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Invited critical review

Non-oxidative ethanol metabolites as a measure of alcohol intake

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ABSTRACT

Recent alcohol intake can be monitored by the measurement of indirect biomarkers. Elevated levels of liver enzymes (i.e. gamma-glutamyl transferase (GGT), alanine amino transferase (ALT) and aspartate amino transferase (AST)) in blood are commonly used in clinical practice as an indicator of alcohol-induced liver damage. With the exception of carbohydrate-deficient transferrin (CDT), the specificity of indirect markers is only moderate because many cases of elevated levels are unrelated to alcohol consumption. Because of their intermediate half-life and tendency to accumulate in hair, non-oxidative ethanol metabolites can be used as markers with an intermediate timeframe between ethanol measurements and GGT and CDT with regard to recent alcohol consumption occurring between hours to 1 week. Additionally, these biomarkers offer a high ethanol-specificity in combination with approximately a two-fold higher sensitivity in comparison with indirect alcohol markers. In case of forensic use of direct ethanol metabolites, caution has to be taken in interpretation and pre-analytical pitfalls should be considered.

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Contents

Abbreviations: BAC, blood alcohol concentration; BMI, body mass index; CDT, carbohydrate-deficient transferrin; CYP 2E1, cytochrome P450 2E1; CZE, capillary zone electrophoresis; ELISA, enzyme-linked immunosorbent assay; ELSD, evaporative light scattering detection; ESI, electrospray ionization; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEE, fatty acid ethyl esters; GC, gas chromatography; HPLC, high-performance liquid chromatography; LoQ, limit of quantification; MS, mass spectrometry; PEth, phosphatidyl ethanol; SoHT, Society of Hair Testing; UDP, uridine diphosphate; WHO, World Health Organization; ISBRA, International Society on Biomedical Research on Alcoholism.

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1. Introduction

The 2011 Global Status Report on Alcohol from the World Health Organization (WHO) states that the harmful use of alcohol is one of the world's leading health risks. It is a causal factor in more than 60 major types of diseases and injuries and results in approximately 2.5 million deaths each year [1]. Many subjects misusing alcohol can be identified based on clinical history and examination and self-report questionnaires, but sensitivity is generally poor with deliberate under-reporting being common [2]. Currently available biological state markers are limited in two basic respects: (a) time window for alcohol drinking reflected by direct measures (e.g. serum ethanol detects only recent use within hours) and (b) confounding factors such as age, gender, other ingested substances and non-alcohol-associated diseases for traditional liver function tests [3]. Overall, hazardous and harmful drinking patterns, such as drinking to intoxication and binge drinking, seem to be on the rise among adolescents and young adults [4]. There is, therefore, a need for a biomarker that will bridge the gap in the time window, between one day and one week, left by the current biomarkers of alcohol consumption.

A positive blood alcohol concentration (BAC) provides a highly specific indication of recent drinking. Ethanol is rapidly absorbed across both the gastric mucosa and the small intestines, reaching a peak concentration 20–60 min after ingestion. The bloodstream transports ethanol to the body and after equilibration, most tissues are exposed to the same concentration as in the blood. The rate of equilibration is governed by the ratio of blood flow to tissue mass, which depends on volume of distribution and time after alcohol ingestion [5].

Breath-analyzers provide an intermediate result and the levels correlate well with the BAC [6]. Breath alcohol is a representation of the equilibrium of alcohol concentration as the blood gasses pass from the blood into the lungs to be expired in the breath. However, the airway alcohol exchange process is diffusion and perfusion limited, leading to variation in measured breath alcohol concentration measurements [7]. A major limitation of this test is the short detection window (typically <12 h), due to rapid ethanol elimination (0.15 g/L/h for men and 0.18 g/L/h for women) [8]. Urine alcohol gives an indication of the BAC at the time the urine was produced [5]. Transdermal alcohol sensors are promising as a means of prospectively measuring alcohol intake over several days [9].

Recent alcohol intake can be monitored by the measurement of indirect biomarkers. Elevated levels of liver enzymes (i.e. gamma-glutamyl transferase (GGT), alanine amino transferase (ALT) and aspartate amino transferase (AST)) in blood are commonly used in clinical practice as an indicator of alcohol-induced liver damage [5]. However, these tests suffer from low sensitivity for early detection of risky drinking, and the specificity is only moderate. In most studies, GGT sensitivities exceed those of the other commonly used markers [10]. The WHO/ISBRA collaborative project on markers of alcoholism indicated elevated serum GGT concentrations in 52% of alcohol-dependent subjects [11]. GGT is significantly correlated to ethanol intake only in high alcohol consumers. Detection times of liver enzymes in serum depend on the amount and frequency of alcohol intake. AST, ALT and GGT have an elimination time of 2–3 weeks [10].

Alcohol and its metabolites have toxic effects on hematologic precursor cells. Macrocytosis, indicated by an increased mean corpuscular erythrocyte volume (MCV), is a common finding in chronic alcoholics. Population studies have reported elevated MCV levels in 4% of adults, 65% of these being likely alcohol-related [12]. Because the red blood cell has a lifespan of ±120 days, MCV may remain elevated for 3 months after alcohol withdrawal [5]. This makes it less useful for monitoring abstinence. MCV has limited specificity in patients with malnutrition, liver diseases, hematological diseases, hypothyroidism or reticulocytosis [11].

Among the currently used indirect diagnostic laboratory tests, carbohydrate-deficient transferrin (CDT) is regarded as the parameter with the highest diagnostic efficiency [13]. The dose–response relation between daily ethanol intake in the range 0–70 g and the CDT value is characterized by a rather broad variation [14]. The mean half-life of CDT is approximately 14–17 days [13]. Due to the rapid decline of CDT values compared with indicative liver enzymes and MCV, CDT is a valuable parameter in the early stage of alcohol withdrawal [14]. Nevertheless, there are numerous caveats in the interpretation of a CDT value and falsely high values have been found in the serum of patients with a congenital disorder of glycosylation (CDG). False-positive results may occur because of genetic D-variants of transferrin and primary biliary cirrhosis [15]. CDT suffers from low sensitivity because some individuals show no or low increase in CDT (none or low responders) despite excessive ethanol intake [16].

With the exception of CDT, the specificity of indirect markers is only moderate because many cases of elevated values are unrelated to alcohol consumption. About 92–95% of the consumed ethanol undergoes biotransformation via oxidative metabolism (Fig. 1). Non-metabolized alcohol is eliminated in small quantities by the kidneys (0.5–2%), lungs (1.6–6%) and the skin (<0.5%) (Table 1) [17]. A small proportion of the ingested ethanol, undergoes non-oxidative metabolism. The latter, i.e. ethyl glucuronide (EtG) [18], ethyl sulfate (EtS) [19], phosphatidylethanol (PEth) [20] and fatty acid ethyl esters (FAEE) [21], allow to detect a single alcohol intake several hours up to some days afterwards, the time window largely being dose-dependent [11]. In the present review, the methodology, possibilities and limitations of these biomarkers are discussed.

2. Ethyl glucuronide

2.1. A non-oxidative metabolite of ethanol

The use of ethyl glucuronide (ethyl β-D-6-glucuronide; EtG) as a possible marker for alcohol intake was first discovered in 1995 by Schmitt [18]. The hepatic clearance of ethanol is primarily catalyzed by alcohol dehydrogenase, the microsomal ethanol-oxidizing system (CYP 2E1) and peroxisomal catalase (Fig. 1). Only a small proportion (0.6–1.5%) of ethanol is conjugated with glucuronic acid [17]. The latter is catalyzed by the UDP-glucuronosyltransferase (UGT) superfamily of enzymes, which utilize UDP-glucuronic acid as a cofactor [22]. Approximately 0.02–0.06% of the total amount of ethanol consumed is eliminated as EtG in the urine [23]. Although the relative amount of glycated ethanol is small, it represents a useful tool as EtG becomes detectable up to 4 days after complete elimination of alcohol from the body [3]. EtG formation is catalyzed by multiple UGTs which implies that any functional differences due to UGT polymorphisms would most likely be masked by a combination of other UGT isoforms [22]. Therefore, there is no pharmacogenetic reason why EtG cannot be used as a biomarker for ethanol consumption.

In recent years, it was demonstrated that the consumption of alcohol can be indirectly determined by analyzing the hair for EtG [24,25]. The solid and durable nature of hair ensures a substantially longer detection time for chemical substances. During the growth period, substances can enter the hair either via incorporation by diffusion from blood into growing cells or by deposition from sweat or sebum into the completed hair shaft [26]. The level of incorporation is affected by the amount of exposure to the hair from each of these sources, the pH of the surrounding mediums, physicochemical properties of the analyte, its opportunity and ability to penetrate the hair and its binding sites.

2.2. Pre-analytical aspects and confounding factors

The stability of EtG in urine samples is satisfying. When stored at 4 °C proved, the concentration remains stable for 5 weeks [27]. Bacterial contamination of urine may cause false-negative EtG test results [28]. Conversely, EtG can be formed in a biological specimen after

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