Modulating Dietary Iron to Enhance Metabolic Fitness – A Preclinical Study

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Background: Diabetic patients with iron overload benefit from bloodletting (phlebotomy), which improves insulin sensitivity and reduces HbA1c (diabetes marker). However, the effects are not sustainable, and practice of repetitive phlebotomy is limited. In the United States, 40.1 million people have diabetes (12% of the total population) and 115.2 million people have prediabetes (a state of high diabetes risk), making it of timely significance to develop dietary interventions for effective treatment of the metabolic disease.

Methods: We modulated iron contents (50, 20, and 4 ppm) in the diet and investigated how the interventions affected metabolic functions in a widely used preclinical model - obese mice.

Results: We found that 20-ppm iron (i.e., iron moderately restricted) diet enhanced insulin sensitivity, function of mitochondria (the powerhouse in the cell), and energy expenditure compared to 50-ppm iron (i.e., iron adequate) diet. By contrast, severe iron restriction (4-ppm iron diet) caused anemia, underweight, and metabolic disorder. Mechanistically, moderate iron restriction induced a condition of subcellular “iron deficiency” due to iron redistribution into mitochondria in fat tissues, which increased H3K4 methylation possibly by suppressing iron-dependent histone demethylase JARID. H3K4 methylation enrichment induced the expression of GDF15, a nutrient sensor that promotes metabolic functions. Pharmacological inhibition of H3K4 methylation or genetic ablation of GDF15 abolished iron restriction-induced benefits.

Conclusions: This study reveals a potential strategy of targeting dietary iron to prevent metabolic disorder. Our discovery of the iron-H3K4 methylation-GDF15 pathway may inform future development of epigenetic therapeutics for diabetes and iron-overload related metabolic disease.