Usefulness of Biochemical Screening of Diabetic Patients for Hemochromatosis

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We assessed the prevalence of previously unrecognized hemochromatosis among patients in whom diabetes mellitus was diagnosed after the age of 30 yr, and we evaluated the positive predictive value of biochemical screening tests for hemochromatosis in diabetic subjects. Thirty-eight of 572 patients screened (6.6%) had a serum ferritin level >324 μg/L; 16 patients had normal levels on repeat testing. Four patients' serum ferritin levels fell to <400 μg/L. Seven of 18 patients with a persistently elevated serum ferritin level did not undergo a liver biopsy because of a recognized cause of hyperferritenemia (carcinoma, alcoholism, or systemic lupus erythematosus). The diagnosis of hemochromatosis seemed certain in 1 of 3 patients who were not biopsied for technical reasons. Of 8 patients biopsied, 2 had hemochromatosis, 4 had fatty liver, 1 had hemosiderosis, and 1 had a chronic inflammatory cell infiltrate with no iron deposition. Of 4 patients with a raised transferrin saturation level, 2 had raised serum ferritin levels and hemochromatosis, 1 had raised serum ferritin and hemosiderosis on liver biopsy, and 1 had a normal transferrin saturation level on repeat testing. Two of 3 cases of hemochromatosis had other clinical markers of the condition. Therefore, routine screening of diabetic patients for hemochromatosis is not necessary, because patients with hemochromatosis will often have other clinical features of the disease. When screening diabetic patients for hemochromatosis, it should be remembered that a persistently raised serum ferritin level has a low positive predictive value (16.6%) and that a normal transferrin saturation level does not exclude the diagnosis. *Diabetes Care* 13:532–34, 1990

Idiopathic hemochromatosis is a disorder in which there is an increase in total-body iron stores that leads to a progressive parenchymal deposition of iron in the liver and other organs (1). It is an autosomal-recessive condition (2). The clinical manifestations have been previously documented (3). Overt diabetes occurs in 60–80% of patients with hemochromatosis (4). The incidence of the condition was previously underestimated. Based on HLA studies, it is now thought to occur in ~1 in 200 people (5–7).

Thirteen patients attending our diabetes clinic had been previously diagnosed to have hemochromatosis. All patients had clinical stigmata due to the disorder when they presented with diabetes mellitus. In this study, we sought to determine whether there were undiagnosed people with hemochromatosis attending our clinic. In addition, we wanted to evaluate the screening tests for detecting hemochromatosis in a diabetic population.

RESEARCH DESIGN AND METHODS

Serum ferritin, iron, and transferrin levels were assayed in all diabetic subjects diagnosed after age 30 yr who attended our clinic. Iron was assayed by a standard ferrozine calorimetric technique (8). Transferrin was measured by an immunoturbidometric assay with Dako antiserum and the encore centrifugal analyzer (9). Transferrin saturation was then calculated with a previously published and validated conversion formula (10). Ferritin was assayed by use of a two-site immunoradiometric assay (11). Results were considered abnormal if the ferritin level was >324 μg/L or the transferrin saturation level was >62%. A serum ferritin level of 324 μg/L was the upper limit of normal for our laboratory. A transferrin saturation of 62% was selected on the basis of work conducted by Dadone et al. (12).

In most cases, blood was drawn concurrently with routine blood samples for glucose and glycosylated hemoglobin at the clinic; the patients were not fasting. If a separate venesection was required, verbal consent was obtained from the patient. Patients with abnormal results were reviewed clinically. Tests were repeated, and, if found abnormal, a liver biopsy was performed via a Menghini needle after informed consent was obtained and contraindications were ruled out. The specimens obtained were assessed histochemically. Patients in whom the serum ferritin level fell to <400 μg/L on repeated testing did not have a liver biopsy because it was believed that a biopsy would be clinically unjustified in such cases.

Statistics. A χ^2-test was used to assess differences between proportions. $P < 0.05$ was significant.

RESULTS

Of 572 diabetic subjects screened, 38 (6.6%) had a serum ferritin level >324 μg/L; 16 patients had normal levels on repeat testing. Four patients had serum ferritin levels between 324 and 400 μg/L on repeat testing, and all 4 had a transferrin saturation level <36%. Because these patients had minimally elevated serum ferritin and tansferrin saturation levels in the low normal range, it was believed that a liver biopsy was not clinically indicated. Of 18 (3%) patients with persistently elevated serum ferritin levels, 7 were not biopsied due to the presence of other causes of hyperferritinemia (patients 1–7, Table 1). One patient was unsuitable for biopsy due to the presence of severe chronic obstructive pulmonary disease and a large gallbladder that was deter-

TABLE 1
Patients who did not have liver biopsy

Patient	Age (yr)	Sex	Serum ferritin	Transferrin saturation (%)	Diagnosis
1	56	M	455	25.0	Carcinoma lung
2	65	F	2000	24.5	Carcinoma kidney
3	74	M	1929	29.0	Hepatoma
4	70	M	334	11.8	Carcinoma prostate
5	60	M	500	32.0	Alcoholism
6	66	M	399	28.0	Alcoholism
7	54	M	644	35.0	Systemic lupus erythematosus
8	64	M	620	25.0	Chronic obstructive pulmonary disease
9	60	M	672	38.0	Lost to follow-up
10	74	F	1280	100.0	Pigmented, insulin-dependent diabetes mellitus, raised liver function tests

mined ultrasonically (patient 8, Table 1). One patient was lost to follow-up (patient 9, Table 1). Another patient was not biopsied because of the presence of other medical conditions and because the degree of elevation of her serum ferritin and transferrin saturation levels made the diagnosis of hemochromatosis extremely likely (patient 10, Table 1). Of 8 patients who had liver biopsies, 2 had hemochromatosis, 1 had hemosiderosis, 4 had steatosis, and 1 had moderate chronic inflammatory cell infiltrate (Table 2).

Four patients had elevated transferrin saturation levels; two of them also had elevated serum ferritin levels and hemochromatosis. The third patient had a normal serum ferritin level, and his transferrin saturation level was normal on repeat testing. The fourth patient had elevated serum ferritin levels and hemosiderosis on biopsy. The positive predictive value of a persistently elevated transferrin saturation level was 66%, whereas the positive predictive value for an elevated serum ferritin level was 16.6% (3 of 18 patients; $\chi^2 = 1.6$, NS, 95% confidence interval −1 to +95%). Of the three patients diagnosed as having hemochromatosis, one had no other clinical features of this condition, one had atrial fibrillation and hepatomegaly, and one had hepatomegaly and was markedly pigmented.

TABLE 2
Patients who had liver biopsy

Patient	Age (yr)	Sex	Serum ferritin	Transferrin saturation (%)	Histology
1	73	M	917	80.0	Cirrhosis, marked iron deposition
2	68	M	608	39.0	No cirrhosis, marked iron deposition
3	58	M	466	71.8	Mild periportal iron deposition
4	70	M	512	20.3	Fatty liver
5	70	F	469	56.0	Fatty liver
6	62	F	458	30.0	Fatty liver
7	55	M	472	19.0	Fatty liver
8	56	M	401	14.0	Portal inflammation

DISCUSSION

Idiopathic hemochromatosis is inherited in an autosomal-recessive fashion (2). The frequency of the carrier state has been estimated to be 10–16% from HLA studies (13). It is now believed that idiopathic hemochromatosis is more common among the general population than was previously believed. Some studies have found a prevalence of 1 in 200 people (5–7). Because of this increase in the estimated prevalence of the condition, it is believed by some that screening of the general population is warranted. This has not been conclusively shown to be necessary or cost effective.

The prevalence of diabetes in hemochromatosis has been reported to be 60–80% (4). The prevalence of hemochromatosis among diabetic subjects has not been studied extensively. One recent study reported the prevalence to be 9.6/1000 (14); this is higher than in the general population. It is not known if screening of patients with diabetes mellitus for hemochromatosis is worthwhile. Our goal was to determine the prevalence of unrecognized hemochromatosis in our diabetic clinic.

Three of 572 patients screened had hemochromatosis that was previously unrecognized. Of these, 2 patients had other clinical features of hemochromatosis. Clinical manifestations of the condition have been well documented. We believe that routine screening of diabetic subjects for hemochromatosis is not warranted, because most patients presenting with diabetes mellitus secondary to iron overload will have other clinical features of hemochromatosis. However, the diagnosis should be considered in all diabetic patients and clinical features determined.

There is some controversy regarding the best method of screening for hemochromatosis. Serum iron is not thought to be useful because it is often elevated in people with normal body iron stores (15). Dadone et al. (12) found a transferrin saturation level >62% to be the best predictor of iron overload, whereas Bassett et al. (16) used a transferrin saturation level >50%. However, Halliday et al. (15) found serum ferritin to be a more useful noninvasive test. None of the studies, however, looked at screening tests in the diabetic population.

Therefore, we evaluated the predictive accuracy of biochemical screening tests for hemochromatosis in a diabetic population. Bassett et al. (16), looking at first-degree relatives of patients with hemochromatosis, reported the positive predictive value of an elevated serum ferritin level (150 μg/L in females, 200 μg/L in males) to be 88% for the diagnosis of hemochromatosis. In contrast, in a population of blood donors, Edwards et

al. (17) found serum ferritin to be an insensitive marker for hemochromatosis. However, regular blood donations may have lowered the ferritin levels of these patients and thus reduced the sensitivity of serum ferritin as a screening tool in this population. In our diabetic subjects, the positive predictive value of an elevated serum ferritin level for hemochromatosis was 16.6%. This low value may be due to the diabetic state. It is known that diabetes mellitus can lead to fatty infiltration of the liver (18). It is also recognized that acute and chronic hepatic damage can lead to hyperferritinemia (19). Although it has not been shown that fatty liver of diabetes mellitus can lead to hyperferritinemia, this is a possible explanation for the high false-positive rate in diabetic subjects.

In our population, a transferrin saturation level persistently >62% had a positive predictive value of 66% compared to 16.6% for an elevated serum ferritin level. Although this does not achieve statistical significance, due to the small numbers involved, it does suggest that transferrin saturation may be a more useful screening tool than serum ferritin in diabetic subjects. However, one of three patients with hemochromatosis had a normal transferrin saturation level. Our results for transferrin saturation are comparable to the results reported by Bassett et al. (16) (74%) in a nondiabetic population. In a population of blood donors, Edwards et al. (17) reported a positive predictive value for men and women to be 62 and 100%, respectively, when fasting transferrin saturation was >62%. In contrast to the findings of Bassett et al. (16), we did not find a high incidence of false-positive results when samples were taken for transferrin saturation after patients had consumed a meal.

A weak correlation has been found between serum iron and transferrin saturation and mobilized body iron stores (16). In addition, the same study showed a strong correlation between serum ferritin and mobilized body iron stores. It has also been suggested that serum ferritin may be a guide to the degree of liver damage (13). In our study serum ferritin was highest in the patient with cirrhosis, intermediate in the patient with marked iron deposition and no cirrhosis, and lowest in the patient with mild periportal iron deposition (Table 2). These results are in agreement with the hypothesis that serum ferritin is a marker for the degree of liver damage.

In conclusion, it appears that diabetic patients do not need to be screened routinely for hemochromatosis because most patients will have other clinical features of the condition. Transferrin saturation is a more useful screening tool than serum ferritin among diabetic patients because of its lower incidence of false-positive results.

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