Effects of heavy alcohol consumption on serum ferritin concentrations

T. E. MEYER, C. KASSIANIDES, T. H. BOTHWELL, A. GREEN

Summary

Serum ferritin and hepatic enzyme concentrations were measured in 30 alcoholic subjects. Both the serum ferritin and γ-glutamyltranspeptidase (GGT) values were raised in 23 subjects and a significant correlation was noted between the two measurements \((r = 0.51; P < 0.01)\). There was, however, no correlation between the initial serum ferritin concentration and the serum alanine transaminase and serum aspartate transaminase concentrations. The serum ferritin and GGT levels were followed serially during a period of abstinence in 9 subjects; values fell in parallel in all of them. The data indicate that a serum ferritin level above 300 \(\mu g/l\) is very unlikely to be the result of alcohol-induced liver damage if the serum GGT value is less than 50 U/l. The combined measurement of serum ferritin and GGT values should therefore prove useful in epidemiological studies concerned with defining the prevalence in different population groups of the HLA-linked iron-loading gene that leads to the clinical disorder of idiopathic haemochromatosis.

There is now abundant evidence that the serum ferritin concentration bears a linear relationship to body iron stores, with each microgram of ferritin per litre serum equivalent to about 10 mg storage iron. The measurement has therefore been widely used to identify the prevalence of both iron deficiency and iron overload in population studies. There are, however, certain situations in which the serum ferritin level is inappropriately raised. These include liver disease, the leukaemias, lymphomas, cancers and infections. While most of these diseases would have little effect on the results of studies carried out on apparently healthy subjects in Western countries, this is not true of all of them. Kristenson et al. found that 67% of heavy drinkers had raised serum ferritin concentrations. The fact that serum γ-glutamyltranspeptidase (GGT) concentrations were also raised in these subjects suggested that the liver was the source of the ferritin.

These various observations have relevance to a number of studies which are being undertaken in several Western countries to document the prevalence of iron overload in different population groups. It is now apparent that the disease idiopathic haemochromatosis is inherited in an autosomal recessive fashion and that the heterozygotic state may be present in as many as 10% of some White populations. This means that in such populations approximately 3:1000 are homozygous for the iron-loading gene and are therefore at risk of severe iron overload. If the gene frequency is as prevalent as the present evidence suggests, then concerted attempts should be made to identify affected homozygotes. In this context, the serum ferritin concentration has been particularly helpful. However, a number of subjects identified in this way have been found not to be homozygous carriers of the gene and Kristenson et al.'s data suggest that at least a proportion of them may have had raised serum ferritin concentrations because they were consuming large amounts of alcohol. The present study was therefore undertaken to examine serum ferritin concentrations in alcoholic subjects in more detail in an attempt to define criteria by which such subjects can be differentiated from homozygous haemochromatotics in future epidemiological studies.

Patients and methods

The 30 subjects who were studied were all admitted to the Johannesburg Hospital because of excessive alcohol consumption. Special note was taken of the amount and type of alcohol that had been consumed and of the duration of alcohol abuse. Initial investigations included a full blood count, measurement of serum ferritin levels and liver function tests. Serial measurements of serum ferritin and liver enzyme levels were carried out in 9 of the patients during periods of abstinence varying between 8 and 71 days.

Blood counts and haematological indices were measured in a Coulter Model S Plus counter. The serum ferritin level was measured by an enzyme-linked immunosorbent assay, while liver enzyme levels were determined using the following methods: serum GGT by the method of Persijn and van der Lil and serum aspartate transaminase (AST) and serum alanine transaminase (ALT) on the SMA 12/60 by standard Technicon methods.

Since data for serum ferritin and hepatic enzyme levels were not normally distributed, all results were expressed as geometric means and standard deviation (SD) ranges. In addition, correlations between different measurements were determined on logged data.

Results

All subjects (21 males and 9 females aged 28–70 years) admitted to a recent alcohol intake of greater than 130 g/d. They had haemoglobin values ranging from 5.4 to 18.3 g/dl (mean 14 g/dl). The average initial mean corpuscular volume (MCV) was 100 fl (range 87–124 fl).

The initial serum ferritin concentration varied between 110 and 10315 \(\mu g/l\). It was above the upper limit of normal (200 \(\mu g/l\)) in 23 of the 30 patients, above 300 \(\mu g/l\) in 20, above 400 \(\mu g/l\) in 19 and above 1000 \(\mu g/l\) in 9. Hepatic enzyme levels were also raised in the majority of subjects. The GGT level was above 50 U/l in 23 of 30 subjects, the AST level was above 40 U/l in 22

---

MRC Iron and Red Cell Metabolism Unit, Department of Medicine, University of the Witwatersrand, Johannesburg

T. E. MEYER, M.B.B.CH., F.C.P. (S.A.)
C. KASSIANIDES, M.B.B.CH.
A. GREEN, B.S.C.

Reprint requests to: Prof. T. H. Bothwell, Dept of Medicine, University of the Witwatersrand Medical School, York Road, Parktown, 2193 RSA.
of 26 subjects for whom values were available and the ALT level was above 35 U/l in 20 of 26 subjects. Also, the total bilirubin value was above 22 µmol/l in 18 of 26 subjects.

The degree of derangement of the various measurements was calculated by estimating the geometric mean increase of each above the upper limit of normal. Expressed in this way the figures were as follows: serum ferritin level 3.02 x normal (SD range 0.95 - 9.57), GGT level 3.97 x normal (SD range 0.84 - 18.69), serum AST level 2.44 x normal (SD range 1.06 - 5.61), serum ALT level 1.73 x normal (SD range 0.80 - 3.175) and serum bilirubin level 1.47 x normal (SD range 0.51 - 4.28).

In a further analysis the initial serum ferritin concentrations were correlated with those of the three hepatic enzymes using the logged data. The correlation between the serum ferritin and GGT levels was significant \( r = 0.51, P < 0.01 \) (Fig. 1), while those between the serum ferritin level and the AST and ALT levels were not \( r = 0.28, P > 0.1 \) and \( r = 0.37, P < 0.1 \) respectively.

The relationship between the serum ferritin and GGT concentrations was further explored in 9 subjects in whom serial measurements were carried out for varying periods of time (Fig. 2). There was a parallel decrease in the concentrations of the two measurements in all 9 subjects during the period of observation.
Discussion

Current evidence suggests that the minute quantities of ferritin that circulate in the plasma are secreted by the reticuloendothelial system. In common with many other plasma proteins, carbohydrate residues are added during secretion. In contrast, liver injury is associated with the release of non-glycosylated tissue ferritin into the circulation. This is the source of the high concentrations found in patients with massive hepatic necrosis. The serum ferritin level has also been reported as being raised in a number of other acute and chronic liver diseases, including acute hepatitis, alcoholic cirrhosis and cryptogenic cirrhosis. In these conditions a significant correlation has been noted between the serum ferritin concentration and the serum AST level. In another detailed study on alcoholic subjects, Lundin et al. found that low-grade but significant correlations existed between the serum ferritin level and the serum AST, ALT and GGT levels. When 19 alcoholics were followed up during a 2-week abstinence period, the serum ferritin levels dropped progressively, as did the serum AST and bilirubin levels. In contrast, there was no significant change in the levels of the other two enzymes.

The present study was undertaken from a somewhat different standpoint. At present there is widespread interest in defining the prevalence in different population groups of the iron-loading gene which in the homoyzogous state leads to the clinical disease of idiopathic haemochromatosis. The identification of homozygous individuals on the basis of raised serum ferritin concentrations is, however, bedevilled by the fact that similar raised levels may be found in alcoholic liver disease. Indeed, in one recent study the majority of apparently healthy heavy drinkers were found to have raised serum ferritin concentrations. It was noteworthy that the serum GGT level was raised in all subjects with serum ferritin concentrations above 400 μg/L. Serum AST and ALT levels were less sensitive markers of excessive alcohol consumption, being raised in only 35% and 51% respectively of those patients with raised GGT concentrations.

In the present study, the relationship between serum ferritin and hepatic enzyme concentrations were examined in further detail. A significant correlation between the initial serum ferritin and GGT levels was noted but this was not true for the other two enzymes. In addition, the geometric mean increases in the serum ferritin (3.02 x normal) and GGT (3.97 x normal) levels were greater than for either ALT (1.73 x normal) or AST (2.44 x normal) levels. This finding raises the possibility that the rise in serum ferritin and GGT levels may not only be the result of liver cell death or increased membrane permeability but may also reflect alcohol-induced synthesis of the two secretory proteins. If so, the ferritin might be expected to be iron-free and glycosylated, but no information on this point was obtained in the present study. Alternatively it is possible that the disproportionate rise in the concentrations of serum ferritin and GGT was the result of their slower clearance rates from the plasma.

Other factors may also be involved. Whatever the explanation, it is apparent that the serum ferritin concentration is as sensitive an indicator of alcohol abuse as is the GGT concentration.

A striking finding in the present study was the close correlation between the progressive drop in the serum ferritin and GGT levels that occurred during a period of abstinence. It was noteworthy that this relationship was independent of the original concentration of serum ferritin. For example, in one subject (case 1, Fig. 2) who had depleted bone-marrow iron stores, the initial ferritin value was only 152 μg/L. It declined to 32 μg/L over the next 32 days, during which time there was a corresponding fall in the GGT level from 1673 to 330 U/L (r = 0.97, P<0.01). When these various results are considered in conjunction with those of Kristenson et al., it is apparent that a serum ferritin value above 300 μg/L is extremely unlikely to be the result of excessive alcohol consumption if the serum GGT level is less than 50 U/L. There was only one such case in the present study and none in the Scandinavian investigation. The serum GGT level should therefore prove a useful additional screening measurement in studies undertaken to define the prevalence of genetically related iron overload. In this regard, the preliminary results of a survey in the Western Cape (unpublished data) are of interest. Serum ferritin concentrations were measured in 600 adults, most of whom were of Afrikaner descent. The concentrations were above 300 μg/L in 24 and above 400 μg/L in 17 subjects. Serum GGT concentrations were then measured in 15 of the subjects with ferritin values above 400 μg/L and were found to be less than 50 U/L in 11. These findings suggest that the iron-loading gene responsible for idiopathic haemochromatosis may be common in the Western Cape and also underline the need for more detailed family studies.

REFERENCES

3. Dolan MJ, Humber PA, Staugard F. Prevalence of iron deficiency and anemia in Iran, U.S. Hallgren a,a is extremely unlikely to be the result of excessive alcohol consumption, being raised in only 35% and 51% respectively of those patients with raised GGT concentrations.