OVERESTIMATION OF "PURE" NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AS A CAUSE OF LIVER FIBROSIS (AF) USING ALCOHOL CONSUMPTION ESTIMATED BY SELF-DECLARATION (SD)

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ABSTRACT

Background: Studies on NAFLD included subjects not at risk of alcoholic liver disease (ALD), generally defined as a **self declared** consumption >10g/day for female and >20g for male (**SDrisk**). The risk of erroneous conclusion due to false negative of SD is unknown. The aim was to compare SD versus measurement of carbohydrate deficient transferin (CDT) for attributing the cause of fibrosis to NAFLD or ALD in a general population.
Methods: We prospectively enrolled 1,096 consecutive volunteers, 40yrs or older, without history of liver disease consulting for a screening in Social Security Examination Center. The following items were included: duration of alcohol abuse, daily or weekend consumption of beer, wine, before dinner drinks, and spirits. FibroTest (FT) and CDT assays were performed on nephelometer BN2 (Dade Behring, Marburg). Risk of ALD was compared using either SDrisk, or CDT over 1.6% (CDTrisk) as previously validated (Imbert 2008). Subjects with presumed advanced fibrosis AF (FT greater than 0.48) were re-investigated in a tertiary center including elastography (LSM).
Results: The prevalence of subjects at risk for ALD using SD was 21.0% (230/1096) lower than 31.7% (347/1096; P< 0.0001) using CDT. 74 subjects with presumed AF were identified (6.8%), 72 accepted re-investigation, 32 had confirmed AF (LSM>7.1kPa) and 17 highly suspected AF (LSM>5kPa). CDT identified more confirmed AF 75% (24/32) than SD 41% (13/32 P=0.01), with higher AUROC 0.72 vs 0.58 (P=0.002). In multivariate analysis including age, gender, HCVab, and metabolic factors, CDT was associated with confirmed AF (OR=2.3;P=0.0001) and not SD (OR=0.99). The significant association between triglycerides (a marker of both metabolic and alcoholic risks) and AF disappeared after adjustment using CDT. Subjects with possible underestimation of their alcohol consumption (CDTrisk without SDrisk) represented 41% (30/74) of subjects with AF versus 21% (216/1022; P=0.0001) without AF. Using CDT versus SD, the attributable cause of AF was ALD in 16% (12/74) versus 5% (4/74), mixed ALD/NAFLD in 45% (33/74) versus 23% (17/74), and NAFLD in 34% (25/74) versus 55% (41/74) (P=0.01).
Conclusions: Prevalence of "pure NAFLD" is probably overestimated in countries with high alcohol consumption. Research must individualize subjects with both alcohol consumption and metabolic risk factors.

PATIENTS and METHODS

Cohort
Prospective n=1096 informed random subjects aged 40 years or older from a cohort of n=7554 screened for advanced fibrosis in two Social Security Examination Center in Paris.

Exclusion criteria
Subjects with known history of liver disease were excluded

Parameters:
- 70 epidemiological, clinical, biological characteristics
- **Self declared alcohol consumption** (**SD**) with the following items included: duration of alcohol abuse, daily or weekend consumption of beer, wine, before dinner drinks, and spirits.
- **Biomarker (FibroTest)** – on fresh serum centralized
- **Carbohydrate deficient transferin (CDT)** on fresh serum centralized

FibroTest and CDT assays were performed on fresh sera using a BN2 nephelometer (Dade Behring, Marburg).

Study strategy

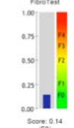
Risk of alcoholic liver disease (ALD) was compared using either self declared alcohol consumption (called SDrisk), or CDT over 1.6% (called CDTrisk) as previously validated (Imbert-Bismut 2009, see reference 1).

- Subjects with presumed advanced fibrosis according to **FibroTest** (>0.48) were re-in a tertiary center using: **Fibroscan (FS) using 7.1 kPa cut-off for advanced fibrosis**, **ultrasonography**, **endoscopy** if necessary, **liver biopsy** if accepted, **serum markers of chronic liver disease** (HBsAg, HCV antibody, hemochromatosis gene mutation, antibody anti-actin, anti-LKM1, anti DNA, anti-mitochondria, ceruleoplasmin). The efficacy of this non-invasive screening strategy of fibrosis was already validated in a prospective diabetic population without history of liver disease (Jacqueminet et al 2008, see reference 3).

- High-risk profiles of false negative and positive FibroTest were excluded by security algorithms provided with results

CDT = % of carbohydrate deficient transferin from the total transferin amount
- Normal values <1.6%

FibroTest™ - patented algorithm (Halfon et al, see reference 3)
- scoring from 0.00 to 1.00 (advanced fibrosis >0.48)
- Combines:
  - age and gender
  - Total bilirubin,
  - GGT,
  - Haptoglobin,
  - Alpha2-macroglobulin,
  - Apolipoprotein A1



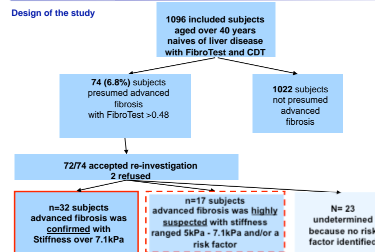
BACKGROUND & AIMS

Studies on non alcoholic fatty liver disease (NAFLD) included subjects not at risk of alcoholic liver disease (ALD) generally defined as a **self declared consumption** >10g/day for female and >20g for male (**SD**risk). The risk of erroneous conclusion due to false negative of self declared risk is unknown.

Aim: to compare the self declared (SD) alcoholc onsumption -SDrisk - versus the measurement of carbohydrate deficient transferin (CDT) for attributing the cause of fibrosis to NAFLD or ALD in a general population.

RESULTS

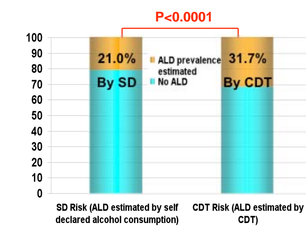
Design of the study



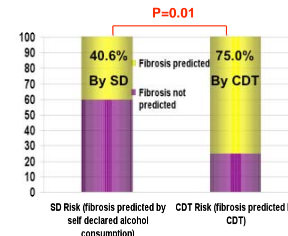
Characteristics of included subjects	Subjects with presumed fibrosis N=74	Subjects without presumed fibrosis N=1022	P value
Number of subjects	**74**	**1022**	
Age at serum, median years	66.9	57.8	P<0.0001
Male (%)	92%	50%	P<0.0001
High Education level	29.7%	24.6%	P=0.13
Self-declared alcohol consumption at risk**	28.4%	20.4%	P=0.11
Elevated CDT (>1.6%)	60.8%	29.8%	P<0.0001
BMI >= 27.0	51.4%	30.8%	P=0.003
Metabolic factor of ATP-III classification			
Glucose >= 6.1 mmol/L or diabetes treatment	33.3%	9.3%	P<0.0001
Central obesity waist >102cm male >88cm female	24.3%	14.4%	P=0.021
Triglycerides >=1.7 mmol/L or fibrate treatment	42.9%	22.3%	P<0.0001
Hypertension or treatment	35.1%	29.5%	P=0.31
HDL-chol <1.03 mmol/L male <1.29 mmol/L female	22%	7.1%	P<0.0001

RESULTS *continued*

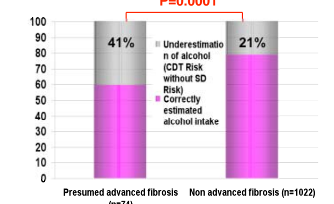
Higher ALD prevalence estimated using CDT versus self-declared alcohol consumption (SD)



Better prediction of *confirmed* advanced fibrosis by using CDT versus SD Risk



Alcohol intake was more often underestimated (CDT Risk without SD Risk) among subjects with presumed fibrosis compared to others



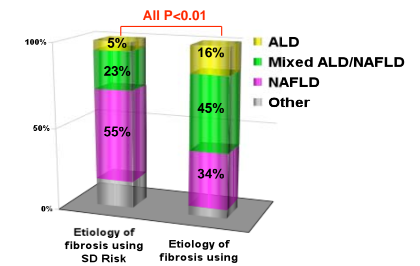
Multivariate analyses: CDT predicted advanced fibrosis stronger than self declared (SD) risk

Factors	Odds ratio (OR)	P value
CDT	2.3	0.001
Self Declared consumption (SD)	0.99	NS

*Multivariate analyses included age, gender, metabolic factors

Triglycerides (a common marker of both metabolic and alcoholic risks) were no longer associated with advanced fibrosis after adjustment using CDT.

Causes of advanced fibrosis taking according to SD Risk versus CDT Risk



CONCLUSIONS

Prevalence of "pure NAFLD" is probably overestimated in countries with high alcohol consumption. Research must individualize subjects with both alcohol consumption and metabolic risk factors.

References

1. Imbert-Bismut F, et al. The diagnostic value of combining carbohydrate deficient transferin, fibrosis and steatosis biomarkers for the prediction of excessive alcohol consumption. Eur J Gastro Hepatol 2009;21:18-27.
2. Jacqueminet S et al. Screening for liver fibrosis by using a noninvasive biomarker in patients with diabetes. Clin Gastroenterol Hepatol. 2008;6:828-31.
3. Halfon P et al. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. Gastroenterol Clin Biol 2008;32:22-38.

DISCLOSURE: TP is the inventor and has a capital interest in Biopredicitve the company marketing FibroTest. MM is employee of Biopredictive. Patents belong to the public organization Assistance Publique Hôpitaux de Paris