Understanding how hormones influence anemia

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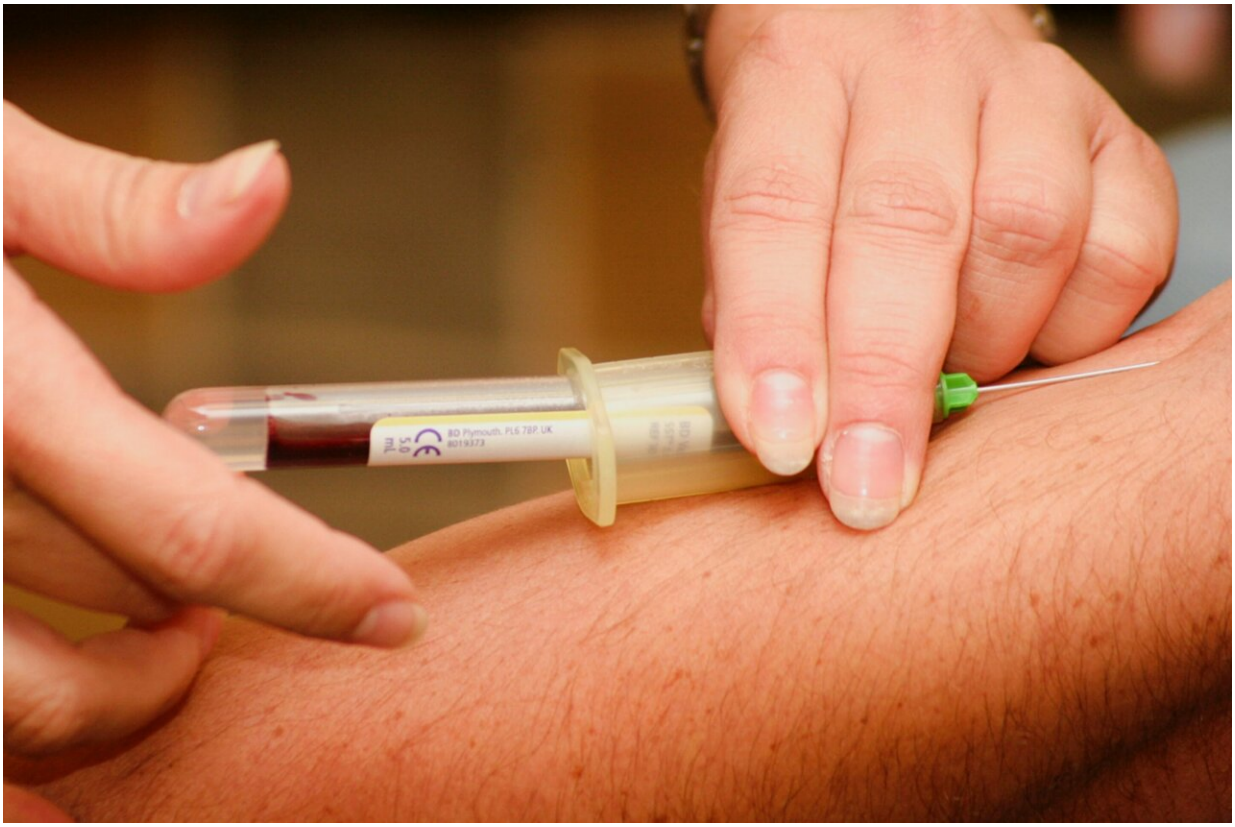

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Northwestern Medicine scientists have uncovered how peptides produced by bones during inflammation prevent anemia in mice, according to a recent study published in the journal *Blood*.

Inflammation, a feature of many chronic illnesses, is known to lead to the concomitant increased production and cleavage of fibroblast growth factor 23 (FGF23), a hormone previously linked to iron dysregulation.

Particularly in patients with chronic kidney disease, the increase of FGF23 is associated with a reduction in iron levels, leading to anemia and increased morbidity, said Valentin David, Ph.D., the Frank Krumlovsky, MD, Professor of Medicine in the Division of Nephrology and Hypertension and senior author of the study.

"Intact FGF23 is a phosphaturic hormone mainly secreted by bone cells," David said. "It was first discovered in 2000, and we have been following it closely since then. We have studied heavily the role of FGF23 in regulating classical mineral metabolism factors, including phosphate and vitamin D. In this paper, we wanted to know if there was a physiological role for the cleaved carboxy terminal FGF23 peptides."

To better understand the role of these carboxy terminal FGF23 peptides, or C-terminal FGF23, investigators first set out to identify which cells produce it under inflammatory conditions.

Utilizing mouse models, investigators induced acute inflammation and found that mature osteocytes, a type of bone cell, were the main producers of C-terminal FGF23 (Cter-FGF23).

To better understand the role of Cter-FGF23 peptides in the regulation of iron, scientists then developed a mouse model with an osteocyte-specific deletion of the FGF23 gene and observed that circulating iron levels dropped by 90 percent compared to wild-type mice. An injection of Cter-FGF23, however, restored iron levels to normal, according to the study.

The findings could represent a new treatment direction for anemia and

bone mineral disorder in chronic kidney disease, David said.

"Our findings are significant for multiple reasons: First, because this is the first evidence that peptides derived from the intact FGF23 have a physiological role, which we can then start exploring as a potential therapeutic option," David said. "Second, because it shows that the secretion of Cter-FGF23 peptides is an active mechanism that maintains balanced phosphate and iron homeostasis. And three, because it also provides us a pathological context in chronic kidney disease, in which patients not only suffer from excess intact FGF23, therefore lack of C-terminal FGF23 peptides, but these patients also have disordered iron metabolism and are anemic."

Branching off this new discovery, David and his colleagues plan to further investigate the role of other peptides created from FGF23 cleavage, he said.

"When FGF23 is cleaved, it not only gives rise to the C-terminal peptides, but also amino terminal peptides, or Nter-FGF23," David said. "To our knowledge, nobody has investigated the role of these Nter-FGF23 peptides and we have evidence that it has very fascinating effects in vivo. We also aim to further understand the source of FGF23. In chronic kidney disease, there are multiple sources of intact FGF23 and cleaved peptides, so we think understanding these sources is quite significant."

More information: Guillaume Courbon et al, Bone-derived C-terminal FGF23 cleaved peptides increase iron availability in acute inflammation, *Blood* (2023). DOI: 10.1182/blood.2022018475

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