Incidence and Natural Course of Fatty Liver in the General Population: The Dionysos Study

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Using the general population of the Dionysos Study, we followed up 144 subjects without fatty liver (FL^-) and 336 with fatty liver (FL^+) for a median time of 8.5 years. All subjects had suspected liver disease (SLD) defined as altered liver enzymes, high mean corpuscular volume, or low platelet count in the absence of HBV and HCV infection. Ethanol intake was assessed using a food frequency questionnaire, and FL was diagnosed using ultrasonography. The incidence and remission rates of FL were 18.5 and 55.0 per 1,000 person-years. Progression to cirrhosis or HCC was rare in both cohorts (incidence rate: 1.7 versus 1.1 and 0.8 versus 0.4 per 1,000 person-years for FL^- versus FL^+). Multivariable Poisson regression was performed to identify predictors of FL incidence and remission among sex, age, body mass index, ethanol, and liver enzymes. Every increase of 20 g/day of ethanol intake at baseline was associated with a 17% increase in the rate of incident FL ($P = 0.019$), a 10% decrease in the rate of remitting FL and SLD ($P = 0.043$), a 19% decrease in the rate of remitting FL with persistent SLD ($P = 0.002$), and a 10% increase in mortality rate ($P = 0.005$) in the FL^+ cohort. *Conclusion:* In the general population of the Dionysos Study, FL regressed in nearly 1 of every 2 cases and had a substantially benign course. Ethanol intake was the most important risk factor for FL remission and incidence and a predictor of mortality in subjects with FL. (HEPATOLOGY 2007;46:1387-1391.)

Recent studies performed in representative samples of the general population have shown that fatty liver (FL) is highly prevalent and that anthropometric and metabolic indicators are better predictors of FL than ethanol intake.[1-4] Data are still lacking, however, on the incidence and natural course of FL in the general population.[5] The incidence and remission rates of nonalcoholic fatty liver disease (NAFLD) were 10% and 16%, respectively, in a convenience sample of 4,401 Japanese employees followed for a mean time of 1.1 years.[6] The survival of a community-based sample of NAFLD patients was lower than that of the general population (standardized mortality rate [SMR], 1.34; 95% CI, 1.003-1.76) and 5% of them developed cirrhosis after a mean (SD) time of 7.6 (4.0) years.[7] In the largest clinical study performed to date, 5% of a convenience sample of 129 hospitalized NAFLD patients developed end-stage liver disease after a mean follow-up time of 13.7 years.[8] Referral bias may be responsible for the relatively high incidence of cirrhosis observed in community- and hospital-based cohorts.[5,7,9] Indeed, there is an ongoing controversy as to whether NAFLD should be considered a benign disease.[10,11] Using data from the follow-up of the Dionysos Study, we evaluated the incidence and natural course of FL in a representative sample of the general population.

Patients and Methods

Study Design. The purpose of the Dionysos Study was to assess the prevalence, incidence, and natural course of liver disease in the general population of 2 towns of Northern Italy.[12,13] Between 1991 and 1992, we evaluated 6,917 (68%) of 10,151 individuals aged 12-65 years living in Campogalliano (Modena, Emilia-Romagna) and Cormons (Gorizia, Friuli-Venezia-Giulia). Suspected

Abbreviations: BMI, body mass index; FL, fatty liver; GGT, γ-glutamyltransferase; NAFLD, nonalcoholic fatty liver disease; PY, person-years; RR, rate ratio; SLD, suspected liver disease; SMR, standardized mortality rate; US, ultrasonography.

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liver disease (SLD) was operationally defined as 1 or more of the following: (1) ALT >40 U/L; (2) AST >37 U/L; (3) γ-glutamyltransferase (GGT) >50 U/L; (4) mean corpuscular volume >100 fL; (5) platelets $<100 \times 10^9$/L; (6) positivity to anti-HCV antibodies; and (7) positivity to HBV surface antigen. All subjects with SLD underwent liver ultrasonography (US) and were evaluated at the Liver Research Center every 6 months for the duration of the study. After exclusion of subjects with HBV and HCV infection, 210 subjects with SLD showed absence of FL at US and 483 showed presence of FL at US. We re-evaluated these 2 cohorts in 2001-2002 to define the incidence rate, remission rate, and natural course of FL in the general population.

Methods. The methods employed by the Dionysos Study have been described in detail elsewhere.[12,14,15] Briefly, each subject underwent a clinical and laboratory evaluation, liver US, and a food frequency questionnaire for the assessment of food and ethanol intake. The questionnaire was developed in Italy and has good validity (Spearman's rho ≥ 0.73) and repeatability (rho ≥ 0.81) for the assessment of ethanol intake and has been used in epidemiological studies of alcohol consumption.[16,17] The diagnosis of FL was performed via US using standardized criteria.[1,15] The same trained physicians in Campogalliano and Cormons performed US at the basal and follow-up visits. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Vital status was ascertained using municipal registries. Cirrhosis and HCC were diagnosed via liver biopsy. The study protocol was approved and supervised by the Scientific Committee of the Fondo per lo Studio delle Malattie del Fegato-ONLUS (Trieste, Italy). All subjects gave written consent to participate in the study.

Statistical Analysis. Continuous variables are given as medians and interquartile ranges because of skewed distributions. Between-group comparisons of continuous variables were performed with the Mann-Whitney *U* test; those of categorical variables were performed with the Fisher exact test. Incident FL was defined as FL absent at baseline and present at follow-up; remitting FL was defined as FL present at baseline and absent at follow-up; persistent SLD was defined as SLD present at both baseline and follow-up; remitting SLD was defined as SLD present at baseline and absent at follow-up; and death was defined as death occurring anytime between March 18, 1991 (first baseline visit of Dionysos Phase 1), and June 30, 2002 (last follow-up visit of Dionysos Phase 2). Rates are expressed as the number of cases per 1,000 person-years (PY). Multivariable Poisson regression with robust 95% CI was used to evaluate the contribution of sex, age, BMI, ethanol intake, ALT, AST, and GGT to the outcomes of interest.[18] All predictors besides sex were evaluated as continuous. Ethanol intake was divided by 20 because 20 g/day is the cutoff currently employed to separate NAFLD from alcoholic FL disease.[19] In addition to avoiding the loss of information caused by dichotomization of continuous variables,[20] this approach allows a better modeling of the relationship between ethanol intake and the outcomes of interest.[21] ALT, AST, and GGT were divided by 40, 37, and 50 (i.e., their upper normal limits at the time of Dionysos Study Phase 1), respectively. Fractional polynomials were used to test whether the prediction of the outcomes could be improved by transformation of covariates.[21] Because there was no increase in the accuracy of the prediction, covariates were left untransformed in the final model. The SMR was calculated using age- and sex-specific mortality rates for Northern Italy. Statistical significance was set to a 2-tailed value of $P < 0.05$ for all tests. Statistical analysis was performed using STATA 9.2 (STATA Corp., College Station, TX).

Results

FL⁻ Cohort. Of the 210 members of the FL⁻ cohort, 134 were re-evaluated and 10 died. These 144 (68.6%) subjects were older than those not available at follow-up but had the same sex and same values of ALT, AST, GGT, mean corpuscular volume, platelets, ethanol intake, and BMI (Table 1). The median (interquartile range) follow-up time of the FL⁻ cohort was 8.5 (0.7) years, and the total follow-up time was 1,191 PY.

Twenty-two FL⁻ subjects developed FL (rate, 18.5/1,000 PY), 13 with persistence and 9 with remission of SLD (Table 2). At multivariable analysis, ethanol intake was the only baseline predictor of incident FL (rate ratio [RR], 1.17 every 20 g/day increase [$P = 0.019$]) (Table 3).

One male FL⁻ subject developed alcoholic cirrhosis and 1 developed cryptogenic cirrhosis, for an overall incidence rate of cirrhosis of 1.7/1,000 PY (Table 2). The FL⁻ subject with alcoholic cirrhosis developed HCC (incidence rate, 0.8/1,000 PY). All cases of cirrhosis and HCC developed in subjects with persistent SLD. The baseline alcohol intake of the subject who developed alcoholic cirrhosis was 39 g/day.

Ten FL⁻ subjects died, yielding a mortality rate of 8.4/1,000 PY (Table 2) and corresponding to an SMR of 1.24 (95% CI, 0.7-2.3). The causes of death were: cancer (n = 3), pulmonary disease (n = 2), cardiovascular disease (n = 2), cirrhosis (n = 1), HCC (n = 1) and diabetes (n = 1). Eighty percent of deaths occurred in subjects with persistent SLD. At multivariable analysis, only age

Table 1. Baseline Characteristics of Subjects Available and Not Available at Follow-Up

	FL⁻ Cohort (n = 210)			FL⁺ Cohort (n = 483)		
	Available (n = 144)	Not Available (n = 66)	*P* Value*	Available (n = 336)	Not Available (n = 147)	*P* Value*
Sex (M/F)	82/62	41/25	0.547	269/67	119/28	0.901
Age (years)	47 (22)	36 (20)	<0.001	48 (16)	43 (19)	0.003
ALT (U/L)	42 (22)	42 (24)	0.975	45 (25)	47 (29)	0.127
AST (U/L)	30 (13)	29 (14)	0.966	30 (14)	30 (17)	0.899
GGT (U/L)	62 (62)	55 (52)	0.438	63 (45)	64 (43)	0.876
Mean corpuscular volume (fL)	89 (7)	90 (6)	0.596	90 (7)	89 (6)	0.150
Platelets ($U \times 10^9$/L)	248 (64)	246 (75)	0.377	238 (72)	237 (62)	0.993
Ethanol intake (g/day)	16 (30)	10 (30)	0.846	32 (51)	32 (54)	0.503
BMI (kg/m^2)	24 (4)	23 (5)	0.339	28 (5)	28 (5)	0.546

Values are given as median and interquartile range.

*Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables.

(RR, 2.94 every 10-year increase [$P = 0.005$]) was a predictor of death in the FL⁻ cohort (Table 3).

FL⁺ Cohort. Of the 483 subjects in the FL⁺ cohort, 307 were re-evaluated and 29 died. These 336 (69.6%) subjects were older than those not available at follow-up but had the same sex and same values of ALT, AST, GGT, mean corpuscular volume, platelets, ethanol intake, and BMI (Table 1). The median (interquartile range) follow-up time of the FL+ cohort was 8.5 (0.9) years, and the total follow-up time was 2,817 PY.

One hundred fifty-five FL⁺ subjects had regression of FL, 85 with persistence (rate, 30.2/1,000 PY) and 70 with remission of SLD (rate, 24.8/1,000 PY) (Table 2). At multivariable analysis (Table 4), ethanol intake was the only baseline predictor (inversely) associated with remission of both FL and SLD (RR, 0.90 every 20 g/day increase [$P = 0.043$]). Ethanol intake was also (inversely) associated with remission of FL in subjects with persistent SLD (RR, 0.81 every 20 g/day increase [$P = 0.002$]), and the same was observed for BMI (RR, 0.95 every kg/m^2 increase [$P = 0.043$]).

Three male FL⁺ subjects developed alcoholic cirrhosis (rate, 1.1/1,000 PY), and 1 developed HCC (rate, 0.4/1,000 PY) (Table 2). Two cases of cirrhosis and 1 of HCC developed in subjects with persistent SLD at the follow-up visit. The baseline ethanol intake of the subjects who developed alcoholic cirrhosis was 79, 104, and 130 g/day.

Twenty-nine FL⁺ subjects died, yielding a mortality rate of 10.3/1,000 PY (Table 2) and corresponding to an SMR of 1.47 (95% CI, 1.02-2.11). The causes of death were cancer (n = 13), cardiovascular or cerebrovascular disease (n = 9), cirrhosis (n = 2), HCC (n = 1), perforated ulcer (n = 1), trauma (n = 1), pneumonia (n = 1), and unknown (n = 1). In a preliminary Poisson regression model (data not shown), age and GGT but not ethanol intake were independent predictors of death. Because GGT is often increased as a consequence of eth-

Table 2. Incidence and Natural Course of Fatty Liver

	FL⁻ Cohort (n = 144)			FL⁺ Cohort (n = 336)		
	n	%	Rate* (95% CI)	n	%	Rate* (95% CI)
FL remission	–	–	–	155	46.1	55.0 (47.0-64.4)
SLD persistence	–	–	–	85	25.3	30.2 (24.4-37.3)
SLD remission	–	–	–	70	20.8	24.8 (19.7-31.4)
FL incidence	22	15.3	18.5 (12.2-28.1)	–	–	–
SLD persistence	13	9.0	10.9 (6.3-18.8)	–	–	–
SLD remission	9	6.3	7.6 (3.9-14.5)	–	–	–
Cirrhosis incidence	2	1.4	1.7 (0.4-6.7)	3	0.9	1.1 (0.3-3.3)
SLD persistence	2	1.4	1.7 (0.4-6.7)	2	0.6	0.7 (0.2-2.8)
SLD remission	–	–	-	1	0.3	0.4 (0.1-2.5)
HCC incidence	1	0.7	0.8 (0.1-6.0)	1	0.3	0.4 (0.1-2.5)
SLD persistence	1	0.7	0.8 (0.1-6.0)	1	0.3	0.4 (0.1-2.5)
SLD remission	–	–	–	–	–	–
Mortality	10	6.9	8.4 (4.5-15.6)	29	8.6	10.3 (7.2-14.8)
SLD persistence	8	5.5	6.7 (3.4-13.4)	14	4.2	5.0 (2.9-8.4)
SLD remission	2	1.4	1.7 (0.4-6.7)	15	4.4	5.3 (3.2-8.8)

*Rate is number of cases per 1,000 PY.

Table 3. Predictors of Fatty Liver Incidence and Death in the Cohort Without Fatty Liver

	FL Incidence (n = 22)		Death (n = 10)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Male sex	1.17 (0.47-2.88)	0.734	3.33 (0.82-13.55)	0.093
Age (years/10)	0.99 (0.69-1.41)	0.944	2.94 (1.38-6.27)	0.005
BMI (kg/m^2)	1.10 (0.98-1.24)	0.109	0.93 (0.72-1.20)	0.590
Ethanol (g/day/20)	1.17 (1.03-1.34)	0.019	1.13 (0.88-1.44)	0.335
ALT (U/L/40)	1.69 (0.53-5.41)	0.371	1.15 (0.09-14.46)	0.913
AST (U/L/37)	0.90 (0.55-1.47)	0.669	1.29 (0.83-2.01)	0.252
GGT (U/L/50)	1.05 (0.79-1.38)	0.747	1.30 (0.63-1.69)	0.895

anol intake and may help discriminate NAFLD from alcoholic FL disease,[1] we added an interaction between alcohol and GGT to the model, which revealed an independent effect of ethanol intake on death. In the final model (Table 4), age (RR, 2.78 [$P < 0.0001$]), ethanol intake (RR, 1.10 [$P = 0.005$]), and GGT (RR, 1.21 [$P < 0.0001$]) were independent predictors of death.

Discussion

The Dionysos Study is the first study on the incidence and natural course of FL performed in a representative sample of the general population. It adds to previous studies performed on convenience subjects,[6] community patients,[7] and hospital patients[8] by showing that FL has a benign course in the general population.

Fifteen percent of our FL$^-$ subjects developed FL after 8.5 years of follow-up. In comparison, 10% of a convenience sample of Japanese employees developed FL after 1.1 years.[6] Differences in study design, follow-up length, and possibly ethnic factors may explain this discrepancy. In our study, the risk of FL after 8.5 years of follow-up increased 17% for every 20-g/day increase of ethanol intake at baseline. Baseline BMI was not a predictor of incident FL. This is in contrast with the finding that BMI, not ethanol intake, was an independent predictor of FL in the cross-sectional Dionysos Nutrition & Liver Study performed in Campogalliano 8.5 years after phase 1 of the Dionysos Study.[1,4] In addition to the different study design, the fact that ethanol intake was reduced by half in Campogalliano during this period is the most likely explanation of this finding.

Forty-six percent of our FL$^+$ subjects had remission of FL after 8.5 years of follow-up. Remission of FL was thus more common than incidence. In comparison, only 16% of a convenience sample of Japanese employees had regression of FL after a follow-up of 1.1 years.[6] Differences in study design, follow-up length, and possibly ethnic factors may explain this discrepancy. It is notable, however, that remission was more common than incidence in both studies. For every 20-g/day increase of ethanol intake at baseline, the remission rate of FL was 10% lower in subjects with SLD remission and 19% lower in those with SLD persistence. Every increase of 1 kg/m^2 of BMI at baseline further lowered the remission rate of FL of 5% in subjects with SLD persistence. The fact that BMI was a predictor of FL remission only in subjects with SLD persistence is likely due to the fact that, given the same number of subjects (n = 336), the power to detect a significant effect is greater for 85 versus 70 positive outcomes.

The incidence of cirrhosis was very low in both subjects with (0.9%) and without (1.4%) FL. Approximately 1% of our subjects with FL developed cirrhosis compared with 5% of community patients with NAFLD.[7] Referral bias may be responsible for these differences, because subjects with more severe disease are more likely to be included by community sampling. The incidence of HCC was likewise low in both subjects with (0.3%) and without (0.7%) FL.

Approximately 9% of FL$^+$ and 7% of FL$^-$ subjects died during the study. This mortality rate is lower than that reported in community patients with NAFLD (13%).[7] Again, referral bias may be the most likely explanation for this difference. Even if the SMR of the FL$^+$ subjects was 1.47, its 95% CI was too wide (1.02-2.11) to draw any solid conclusion on the association between FL

Table 4. Predictors of Fatty Liver Remission and Death in the Cohort With Fatty Liver

	FL Remission With SLD Remission (n = 70)		FL Remission With SLD Persistence (n = 85)		Death (n = 29)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Male sex	0.67 (0.42-1.08)	0.100	1.02 (0.65-1.58)	0.935	6.05 (0.62-58.9)	0.121
Age (years/10)	1.15 (0.93-1.42)	0.201	0.97 (0.82-1.15)	0.734	2.78 (1.83-4.22)	<0.0001
BMI (kg/m^2)	0.99 (0.94-1.04)	0.663	0.95 (0.89-0.99)	0.043	0.95 (0.87-1.04)	0.266
Ethanol (g/day /20)	0.90 (0.81-.99)	0.043	0.81 (0.71-0.93)	0.002	1.10 (1.02-1.17)	0.005
ALT (U/L/40)	1.08 (0.71-1.66)	0.711	0.83 (0.52-1.34)	0.450	0.74 (0.34-1.62)	0.458
AST (U/L/37)	1.07 (0.62-1.83)	0.811	0.86 (0.40-1.84)	0.693	1.05 (0.31-3.57)	0.926
GGT (U/L/50)	0.95 (0.85-1.06)	0.335	0.92 (0.76-1.09)	0.323	1.21 (1.11-1.32)	<0.0001
Ethanol (g/day/20) × GGT (U/L/50)	–	–	–	–	0.99 (0.98-1.00)	0.077

and mortality.[11] Ethanol intake was an independent predictor of mortality in FL^+ but not FL^- subjects. This may have practical implications, because the risk of death of FL^+ subjects increased 10% for every 20-g/day increase of ethanol intake. This implies that subjects with alcoholic FL disease have a 10% increase of mortality compared with those with NAFLD. It is also of some interest that GGT was an independent predictor of mortality in FL^+ but not FL^- subjects. In addition to being increased as a consequence of ethanol intake, GGT is emerging as an independent risk factor of metabolic and cardiovascular disease; this may partly explain its ability to predict mortality in FL^+ subjects.[22]

Although this is the first study on the incidence and natural course of FL performed in a representative sample of the general population, it has several limitations. First, approximately 30% of the subjects with or without FL at baseline were not available at the 8.5-year follow-up. Even if they were younger than those available at follow-up, they nonetheless had the same sex and same values for liver enzymes, ethanol intake, and BMI. Second, US is not a reference method for the assessment of FL, even if at present there are no alternatives for field studies.[1] US is highly specific only for the detection of fatty infiltration greater than 30%, and the interpretation of our operational definition of FL must take this into account. More importantly, US cannot detect inflammation and/or fibrosis; therefore, we cannot make any inference on the severity of FL. Third, we were unable to test for the contribution of metabolic parameters (insulin, triglycerides, glucose) that have been associated with FL prevalence, incidence, and course, because they were not measured at baseline in all subjects.[1,4,7] Finally, our data may not apply to subjects with fatty liver and normal liver enzymes, which are quite common in the general population.[1]

In the general population of the Dionysos Study, FL regressed in nearly 1 of every 2 cases and had a substantially benign course. Ethanol intake was the most important risk factor for FL remission and incidence and was a predictor of mortality in subjects with FL.

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