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**Hair ethyl glucuronide is a highly accurate biomarker of chronic excessive alcohol use
in patients with alcoholic cirrhosis**

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Abbreviations

EDI, estimated daily intake; hEtG, hair ethyl glucuronide; MELD, model for end-stage liver disease; NPV, negative predictive value; PPV, positive predictive value.

Disclosures

The authors declare having no conflict of interest regarding the presented data in this manuscript.

Author contributions

JV: concept and design, experiments and procedures, interpretation of data and writing the manuscript. CLC, GLS, PPM, TR: experiments and procedures and critical revision of the manuscript. MDD: experiments and procedures. DM, JP, SvdM and DC: critical revision of the manuscript. HN: experiments and procedures, interpretation of data and critical revision of the manuscript. FN: concept and design, writing the manuscript.

Key words

Ethanol; alcohol; screening; liver transplantation

INTRODUCTION

The assessment of ongoing alcohol use in patients with alcoholic liver disease remains a major diagnostic challenge.^{1,2} Ethyl glucuronide in scalp hair (hEtG) is an attractive direct alcohol biomarker with a diagnostic time window of several months, but validation in patients with cirrhosis is required.³ In this study, we tested the diagnostic accuracy of hEtG in a cohort of healthy volunteers and patients with alcoholic cirrhosis and a reliable self-reported alcohol intake. After this validation step, we explored the diagnostic potential of hEtG in random patients with alcoholic cirrhosis referred for liver transplantation screening.

METHODS

The validation cohort (n=101) consisted of 43 healthy volunteers and 58 patients with alcoholic cirrhosis. Abstinence in this group was defined as the absence of any clinical sign of alcohol use during a 1-year follow-up. The clinical application group consisted of 43 random patients with alcoholic cirrhosis, who denied chronic excessive alcohol use in the previous 3 months. A detailed questionnaire, proximal 3 cm scalp hair strand to measure hEtG and blood were collected.³ Thirteen patients in the validation cohort and 16 patients in the clinical application group underwent liver biopsy to assess the presence of Mallory-Denk bodies and polymorphonuclear leucocytes as histological signs of ongoing excessive alcohol use.⁴ Continuous variables were analyzed using independent samples t or Mann-Whitney test, dichotomous variables using Chi-square and Fisher's exact tests and correlations by calculation of Pearson's or Spearman's correlation coefficients. A *P*-value < .05 was considered statistically significant.

RESULTS

Patients with alcoholic cirrhosis in the validation cohort (n=58) and the clinical application group (n=43) did not differ regarding age, gender, body mass index, liver tests, renal function, model for end-stage liver disease (MELD) score and use of hair cosmetics (for all $P > .05$).

Absolute hEtG levels of the patients in the validation cohort together with the corresponding diagnostic values are given in Figure 1.

Taken together all cirrhotic patients included in the study (n=101), total bilirubin, INR, MELD score and creatinine did not differ between patients with low hEtG (< 50 pg/mg; n=67) and high hEtG levels (≥ 50 pg/mg; n=34) (for all $P > .05$). Hair EtG levels did not correlate with MELD scores, total bilirubin or creatinine levels in the abstinent cirrhotic patients in the validation cohort (for all $P > .75$).

Cirrhotic patients with low hEtG levels (< 50 pg/mg) (n=22) did not show histological signs of ongoing excessive alcohol use, except one abstinent patient with a hEtG level of < 0.7 pg/mg and prior bariatric surgery.

In the clinical application group of patients with alcoholic cirrhosis, 15/43 (35%) patients (5/32 self-declared abstainers and 10/11 self-declared moderate users) had hEtG levels of ≥ 50 pg/mg, indicating chronic excessive alcohol use in the previous 3 months.

DISCUSSION

We assessed whether the hEtG cut-off levels proposed by international guidelines to categorize patients into different drinking groups are also applicable to patients with alcoholic cirrhosis.⁵ Hair EtG levels of ≥ 30 pg/mg have indeed a high diagnostic accuracy for chronic excessive alcohol use in the previous 3 months, but hEtG even reaches a perfect diagnostic accuracy when a cut-off of ≥ 50 pg/mg is applied.

We advocate to interpret hEtG levels below 50 pg/mg with caution. This hEtG range excludes chronic excessive alcohol use, but does not allow distinction between abstinence or ongoing moderate alcohol use in patients with alcoholic cirrhosis. Possibly, these issues can be redressed by serial or segmental hair analyses and the additional testing of urinary EtG.^{3,6}

Although EtG is synthesized in the hepatocyte, hEtG levels seem not to be influenced by the degree of liver impairment.^{7,8} Hair EtG results should be interpreted with caution in patients with severe renal impairment, since this may lead to false positive results by decreased elimination of blood EtG.^{3,6} Moderate renal impairment, present in 27/101 (26.7%) of the included cirrhotic patients, did not have a significant impact on hEtG levels. The rate of cosmetic hair treatment in our study was too low to draw firm conclusions, but always should be suspected as a cause for false negative results.³

Interestingly, the exclusion of chronic excessive alcohol use based on the hEtG level corresponded in all patients with the absence of histological hallmarks of ongoing excessive alcohol use, except in one abstinent patient with non-alcoholic steatohepatitis.

In conclusion, hEtG is a highly sensitive and specific biomarker for the detection of chronic excessive alcohol use over a large time window of 3 months in patients with alcoholic cirrhosis. Therefore, hEtG is a useful tool in the liver clinic.

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Figure 1. Hair EtG results of patients in the validation cohort. Absolute values of (A) healthy volunteers and (B) patients with alcoholic cirrhosis. (C) Diagnostic accuracy of hEtG in healthy volunteers and patients with alcoholic cirrhosis.

hEtG: hair ethyl glucuronide; PPV: positive predictive value; NPV: negative predictive value.

Abstinence was defined as no use of any alcoholic beverages in the previous 3 months, moderate use as a mean use of > 0 g/day and < 60 g/day in the previous 3 months and excessive alcohol use as a mean use of ≥ 60 g/day in the previous 3 months.⁵

*Reference values as proposed by the Society of Hair Testing⁵: hEtG level < 7 pg/mg is considered to indicate abstinence, hEtG level ≥ 7 pg/mg and < 30 pg/mg would indicate moderate use and hEtG level ≥ 30 pg/mg would indicate chronic excessive alcohol use in the previous 3 months.

A **B** **C**

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
hEtG in healthy volunteers				
Moderate use (hEtG ≥ 7 and < 30 pg/mg)*	47	100	100	19
hEtG in patients with alcoholic cirrhosis				
Moderate use (hEtG ≥ 7 and < 30 pg/mg)*	67	66	38	86
Excessive use (hEtG ≥ 30 pg/mg)*	100	97	95	100
Excessive use (hEtG ≥ 50 pg/mg)	100	100	100	100