False-Positive CDTect Values in Patients with Low Ferritin Values

To the Editor:

The determination of carbohydrate-deficient transferrin (CDT)—for example, by assays such as CDTect® (Pharmacia & Upjohn)—is currently widely accepted as a valuable marker for the detection of chronic alcohol abuse (1, 2). The major reason for this is high specificity (>95%) in combination with good sensitivity (>75%). False-positive CDT determinations are scarce but do occur in patients with some liver diseases, with the rare genetic D variant of transferrin, and with the carbohydrate-deficient glycoprotein syndrome. Because it can be anticipated that the amount of CDT will also be influenced by the rate of transferrin synthesis, we studied CDT values measured by CDTect in a group of anemic patients with various causes and treatments and subsequently in nonanemic patients with low ferritin values. The study was approved by the Medical Ethical Committee of our hospitals.

CDT (CDTect, Pharmacia & Upjohn; reference values <20 units/L for men and <26 units/L for women), ferritin (AxSYM, Abbott; reference values, 25–300 µg/L), serum iron (Hitachi 704, Boehringer Mannheim; reference values, 10–32 µmol/L), and transferrin (Tinaquant, Hitachi 704, Boehringer Mannheim; reference values, 1.84–3.60 g/L) were measured in 99 anemic patients (46 men and 53 women) with a hemoglobin monomer concentration <7.0 mmol/L for at least 3 months. Several patients had persistent iron deficiency, and others were treated with oral iron supplementation. Transferrin concentrations were 0.36–4.39 g/L (mean, 2.26 g/L). Serum iron was 1.4–39.2 µmol/L (mean, 10.2 µmol/L), and ferritin was 8–14904 µg/L (mean, 647 µg/L). CDTect values are expressed in arbitrary units/L, which is approximately equivalent to mg/L. Calculations were carried out by standard linear regression analysis.

We found statistically significant correlations between transferrin and ferritin, between CDT and ferritin, and between CDT and transferrin but not between any of these analytes and serum iron. Because the ferritin concentration covered a very large range, the use of the logarithm of ferritin concentrations was necessary. In this manner, we found a semilogarithmic correlation of transferrin with ferritin (transferrin in g/L = 3.82 – 0.69 × log[ferritin in µg/L]; r = −0.71) and a semilogarithmic correlation of CDT and ferritin (CDTect in units/L = 26.95 – 6.52 × log[ferritin in µg/L]; r = −0.70; Fig. 1A). Obviously, there was also a linear correlation of CDT with transferrin (CDTect in units/L = 6.38 × transferrin in g/L – 2.34; r = 0.66). As can be seen in Fig. 1, CDT values frequently exceed the cutoff value of CDTect (20 units/L for men, 26 units/L for women) at low ferritin concentrations (<25 µg/L). The ratio of CDT/transferrin correlated only weakly with the logarithm of ferritin concentrations (CDTect/transferrin in units/g = 7.88 – 1.13 log[ferritin in µg/L], r = 0.3).

To check if the false-positive CDT results happened merely in anemic patients with low ferritin values, 16 nonanemic patients (6 men and 10 women) with low ferritin values were taken at random for CDTect analyses; ferritin concentrations were 0.4–21.6 µg/L (mean, 10.0 µg/L).

Fig. 1. Correlation of CDTect and transferrin vs ferritin.

(A) Negative semilogarithmic correlation of CDTect (■) and transferrin (○) concentrations with ferritin concentrations. (B) CDTect concentrations vs low ferritin values (<25 µg/L). The upper limits of CDTect for men (□) and women (●) are shown by lines at 20 units/L and 26 units/L, respectively.
The results are depicted in Fig. 1B together with the results of the low ferritin patients of the previously mentioned anemic cohort (five men and eight women). In the group with ferritin values below the reference interval (<25 μg/L), 5 out of 11 men had CDT values ≥20 units/L and 8 out of 18 women had CDT values ≥26 units/L. Therefore, a disproportionate number of high CDT values were observed in anemic and nonanemic patients with low ferritin values. Retrospectively, these patients showed no indications for alcohol abuse. In the literature, the specificity of CDT for nondrinking alcohol abuse has been reported as high as 100% [1, 2].

From these results it can be concluded that higher transferrin production (to cope with higher iron demand, for example) involves higher CDT concentrations, which frequently exceed the cutoff values. It can be expected that other conditions with low iron stores also show an increased percentage of false-positive CDT values. This was actually shown in hereditary hemochromatosis, where iron depletion with phlebotomy caused an increase in serum CDT, also above the reference interval [3].

Finally, we recently found that reference values of CDTect in nondrinking perimenopausal women were dependent on the frequency of menstruation in the past year. The upper limit of the reference values was 26 units/L for pre- and perimenopausal women (in accordance to the manufacturer) but was significantly lower for postmenopausal women (22 units/L, P < 0.0001) [4].

In conclusion, low iron status or high iron demand involves higher transferrin synthesis, probably with a proportional increase of CDT isoforms. Therefore, low ferritin status should be taken into account as a cause for unexplained high CDT results. The use of the ratio CDT/transferrin seems to have an advantage in this situation; however, it can induce false-positive outcomes if transferrin concentrations are low [5].

References

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Suitability of Plastic Collection Tubes for Cyclosporine Measurements

To the Editor:

The recommended specimen for measuring cyclosporine concentrations is whole blood anticoagulated with EDTA (1). Traditionally, these specimens have been collected in glass tubes. Because of safety issues, evacuated plastic tubes are now available for blood collection. However, because it is known that cyclosporine is adsorbed by some kinds of plastics (2), there is no guarantee that cyclosporine concentrations in specimens collected in plastic tubes will remain stable.

Dasgupta et al. (3) examined the effect of plastic collection tubes on 13 therapeutic drugs. One of the drugs they examined was cyclosporine. However, no cyclosporine data were exhibited in their paper, and the stability was monitored for only 24 h. We wished to undertake a more complete study. Additionally, because some of our specimens are shipped to us from remote locations, we sought to examine the stability of cyclosporine in plastic tubes for longer than 1 day.

Sterile 3-mL glass and plastic evacuated blood collection tubes (Vacutainer® and Vacutainer PLUS, respectively) with EDTA anticoagulant were obtained from Becton Dickinson Vacutainer Systems. Specimens in glass and plastic tubes were collected simultaneously from renal transplant patients receiving cyclosporine to prevent rejection. Specimens were collected only from patients whose physicians had requested cyclosporine measurements. Tubes were stored at 4 °C or room temperature after collection and between analyses. Specimens were analyzed for cyclosporine concentrations within 24 h of collection (day 0), and 1, 4, and 7 days thereafter (days 1, 4 and 7, respectively). Specimens were mixed by rocking for at least 10 min at room temperature before analysis. Cyclosporine concentrations were measured by fluorescence polarization immunoassay on an Abbott TDX using the Abbott Cyclosporine Monoclonal Whole Blood assay kit (Abbott Laboratories). Assays were performed according to the manufacturer’s procedure.

In the first experiment, 14 specimens from 12 patients were stored at 4 °C and analyzed over 7 days. Cyclosporine concentrations ranged from 91 to 611 μg/L (glass tubes, day 0). For most samples, the value in the plastic tube was slightly higher than the value from the glass tube (individual data not shown). The paired t-tests on each day were statistically significant (P < 0.05). The average concentrations for these 14 specimens on each day for the two specimen containers (glass vs plastic) are shown in Table 1. As can be seen, the means of the concentrations from the specimens collected in plastic tubes were slightly higher than the specimens collected in glass tubes, although the means were not statistically different (unpaired t-tests). The average percentage difference between the plastic and glass tubes