

LETTER TO EDITOR

Iron homeostasis alterations and erectile dysfunction: A new issue in erectile dysfunction treatment?

Claudio Marino¹, Salvatore Iaconis¹, Francesco Di Bello¹, Gianluigi Cacace¹, Giovanni Fusco¹, Lorenzo Romano¹, Ernesto Di Mauro¹, Luigi Cirillo¹, Vincenzo Maria Altieri^{2, 3}, Francesco Mastrangelo¹, Luigi Napolitano¹, Alessandro Palmieri¹

¹ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy;

² Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy;

³ Department of Urology, Humanitas Gavazzeni, Bergamo, Italy.

KEY WORDS: *Erectile dysfunction; Nitric oxide; Iron.*

Submission 31 December 2023; Accepted 17 January 2024

To the Editor,

Erectile dysfunction (ED) is one of the most prevalent conditions affecting men globally, with significant psychological and social consequences (1-2).

The prevalence varies across different populations, and it is estimated around 50% in men aged between 40 to 70 (3). The etiology of ED is multifactorial, involving a complex crosstalk between psychological, hormonal, neurogenic, vascular, and structural factors (2, 4, 5) Recently, the role of *iron homeostasis* (IH) is emerging. Indeed, it is known that in hereditary hemochromatosis patients, the iron overload accumulated in the penis tissue, resulting in oxidative stress, tissue damages and consequently ED. To date, IH is an essential aspect of human health, and its dysregulation has been historically implicated in neurodegenerative disorders, anemia, or cardiovascular diseases (6). Albeit the novel evidence on iron overload consequences on penis tissues, the underlying mechanisms of iron-related-ED remains unknown (7). Several hypotheses have been postulated, such as endothelial dysfunction related either to iron overload and deficiency, the anemia, oxidative stress overproduction, and neurogenic dysfunction. First, in hemochromatosis patients the ED could occur due to the storage of iron in penis tissue, endocrine dysfunction as well as decreased serum testosterone level (8). Furthermore, also the iron deficiency has been associated with ED. The mechanism underlying the above observations is due to the reduced *nitric oxide* (NO) bioavailability (9). *Reactive oxygen species* (ROS) may be involved in the iron-related-ED. Indeed, ROS disrupt the oxidative balance, affecting the *hypothalamic-pituitary-gonadal axis* (HPG) functionality (10). Moreover, the reaction of superoxide ($O_2^{\cdot-}$) with NO, resulting in acute impairment of cavernosal relaxation and in long-term penile vasculopathy due to a cellular damage. Additionally, iron deficiency can also increase the oxidative stress, compromising antioxidant defense mechanisms (11). Indeed, super-Oxide dismutase, one of the most antioxidants enzymes, is increased in patients with iron deficiency anemia, due to a compensatory reaction to the oxidative stress. Moreover, Iron accumulation in the central nervous system can lead to neurodegeneration, and potentially affecting the neural pathways involved in erectile function with reduction of dopamine synthesis (12). In conclusion, IH represents a key role in endothelial and cavernous nerves function. Both iron overload and deficiency could impair endothelial function, reducing NO bioavailability and vasodilation in the penile vasculature (13). Furthermore, the iron storage in the nervous plex could determine nerve injury, leading to ED. The relationship between IH alterations and ED represent a promising research area, with potential implications for the diagnosis and treatment of ED. Further research is needed to determine the effective mechanism of neurogenic dysfunction which contributes to ED in the context of IH alterations and whether targeting this mechanism could lead to novel therapeutic interventions.

REFERENCES

1. Mirone V, Napolitano L, D'Emmanuele di Villa Bianca R, et al. A new original nutraceutical formulation ameliorates the effect of Tadalafil on clinical score and cGMP accumulation. *Arch Ital Urol Androl.* 2021; 93:221-226.
2. Napolitano L, Fusco GM, Cirillo L, et al. Erectile dysfunction and mobile phone applications: Quality, content and adherence to European Association guidelines on male sexual dysfunction. *Arch Ital Urol Androl.* 2022; 94:211-216.
3. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994; 151:54-61.

4. Cirillo L, Fusco GM, Di Bello F, et al. Sexual dysfunction: Time for a multidisciplinary approach? *Arch Ital Urol Androl.* 2023; 95:11236.
5. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet.* 2013; 381:153-65.
6. Camaschella C. Iron-deficiency anemia. *N Engl J Med.* 2015; 372:1832-43.
7. Brissot P, Ropert M, Le Lan C, Loréal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. *Biochim Biophys Acta.* 2012; 1820:403-10.
8. Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med.* 1998; 129:932-9.
9. Choi JW, Pai SH, Kim SK, et al. Iron deficiency anemia increases nitric oxide production in healthy adolescents. *Ann Hematol.* 2002; 81:1-6.
10. Darbandi M, Darbandi S, Agarwal A, et al. Reactive oxygen species and male reproductive hormones. *Reprod Biol Endocrinol.* 2018; 16:87.
- 11, et al. Atli G, Canli M. Response of antioxidant system of freshwater fish *Oreochromis niloticus* to acute and chronic metal (Cd, Cu, Cr, Zn, Fe) exposures. *Ecotoxicol Environ Saf.* 2010; 73:1884-9.
12. Simonsen U, Rodriguez-Rodriguez R, Dalsgaard T, et al. Novel approaches to improving endothelium-dependent nitric oxide-mediated vasodilatation. *Pharmacol Rep.* 2009; 61:105-15.
13. He H, Qiao Y, Zhou Q, et al. Iron Overload Damages the Endothelial Mitochondria via the ROS/ADMA/DDAHII/eNOS/NO Pathway. *Oxid Med Cell Longev.* 2019; 2019:2340392.

Correspondence

Claudio Marino, MD
marinoclaudio88@outlook.it

Salvatore Iaconis, MD
salvatore.iaconis@gmail.com

Francesco Di Bello, MD
fran.dibello12@gmail.com

Gianluigi Cacace, MD
cacace.gianlu@gmail.com

Giovanni Maria Fusco, MD
giom.fusco@gmail.com

Lorenzo Romano, MD
lorenzo.romano@unina.it

Ernesto Di Mauro, MD
ernesto.dimauro@unina.it

Luigi Cirillo, MD
cirilloluigi22@gmail.com

Francesco Mastrangelo, MD
fmastrangelo91@gmail.com

Alessandro Palmieri, MD
info@alessandropalmieri.it

Luigi Napolitano, MD (Corresponding Author)
dr.luiginapolitano@gmail.com

Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, 80100, Italy

Vincenzo Maria Altieri, MD
vincenzomaria.altieri@gmail.com

Department of Medicine and Health Sciences "V. Tiberio", University of Molise, 86100 Campobasso, Italy

Conflict of interest: The authors declare no potential conflict of interest.