

**Principal Investigator:** James G. Wilson

**Ancillary Study Title:** Relationship of elevated iron stores to diabetes mellitus and nephrology in African Americans

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**Project Overview:**

African Americans have substantially higher incidence and prevalence of diabetes mellitus (DM) and diabetic nephropathy than Caucasians. In 1997 the incidence of end stage renal disease (ESRD) attributed to diabetes was four-fold higher in African Americans than Caucasians. Between 1993 and 1997, about 40% of ESRD in African Americans was attributable to diabetes.

Pathologic iron excess in hereditary hemochromatosis (HH) and transfusional iron overload is frequently accompanied by glucose intolerance and diabetes. In HH, glycemic control has been observed to improve in 30-40% of diabetic patients after therapeutic reduction of body iron stores, providing strong evidence that iron is causally related to diabetes in these patients. The finding that serum ferritin levels in healthy adults and patients with type II DM are positively correlated with fasting glucose, insulin, and glycosylated hemoglobin suggests that even moderately elevated body iron stores may contribute to impaired glycemic control. In multiple studies, about a third of patients with DM have had serum ferritin concentrations above the normal range.

Basic studies have demonstrated mechanisms through which tissue iron, by promoting the generation of reactive oxygen species, may lead to oxidative damage of vascular and parenchymal tissue. In a rat model of diabetes, iron reduction by treatment with deferoxamine was found to ameliorate abnormal nerve conduction and blood flow. Thus, iron may have a role in producing diabetic complications, including diabetic nephropathy, in addition to any adverse effects on glycemic control.

Moderately elevated body iron stores, as indicated by serum ferritin levels, appear to be present in African Americans at least as frequently as Caucasians. Correlations between these levels and those of glucose, insulin, and glycosylated hemoglobin also resemble the findings in Caucasians. Thus available data suggest that relative iron excess could contribute to the occurrence of diabetes and its complications in a significant subset of African Americans. Accordingly, we propose the following:

- 1) To assess whether biochemical measures of body iron status (transferrin saturation and serum ferritin) correlate with measures of glycemic control or with the occurrence of diabetes in a large, community-based observational study of diabetes, hypertension, and cardiovascular disease in African Americans (the Jackson Heart Study);
- 2) To assess whether transferrin saturation and/or serum ferritin correlate with the occurrence of microalbuminuria, diabetic nephropathy, and renal functional decline in African Americans with diabetes;
- 3) To assess whether elevated iron stores are associated with an increased prevalence of insulin resistance syndrome in African Americans.

