

Iron supplementation for fatigue in non-anemic women with ferritin ≤ 20 $\mu\text{g/L}$: follow-up study after a double-blind randomized placebo-controlled trial

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Background: Iron supplementation may be beneficial to women complaining of unexplained fatigue as shown by a one-month randomised clinical trial that we published previously. Intensity of fatigue decreased significantly after a one-month iron supplementation but we do not know what could be the impact of a 2 or 3-months iron treatment on fatigue.

Methods: The design is a 2-month open follow-up study immediately after the one-month double-blind, placebo-controlled prospective trial. Subjects were recruited in an academic primary care center and in 8 general practices. The inclusion criteria were women between 18 and 55 years old, complaining of unexplained fatigue after ruling out somatic disorders, chronic fatigue syndrome or evidence of depression; 144 participants were randomly assigned either to oral ferrous sulfate (80 mg once daily) or placebo for 4 weeks. After one month, women (n=65) with a low serum ferritin concentration (below or equal to 20 $\mu\text{g/L}$) received iron for two additional months in an open design. The effect of iron treatment was assessed by questionnaires (a 10-point Likert scale of fatigue). Adherence to treatment was verified by an electronic device.

Results: The level of fatigue after one month decreased by 29% ($-1.82 \pm 1.7 / 6.37 \pm 1.5$ points) in the group receiving iron vs 13% ($-0.85 \pm 2.1 / 6.46 \pm 1.5$ points) in the placebo group ($p=0.0037$). Among the group of 65 women with ferritin ≤ 20 $\mu\text{g/L}$ at baseline, 35 who were in the treatment group for the first month received two additional months of iron supplementation. In this group the intensity of fatigue decreased by 50% after 3 months of iron supplementation. The mean serum ferritin level increased from 10.3 ± 5 to 27.8 ± 11.5 $\mu\text{g/L}$. Iron retention calculated by Walters formula decreased from 4.2 % the first month to 1.3% the last 2 months. The 30 subjects with ferritin ≤ 20 $\mu\text{g/L}$ who were in the placebo group over the first month received two months of iron supplementation. Fatigue decreased by 48%. Mean serum ferritin went from 11.5(5) to 23.6 (8.3) $\mu\text{g/L}$.

Conclusion: This observational study following an RCT showed that iron supplementation for at least 2 months is necessary to decrease the intensity of fatigue by approximately 50% in non-anemic iron deficient women.