to the food supplement used in the study (Captafer, Medestea, Torino, Italy). Ingredients: hydrolyzed sea fish cartilage, microcrystalline cellulose, zinc gluconate, vitamin C, vitamin E, vegetable magnesium stearate, copper gluconate; anti-caking agent: silicon dioxide; folic acid; coating agents: hydroxypropylmethylcellulose, microcrystalline cellulose; stearic acid, lemon flavouring.***

	Nutritional information		
	2 tbl	% RDA	100 g
Energy (Nx6,25)	2,3kcal		143 kcal
	9,7 kj		604 kj
Proteins (pd)	0,38 g		23,8 g
Carbohydrates	0,10 g		6,1 g
Fats	0,02 g		2,31 g
Vitamin C	90 mg	150	5,62 g
Vitamin E	30 mg	300	1,87 g
Folic Acid	150 µg	75	0,01 g
Zinc	7,5 mg	100	0,98 g
Copper	1,2 mg		0,07 g
Hydrolized Sea Fish Cartilage	800 mg		50 g

(Captafer®, Medestea, Torino, Italy). The nutritional composition is detailed in Table I;
- Treatment B: 28 patients took a placebo (2 tablets/day).

All patients were given an information booklet which included dietary advice and suggestions of ways to increase iron absorption through the daily diet, according to internationally recognized guidelines [30].

Of the 58 patients who enrolled, 49 completed the study: 25 from the Treatment A group and 24 from the Treatment B group. The other 9 patients chose to leave the study solely for personal reasons.

Statistical analysis

In order to evaluate the difference in the haematochemical parameters after 30 days and after 60 days in comparison with the baseline values, the 2-tail Student t-test was used. P values of less than 0.05 were considered statistically significant.

Results

Table II records all the haematochemical data of the 49 patients who were evaluated. The patients were then sub-divided into 2 groups according to the blood iron values (<60µg/dl: Group 1) and blood ferritin values (<20ng/dl: Group 2) recorded at the baseline examination.

	T0 Trattamento A	T1 Trattamento A	T2 Trattamento A	T0 Trattamento B	T1 Trattamento B	T2 Trattamento B
WBC 10^3/Ul	7,23±1,87	6,86±1,45	6,92±1,64	7,88±1,45	7,46±1,65	6,99±1,55
RBC 10^6/uL	4,47±0,37	4,46±0,35	4,51±0,33	4,55±0,48	4,49±0,66	4,48±0,53
HGB g/dl	13,18±1,43	13,30±1,46	13,22±1,29	13,24±1,47	13,28±1,66	13,43±1,54
HCT %	38,70±3,65	38,64±3,65	39±3,15	38,66±3,45	38,98±3,49	38,48±3,18
MCV fL	86,70±6,83	86,87±7,40	84,07±14,55	85,40±7	86±8,53	85,65±9,66
PLT 10^3/uL	264,79±70,80	273±60,22	275,55±67,80	275,89±60,48	272±65,44	275,45±66,88
Linf. Tot %	2,15±0,54	2,05±0,62	2,08±0,56	2,25±0,59	2,17±0,53	2,22±0,66
Linf. 10^3/uL	30,66±7,07	29,69±6,93	30,70±6,18	29,46±6	30,59±7,11	29,55±6,48
Folati ng/ml	6,64±3,45	5,94±3,36	6,60±2,96	5,99±3,34	6,50±3,66	6,34±3,56
Vitamin B12 pg/ml	337±80,60	385,50±106,33	407,50±108,82	344,60±90,50	356,40±99,45	390,44±100,72
TSH mU/L	1,45±0,70	—	—	1,98±0,45	—	—
FT3 pmol/L	6,96±0,62	—	—	7,06±0,44	—	—
FT4 pmol/L	11,82±2,62	—	—	12±1,99	—	—
Sideremia µg/dl	50,9±19,9	69,8±11,2	70,7±2,1	60,4±26,8	60,7±25,1	61,2±27
Transferrin mg/dl	307,36±61,07	309,76±58,98	315,43±62,69	305,48±59,77	308,54±59,47	307,42±60,42
Ferritin ng/ml	19,2±9,6	20,6±7,3	20,6±7,5	21,1±8,9	19,9±7,5	20,3±7,1
TIBC µg/dl	398,27±79,06	402,43±76,31	413,80±78,30	390,4±80,5	400,6±84,4	411,9±85,4

Table II - Average ± DS of the hematochemical parameters evaluated in the study, from the first (T0), second (T1) and third (T20) assessments in Group 1 and Group 2.

Table III - Average ± DS of blood iron, transferrin and ferritin in the patients with blood iron <60mg/dl at the first (T0) second (T1) and third (T2) evaluations in Group 1 and Group 2

	T0 Trattamento A	T1 Trattamento A	T2 Trattamento A	T0 Trattamento B	T1 Trattamento B	T2 Trattamento B
Sideremia mg/dl	36,4±9,8	65,3±11,8	57±28,2	38,6±8,8	40,7±8,1	39,2±7
Transferrin mg/dl	315,35±61,17	316,41±60,91	321,64±64,61	320,45±63,22	319,36±69,88	320,76±69,45
Ferritin ng/ml	26,4±2,2	25±3,7	23,7±2,1	28±5,4	26±3,8	25,9±3,8

Table IV - Average ± DS of blood iron, transferrin and ferritin in the patients with ferritin <20ng/ml at the first (T0) second (T1) and third (T2) evaluations in Group 1 and Group 2

	T0 Trattamento A	T1 Trattamento A	T2 Trattamento A	T0 Trattamento B	T1 Trattamento B	T2 Trattamento B
Sideremia mg/dl	72,7±7,6	76,6±8,3	71,6±8,9	86,1±14,7	84,2±15,5	87,1±16,5
Transferrin mg/dl	324,29±57,80	328,47±53,76	329,29±57,18	291,34±60,45	296,03±59,25	301,12±59,39
Ferritin ng/ml	8,6±4,4	13,9±6,6	15,5±10,5	12,9±3,6	12,7±2,9	13,8±3,3

Table III lists the values of blood iron, blood transferrin and blood ferritin of the patients in Group 1 (15 treated with the food supplement and 13 with the placebo). Analysis of the results shows that, after 30 days of treatment, only Treatment A patients demonstrated a significant ($P<0.001$) and considerable improvement in blood iron, which was also the case after 60 days ($P<0.005$). One very important aspect arising from analysis of the results obtained was the fact that after 60 days of treatment with the food supplement, 100% of the patients responded to the treatment, producing an increase in blood iron. The patients in the Treatment B group (placebo) did not show any significant improvement in blood iron levels either after 30 days or after 60 days. Table IV lists the blood iron, blood transferrin and blood ferritin values of the patients in Group 2 (10 treated with the food supplement and 11 with the placebo), who showed baseline blood ferritin values lower than 20ng/ml. All these patients turned out to have normal blood iron (< 60 µg/dl). Analysis of the results recorded after 60 days of treatment with Captafer shows a significant increase ($P<0.05$) in blood ferritin values; however, the patients treated with the placebo showed no significant variation. No side effects of any type were noted during the consumption of the food supplement; furthermore, the compliance of the patients who took the product was excellent.

In terms of evaluation of the patients' mood using the Beck Questionnaire, a statistically significant improvement in comparison with the baseline level (7 ± 2 vs 3 ± 1, $P<0.05$) was noted after 60 days of treatment exclusively in the patients receiving the Captafer treatment. Meanwhile, the scores from the 2 evaluations were virtually identical for the patients who received the placebo (6 ± 3 vs 6 ± 1).

Discussion and conclusions

The treatment of iron deficiency by consuming a food supplement composed of nutrients which facilitate iron absorption and promote the correct use of iron by the organism [14] could offer a valid alternative to the classic treatment using iron salts [14] which, unfortunately, frequently presents significant side effects relating to the gastrointestinal tract [15]. This study has in fact demonstrated the efficacy, in comparison with the placebo, of taking a 60-day course of a food supplement (composed of hydrolyzed sea fish cartilage, vitamin C, vitamin E, folic acid, zinc and copper), in improving the blood iron and blood ferritin values in a group of fertile patients suffering from iron deficiency. This is an original result in the sense that previous studies carried out to demonstrate the efficacy of taking specific nutrients in improving iron absorption and bioavailability were often

carried out using individual nutrients only. In contrast, this study considers for the first time the efficacy of consuming a variety of nutrients together, all of which have a positive effect on iron metabolism. Furthermore, this study goes on to prove the efficacy within the human body of a certain compound - hydrolyzed marine fish cartilage - which produced excellent *in vitro* results in improving the bioavailability of iron [27]. Finally, it is important to underline the significant improvement in mood which was encountered exclusively in the group which took the food supplement. This finding is a factor which must be given serious consideration, in light of the fact that iron deficiency is often associated with mood changes [5-13]. This food supplement treatment therefore presents a valid alternative to martial therapy, and further studies must be carried out in order to develop this very promising area, especially given the high number of patients believed to be affected by iron deficiency [2, 3].

Summary

Aim: The term iron deficiency is used to indicate a condition where iron (Fe) content within the organism is low, prior to the determination of a consequent reduction in erythropoiesis. This clinical scenario is often encountered in fertile female patients. The most commonly used therapy (Fe salts) is often poorly tolerated. This use of a well-tolerated food supplement containing nutrients that can improve Fe bioavailability could offer a valid alternative to martial therapy. *Method*: 49 fertile female patients suffering from iron deficiency were evaluated in this study, all of normal weight and not receiving estroprogestin therapy. The patients underwent 3 evaluations: baseline, after 30 days and after 60 days, in order to determine complete haemochrome, blood iron, blood ferritin, blood transferrin, iron binding capacity, folates, TSH, FT3 and FT4. After the baseline evaluation, the patients were randomly assigned to one of 2 treatment groups: Treatment A (25 patients): food supplement containing hydrolyzed sea fish cartilage, vitamin C, vitamin E, folic acid, zinc and copper (Captafer); or Treatment B (24 patients): placebo.

Results: The patients were then sub-divided into 2 groups according to baseline values of blood iron (<60 mg/dl) or blood ferritin (<20ng/ml). In the group of patients who presented a blood iron value of <60mg/dl, only treatment A (food supplement) showed a significant improvement in blood iron values after 30 days ($P<0.001$) and after 60 days ($P<0.004$) of treatment. The group of patients with baseline blood ferritin levels <20ng/ml had blood iron values >60mg/gl. After 60 days of treatment with the food supplement, these patients showed a significant increase in blood ferritin ($P<0.05$). In contrast, the patients treated with the placebo showed no significant difference in comparison with the baseline values. *Conclusions*: This study proved that in female patients with iron deficiency, use of a food supplement composed of nutrients which improve Fe bioavailability produces a significant improvement in blood iron and blood ferritin values.

Key words: Iron deficiency - iron - folic acid - vitamin C - Vitamin E - Sea fish cartilage.

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