Abstinence in alcoholism. Changes in carbohydrate--deficient transferrin (CDT)

Jorge Peneda*, Aidil Fonseca**, Cristina Ribeiro***, Teresa Sá Nogueira****, M. Celeste Dias*****, Soledade Gomes******, Domingos Neto*******

Abstract

Carbohydrate-deficient transferrin – CDT is currently the most specific biological marker for chronic alcohol consumption.

After 4 weeks of monitored abstinence, a population of 55 alcoholic patients, admitted to the Centro Regional de Alcoologia in Lisbon for treatment and recovery, had significant decreases in their average levels of abnormal transferrin. Yet, at this stage, the values of this marker remained higher than the conventional reference levels, namely in heavy drinkers with viral hepatitis (HBV, HCV). These values became significantly lower than the traditional markers (AST/ALT/GGT) of abstinent heavy drinkers, particularly those with hepatitis. This reflects the better specificity of CDT for alcoholism/abstinence. The abnormal index values of iron status are also higher in heavy drinkers in the abstinence period, again particularly those with viral hepatitis infection, in comparison with the reference population. The evaluation of the critical transferring level is helpful, as it correlates with the isoforms induced by alcohol.

This data recommends the absolute need for determination of abnormal transferrin levels in heavy drinkers under monitored abstinence, which should be the indicated reference marker for the subsequent surveillance of alcohol abstinence.

Key words: alcoholism, abstinence, carbohydrate deficiency transferrin, iron status.

Introduction

Over the last ten years, the usefulness of the gradual introduction into clinical practice of measuring abnormal levels of serum transferrin (isoforms) induced by persistent consumption of alcohol[1-3] has become more consistent, due to its higher sensitivity and better specificity than the traditional biological indices (AST, ALT, GGT), and its promising predictive value in societies, like ours, with high frequencies of alcohol consumption.[4-7]

Moreover, this parameter has recently been shown to be relevant in the monitoring of abstinence over time (individual reference cut-off) in alcoholic patients undergoing treatment,[7-13] acting as an early indicator of relapse (a return to drinking often precedes typical clinical symptoms by several weeks) and, therefore, as a useful guide in the timely intervention of medical treatment for reconversion to abstinence.[12,13]

Normal transferrin is glycoprotein that is synthesized and glycosylated in the hepatocytes and secreted by the liver. Ethanol and acetaldehyde lead to the induction of insaturation through a deficit in the incorporation of oligosaccharide radicals in the iron transport protein – transferrin - in the Golgi complex, through a major reduction in the sialyltransferase activity, and by reinforcing the activity of the sialydases in the serum of the alcoholic patient.[1,14-16] This immature form of transferrin acquires its detectable isoforms with persistent active alcohol consumption of about sixty grams/day for seven to ten consecutive days, reaching high levels of sensitivity and specificity, ranging from 70 to 80% and 90 to 95% respectively,[1] although there is no consensus on these levels. Since the half-life is about fifteen days,[4] much shorter than that of the classic markers of alcoholism, it is useful in their relative interpretation.

The strongest feature of this test is its specificity, since few medical conditions that are easily detectable in clinical practice and not alcohol-related, yield false positives with low frequency, and it also seems to be independent of the nature of the liver disease and the severity of the liver damage.[18-21,42] In a previous work, as in other series, the measurement of the absolute value of abnormal transferrin is influenced by the level of total serum transferrin, which is important in eva-

*Head Researcher at the Núcleo de Alcoologia do Instituto Nacional de Saúde
**Senior Technician at the Instituto Nacional de Saúde
***General Clinical Asssistant at the Centro Regional de Alcoologia de Lisboa
****Senior Psychiatry Assistant at the Centro Regional de Alcoologia de Lisboa
*****Head Nurse at the Centro Regional de Alcoologia de Lisboa
******Dietician at the Centro Regional de Alcoologia de Lisboa
*******Director of the Centro Regional de Alcoologia de Lisboa
Received for publication on the 20th April 98

TABLE I

Carbohydrate deficient transferrin in alcohol-dependency and in abstinence

	Axis n = 55	CDT n = 23	CDT/Tf n = 23
T0	6.58 ± 4.07	27.11 ± 13.98	10.67 ± 5.46
	n = 50		
T1	3.45 ± 1.53	13.73 ± 5.32	5.11 ± 2.34
	p<0.01	p<0.01	p<0.01

T0 - At admission
T1 - At discharge after four weeks of controlled abstinence; five patients did not complete this time period
Tf - Total transferrin. Axis CDT carbohydrate deficient transferrin (methodology)

luating the iron status in the alcoholic patient.[22-25,42]

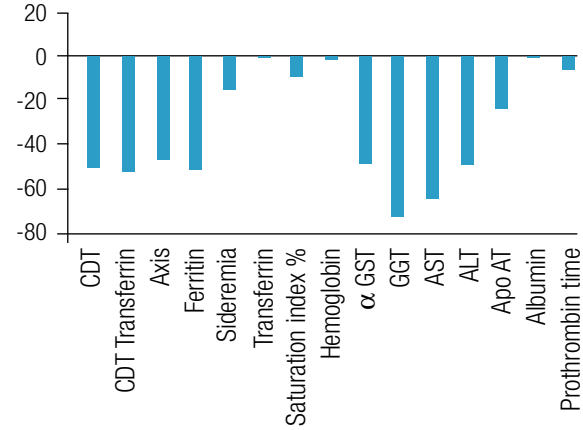
The present study aims to assess the behavior of abnormal serum transferrin in a chronic dependent user population, subject to controlled abstinence in an alcoholism treatment and recovery center.

Material and methods

The target population consisted of fifty-five patients (in random temporal order) hospitalized at the Centro Regional de Alcoologia de Lisboa (CRAL, Lisbon Regional Center for Alcoholism) in the period 1996-97.

As part of the routine clinical and laboratory study, the patients, duly informed about the additional tests, had blood drawn on the date of admission (time 0) and again on the date of discharge (time 1) following four weeks of controlled abstinence. Multiple biological variables for the study of the metabolic behavior of lipids, glucose, proteins, iron, and liver function, including the measurement of selective biological variables for the calculation of the PGA index (prothrombin time + gamma-glutamyl transpeptidase + apolipoprotein A1), were considered, in addition to the quantification of serum carbohydrate deficient transferrin (CDT).

We used the first generation CDTect Pharmacia (Uppsala) test, with results expressed as absolute values, and the second generation AXIS % CDTria TIA (Oslo) test, which also includes the calculation of the transferrin ratio in the procedure, and expresses the results as percentages, involving asialo-, monosialo-, and disialo-transferrin forms in the prototype test, as well as trisialo-transferrin.



% deviation from mean values of biological indices in the serum of alcoholic patients after four weeks of abstinence from alcohol.

FIG. 1

All patients were screened for the existence of viral infections (HBV and HCV).

For an accessible, global determination of morphological liver status (limited to non-invasive options),[43] the patients underwent ultrasound imaging exams (liver, splenoportal axis, and peritoneal cavity).

Reference values used for the variables studied were: GSTa (a glutathione S transferase) mg/L <4; GGT (gamma-glutamyl transpeptidase) U/L H<37 M<24; AST (aspartate aminotransferase) U/L H<29 M<21; ALT (alanine aminotransferase) U/L H<25 M<21; ApoA1 (apolipoprotein A1) g/L 120-172; sideremia mg/d H 59-158 M 37-145; transferrin mg/d H 223-244 M 197-395; transferrin saturation % 16-60; ferritin ng/dL H 52-352 M 8-110; hemoglobin g/dL H 14-18 M 12-16; prothrombin time % 70-120; albumin g/dL 3.63-4.79; CDT UL <20.5; Axis % 2.5-5; CDT/Tf % < 7.5.

Laboratory techniques

Axis % CDTri TIA (turbidimetric immunoassay), LP400 Microplate Reader (reading apparatus, SANOFI Diagnostics Pasteur), Axis Biochemicals reagents. The serum transferrin of the sample is saturated with Fe^{3+} ions, followed by the separation of the different isoforms using ion-exchange microchromotography, given that the different concentrations of sialic acid residues present in the transferrin isoforms have different charges enabling their separation. The

TABLE II

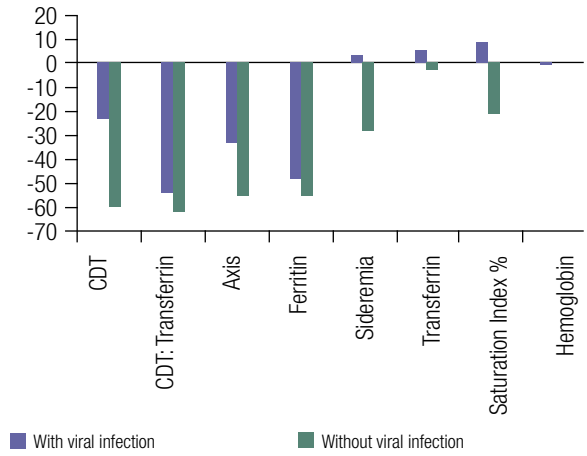
Carbohydrate deficient transferrin in alcohol-dependency and in abstinence without and with viral infection (HBV, HCV)

Subgroup of alcohol-dependents without viral infection			
	Axis n=30	CDT n=15	CDT/Tf n=15
T0 T1	6.9 ± 4.3 3.3 ± 1.3	29.4 ± 15.1 12.8 ± 4.0	11.1 ± 5.9 4.5 ± 1.5
	p<0.01	p<0.01	p<0.01
Subgroup of alcohol-dependents with viral infection			
	Axis n=25	CDT n=8	CDT/Tf n=8
T0 T1	5.8 ± 3.8 n=20 3.9 ± 1.9	25.2 ± 12.1 15.6 ± 7.1	10.4 ± 4.6 6.2 ± 3.2
	NS	NS	NS

T0 - At admission
T1 - At discharge, after four weeks of controlled abstinence
Tf - Total transferrin. Axis CDT carbohydrate deficient transferrin (methodology)

eluted isoforms (asialo-, monosialo-, disialo-, and trisialo-transferrin), together with human antitransferrin antibodies, form immunocomplexes that are measurable by turbidimetry. The total transferrin of the sample is determined separately, using the same antibody. The result is evaluated using a calibration curve and expressed as a percentage relative to the concentration of total transferrin. CDTect Pharmacia (second radioimmunological method), Beckman 5500 GAMMA Counting System (reading apparatus), Pharmacia CDTect RIA regents, procedural description in previous work.[42] Hematological parameters quantified using a Coulter MAXM Auto Loader. Prothrombin time, automatic method, STA Compact reading device (Boehringer Mannheim). Activity of transaminases and gamma-glutamyl transpeptidase analyzed by the Hitachi 911 autoanalyser, Boehringer Mannheim reagents, transferrin by the immunoturbidometric method, and sideremia using the direct ferrozine method. Procedures are described in a previous work.[42]

Statistical analysis used the Student's t-test to check for null hypothesis of differences between means. Microsoft Excel software was used.



% deviation from mean values of biological indices of the status of iron in the serum of alcoholic patients (groups with and without viral infection) after four weeks of abstinence from alcohol.

FIG. 2

Results

The group studied consisted of forty-three male and twelve female patients, fifty-two of whom were Caucasians and three of whom were Black, with an average age of forty-two years (28 to 49 years of age) and estimated consumption of 100-490 g/day for a period of more than six years.

Table I and *Fig. 1* show the behavior of the Axis, CDT, and CDT/transferrin readings of biological alcohol consumption markers, with abnormal average levels of serum transferrin in the longitudinal study, at time 0 and at time 1 (from consumption to completion of four weeks of controlled abstinence). A comparison of these levels shows a significant decrease ($p < 0.01$) in each of the variables, with decreases of -47.6% Axis, -50.9% CDT and -52.2% CDT/transferrin.

Despite the controlled abstinence (T1), values higher than the conventional cut-off values were still found (13.8% Axis, 4.3% CDT, and 18% CDT/transferrin). In this series, the mean serum levels of alcohol-dependent after four weeks of controlled abstinence were eleven percent higher than readings taken in a control population that did not consume alcohol.

In the present case series, twenty-five of the fifty-five patients (45.4%) were identified as being infected or co-infected with the HBV and/or the HCV.

In the stratification (*Table 2* and *Fig. 2*) of this uni-

TABLE III

Iron status indices in alcohol dependency and in abstinence

	Ferritin	Sideremia	Transferrin	Saturation Index	HB
T0 N=55	562.5 ± 962.0	130.6 ± 70.0	302 ± 66.1	34.0 ± 20.1	14.6 ± 1
T1 N=50	269.6 ± 338.9	110.3 ± 47.4	304 ± 66.3	30.7 ± 15.3	19.5 ± 1
	p<0.05	NS	NS	NS	NS

T0 - At admission
T1 - At discharge, after four weeks of controlled abstinence. Five patients were lost because they did not complete the hospitalization period.
HB - Hemoglobin

TABLE IV

Iron status indices in alcohol-dependency and in abstinence without and with viral infection (HBV, HCV)

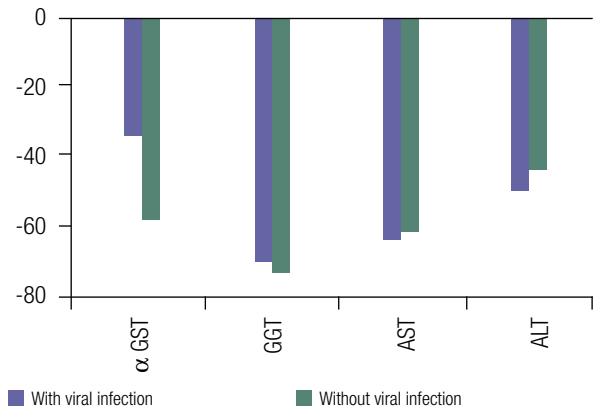
Without viral infection				
	Iron	**Transferrin**	**Saturation Index**	**Ferritin**
T0 n=30	140.4 ± 67.3	314.6 ± 68.1	35.4 ± 18.3	40.7 ± 449.9
T1 n=30	102 ± 34.8	306.4 ± 58.9	27.9 ± 12.4	193.4 ± 214.7
	p<0.01	NS	NS	p<0.05
With viral infection				
	Iron	**Transferrin**	**Saturation Index**	**Ferritin**
T0 n=25	118.8 ± 727	287.2 ± 61.7	32.4 ± 22.3	730.3 ± 1300
T1 n=20	122.7 ± 60.7	301.2 ± 77.5	35.1 ± 18.8	383 ± 450.4
	NS	NS	NS	NS

T0 - At admission
T1 - At discharge, after four weeks of controlled abstinence. Five patients were lost because they did not complete the hospitalization period

verse, in the subgroup of alcohol-dependents without infection (absence of HBV, HCV), the longitudinal evolution of behavior of the marker indices of alcohol consumption, in relation to the levels of existence of abnormal transferrin highlights decreases of -52.1% Axis, -57.0% CDT, and -59.5% CDT/transferrin in mean serum levels after four weeks of controlled abstinence as statistically significant differences (p <0.01). However, in the subgroup of alcohol-dependents with viral infection (the presence of HBV and HCV), less pronounced differences were found in the average serum levels after controlled abstinence (-32.8% Axis, -38.1% CDT and -52.1% CDT/transferrin) than in the other subgroup, and these differences were not significant.

The frequencies of abnormal values (higher than conventional reference values) at T0 in the alcohol-dependent subgroup without viral infection were 56.7% Axis and 60% CDT, while in the subgroup of alcohol-dependents with viral infection they were 43.5% Axis and 62.5% CDT. After controlled abstinence for a period of four weeks, the frequencies of abnormal values of carbohydrate deficient transferrin in the alcohol-dependent subgroup without viral infection were 13.3% Axis and 0% CDT, while in the alcohol-dependent subgroup with viral infection, these frequencies, at 25% Axis and 12.5% CDT, were clearly higher than in the other group.

The indices for iron status (*Table 3* and *Fig. 1*) show that abstinence promotes a decrease by -52.0% (p <0.05), -15.5%, and -9.7% respectively, in the average serum ferritin, sideremia, and saturation index levels, with no change in transferrin levels. The levels of hemoglobin endowment were normal and invariable. After four weeks of abstinence, the frequencies of values higher than the conventional references were 30% for ferritin, 12% for sideremia, 8% for the transferrin saturation index, and 8% for transferrin. The average value of transferrin in this series is higher than that in the other series of twenty-one patients with advanced alcoholic cirrhosis of the



% deviation from mean values of biological indices of liver dysfunction in the serum of alcoholic patients (groups with and without viral infection) after four weeks of abstinence from alcohol

FIG. 3

liver hospitalized in a central general hospital, HCL 302 ± 66.1 E.S.R. 254 ±621.7.[42]

In the stratification of patients studied (*Table 4* and *Fig. 3*), decreases in average serum values in the subgroup of alcohol-dependents without viral infection of -27.4% (p <0.01), -2.6%, -21.2%, and -52.5% (p <0.01), respectively, for sideremia, transferrin, transferrin saturation index, and ferritin, were noted following abstinence, with frequencies of abnormal values (higher than reference values) of 3.6%, 7.1%, 3.4%, and 20%, respectively, for sideremia, transferrin, transferrin saturation level, and ferritin. In the subgroup of alcohol-dependents with viral infection, frequencies of abnormal values following abstinence were 28.7% sideremia, 10% transferrin, 15.2% transferrin saturation index, and 45.2% ferritin. Following abstinence, iron status was the highest of the indices of the subgroup of alcohol-dependents with viral infection, though significant decreases were not measured in any of the indices of the group of patients with this condition.

In the study of liver dysfunction (*Table 5* and *Fig. 1*), the average serum values of enzymatic activity indices decreased significantly after four weeks of abstinence: -49.2% (p <0.05), -73.4% (p <0.01), -65.1% (p <0.01), and -49.4% (p <0.05) for GTSa, GGT, AST, and ALT respectively. Following abstinence, frequencies of abnormal values (higher than conventional references) were noted as 52.1%, 54%, 14%, and 23.6% for GSTa, GGT, AST and ALT respectively, these being well above the frequencies of abnormal values of carbohydrate deficient transferrin normally found in an identical situation of absence of alcohol.

In a stratification of the total population studied (*Table 6* and *Fig. 3*), the subgroup of alcohol-dependents without viral infection and in abstinence shows significant decreases (p <0.01) in the average levels of GGT, AST, and ALT, biological indices of liver dysfunction. In regards to the differences in the average levels in the subgroup of alcohol-dependents with viral infection, abstinence is not sufficient to cause statistical significance in any of them. In the latter subgroup, following abstinence, the frequency of abnormal levels (higher than the conventional cut-off values) is higher than in the subgroup of alcohol-dependent patients without viral infection, under the same conditions.

In a comparison of the behavior of serum levels of these enzymatic indices between the two subgroups, there were no significant differences in any of them at time 0. However, in a condition of abstinence, at time 1, there were significant differences between the subgroups with and without viral infection: ALT p<0.05, GGT p<0.05, GTSa p<0.01, and AST p<0.01.

A non-invasive, conditioned of the status of the liver under the persistent effect of alcohol (*Table 7*) shows that in this series of alcohol-dependent patients hospitalized for alcoholism treatment in the Centro Regional de Alcoologia de Lisboa, only 2.5%

TABLE V

Liver dysfunction in alcohol-dependency and in abstinence

	GSTa	GGT	AST	ALT
T0 N=55	12.2 ± 18.0	231.4 ± 70.0	51.9 ± 86.7	42.5 ± 65.8
T1 N=50	6.2 ± 5.4	61.6 ± 71.5	18.1 ± 11.9	21.5 ± 15.6
	p<0.05	p<0.01	p<0.01	p<0.05

T0 - At admission
T1 - At discharge, after four weeks of controlled abstinence
Five patients were lost because they did not complete the hospitalization period
GSTa, GGT, AST, ALT (methodology)

TABLE VI

Liver dysfunction in alcohol-dependency and in abstinence without and with viral infection (HBV, HCV)

Without viral infection				
	GGT	**GSTa**	**AST**	**ALT**
T0 N=30	159.3 ± 18.6	11.2 ± 11.3	38.1 ± 33.5	32.2 ± 26.3
T1 N=30	42.5 ± 30.8	4.6 ± 3.1	14.3 ± 3.2	17.9 ± 8.3
	p<0.01	NS	p<0.01	p<0.01
Without viral infection				
	GGT	**GSTa**	**AST**	**ALT**
T0 n=25	317.8 ± 512.7	21.4 ± 22.2	68.4 ± 112.5	54.8 ± 92.9
T1 n=20	90.4 ± 101.5	12.2 ± 5.5	23.8 ± 17.0	26.8 ± 21.7
	NS	NS	NS	NS

T0 - At admission
T1 - At discharge, after four weeks of controlled abstinence
Five patients were lost because they did not complete the hospitalization period
GSTa, GGT, AST, ALT (methodology)

TABLE VII

PGA index in alcohol-dependency and in abstinence (morpho-functional equivalency)

Score	CRAL (n=55)	HSAC/HCL (n=21) 42
<6	64.2%	0%
>6 <8	33.3%	10%
>9	2.5%	90%
Scale correspondence:		
	without damage/minimal damage	3 - 5 points
	fibrosis with/without hepatitis	6 - 8 points
	cirrhosis with/without hepatitis	9 - 12 points

CRAL: Centro de Alcoologia de Lisboa (patients hospitalized for alcoholism)
HSAC/HCL: H.Sto.A. Capuchos/Hospitais Civis de Lisboa (patients hospitalized for alcoholic cirrhosis)
PGA:38 Prothrombin time + gamma-glutamyl transpeptidase + apolipoprotein A1
Point system equivalencies/serum levels of APO A1, GGT, Prothrombin time 38,42

of cases had a PGA index score (severity of alcoholic liver disease) higher than 9, while 64.2% had scores lower than 6 (compared to 90% of patients with scores higher than 9 in a series of twenty-one patients hospitalized for advanced alcohol-related cirrhosis of the liver in a central general hospital - HCL).[42]

The ultrasound imaging study of the series at CRAL resulted in 21.7% of cases with normal results and 78.3% with diagnoses of hepatomegaly/steatosis, without any imaging results across the entire series suggestive of nodular structures in the liver, portal hypertension, splenomegaly, or ascites.

Discussion

In this series, the quantification of transferrin isoforms in the blood serum of alcohol-dependent patients, hospitalized for alcoholism treatment and recovery, proved to be a better interpretive tool than traditional indicators. The results of the three indices studied, Axis, CDT, and CDT/transferrin, were equally effective in terms of the detailed analysis of alcohol consumption.[26] The absence of alcohol results in a significant decrease in each of the indices.[4,8,9,12]

At the beginning of treatment, the alcohol-dependent patients in this series had percentages of abnormal transferrin similar to those measured in other series conducted under similar conditions.[27] On the other hand, and as in other case series, the serum isoform levels in alcohol-dependents under controlled abstinence may be higher than the values of the general consumer population.[9,17] This shows the advantage of determining the individual level of the alcoholic in abstinence, as an appropriate and more accurate benchmark for the subsequent monitoring of supervised abstinence.

Here in Portugal, the frequency of viral infection (HBV and HCV) in alcohol-dependent patients is high. A comparison of the results of the subgroups that make up the total shows that while the absence of alcohol is sufficient to cause a significant decrease in serum levels of carbohydrate deficient transferrin, in the subgroup of alcohol-dependent patients with viral hepatitis infection, abstinence by itself is

not enough to induce significant decreases in these indicators of consumption, which suggests that other factors interfere in this behavior, particularly through direct or indirect intervention with the virus/iron metabolism interaction,[22,28-36] particularly with abnormal transferrin, which highlights the need for individualized reference values for the subsequent control of abstinence.

In the alcoholic, variability in iron homeostasis is expressed clinically in symptoms ranging from anemia to siderosis, and there is a known positive association between serum levels of transferrin and its induced isoforms.[23-26,42] In this series, normal hemoglobin endowment and assumed mild to moderate alcoholic liver disease (a pathobiological discriminator of morphofunctional suspicion with a low score on the PGA index),[37-42] age group, imaging tests,[43] and induced variability/reversibility of enzymatic activity in most patients, support a probable increase in the synthesis of transferrin in the liver.[36] This, it makes sense to study the ratios of abnormal transferrin. Controlled abstinence is sufficient to cause a decrease in all the iron status indicators, with significance for ferritin.

The effects of the absence of alcohol on the alcoholic undergoing treatment are more significant in the absence of viral infection of the liver, and it is known that this alone is frequently associated in clinical practice with an increase in iron status.[34] In fact, in the subgroup of alcohol-dependents with viral infection under abstinence, the frequency of abnormal serum levels is higher than in the group of alcohol-dependents without viral infection under the same study conditions, which suggests the influence of an unknown mechanism other than alcohol.[34] Abstinence causes a significant reduction in liver dysfunction as measured by the enzymatic activity indices. But even in the absence of alcohol, high frequencies of these markers, traditionally used as potential indicators of consumption, are found and since these are higher than the abnormal frequencies of carbohydrate deficient transferrin, this latter marker of alcohol consumption turns out to be more useful for the proper individual control of abstinence.[1,28,42] The frequency of abnormal values of liver function in the subgroup of alcohol-dependents with viral infection under controlled abstinence distinguishes the pathogenesis attributable to the dysfunction, explaining the significant differences between the two subgroups of alcohol-dependents for all indicators of liver dysfunction.

This study supports the usefulness of individualized CDT measured during controlled abstinence for the timely detection of possible relapses in alcoholism (relative increase in abnormal transferrin) during the process of monitored recovery. ■

Acknowledgements

Prestifarma (Biotrin-Dublin, Axis-Oslo) for providing various kits for the determination of % CDT and GSTa. Pharmacia (Uppsala) for providing the CDTect RIA kit. Sra. D. Lídia B. Ferreira, laboratory technician (INSA), for her excellent collaboration.

References

1. Stibler H. Carbohydrate-deficient Transferrin in serum: a new marker of potentially harmful alcohol consumption reviewed. Clin Chem 1991; 37: 2029-2037.

2. Allen JP, Litten RZ, Anton RF, Gross GM. Carbohydrate-deficient Transferrin as a measure of immoderate drinking: remaining issues. Alcohol Clin Exp Res 1994; 18: 799-812.

3. Sillanaukee P. Laboratory markers of alcohol abuse. Alcohol Alcohol 1996; 31: 613-616.

4. Wetterling T, Kanitz RD. Clinical value of laboratory findings in alcoholics. Eur Addict Res 1996; 2: 140-146.

5. Meerkerk GJ. CDT in general practice. Alcohol Alcohol 1997; 32:312 S.

6.Fanske S. The use of CDT in primary health care. Alcohol Alcohol 1997; 32:314 S.

7. Sillanaukee P, Aalto M. Prevalence and detection of heavy drinking among primary health care patients – experience from the Lakti Brief Intervention Study. Alcohol Alcohol 1997; 32:319 S.

8. Borg S, Helander A, Carlsson AV, et al. Detection of relapses in alcohol dependent patients using carbohydrate-deficient transferrin: improvement with individualized reference levels during long-term monitoring. Alcohol Clin Exp Res 1995; 19:961-963.

9. Helander A, Carlsson AV. Borg S. Longitudinal comparison of CDT and GGT levels in alcohol dependent subjects. Alcohol Alcohol 1995; 30:557.

10. Anton RF, Moak DH, Lathan PK. Carbohydrate-deficient Transferrin (CDT) as a marker for relapse drinking in a pharmacologic treatment study of alcohol dependence. Alcohol Clin Exp Res 1995; 19 :43 A.

11. Decrey H, Fellrath F, Van Melle G, et al. Usefulness of carbohydrate--deficient transferrin in follow-up after alcohol withdrawal. Alcohol Alcohol 1995; 30:555.[A]

12. Rosman AS, Basul P, Gavin K, Lieber CS. Utility of carbohydrate-deficient transferrin as a marker of relapse in alcoholic patients. Alcohol Clin Exp Res 1995; 19:611-616.

13. Anton RF. The use of carbohydrate-deficient transferrin as an indicator of alcohol consumption during treatment and follow-up. Alcohol Clin Exp Res 1996; 20:54[A]–56[A].

14. De Jong G, van Dijk JP, van Eijk HG. The biology of transferrin. Clin Chem Acta, 1990; 190:1-46.

15. Durand G. Overview on pathological glycosylation. Alcohol Alcohol 1997; 32:310S.

16. Bean P, Peter JP. Allelic D. Variants of transferrin in evaluation of alcohol abuse: differential diagnosis by isoelectric focusing-immunoblotting-laser densitometry. Clin Chem 1994; 40: 2078-2083.

17. Xin Y, Lasker J, Lieber CS. Serum carbohydrate-deficient transferrin: mechanism of increase after chronic alcohol intake. Hepatology 1995; 22: 1462-1468.

18. Bell H, Talleksen C, Sjaheim T, et al. Serum carbohydrate-deficient transferrin with chronic liver diseases. Alcohol Clin Exp Res 1993; 17: 246-252.

19. Caldwell SH, Hallyday JW, Fletcher LM. Carbohydrate-deficient transferrin in alcoholics with liver disease. J Gastroent and Hepat 1995; 10: 174-178.

20. Niemela O, Sorvajarvi K, Blake JE, Israel Y. Carbohydrate-deficient transferrin as a marker of alcohol abuse: relationship to alcohol consumption, severity of liver disease, and fibrogenesis. Alcohol Clin Exp Res 1995; 19: 1203-1208.

21. Niemela O, Sorvajarvi K, Blake JE, Israel Y. Relationship of carbohydrate--deficient transferrin to the severity of alcoholic liver disease. Alcohol Alcohol 1995; 30: 561.

22. Bell, Heller K, Harthing S et al. Different levels of serum carbohydrate--deficient transferrin (CDT) in chronic hepatitis C and haemochromatosis. Alcohol Alcohol 1995; 30: 555[A].

23. Sorvajarvi K, Blake JE, Israel Y et al. Sensitivity and specificity of carbohydrate deficient transferrin as a marker of alcohol abuse are significantly influenced by alterations in serum transferrin: comparison of two methods. Alcohol Clin Exp Res 1996; 20: 449-454.

24. Bell H, Tallaksen ME, Try K, Hang E. Carbohydrate-deficient transferrin and other markers of high alcohol consumption: a study of 502 patients admitted consecutively to a medical department. Alcohol Clin Exp Res 1994, 18: 1103-1108.

25. Yamauchi M, Hirakawa J, Maezawa Y et al. Serum level of carbohydrate--deficient transferrin as a marker of alcoholic liver disease Alcohol Alcohol 1993; 28: 3-8.

26. Gordon HM, Sherwood R, Morgan MY. Serum carbohydrate-deficient transferrin (CDT) comparison of methodologies. Alcohol Alcohol 1997; 32: 331 S.

27. Rommelspacher H, Spies C, Schmidt K. Laboratory marker monitoring in an intensive care unit and in a long-term rehabilitation program. Alcohol Alcohol 1995; 30: 492[A].

28. Bell H, Skimingsrud A, Raknerud N, Try K. Serum ferritin and transferrin saturation in patients with chronic alcoholic and non-alcoholic liver diseases. J Intern Med 1994; 236: 315-322.

29. Vernet M, Bried A, Simplot A. Metabolisme du fer et infection à VIH: étude préliminaire. Ann Biol Clin 1997; 55: 477-480.

30. Weinberg ED. Iron withholding: a defence against viral infections. Bio Metals 1996; 9: 393-399.

31. Moirand R, Lescoat G, Delamaire D et al. Increase in glycosylated and non--glycosylated serum ferritin in chronic alcoholism and their evolution during alcohol withdrawal. Alcohol Clin Exp Res 1991; 15: 963-969.

32. Lee MH, Means RT. Extremely elevated serum ferritin levels in a University hospital: associated diseases and Clinical Significance. Am J Medicine 1995; 98: 566-571.

33. Grossard AA, Gross JR, Burgaret LJ et al. Significance of iron indices in hepatitis C, alcoholic liver diseases, and non-C, non-alcoholic liver disease. Gastroenterol 1995; 108: A 1075.

34. Bronkovsky H, Banner BF, Rothman AL. Iron and chronic viral hepatitis. Hepatology 1997; 25: 759-768.

35. Dibisceglie AM, Axiotis CA, Hoofnagle JB, Bacon BR. Measurements of iron status in patients with chronic hepatitis. Gastroenterol 1992; 102: 2108-2113.

36. Potter BJ, Chapman RWG, Nunes RM. et al. Transferrin metabolism in alcoholic liver disease. Hepatology 1985; 5: 714-721.

37. Bedossa, P, Poynard T, Abella et al. Apolipoprotein A1 is a serum and tissue marker of liver fibrosis in alcoholic patients. Alcohol Clin Exp Res 1989; 13: 829-833.

38. Poynard T, Aubert A, Bedossa P et al. A simple biological index for detection of alcoholic liver disease in drinkers. Gastroenterol 1991; 100: 1397-1402.

39. Paradis V, Mathurin P, Ratziu V et al. Binding of Apolipoprotein A1 and acetaldehyde-modified Apolipoprotein A1 to liver extracellular matrix. Hepatology 1996; 23: 1232-1238.

40. Poynard T, Abella A, Pignon JP et al. Apolipoprotein A1 and alcoholic liver disease. Hepatology 1987; 6: 1391-1395.

41. Mathurin P, Vidaut D, Bedossa P et al. Quantification of apolipoprotein A1 and B messenger RNA in heavy drinkers according to liver disease. Hepatology 1996; 23: 44-51.

42. Peneda JA, Fonseca A, Neves M et al. Asialo-Transferrina discriminante do consumo excessivo activo de álcool, subagudo e crónico – Utilidade clínica na doença hepática. Acta Médica 1996; 9: 103-111.

43. Van Leeuwen DJ, Wilson L, Crowe DR. Liver biopsy in the mid 1990's: questions and answers. Sem Liver Dis 1995; 15: 340-359.