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Effect of iron overload on glucose metabolism in patients with hereditary hemochromatosis

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Abstract

Diabetes mellitus (DM) affects 30% to 60% of patients with hereditary hemochromatosis (HH). The underlying pathophysiology of DM in patients with hemochromatosis has not been fully elucidated. We studied both insulin secretion and insulin sensitivity in a cohort of patients with HH. We studied glucose metabolism in 53 newly diagnosed HH patients using a standard 75-g oral glucose tolerance test. Basal and stimulated insulin sensitivities were calculated using the quantitative insulin sensitivity check index and oral glucose insulin sensitivity index, respectively. β-Cell function was assessed using C-peptide concentrations during the oral glucose tolerance test after adjusting for ambient insulin sensitivity. Twenty healthy subjects served as the control group. Fifteen subjects (28%) with HH had abnormal glucose tolerance (AGT). Seven (13%) had DM, and 8 (15%) had impaired glucose tolerance. As well as higher fasting glucose and glycated hemoglobin, those with AGT had a higher fasting insulin and C-peptide levels compared with those with normal glucose tolerance (NGT) (all Ps < .05). Insulin sensitivity measurements showed that the subjects in HH group with AGT were more insulin resistant than the subjects with NGT and controls subjects (P < .05). No significant changes were observed between the groups with NGT and AGT regarding hepatic insulin extraction and both indices related to insulin release in subjects with HH. Our cohort of patients with hemochromatosis and AGT had features similar to typical type 2 DM patients. These findings challenge the traditional view that DM in hemochromatosis is due primarily to iron-induced β-cell failure.

1. Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism affecting Caucasian populations, with a prevalence of between 1 in 200 and 1 in 500 [1,2]. Hereditary hemochromatosis is associated with mutations of the HFE gene, located on chromosome 6. The HFE gene encodes a complex 343–amino acid molecule. Two missense mutations in this gene were initially identified. The first is a change of the cysteine at position 282 to tyrosine (C282Y). The second is a change of histidine at position 63 to aspartate (H63D). Other mutations are less common. The HFE protein has a wide tissue expression and is involved in the regulation of gastrointestinal iron absorption, although the precise mechanism of its action is not known. The C282Y mutation is postulated to have originated by chance in a single Celtic (or Viking) ancestor in northwestern Europe some 2000 years ago. In Ireland, 93% of HH patients are homozygous for the C282Y mutation [3]. Analysis of Irish neonates identified an allele frequency of 11% for this mutation in the general population, indicating a homozygote frequency of 1 of 83, which is the highest reported frequency worldwide [4,5]. The penetrance of the HFE gene mutations varies considerably. Hemochromatosis may present as a nonspecific syndrome such as unexplained fatigue; or primarily as liver, cardiac, rheumatologic, or endocrine disease; or as an

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incidental laboratory abnormality, namely, elevated ferritin and transferrin saturation without end-organ damage [6-8].

Diabetes mellitus develops in 30% to 60% of patients with hemochromatosis [9]. The mechanisms underlying the association of iron overload with the progression to diabetes have not yet been completely elucidated [10]. Hereditary hemochromatosis has been thought to relate to iron-induced β-cell failure. There is evidence that iron excess results in β-cell oxidant stress and decreased insulin secretory capacity secondary to β-cell apoptosis and desensitization of glucose-induced secretion. This abnormality alone is believed to be insufficient to cause diabetes [11]. One study of human subjects with hemochromatosis demonstrated a significant decrease in the acute insulin response to glucose during intravenous glucose tolerance tests, but this was found to be the case in subjects both with and without diabetes [12]. Hereditary hemochromatosis is also associated with insulin resistance. It has been hypothesized that elevated iron stores may interfere with hepatic insulin extraction leading to peripheral hyperinsulinemia [10,13]. Some authors have suggested that iron may catalyze the formation of hydroxyl radicals, which contribute to the development of insulin resistance [14,15]. Insulin resistance has also been documented in subjects with diabetes resulting from hemochromatosis [16,17] or iron overload [18].

Therefore, many questions regarding the underlying pathophysiology of diabetes in this group of patients remain unanswered. To address these questions, we have studied some of the key contributors to abnormal glucose metabolism in Irish subjects with HH. We recruited newly diagnosed patients with hemochromatosis and prospectively studied the effect of their iron overload on insulin secretion and sensitivity in the context of standard anthropometric and clinical variables.

2. Subjects and methods

2.1. Subjects

Subjects with recently diagnosed HH were recruited prospectively from the hemochromatosis clinic at St James's Hospital. The diagnosis of HFE mutations was genetically confirmed by real-time polymerase chain reaction (Cys282Tyr, His63Asp). All eligible patients agreed to participate in the study. However, those with severe heart failure, liver cirrhosis, pre-existing diabetes, and hypopituitarism were excluded from the study because of the likely confounding effects of these conditions on metabolic measurements. Data from 6 female and 14 male otherwise-healthy subjects previously studied at our laboratory were included as a historical control group. The study was approved by the Research Ethics Committee, and all subjects gave written consent to participate.

All subjects attended the Metabolic Research Unit on one morning between 8:00 and 10:00 AM for full medical history and physical examination. Weight, height, and body mass index were measured. Routine blood samples were taken for blood count, renal, liver, bone profile, thyroid function tests, and fasting lipids. Blood pressure was measured using the left arm after the subject had been sitting comfortably for 5 minutes, using an oscillometric device (Omron 705 CP; Omron, Matsusaka, Japan). Three readings were taken, and the lowest one was recorded.

2.2. Assays, tests, and calculations

Serum insulin and C-peptide were measured using commercially available fluoroimmunoassays (Auto-Delfia, Wallac-Oy, Finland). Plasma total cholesterol and triglycerides were measured using enzymatic methods (Human liquicolor kits/Hitachi Modular). Plasma high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were measured directly with enzymatic methods (Randox direct kits/Hitachi Modular). Plasma glucose was measured using glucose oxidase method (bioMerieux kit/Hitachi Modular), and glycated hemoglobin (HbA_{1c}) was measured using a Hi-Auto A_{1c} analyzer (Menarini HA 8140).

2.3. Oral glucose tolerance test

After a 12-hour overnight fast, a standard 2-hour 75-g oral glucose tolerance test (OGTT) was performed, with blood samples taken every 30 minutes for plasma glucose, insulin, and C-peptide. Glucose tolerance status was defined according to the World Health Organization [19]. The areas under the concentration curve (AUCs) were calculated with the trapezoidal rule. Insulin sensitivity was assessed in fasting conditions with the quantitative insulin sensitivity check index (QUICKI) [20] and with the oral glucose insulin sensitivity (OGIS) index [21] during the OGTT, that is, in dynamic "postprandial" conditions. Both indices have been previously validated against the tracer glucose clamp and are widely used [22]. The capacity of the β-cell to adapt to changes in insulin sensitivity was calculated as the product of OGIS times the total incremental C-peptide released during OGTT ($\Delta AUC_{C\text{-}peptide}$). Analogously, the ability of insulin to dispose of glucose in relation to the prevailing insulin concentration was given by OGIS $\times$ $\Delta AUC_{insulin}$. These indices, sometimes referred to as the *adaptation* and *disposition indices*, have been already used in several previous studies (eg, Stadler et al [23] and Ludvik et al [24], respectively). They provide a quantitative figure of the overall metabolic status by simultaneously accounting for insulin action and secretion. Hepatic insulin clearance was calculated from insulin and C-peptide data as described in Stadler et al [23].

2.4. Statistics

Data were presented as mean ± SD. Before statistical analysis, normal distribution and homogeneity of the variances were tested. Data were compared using independent t test and χ^2 analysis. Levels of statistical significance were set at $P < .05$. Statistical analyses were performed using SPSS (Chicago, IL).

3. Results

Thirty-eight subjects (72%) of the 53 recruited were homozygous for C282Y, 10 (19%) were compound C282Y/H63D heterozygous, and 5 (9%) were homozygous for the H63D HFE mutation. The results of OGTT showed that 38 (72%) subjects with HH had normal glucose tolerance (NGT) and 15 subjects (28%) had abnormal glucose tolerance (AGT). Of these, 7 (13%) had diabetes and 8 (15%) had impaired glucose tolerance (IGT).

Baseline characteristics of the participants are shown in Table 1. Most subjects were male, and there was no statistical difference in sex between the groups by χ^2 test. There was no difference in HH group between subjects with NGT and AGT and control group in blood pressure, body mass index, and fasting lipids. Transferrin saturation or ferritin was not different in subject with HH and AGT or NGT. Hereditary hemochromatosis–AGT subjects were older than HH-NGT but younger than control subjects. The mean fasting glucose and 2-hour glucose from OGTT in subjects with HH-AGT were higher than those in HH-NGT and control group. The HbA_{1c} was higher in HH-AGT than in HH-NGT and control group; as well, fasting insulin and C-peptide were higher in HH-AGT than HH-NGT and control group (Table 1).

To test whether HH-AGT was associated with decreased insulin secretion or increased insulin resistance, QUICKI and OGTT-derived OGIS were evaluated for fasting and dynamic postprandial insulin sensitivity, respectively. Those with HH-AGT were more insulin resistant under both conditions than HH-NGT (OGIS: 369 ± 56 vs 451 ± 56, $P < .05$, Fig. 1A; QUICKI: 0.57 ± 0.02 vs 0.7 ± 0.02, $P < .05$, Fig. 1B). Subjects with HH-AGT were more insulin resistant when compared with the control subjects with normal glucose metabolism and without HH (OGIS: 439 ± 49, QUICKI: 0.65 ± 0.1), whereas there was no difference between the HH subjects with NGT and the healthy controls (Fig. 1A, B). Metabolic parameters related to insulin release are presented in Table 2. The total glucose AUC was higher in HH-AGT than in HH-NGT group. Despite the difference in fasting levels of insulin and C-peptide, there were no differences between the groups in any of the derived indices relating to β-cell function and insulin degradation. We subdivided the HH-AGT group into those with DM and those with IGT. When comparing subjects in the DM and IGT subgroups, there was no statistical difference in BMI

Table 1
Baseline characteristics (mean ± SD) of the subjects

	HH-NGT	HH-AGT	Control subjects
n	38	15 (7/8)	20
Male (%)	71	87	70
Age (y)	46 ± 10	57 ± 9.0*	52 ± 4.9‡
Systolic BP (mm Hg)	127 ± 17	130 ± 16	129 ± 16
Diastolic BP (mm Hg)	78 ± 9.0	80 ± 10	80 ± 9.0
Body mass index (kg/m^2)	26 ± 5.1	28 ± 3.7	27 ± 1.9
FPG (mmol/L)	4.8 ± 0.3	6.0 ± 1.1*	5.1 ± 0.3†
2-h PG (mmol/L)	5.4 ± 1.3	11.7 ± 3.6*	5.2 ± 1.0†
Fasting insulin (μU/mL)	6.5 ± 2.9	10.6 ± 3.6*	8.1 ± 6.3†
Fasting C-peptide (μg/L)	2.3 ± 0.7	3.2 ± 1.3*	2.5 ± 1.0†
HbA_{1c} (%)	5.4 ± 0.3	6.0 ± 0.7*	5.2 ± 0.4†
Total cholesterol (mmol/L)	4.8 ± 0.8	4.2 ± 1.3	4.6 ± 1.0
HDL (mmol/L)	1.4 ± 0.7	1.2 ± 0.6	1.2 ± 0.7
LDL (mmol/L)	2.7 ± 0.7	2.2 ± 0.9	2.4 ± 0.7
Triglycerides (mmol/L)	1.4 ± 0.7	1.7 ± 0.8	1.6 ± 0.8
Ferritin (g/L)	735 ± 809	1266 ± 1201	NA
Transferrin saturation (%)	78 ± 24	74 ± 20	NA

BP indicates blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NA, not applicable.

* $P < .05$ between HH AGT and NGT.

† $P < .05$ between HH AGT and controls.

‡ $P < .05$ between HH AGT and NGT and controls.

Table 2
OGTT-derived metabolic parameters (means ± SD) in subjects with HH

	NGT	AGT
$AUC_{glucose}$ (mmol/L 120 min)	810 ± 146	1362 ± 343*
$AUC_{insulin}$ (μU/mL 120 min)	5590 ± 3534	6952 ± 5391
$AUC_{C\text{-}peptide}$ (ng/L 120 min)	847 ± 212	954 ± 296
Hepatic insulin extraction (%)	58 ± 15	53 ± 19
Disposition index (nmol/m^2)	7.4 ± 6	7.3 ± 14
Adaptation index (nmol/[min m^2])	0.7 ± 0.3	0.6 ± 0.1

* $P < .05$.

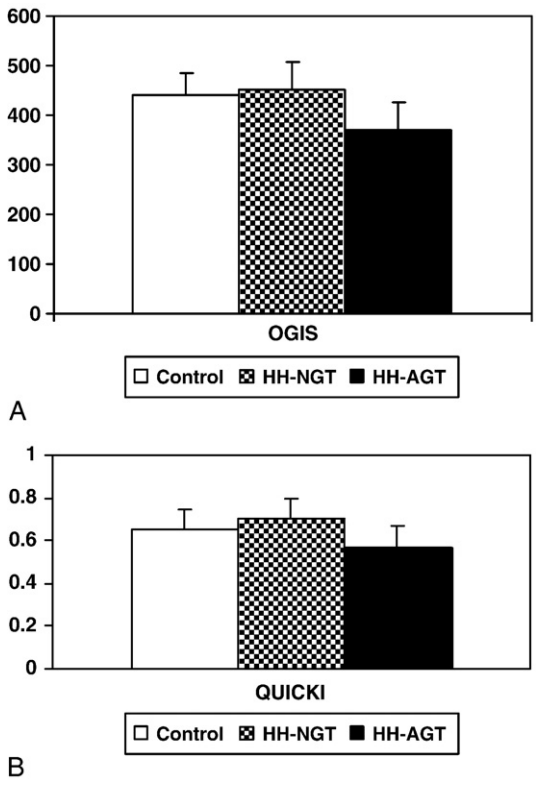

Fig. 1. Dynamic (OGIS, in milliliter per minute per square meter) (A) and fasting (QUICKI, conventional units) (B) insulin sensitivity (mean ± SD) in NGT and AGT subjects with HH. Both parameters in HH-AGT group were lower ($P < .05$) than in control and HH-NGT groups.

(28 ± 4.4 vs 29 ± 3.1, respectively, not significant [NS]), AUC insulin (6937 ± 7047 vs 6964 ± 3942, NS), or the insulin sensitivity indices (OGIS: 354 ± 57 vs 382 ± 54, NS; QUICKI: 0.57 ± 0.05 vs 0.57 ± 0.07, NS).

4. Discussion

Hereditary hemochromatosis is a polygenic disease characterized by inappropriate iron absorption and progressive parenchymal iron deposition with potential for severe organ damage. Disturbance of glucose metabolism is a frequent endocrine abnormality in patients with HH [25]. The pathophysiology of abnormal glucose metabolism in patients with HH is still poorly understood. In this prospective study, we have focused on separate components of the relationship between HH and glucose metabolism in Irish HH patients We found that 28% of newly diagnosed patients had AGT, 13% had diabetes mellitus, and 15% had IGT. Although our study was not designed to assess the prevalence of diabetes in HH patients, it suggests that increased total iron body stores are an independent risk factor for AGT and that screening for AGT in HH is warranted. In addition, the use of dynamic testing with the OGTT rather than fasting glucose alone is more sensitive to detect changes of glucose metabolism [26]. We found that the patients with AGT were more insulin resistant than the patients with NGT and had higher fasting insulin and C-peptide levels. However, no differences were detected in the derived indices relating to β-cell function and insulin degradation. These findings are consistent with many studies in populations at risk for type 2 diabetes mellitus where increased β-cell secretion compensates for insulin resistance. In the current study cohort, most patients with HH were male. In a recently published study, men were found to be more prone to hemochromatosis-associated glucose abnormality than women [27]. This is probably due to shorter and/or less severe exposures to iron overload in women, perhaps as a consequence of menstrual blood loss or other protective effects of estrogen on diabetes risk. A substantial proportion of the subjects with significant iron overload had no detectable abnormality of glucose homeostasis. This is consistent with the large degree of phenotypic variation in terms of other morbidities in subjects with HH that has been attributed at least in part to other genetic modifiers [28,29].

Iron is a transition metal that can catalyze the conversion of poorly reactive free radicals into highly active free radicals. It has been suggested that formation of hydroxyl radicals catalyzed by iron may play a role in the development of diabetes because the highly active radicals can attack cell membrane, lipids, proteins, and DNA and cause tissue damage [15,30-32]. Excess iron deposition in muscle has been reported to decrease glucose uptake because of muscle damage [33], whereas iron accumulation interferes with hepatic insulin extraction [13] and affects insulin synthesis and secretion in the pancreas [34]. Taken together, these findings suggest that iron excess may contribute both to insulin resistance and to decreased insulin secretion [34]. The present study instead indicates that HH seems to affect only insulin action and only in those HH patients with abnormal glucose metabolism.

A limitation of this study is the potential confounding effect of obesity. In our cohort, patients with HH-AGT have similar but slightly higher (albeit not statistically significant) BMI than patients with HH-NGT. The patients with HH-AGT were older than patients with HH-NGT, although presenting with similar degree of iron overload. It is known that prognosis of hemochromatosis and most of its complications depend on the duration of iron excess [35].

In summary, we have demonstrated that a significant proportion of patients with newly diagnosed hemochromatosis have AGT with insulin resistance. This justifies glucose tolerance testing of individuals with hemochromatosis. Thus, in the future, it would be preferable to diagnose hemochromatosis with abnormal glucose metabolism in its early stages and to apply appropriate treatment to improve metabolic control and prevent progression to diabetes. This is especially important for the prevention of diabetes-related cardiovascular comorbidities that can occur very early or even at prediabetic stages of the disease.

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