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Clinical Research Study

Screening for Hereditary Hemochromatosis in Newly Referred Diabetes Mellitus

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ABSTRACT

Aims: Hereditary hemochromatosis (HH) is the most common inherited disease in European populations. It is particularly common in people of Irish heritage, approximately 2% of whom will be at risk of iron overload as a result of human homoeostatic iron regulator protein (*HFE*) gene mutations. We aimed to evaluate the utility of screening for HH in newly referred patients with DM of Irish heritage in a prospective study.

Methods: Of 575 patients newly referred between March 2018 and March 2021, 556 attended for blood testing, to include fasting transferrin saturations, prior to their first clinic visit. Patients with elevated transferrin saturations were further screened for hereditary hemochromatosis (HH) with *HFE* gene analysis.

Results: Transferrin saturations were elevated in 13 of 556 patients (2.3%), 3 of whom had a preexisting diagnosis of HH. Of the remaining 10 patients, 7 had *HFE* gene mutations suggestive of HH (2 C282Y homozygous, 3 C282Y/H63D compound heterozygous, and 2 H63D homozygous), 1 was a HH carrier (C282Y heterozygous), and 2 had normal genetics.

Conclusions: The prevalence of HH of 1.8% in this screened DM population is lower than the reported incidence of HH in the Irish population, suggesting a limited utility of routine screening for HH in newly referred patients with DM.

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder characterized by excessive intestinal iron absorption leading to iron overload of parenchymal cells in many organs, including the liver and the pancreas. HH is the most common genetic disease in European populations and is particularly common in people of Irish heritage.[1,2]

Diabetes mellitus (DM) is the commonest endocrine manifestation of HH.[3] The prevalence of DM in HH has declined in recent years, however, likely due to earlier detection of HH prior to development of significant iron overload.[4]

The clinical manifestations of HH can remain subtle, and early diagnosis and treatment of HH can improve diabetes care. Early diagnosis of HH can also reduce the risk of other HH complications. Hence, screening for HH in patients with DM remains common in clinical practice.[5]

Previous studies provided contradictory information regarding the utility of routine screening for HH in patients with DM.[6-14] Many of these studies were carried out in the era prior to the discovery of the *HFE* gene mutation, and the patients studied were attending for routine clinic review of established diabetes, which may have confounded the results.

In this study we aimed to evaluate the utility of screening for HH in newly referred DM patients of Irish heritage in the modern era.

Methods

Connolly Hospital is an academic teaching hospital and tertiary referral center for diabetes care. Sited on the outskirts of Dublin city, it serves a catchment population of approximately 330,000 mixed urban and rural dwellers.

All persons with DM of Irish heritage and over 30 years of age who were newly referred to the diabetes services at Connolly Hospital over a 3-year period were invited to attend for blood testing, to include fasting transferrin saturations, prior to their first clinic visit. Patients with elevated transferrin saturations (>50% for women, >55% for men) were further screened for HH with *HFE* gene analysis. Patients with type 1 diabetes were excluded from the analysis (no patients with detectable antibodies or with a presentation suspicious for type 1 diabetes were included in the study); otherwise, all patients with DM were included. This was a prospective study.

Age, HbA1c, and transferrin saturations are presented as means ± standard deviation and the genetic results presented as frequencies.

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Table 1
Details of Patients With Elevated Transferrin Saturations

	Age	Gender	HbA1c% (mmol/mol)	Ferritin (ng/mL)	Trans sat (%)
C282Y Homozygous (1)	48	F	5.9 (41)	1147	73
C282Y Homozygous (2)	50	F	8.1 (65)	331	63
C282Y/H63D Heterozygous (1)	65	M	8.8 (73)	426	65
C282Y/H63D Heterozygous (2)	44	F	6.5 (47)	47	59
C282Y/H63D Heterozygous (3)	70	M	6.1 (43)	558	59
H63D Homozygous (1)	38	M	6.5 (47)	101	57
H63D Homozygous (2)	51	F	9.8 (84)	328	63
Known HH (Genetics N/A)	68	M	10.4 (90)	2910	97
Known HH (Genetics N/A)	72	M	6.2 (44)	385	73
Known HH (Genetics N/A)	61	M	8.6 (70)	449	94
C282Y heterozygous	57	F	10.6 (92)	1201	61
Normal Genetics (1)	67	F	6.4 (46)	392	61
Normal Genetics (2)	51	M	8.7 (72)	248	57

N/A = Not available.

Prevalence of HH in this study population was compared to the known prevalence of HH mutation in the background Irish population of 2%.[2] $P < .05$ was considered statistically significant. The data were analyzed using Microsoft Excel (2011).

This study was approved by the Connolly Hospital Ethics Committee (reference number JL 150922–01).

Results

A total of 575 patients were invited to attend for blood testing, including transferrin saturations, before their clinic visit. Of these, 556 attended for testing, 204 women and 352 men. Of those tested, the mean (± standard deviation) patient age was 60.9 (± 13.4) years, mean HbA1c 61.3 (± 20.6) mmol/mol, and mean transferrin saturations 28.1% (± 11.9%).

Transferrin saturations were elevated in 13 of 556 patients (2.3%), 3 of whom had a known preexisting diagnosis of HH. They had presented to their GP with fatigue and joint pains in the years prior to their diabetes diagnosis. Subsequent investigations confirmed the HH diagnosis.

Of the remaining 10 patients (1.8%) with elevated transferrin saturations, 7 had abnormal genetics suggestive of HH (2 C282Y homozygous, 3 C282Y/H63D compound heterozygous, and 2 H63D homozygous). One further patient was identified as a HH carrier (C282Y heterozygous), and 2 patients had normal genetic testing. Details of patients with elevated transferrin saturations are in Table 1.

Taking the background Irish population HH prevalence as 2%[2] as a comparator, our result of 1.8% prevalence in this study cohort (10 patients with HH including 3 patients with a preexisting diagnosis) was not statistically significant ($P = .74$).

Discussion

Of 556 newly referred DM patients of Irish heritage older than 30 years of age who were screened for HH with fasting transferrin saturations and, when indicated, subsequently proceeded to genetic testing, 10 patients were found to have a diagnosis of HH, giving a prevalence of HH of 1.8% in this population. This compares to a reported incidence of HH in the Irish population of approximately 2.0%[2] and hence suggests a limited utility of routine screening for HH in newly referred patients with diabetes. There was a prevalence of C282Y homozygous mutation of 0.4% in the screened population (though we do not have access to the genotypes of the three previously diagnosed patients)—Pilling et al. have found that it is C282Y homozygosity in males that carries with it an increased risk of DM, rather than other genotypes.[15] This paper by Pilling et al. found a prevalence of C282Y homozygosity of 0.6%.

Interestingly, 3 of the total 10 patients with HH in the study population had already received a diagnosis of HH in the years prior to their diabetes diagnosis, meaning that the true yield of our screening program was even lower—with only 7 patients newly diagnosed with HH on the basis of our screening. Unfortunately, the genotypes of the three previously diagnosed HH patients were not available to include in the study as they had been carried out in other centers.

Through the mid-20th century, diabetes was observed in almost 80% of patients with HH,[16] with almost 90% of such cases attributable to the C282Y gene mutation in the *HFE* gene.[7] Although the prevalence of DM in HH has declined in recent years[4] the fear of missing a diagnosis of a secondary cause of diabetes, the subtleties of the clinical signs of HH, and the potential significant negative impact on health outcomes of undiagnosed and untreated HH have led many clinicians to routinely screen patients for HH at diagnosis of DM. While this strategy may have been rewarding in the past, when significant iron overload from previously undetected HH was more common and DM less so, our data suggests that it is not warranted in the modern era of diabetes care.

A number of prior studies contradict our results and suggest that routine screening for HH in DM may be warranted. Phelps et al. studied 418 patients attending a diabetes review clinic and measured ferritin and transferrin saturation levels in all patients.[8] Patients with elevated levels proceeded to a liver biopsy, which ultimately led to a confirmed diagnosis of HH in 4 patients. The authors quoted a background rate of HH in their general population of 4 per 1000 patients, compared to 9.6 per 1000 in their diabetic cohort, and argued, therefore, that routine screening for HH in DM patients is worthwhile and cost-effective. Conte et al. in another cross-sectional study examined 777 patients attending for review of established Type 2 Diabetes Mellitus (T2DM).[9] Patients had ferritin and transferrin saturations measured, and liver biopsy was performed if results were suggestive of iron overload. Of the 777 patients, 12 patients were subsequently diagnosed with HH. As matched controls, 467 subjects were drawn from a population attending hospital clinics for nonulcer dyspepsia and irritable bowel syndrome, and 1 new diagnosis of HH was discovered in this cohort. The prevalence of HH in T2DM patients in this study was 1.54%, compared to 0.2% in the control group, giving an odds ratio of 7.7 for HH in DM patients and prompting the authors to conclude that routine screening for HH in DM could be beneficial. Cadet et al. studied 61 patients who needed hospitalization for treatment of DM complications and found a prevalence of HH of 5.8%, suggesting that targeted screening of complicated DM patients may be worthwhile.[10]

A number of other studies, however, provide support for our conclusion that routine screening for HH in DM is not justified. Kirk et al. noted a similar prevalence of the three main genetic variants (C282Y, H63D, and S65C) of HH when comparing 249 control subjects with 249 patients selected from a diabetes database in the Northwest of Ireland.[11] Frayling et al. performed genetic testing on 238 patients with T2DM and 215 controls and found only 1 patient in each group to be homozygous for the C282Y mutation (H63D gene mutations were not tested).[12] O'Brien et al.[13] and Turnbull et al.[14] studied cohorts of 572 and 727

patients attending for routine diabetes clinic reviews, respectively, and discovered 22 and 23 patients with possible HH, and a low yield of HH diagnosis on subsequent liver biopsy. As both studies were performed in the era prior to the discovery of the *HFE* gene mutations, liver biopsy was relied upon to diagnose HH, and only a minority of patients with abnormal iron indices were biopsied. Although the conclusion of both studies—that routine screening for HH in DM is not warranted—tallies with the results of our study, the nature of both earlier studies means that their results are not applicable to modern medical practice.

One of the strengths of our study is that it was performed prospectively. The other above-referenced studies, on the other hand, examined a cross-sectional cohort of patients with established diabetes attending review clinics. This potentially introduces a significant confounding factor whereby patients with established HH may have been removed to other services or conceivably may have had their diabetes successfully reversed by phlebotomy. In our prospective study the patients were having their first encounter with tertiary diabetes services, which in real-world clinical practice is typically an opportunity for case detection, where appropriate. A further strength of our study is that it was carried out in the ethnic group with one of the highest background prevalence rates of HH, where routine screening would be most likely to show a benefit if such a benefit existed.

Notwithstanding the low prevalence of HH in our cohort, one could argue that we identified 7 patients with HH who may not have otherwise received the diagnosis, and that these patients, therefore, benefitted from screening. In this respect it is interesting to review the results of the serum ferritin levels in these 7 patients. Only 1 of the 7 patients had a ferritin level above 1000. A majority, therefore, had minimal degrees of iron overload, and certainly not sufficient to cause a secondary diabetes. Thus, the diagnosis of HH in these patients was likely coincidental. It is also a matter of conjecture, given the lack of a definite link between genotypic diagnosis and clinical penetrance in HH, whether or not these patients would have developed significant degrees of iron overload in the future if the diagnosis of HH had not been made.[17]

We conclude that, although DM and HH can, of course, still coexist (and indeed did so in 10 of our cohort), routine screening for HH in newly referred patients with DM in the modern era is of limited utility. The increasing prevalence of type 2 DM means that the majority of patients referred to DM services will have this condition rather than a secondary form of DM. Furthermore, the discovery of the *HFE* gene mutation, by allowing for improved screening of first-degree relatives of an index case, has resulted in earlier diagnosis of HH, prior to development of degrees of iron overload sufficient to cause DM. In the modern era, therefore, HH and DM are more likely to coexist by coincidence rather than by causation.

Declaration of Competing Interest

No conflicts of interest or funding to declare.

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The authors have no relevant conflicts of interest to disclose.

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