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Ethyl Glucuronide as a Sensitive Marker of Alcohol Abuse

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Abstract

An important strategy for the prevention of alcohol-related problems is the early diagnosis of alcohol abuse. The present paper aims at a systematic review of the current knowledge on ethylglucuronide (EG) in blood as a direct marker of alcohol abuse. The research evidence suggests that EG in the urine is a promising marker of episodic alcohol consumption in large doses, while EG in the hair is a reliable indicator of chronic alcohol abuse.

Keywords

Ethylglucuronide, Biochemical marker, Alcohol abuse

Introduction

Alcohol is considered one of the main risk factors for premature death in many countries of the world [1]. An important strategy for the prevention of alcohol-related problems is the early diagnosis of alcohol abuse [2]. The use of questionnaires does not allow obtaining objective information due to the tendency of respondents to underestimate the level of alcohol consumption in self-reports [3] Since the currently used methods of laboratory diagnosis of alcohol abuse do not have sufficient reliability [4], the development of modern methods of laboratory diagnosis of alcohol abuse seems to be an urgent task.

In recent years, several direct biochemical markers of alcohol consumption have been identified that are more sensitive and specific than indirect markers [5]. One of the promising markers of acute and chronic alcohol intoxication is considered to be ethylglucuronide (EG), which is a direct minor ethanol metabolite formed by its conjugation with glucuronic acid in the endoplasmic reticulum of liver cells [6-11].

The presence of EG in blood and urine indicates recent alcohol use, while its detection in hair indicates chronic alcohol abuse [10]. A dose-dependent relationship has been found between alcohol consumption and the concentration of EG in blood and urine, and its level in urine is higher than in blood [12]. Analysis of blood samples delivered to the laboratory for routine biochemical studies showed that in blood with an alcohol content of less than 0.1 g/l, the average concentration of EG was 85.1 ng/ml; in blood with an alcohol content of 0.1-0.5 g/l, the average concentration of EG was 276 ng/ml; in blood with an alcohol content of 0-1 g/l, the average concentration of EG was 671 ng/ml; in blood with an alcohol content of more than 1 g/l, the average concentration of EG was 2259 ng/ml [13]. The concentration of EG in blood and urine closely correlates with the amount of alcohol consumed during the three days preceding the analysis [14]. One study examined urinary EG concentrations in relation to self-reported levels of alcohol consumption. It was found that the concentration of EG positively correlated with the amount of alcohol consumed, the activity of γ-glutamyl transpeptidase (γ-GGTP), the mean corpuscular volume of erythrocytes (MCV), but did not correlate with the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [15].

The kinetics of EG elimination was studied under conditions of controlled alcohol consumption by volunteers. The use of 1-2 standard doses of alcohol increases the content of EG in the urine above 0.1 mg/l for up to 24 hours. Two hours after drinking 4 standard doses of alcohol, the mean plasma EG concentration was 0.4 μg/mL, and after three hours, the mean urinary concentration was 3.5 mg/g. After taking 8 standard

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doses, the average concentration of EG in plasma was 1.3 μg/ml, and in urine 10 mg/g. Therefore, the detection of EG in urine is a rather sensitive marker for discrimination between withdrawal and moderate alcohol consumption [16].

The results of a study involving alcohol abusers showed that the concentration of EG in the urine is quite reliable (sensitivity 73.9%; specificity 80%) detects the fact of drinking alcohol, as well as drinking alcohol in large doses (sensitivity 83.3%; specificity 66.1%) [17]. EG is a marker of the so-called intoxication-oriented of alcohol consumption, since it is present in the blood up to 36 hours, and in the urine for up to 3-5 days after a single high-dose alcohol consumption [18].

The results of the assessment depend to a large extent on the threshold level used. At present, the threshold concentrations of EG vary widely (from 100 to 1000 ng/mL) [9-15]. The choice of the optimal threshold level continues to be a matter of debate. Using a low threshold provides high sensitivity, but increases the likelihood of a false positive result. At the same time, a higher threshold provides high specificity and positive predictive value by reducing sensitivity [15].

Comparison of different threshold levels of EG in the urine of patients with alcohol dependence 24 and 120 hours after alcohol consumption showed that the threshold level of 100 ng/ml has the highest sensitivity (0.93-0.78) and specificity (0.67-0.85). When using a threshold level of 200 ng/ml, the sensitivity decreased (0.89-0.67) and the specificity increased (0.78-0.94). Cut-off levels of 300, 400 and 500 ng/mL showed the lowest sensitivity (0.86-0.33) and the highest specificity (0.86-0.97). A false positive result at a threshold level of 100 ng/ml was noted in 6.3% of cases; at a threshold level of 200 ng/ml in 2.6% of cases; at a threshold level of 300 ng/ml in 1.4% of cases; at a threshold level of 400 ng/ml in 1.35 cases; at a threshold level of 500 ng/ml in 1.1% of cases [12]. The presented data justify the use of a cut-off level of 200 ng/ml if the analysis is carried out later than 24 hours after alcohol consumption.

In a study on volunteers, urinary EG levels were detected 12, 24, 48, and 72 hours after ingestion of low, medium, and high doses of alcohol [9]. 12 hours after alcohol consumption, the reliability of determination at threshold levels of EG 100 ng/ml and 200 ng/ml was 100%. The cut-off level of 500 ng/mL detected 50% of low-dose alcohol consumption. Therefore, for the detection of alcohol consumption in small and medium doses, it is necessary to use a cut-off level below 500 ng/ml, especially if more than 48 hours have passed since the consumption of alcohol. The cut-off level of 100 ng/mL has the highest correlation with self-reported alcohol consumption compared to higher cut-off levels, but is not sensitive enough to detect low to moderate alcohol consumption at 12 hours. The use of a threshold level of 200 ng/mL provides an optimal balance between sensitivity and specificity in the detection of alcohol consumption. A higher threshold concentration is used to avoid a false positive result when using household alcohol-containing chemicals [9].

The scope of EG as a biochemical marker of alcohol consumption in experimental and clinical practice is quite wide. The detection of EG in urine is used to control the quality of remission in alcohol-dependent patients undergoing rehabilitation [13]. The presence of EG in urine is a reliable (sensitivity 89.2%, specificity 98.8%) marker of alcohol consumption in patients awaiting liver transplantation [19]. At the same time, EG showed its advantage over other markers (methanol, CDT, AST, ALT, GGTP) in monitoring abstinence in patients on the waiting list for liver transplantation [20]. In a study conducted in Italy, it was demonstrated that in 34.3% of pregnant women, the content of EG in the blood exceeded the threshold level. At the same time, the results of the analysis did not correlate with the results of alcohol consumption self-reports, which emphasizes the need to use direct diagnostic methods [21].

The content of EG in hair is a marker of chronic alcohol abuse [12,21]. A linear relationship has been established between the level of alcohol consumption and the content of EG in the hair, both in representatives of the general population and in persons with alcohol dependence [9]. At the same time, gender, age, and body mass index do not significantly affect the content of EG in hair [12]. Therefore, the detection of EG in hair is a fairly reliable indicator of chronic alcohol abuse, with high sensitivity (70-90%) and specificity (80-95%) [9]. A meta-analysis of studies showed that the average concentration of EG in the hair of domestic drunkards is 7.5 pg/mg, in alcohol abusers - 142.7 pg/mg, in people suffering from alcohol dependence - 596.1 pg/mg [17].

Drinking alcohol at a dose of 16 g per day for 3 months does not lead to an increase in the content of EG in the hair above the withdrawal threshold (7 pg/mg), and drinking at a dose of 32 g per day does not lead to an increase in the content of EG in the hair above the threshold level for alcohol abuse (30 pkg/mg) [12]. The detection of EG in hair also makes it possible to discriminate between different groups of alcohol consumers: Those who do not drink; social drunkards (those who consume less than 60g of alcohol in absolute terms); alcohol abusers (those who consume more than 60 g of alcohol in absolute equivalent) [9]. An indicator of chronic alcohol abuse (consumption of more than 60 g for several months) is the threshold level of EG of 30 pg/mg in 0-3 cm of the proximal segment [12]. Hair longer than 3 cm contains more EG, presumably due to its incorporation from sweat after drinking alcohol [7].

In patients with liver damage, detection of EG in hair at a threshold level of > 8 pg/mg reliably detects (sensitivity 92%, specificity 87%) daily consumption of 28 or more grams of alcohol per day [22]. The content of

EG correlates with the total dose of alcohol consumed during the 90 days preceding the analysis. At the same time, the severity of liver disease does not significantly affect the accuracy of the detection [22].

The disadvantages of using EG as a marker include the likelihood of a false positive result in household contact with alcohol-containing liquids (mouthwash, sanitizers) [23]. False-negative results can be obtained with small doses of alcohol (< 3 standard drinks), as well as after a sufficiently long time (> 16 hours) after drinking alcohol [9]. Drinking non-alcoholic beer and sweets can increase EG levels. Hair coloring and treatment with alcohol-containing liquids, as well as the use of vegetable hair tonics, do not affect the EG content, while hair lightening reduces its level by 20-40% due to oxidation with hydrogen peroxide [12]. EG can be degraded in the urine over time (when stored for more than 12 hours) under the influence of bacterial beta-glucuronidase [7]. On the other hand, the microflora can convert sugar into alcohol, which conjugates with glucuronic acid, which is especially important for people with diabetes [12].

EG can be detected using immunological methods, Gas Chromatography - Mass Spectrometry (GC-MS), as well as High-Performance Liquid Chromatography - Tandem Mass Spectrometry (HPLC-MS). The results of EG determination using different methods are in good agreement with each other [24].

In sum, a systematic review of the current knowledge suggests that EG in the urine is a promising marker of episodic alcohol consumption in large doses, while EG in the hair is a reliable indicator of chronic alcohol abuse.

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