Liver, 1990: 10, 65–71
Key words: *alcohol consumption; cirrhosis; galactose elimination capacity; liver function; prognosis*

Analysis of the deterioration rates of liver function in cirrhosis, based on galactose elimination capacity

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ABSTRACT – The prognosis of cirrhotic patients may depend on their liver function, but very few data are available to predict life expectancy in individual subjects on the basis of their liver function tests. The yearly changes in liver function, based on galactose elimination capacity (GEC), were retrospectively analyzed in 76 cirrhotic patients. The first GEC measurement had always been performed at the time of diagnosis. From that time on, mean GEC changes (in mmol/min per year) were +0.13 [SD 0.60] in the 1st year (range: +1.42/−1.35), and −0.03 [0.30] in the 2nd year (P = ns). Only after 36 months could a significant deterioration in liver function be demonstrated, but GEC changes still ranged from +0.14 to −0.35. The trend in liver function was similar in patients with alcoholic and non-alcoholic cirrhosis, but in alcoholics a favourable effect of abstinence was proved. In individual subjects, 2 consecutive GEC measurements, at least 6 months apart, failed to predict the following GEC values. The coefficients of determination between expected and measured GEC or ΔGEC were 0.13 and 0.36, respectively (n = 58). When forecasting was limited to 2 years (n = 38), still only 31% and 55% of GEC values and ΔGEC variance was predictable on the basis of preceding GEC values. The study shows that no definite trends in liver function deterioration rates can be observed in cirrhosis. This limits the usefulness of liver function tests in predicting prognosis in cirrhotic patients.

Accepted for publication 29 March 1989

The life expectancy of patients with liver cirrhosis is extremely variable. Acute events (hemorrages, sepsis, coma, viral superinfection, alcohol abuse) may cause sudden decompensation of the disease and ultimately death. Apart from acute events, which may be largely unpredictable, it would be desirable to know, for any given patient at any given time, the minimum and maximum time before his liver function will be reduced to values no longer compatible with life. This is likely to depend on his actual liver function and on his liver function deterioration rate (1).

In recent years considerable interest has been paid to dynamic liver function tests, able to measure liver cell mass quantitatively. A better quantification of liver function might help to predict the prognosis (2, 3).

Among these tests, the galactose elimination capacity (GEC) is one of the more widely used in research centres. However, GEC values did not permit prediction of the prognosis in the single patient with cirrhosis, and, in the whole population, the predictive value of GEC was not better than that of conventional routine liver tests (4).

During the last 6 year we used GEC extensively in order to measure liver function in patients with cirrhosis. In this study we retrospectively analyzed the GEC values of patients who had 2 or more GEC determinations.

We aimed to answer the following questions: a) Does liver function progressively deteriorate in patients with cirrhosis? b) Is there a maximum and a minimum expected GEC change, which may be used to calculate, for any given patient at any given time and at any given GEC value at entry, the range of life expectancy?

Material and methods

Patients

The present retrospective study is based on the data of 76 cirrhotic patients in whom serial GEC determinations were available from 1982 to 1988. They ranged in age from 18 to 74 years; 61 were male and 15 were female. In all cases the diagnosis of cirrhosis was based on clinical and laboratory data and confirmed by a liver biopsy, in most cases performed during laparoscopy.

In 43 cases the diagnosis had been non-alcoholic cirrhosis. Patients with HBV related cirrhosis, non-A non-B postnecrotic cirrhosis, cryptogenic (autoimmune cirrhosis) and grade 3–4 primary biliary cirrhosis belonged to this group.

In 33 patients the diagnosis had been alcoholic cirrhosis. Patients were included in this group if they consumed more than 70 g (female) or 100 g (male) of alcohol per day for a continuous period of at least 5 years. None of these patients had signs of alcoholic hepatitis. Twenty-two patients stopped their alcohol abuse after the diagnosis. Their compliance with abstinence was based on interviews with relatives and on the reduction in gamma-GT levels or red blood cell volume. Eleven patients continued to drink during follow-up.

In all cases the first GEC determination had been performed at the time of diagnosis. Patients with ascites were treated with diuretics prior to the test. From that time on, the patients had been regularly followed as outpatients or were readmitted to hospital in case of decompensation.

GEC was measured every 1–2 years and a total of 204 determinations were available. For practical purposes, GEC determinations performed during follow up were divided into groups according to the time elapsed since entry into the study: 6–12 months, 12–24 months, 24–36 months, >36 months.

Two patients died within 1 year of the first GEC determination, 5 in the second year after entry, and 2 in the third year. All the remaining 67 survived 36 months or more, except 3 who did not complete the 36 months of follow up by September 1988, but they were still alive after 18, 20 and 21 months, respectively.

Methods

GEC measurement. GEC was measured in fasting patients between 8.30 and 9.30 a.m. Galactose concentrations were determined in capillary blood every 5 min between 20 and 45 min after i.v. injection of 500 mg/kg of body weight of galactose in 30% water solution (w/v). The calculations of galactose elimination capacity were performed according to Tygstrup's method. Urinary losses were considered to be 10% of the injected

Table 1

GEC values and GEC deterioration rates in patients with cirrhosis. The values are given as mean [SD]. The range is in parentheses.

	All cases	No. of cases	Non-alcoholic	No. of cases	Alcoholic	No. of cases
GEC at entry (mmol/min)	1.80 [0.43] (0.85/3.11)	76	1.82 [0.41] (0.85/2.78)	43	1.77 [0.45] (1.18/3.11)	33
Deterioration rates (mmol/min per year):						
5–12 months	+0.12 [0.61] (−1.35/+1.42)	40	+0.04 [0.62] (−1.35/+1.33)	24	+0.25 [0.56] (−0.88/+1.42)	16
12–24 months	−0.03 [0.30] (−0.65/+0.94)	39	−0.03 [0.30] (−0.48/+0.94)	24	−0.04 [0.32] (−0.65/+0.44)	15
24–36 months	0.00 [0.18] (−0.26/+0.46)	17	−0.07 [0.15]§ (−0.26/+0.22)	9	0.09 [0.17] (−0.10/+0.46)	8
>36 months	−0.04 [0.10]* (−0.35/+0.14)	32	−0.06 [0.08]§ (−0.20/+0.08)	18	−0.01 [0.11] (−0.35/+0.14)	14

* Significance of differences from entry values: $P < 0.05$ (paired-t test).

§ Significance of differences from entry values: $P < 0.05$ (Wilcoxon signed rank test).

Table 2

GEC values in alcoholic cirrhosis in relation to drinking habits. Values are given as means [SD]. The range is in parentheses.

	Drinking	No. of cases	Not drinking	No. of cases
GEC at entry (mmol/min)	2.08 [0.52] (1.50/3.11)	11	1.62 [0.32] (1.18/2.28)	22
Deterioration rates (mmol/min per year):				
5–12 months	−0.40 [0.38] (−0.88/+0.06)	4	+0.47 [0.43]§ (−0.30/+1.42)	12
12–24 months	−0.30 [0.26]§ (−0.65/+0.04)	7	+0.19 [0.14]§ (+0.03/+0.44)	8
>24 months	−0.13 [0.12] (−0.35/−0.02)	4	+0.07 [0.12] (−0.10/+0.45)	18

§Significance of differences from entry values: $P<0.05$ (Wilcoxon signed rank test).

dose (5). Normal values in our laboratory are >2.5 mmol/min.

Galactose was determined enzymatically (Test Combination Galactose, Boeringer, Mannheim, West Germany).

Changes in liver function with time. GEC measurements obtained at different intervals since diagnosis were used to calculate the yearly rate of deterioration or improvement, as: $(GEC_n - GEC_1)/t$, where GEC_1 is GEC at diagnosis, GEC_n are the following GEC determinations, and t is time since diagnosis (in years). In subjects where 3 or more GEC determinations were available (n = 58), 3 or more rates of changes in liver function were calculated, always assuming the initial GEC as the starting point. In these patients, two consecutive GEC measurements (GEC_x and GEC_y at time t_x and t_y, respectively) were also used to calculate the expected GEC value (GEC_{exp}) at the time (t_n) when an additional measurement was available (measured $GEC = GEC_m$), assuming a constant change in liver function:

$$GEC_{exp} = GEC_x + \Delta GEC_{exp},$$

where

$$\Delta GEC_{exp} = [(GEC_y - GEC_x)/(t_y - t_x)] \cdot (t_n - t_x)$$

All these calculations assume a linear change of liver function with time.

Statistical analysis

The data in the text and in the tables are given as mean [SD]. The changes in GEC values (in mmol/min per year) in the whole population were tested for significance by means of paired *t*-test. Subgroup analysis was carried out by means of the Wilcoxon signed rank test, in view of the skew distribution of small samples. The coefficients of determination (r^2) between expected GEC values (GEC_{exp}) or GEC changes (ΔGEC_{exp}) and the corresponding measured GEC values and GEC changes (GEC_m and ΔGEC_m) were also calculated (6). P values <0.05 were considered statistically significant.

Results

GEC values at entry were extremely variable (Table 1), both in alcoholic and in non-alcoholic cirrhosis. Only patients with alcoholic cirrhosis who did not stop drinking during follow up had GEC values which were, on average, higher than the other groups (Table 2). The subset of drinking alcoholics included very few patients since most of them were lost at follow up.

The yearly changes in liver function were also extremely variable, mainly when the time between 2 consecutive GEC determinations was less than 12 months. In this case, both a striking increase (up to +1.42 mmol/min per year) or a dramatic deterioration (down to −1.35) in liver function could be measured. No significant trend in the

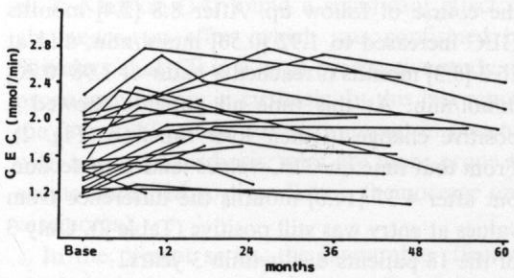

Fig. 1. GEC time-courses in abstaining patients with alcoholic cirrhosis.

population could be observed, except for GEC determinations performed after 36 months or more, but also in this case the limits were wide (from −0.35 to +0.14 mmol/min per year).

The trend was due to a remarkable decline of liver function in non-alcoholic cirrhotics. However, also in this group the yearly changes in liver function, measured by a GEC test performed 56.4 (SD 17.8) months after entry, varied between −0.20 to +0.08 mmol/min per year.

The effects of GEC values at entry on time-course of liver function were assessed by means of a subgroup analysis, dividing the patients according to an arbitrary GEC value of 1.80 mmol/min (the mean value of the entire group). In the 41 patients whose first GEC determination was <1.80 mmol/min (mean 1.50 [0.22]), no significant trend in liver function could be observed, and after 55.9 [18.0] months GEC values were 1.49 [0.40] mmol/min. In subjects with GEC values at entry >1.80 mmol/min (mean 2.17 [0.34]; 35 cases), GEC progressively deteriorated to 1.89 [0.33] mmol/min after 36 months or more ($P<0.05$). The trend was due to a significant decline of liver function in subjects with non-alcoholic cirrhosis (21 cases; GEC at entry, 2.14 [0.28] mmol/min; after 36 months or more, 1.84 [0.37]; $P<0.05$).

In patients with alcoholic cirrhosis GEC changed according to drinking habits (Table 2). In patients who continued to drink, it deteriorated from 2.08 [0.52] mmol/min to 1.69 [0.39] after 8.5 [1.8] months to 1.67 [0.20] mmol/min after 20.5 [3.3] months and to 1.70 [0.21] mmol/min after 37.7 [8.4] months (Fig. 1). Four out of the 11 patients died within 3 years.

In patients with alcoholic cirrhosis who stopped drinking, liver function consistently improved in the course of follow up. After 8.8 [2.4] months GEC increased to 1.92 [0.50] mmol/min, and at 16.3 [3.3] months it reached a nadir of 1.98 [0.20] mmol/min. At this time all patients showed a positive change in their liver function (Fig. 2). From that time on GEC values tended to decline, but after 4.37 [14.0] months the difference from values at entry was still positive (Table 2). Only 3 of the 18 patients died within 3 years.

In patients who had 3 or more GEC determinations, measured and expected GEC values or

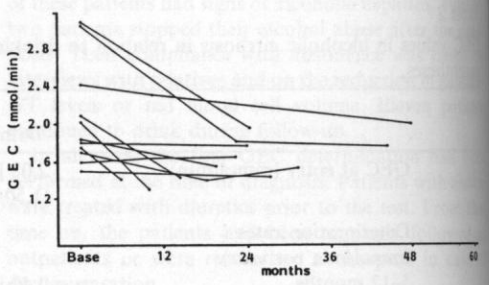

Fig. 2. GEC time-courses in drinking patients with alcoholic cirrhosis.

GEC changes were significantly correlated (Table 3). However, the r^2 coefficients of determination were very low. In 4 out of 58 determinations, GEC_{exp} was <0.7 mmol/min, which is the lowest value compatible with life. In a single patient, GEC_{exp} was negative. Similarly, in 5 patients GEC_{exp} was >3.5 mmol/min, which is the upper limit for normal healthy people. No differences were observed between patients with alcoholic and non-alcoholic cirrhosis.

Limiting the forecasting to GEC values performed within 2 years greatly improved the correlation between GEC_{exp} and GEC_m. However, preceding changes in liver function could still account for only 31% of GEC_m in the whole population or 55% of ΔGEC_m (Fig. 3). The logarithmic transformation of GEC values did not improve the results.

Table 3

R^2 coefficients of determination between measured and expected GEC (GEC_m and GEC_{exp}) or measured and expected GEC changes (ΔGEC_m and ΔGEC_{exp}). The number of cases is in parentheses.

	GEC_{exp}	
GEC_m	All cases	Within 2 years
All cases	0.13 (58)	0.31 (38)
Alcoholics	0.15 (22)	0.30 (13)
Non-alcoholics	0.13 (36)	0.38 (25)
	ΔGEC_{exp}	
ΔGEC_m	All cases	Within 2 years
All cases	0.36 (58)	0.55 (38)
Alcoholics	0.47 (22)	0.65 (13)
Non-alcoholics	0.32 (36)	0.51 (25)

Discussion

This study shows that the time-course of liver function, based on galactose elimination capacity, is variable in patients with cirrhosis. GEC measurement cannot be used to predict liver function in the course of the disease. This limits the usefulness of the test for prognostic evaluations.

The uncertainty in predicting prognosis might be reduced if a systematic decline in liver function were present in cirrhosis. Under these conditions it might be possible in the individual patient, for any measured liver function, to calculate the minimum and the maximum of the expected survival on the basis of data obtained in population studies (1). This hypothesis does not take into account other causes which may affect survival, like gastrointestinal hemorrage or the development of a liver carcinoma. Because of these events, which accounted for 36% of deaths in a prospective study of cirrhosis (7), the minimum life expectancy is difficult to predict. The maximum might really depend on liver function and on liver function deterioration rates, since another 37% of deaths in cirrhotic patients were related to liver failure (7).

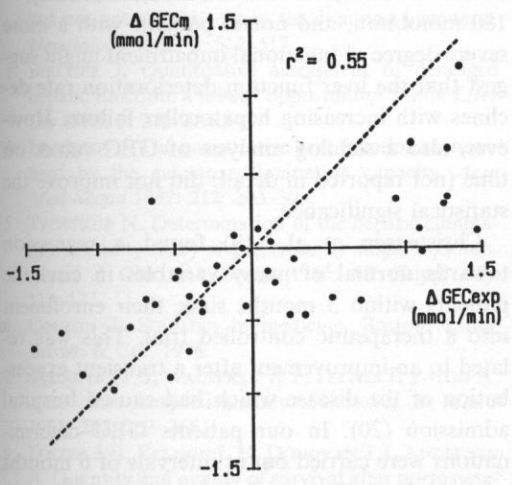

Fig. 3. Regression between ΔGEC expected on the basis of previous GEC changes and ΔGEC measured since entry into the study. The forecasting of two consecutive GEC determinations was limited to values remeasured within 24 months. The line of identity is shown. The equation of the regression [SE of slope and interception] is: $\Delta GEC_m = -0.163\ [0.055] + 0.365\ [0.055] \cdot \Delta GEC_{exp}$. The line does not pass through the origin, and the b slope is significantly different from 1.

Our data show that after 36 months or more from diagnosis, the limits of GEC changes are still so wide, that in a few patients GEC values higher than those at diagnosis may still be measured. From a practical point of view, a GEC change ranging from −0.35 to +0.15 mmol/min per year after a minimum follow up of 36 months means that in our patients, whose average determination at entry was 1.80 mmol/min, the 36-month GEC might vary from 0.75 mmol/min (nearly incompatible with life) to 2.25 which is in keeping with a nearly normal liver function.

Probably, several factors may vary the progression of liver disease. One of them, clearly identified in this retrospective study, was alcohol abuse. Abstinence resulted in a remarkable improvement of GEC, which blurs the usefulness of liver function measurement for prognostic purposes.

Very few studies tried to correlate prognosis with alcohol consumption in patients with cirrhosis. This is probably due to the difficulties in assessing the exact alcohol intake, the contribution of alcohol consumption to liver disease, and finally the compliance of patients with abstinence. Most available data deal with prognosis after portocaval shunt in alcoholic cirrhosis, where abstinence was reported to improve survival (8, 9). Abstinence is probably the reason why patients with alcoholic cirrhosis have a better prognosis than subjects with postnecrotic cirrhosis after shunt (8), while having a poorer immediate prognosis (10). Other studies have failed to document a beneficial effect of abstinence on survival (11–13).

In patients with compensated cirrhosis, Powell & Klatskin (14) found a significant effect of abstinence, an effect which was confirmed by Saunders et al. (7) in a large prospective study on prognostic factors in cirrhosis. In this last report the favourable effect was also present in patients with advanced cirrhosis, who are more prone to events unrelated to liver failure (hemorrage and carcinoma).

In the present series, the favourable effect of alcohol abstinence on galactose elimination capacity was clearly evident. As far as we know, it

is the first time that a clear-cut improvement in liver function has been reported in these patients to support the alleged positive effects of alcohol withdrawal. This effect was confirmed by the lower mortality rate in abstaining alcoholic cirrhotics (17% vs 36% in patients who continued alcohol abuse). Unfortunately, in patients with alcoholic cirrhosis, *a posteriori* selection was probably present in our retrospective series, since only long-term survivors were included, and most of them belonged to the abstaining group. This is also the reason for the lower GEC values at entry in patients who stopped drinking in comparison to drinking alcoholics. Most patients with alcoholic cirrhosis who continued alcohol abuse were lost during follow up, after discharge from hospital, and were not included in the present analysis. This leads to a possible underestimation of mortality in this subgroup.

The improvement in GEC in abstaining patients widened the limits of changes in liver function in our series. However, also excluding patients with alcoholic cirrhosis, a trend in liver function deterioration rate is hardly detectable. No patients with post-necrotic hepatitis B or non-A non-B related cirrhosis had been treated with interferon, and among the 21 patients with autoimmune cirrhosis only 8 were on corticosteroids, which might have affected their liver function (15). In spite of this, in 15 out of the 43 patients in this group, GEC determination increased by 10% or more after diagnosis. The reasons for this unexpected finding are possible effects of therapy or alcohol abstinence also in this group, or to biases in GEC determinations.

In 5 cases the first GEC measurement was performed after gastrointestinal hemorrage and might have been severely reduced because of post-hemorrage hepatic decompensation. However, also the exclusion of these 5 subjects, does not change the results (base: 1.82 mmol/min [SD 0.39]; deterioration rates at 6–12 months, +0.09 [0.56] mmol/min year; at 12–24 months, −0.02 [0.27]; at 24–36 months, −0.05 [0.14]; over 36 months, −0.05 [0.08].

Alternatively, GEC itself might have a low sensitivity in detecting changes in liver function in severely compromised patients. We assumed a 10% urinary loss of injected galactose, but did not check this assumption in any of our patients. Urinary losses are likely to depend on the prevailing plasma galactose concentrations. This might lead to a significant overestimation of GEC in patients with advanced cirrhosis, in whom galactose concentration decay was slower.

More intriguing, a remarkable proportion of injected galactose may undergo a non-renal, non-hepatic removal (16–18). This is probably the reason why in patients with terminal liver failure, while other tests of liver function approach zero, GEC does not decrease to values below 0.7 mmol/min. This galactose removal might be different in individual patients, and change in the course of the disease, leading to imprecise determinations of the actual liver function.

Data obtained in patients who had serial GEC measurements clearly demonstrated that GEC does not allow any forecasting about the possible future changes. Two consecutive GEC measurements failed to predict the measurements performed in the follow up.

The linear dependence of liver function on time, tested in the present study, has never been proved. Indeed, the finding that liver function significantly decreases in subjects with GEC values at entry > 180 mmol/min, and not in patients with a more severe degree of functional impairment might suggest that the liver function deterioration rate declines with increasing hepatocellar failure. However, also a semilog analysis of GEC values on time (not reported in detail) did not improve the statistical significance.

Christensen et al. (19) found a regression towards normal of many variables in cirrhotic patients within 3 months since their enrollment into a therapeutic controlled trial. This was related to an improvement after a transient exacerbation of the disease which had caused hospital admission (20). In our patients GEC determinations were carried out at intervals of 6 months or more, but still the improvement was evident in several cases. This limits the possibility to use time courses of GEC for prognostic purposes. The GEC expected on the basis of time-dependent changes largely overestimated the actual GEC; the regressions had significant interception with the coordinates, and the b slope differed from 1.

Therefore, even if in a prospective study pa-

tients with cirrhosis with a GEC value at entry exceeding 1.37 mmol/min had a better prognosis than patients with more compromised liver function (4), there is no possibility to predict the time course of liver function and life-expectancy in individual subjects. Only serial prospective measurements of GEC at fixed intervals (6–12 months) might be of some help. However, the advantage of GEC over routine liver function tests (albumin, cholinesterase, prothrombin activity), which are cheaper and easier to perform, remains to be determined.

Acknowledgements

Supported by Ministero della Pubblica Istruzione, Rome, Fondi 60%, 1987.

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