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Serum Ferritin and Transferrin Saturation were Independently Associated with Pre-diabetes among U.S. Adults

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OBJECTIVE: Increased serum ferritin concentrations have been reported to be associated with insulin resistance and an increased risk of developing Type 2 diabetes. However, the exact mechanism leading to this association is not well understood. Previous reports have attributed this association to subclinical iron overload. In our study, we examined the correlation of three markers of iron homeostasis with glucose metabolism and the risk of pre-diabetes among U.S. adults without iron deficiency and chronic kidney disease.

RESEARCH DESIGN AND METHODS: Participants in the National Health and Nutrition Examination Survey 1999–2002 aged ≥ 20 years and had no missing data in any covariate were included (n = 2,517; 52.8% male). Adults with diabetes, iron deficiency or chronic kidney disease were excluded. Pre-diabetes was defined as impaired fasting glucose (fasting plasma glucose ≥100 and <126 mg/dl) or HbA1c 5.7-6.4%, or both. Homeostasis model assessment of insulin resistance (HOMA-IR), HbA1c, fasting plasma glucose and insulin level were also measured as secondary outcomes. Three serum iron markers, ferritin level, transferrin saturation and protoporphyrin level, were studied.

RESULTS: Among the three markers tested, serum ferritin level was positively associated with pre-diabetes with an OR of 1.42 (95% CI: 1.03-1.97, p=0.035). Transferrin saturation was inversely associated with pre-diabetes with an OR of 0.46 (95% CI: 0.21-0.97, p=0.042), even after adjusted for age, ethnicity, gender, education level, smoking, drinking, physical activity, BMI, waist circumference, serum CRP, AST, ALT, triglycerides, total cholesterol, HDL, and mean arterial pressure. Higher serum ferritin level (p = 0.012) and lower transferrin saturation (p=0.006) were independent predictors of higher fasting plasma glucose level in the multivariate model. Reduced serum transferrin saturation was further associated with higher HbA1c, HOMA-IR and insulin level with P-values of 0.015, 0.004 and 0.011 respectively. Protoporphyrin level did not show any significant correlation with pre-diabetes or other variables related to hyperglycemia.

CONCLUSIONS: The serum ferritin level is positively correlated with the risk of pre-diabetes. Interestingly, transferrin saturation shows a negative correlation. A lower transferrin saturation is also associated with a higher HbA1c, HOMA-IR and insulin level. The high ferritin levels in this population are not due to subclinical iron overload, in which a high transferrin saturation would be expected. Chronic inflammation can give rise to a high ferritin level and a low transferrin saturation. Thus, the increased serum ferritin level associated with pre-diabetes appears to be due to inflammation rather than iron overload. Further studies are needed to explore the utility of these markers in predicting future diabetes so that preventive measures can be taken.