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COMMENTARY

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Iron and glucose homeostasis: new lessons from hereditary haemochromatosis

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Abbreviations AIRg: acute insulin response to glucose · DI: disposition index · QUICKI: quantitative insulin sensitivity check index · Si: insulin sensitivity

Interest in the relationship between systemic iron stores and glucose homeostasis has existed since the early descriptions of hereditary haemochromatosis [1, 2]. Diabetes is also prevalent in transfusional iron overload and African iron overload, which resembles haemochromatosis clinically but has a different genetic mechanism. These findings, and studies showing that glucose intolerance in iron overload states can sometimes be prevented or ameliorated by iron removal, have left little doubt that increased tissue iron can contribute to glucose intolerance and diabetes. The actual prevalence of diabetes in haemochromatosis is unknown, with a broad range of estimates reported by different studies. Prevalence assessments have been confounded by selection bias, in that diabetes is considered a diagnostic feature of haemochromatosis. To date, studies of the mechanism(s) of haemochromatosis-associated diabetes have been limited. Thus, discussions of its pathogenesis have drawn heavily on findings in transfusional iron overload, and have been influenced by extensive and elegant studies of type 2 diabetes [3, 4]. In this issue of *Diabetologia*, McClain et al. provide a combined report of an extensive chart review and a prospective study of newly diagnosed patients with haemochromatosis, to address both the prevalence and mechanism of impaired glucose tolerance and diabetes in this disorder [5].

First, the McClain group reviewed the records of 505 haemochromatosis homozygotes seen at the University of Utah between 1975 and 1999. Records were included in the study if patients were aged >40 years (because of the age dependence of diabetes), and if adequate information was available to determine the presence or absence of diabetes by either fasting glucose values (137 patients) or unambiguous history (135 patients). The prevalence of diabetes was 26% as determined by fasting glucose and 20% as determined by history alone. Both figures were close to the 23% prevalence of diabetes in the subsequent prospective study (see below). Among patients whose fasting blood glucose had been recorded, those with diabetes were heavily iron loaded. Seventy-two percent had biopsy-proven cirrhosis and 16% had moderate fibrosis, compared with a 40% prevalence of cirrhosis or fibrosis in patients without diabetes. Among 46 clinically unselected patients in whom haemochromatosis had been identified through family screening or screening at blood donation, 6 (13%) had given a history of diabetes.

Next, McClain et al. recruited 30 haemochromatosis patients over a 6-year period from among referrals to the Hemochromatosis Research Clinic at the University of Utah. Fourteen of the patients' relatives who did not have haemochromatosis served as control subjects. All study participants underwent an OGTT, and a frequently sampled IVGTT was performed the following day. About half of the patients with haemochromatosis had normal glucose tolerance, and the rest had overt diabetes or varying degrees of glucose intolerance, impaired fasting glucose, or both. The patients with normal glucose tolerance did not differ significantly from control subjects in either acute insulin response to glucose (AIRg) or insulin sensitivity (Si). In contrast, those with impaired glucose tolerance had significantly decreased AIRg, a marked tendency towards increased Si, and an overall reduction in the mean

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disposition index (DI, calculated as AIRg × Si). The seven patients with diabetes had a similarly reduced mean AIRg, but had a broader range of Si values and markedly reduced mean DI. Fasting glucose and insulin were both significantly elevated in patients with diabetes, and analysis by the quantitative insulin sensitivity check index (QUICKI), which assesses insulin sensitivity based on fasting glucose and insulin concentrations alone, indicated reduced Si. The most striking findings in these studies of patients with haemochromatosis were (1) a marked reduction in insulin secretory responses in patients with impaired glucose tolerance or diabetes; and (2) either normal or increased insulin sensitivity in the patients without diabetes.

These findings have been corroborated by the same investigators in mouse models of haemochromatosis [6]. In mice with a targeted deletion of the *HFE* gene, hepatic iron was increased more than four-fold and the iron content of isolated pancreatic islets was increased by 72%. Islet surface area in the pancreas was reduced by 45%, without an associated lymphocytic infiltrate and without a concomitant loss of alpha cells. Content of carbonyl-modified protein, a marker of oxidative stress, was increased in islets of $HFE^{-/-}$ mice, as were markers typical of apoptosis. Pancreatic insulin content was reduced, and the dose-response for glucose-stimulated insulin secretion of isolated perifused islets was shifted to the right. Compared with wild-type mice, $HFE^{-/-}$ mice had serum insulin concentrations that were reduced by 17% in the fasting state and by 48% 30 min after intraperitoneal glucose administration. Nevertheless, the glucose tolerance of these mice was normal. The AUC for glucose was actually reduced compared with that of wild-type mice, indicating increased insulin sensitivity in the $HFE^{-/-}$ mice. Similar findings were obtained in mice carrying an HFE mutation analagous to the C282Y mutation of human haemochromatosis, and in mice with dietary iron overload. Interestingly, glucose intolerance did not develop in any of these mice up to the ages of 12–14 months. Thus, alone, these abnormalities of insulin secretion were insufficient to cause major derangement of glucose homeostasis. In aggregate, the above findings were interpreted as suggesting that iron accumulation in pancreatic islets of $HFE^{-/-}$ mice promotes oxidative damage and leads to islet cell apoptosis, loss of islet cell mass, and insulin deficiency. This model is also consistent with the McClain group's findings in human haemochromatosis.

Hramiak et al. reported that seven haemochromatosis patients without either diabetes or cirrhosis had reduced AIRg and slightly increased Si compared with healthy volunteers; AIRg returned to normal after adequate phlebotomy [7]. In the same study, six haemochromatosis patients with diabetes had more markedly reduced AIRg, but, in addition, had decreased Si. Thus, all of the findings of Hramiak et al. were consistent with those reported by McClain et al. in the current issue [5]. Apparently conflicting results, however, were obtained in two earlier studies, in which non-diabetic haemochromatosis patients were found by OGTT or IVGTT to have persistent hyperinsulinaemia with normal or elevated serum glucose [8, 9]. In one of these studies [8], insulin resistance may have been explained by the presence of cirrhosis in all patients. The ten patients in the other study [9], however, had normal body weight and did not have cirrhosis. Differences between the findings in these patients and those in the respective studies of Hramiak and McClain are thus not readily explained. Interestingly, close examination of the data presented by the McClain group (see [5] Fig. 2) reveals a marked trend toward increased AIRg and DI in haemochromatosis patients with normal glucose tolerance, though this is not associated with changes in Si. While these data are cross-sectional rather than longitudinal, one wonders whether there may be an 'early stage' of iron-induced beta cell dysfunction that is characterised by increased insulin secretion in response to glucose.

Glucose intolerance in patients with thalassaemia major and transfusional iron overload has generally been associated initially with hyperinsulinaemia and insulin resistance, though early reduction in insulin secretion capacity (as calculated by the homeostasis assessment model) has been described [1, 2, 10]. In clinically advanced iron overload with overt diabetes, insulin resistance persists, and insulin deficiency is common. Iron overload-related insulin resistance has correlated with both the degree of iron overload and the extent of liver damage. Furthermore, liver disease from other causes, including non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and cirrhosis owing to viral hepatitis is also associated with insulin resistance, involving both impaired insulin-induced suppression of hepatic glucose production and reduced glucose uptake. Although ~75% of glucose uptake occurs in skeletal muscle, and iron content of muscle is known to be increased in iron overload syndromes, the role of muscle in related insulin resistance has been a matter of inference alone. It is possible that changes in liver tissue that are correlated with insulin resistance have served, at least to some degree, as a surrogate for changes in muscle.

The current work by McClain et al. [5] clearly shows that reduced insulin secretory responses can be an early component of impaired glucose tolerance in haemochromatosis. Their findings that insulin sensitivity may actually be increased in this setting are interesting and are supported by their animal studies. Importantly, earlier work indicates that impaired insulin secretory responses may be reversed to some extent by therapeutic phlebotomy [7, 11]. While it is inescapable that a diagnosis of haemochromatosis is more likely to be sought in patients with diabetes, the evidence presented in this issue provides further support for a substantial prevalence of diabetes in this disorder, including a 13% prevalence among haemochromatosis patients identified by family or blood donor screening. Also clear from the current studies is the multi-factorial nature of the transition from impaired glucose tolerance to overt diabetes. Six of the seven haemochromatosis patients with diabetes were clinically obese, and the seventh was overweight. In the retrospective component of the study, the presence of diabetes was strongly correlated with that of hepatic cirrhosis or fibrosis. Finally, multiple studies

have found that diabetes is much more likely to occur in haemochromatosis patients with a family history of diabetes, emphasising the importance of genetic background in this manifestation of haemochromatosis.

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