ISSN: 2690-263X

Razvodovsky. Int Arch Subst Abuse Rehabil 2022, 4:014
DOI: 10.23937/2690-263X/1710014
Volume 4 | Issue 1
Open Access

International Archives of
Substance Abuse and Rehabilitation

ORIGINAL ARTICLE

Phosphatidylethanol as a Marker of Alcohol Abuse

Razvodovsky YE*

Institute biochemistry of biologically active substances, Academy of science of Belarus, Republic of Belarus, Russia

***Corresponding author:** *Razvodovsky Y.E, Institute biochemistry of biologically active substances, Academy of science of Belarus, Republic of Belarus, Grodno, Russia*

Abstract

The present paper aims at a systematic review of the current knowledge on phosphatidylethanol (PEth) in blood as a direct marker of alcohol abuse. The research evidence demonstrates a good clinical efficiency of PEth for detecting chronic heavy drinking. A systematic review of the current knowledge indicates a significant variability in the reference threshold of PEth concentration to discriminate between different levels of alcohol consumption, which complicates its use as a biochemical marker of alcohol abuse. Variability in the reference threshold concentration of PEth may be due to various unaccounted variables, such as individual differences in the rate of its formation (determined by phospholipase D activity) and elimination of PEth, the possibility of formation of PEth in vitro, differences in the analytical methods used and detected homologues, consumption pattern, reliability of self-reports alcohol consumption.

Keywords

Phosphatidylethanol, Alcohol abuse, Biochemical markers

Introduction

Early diagnosis of alcohol dependence is an important strategy in the framework of the state alcohol policy [1]. One of the methods for diagnosing alcohol abuse is the use of questionnaires, the advantages of which are ease of use and low cost, and the disadvantages are subjectivity and low reliability [2]. Therefore, methods for laboratory diagnosis of alcohol abuse using biochemical markers are currently being actively developed [3].

Of all currently known methods for the laboratory diagnosis of alcohol dependence, the most promising is the detection of the concentration of PEth in the blood [4]. PEth are a group of abnormal phospholipids formed in various tissues in the presence of ethanol from the cell membrane phosphatidylcholine under the action of phospholipase D [5]. Of the 48 known PEth homologs, the most common are PEth 16:0/18:1 (38%) and PEth 16:0/18:2 (24%). Since there is no system of enzymatic degradation of PE in erythrocytes, it accumulates in the membrane and, therefore, can serve as a marker of chronic alcohol abuse [6].

In earlier studies, the overall level of PEth was detected, i.e. the sum of all its homologues, while recently the detection of its main homologue 16:0/8:1 is carried out [7]. In vitro studies have shown that the amount of PE formed in erythrocytes is directly proportional to the ethanol concentration and exposure time [8]. The formation of PEth begins immediately after drinking alcohol and reaches a peak after 8 hours [8]. There are significant individual variations in the half-life of PEth, which ranges from 3 to 5 days [9]. There are no gender differences in the formation of PEth, however, given that women have a greater proportion of fat, the dose of alcohol sufficient to detect PEth will be lower than in men of the same weight [10].

PE makes it possible to detect an intoxication-oriented style of alcohol consumption, since it correlates with the cumulative dose of alcohol consumed over a certain period of time [11]. The level of PEth strongly correlates with high alcohol consumption during the 1-4 days preceding the analysis [5]. Literature data regarding the “window” for the determination of PEth in chronic alcohol abuse vary from 9 to 28 days after the cessation of alcohol consumption [12]. However, some authors recommend using it to detect a single alcohol consumption to confirm the fact of relapse of alcohol dependence [13].

Citation: Razvodovsky YE (2022) Phosphatidylethanol as a Marker of Alcohol Abuse. Int Arch Subst Abuse Rehabil 4:014. doi.org/10.23937/2690-263X/1710014

Accepted: June 29, 2022: **Published:** July 02, 2022

Given the significant individual variations in the process of PEth formation, it is rather difficult to calculate the amount of alcohol that must be consumed to achieve the threshold level for detection PEth. It has been established that in men who daily consume approximately 2.5 standard doses (35 g) of alcohol per day for 3 months, the concentration of PEth in the blood was > 20 ng/ml [14]. For women, the threshold level can be reached by drinking 1.5-2 standard drinks (21-28 g) of alcohol per day. The United States laboratories adopted a consensus agreement, according to which the threshold level > 35 ng/ml indicates a low level of alcohol consumption [15].

An important task is to assess the threshold concentrations of PEth corresponding to different levels of alcohol consumption: low, moderate, alcohol abuse, alcohol dependence. To date, there has been no consensus on the reference threshold for different alcohol consumption regimens. According to the results of a meta-analysis, the level of PEth in the blood of heavy drinkers (> 60 g per day) was higher than in everyday drunkards (3.9 vs. 0.29 µmol/l) [16]. It has been proposed to use a PEth concentration of 20–200 ng/mL (0.03–0.30 µmol/L) as the threshold for significant alcohol consumption, and a concentration of > 200 ng/mL as the threshold for heavy drinking [6]. Another paper recommended using a threshold level of PE of 221 ng/L for chronic alcohol abuse [17,18]. PEth concentrations of 20-200 ng/ml correspond to moderate alcohol consumption (2 to 4 standard drinks per day), while concentrations > 200 ng/ml correspond to heavy drinking (at least 4 standard drinks per day for several days) [19]. According to the results of another study, the concentration of PEth in the blood of abstainers is below the detection level (0.001 µmol/l), in the blood of social drinkers 0.006-0.085 µmol/l (4.2-60 ng/ml), in the blood of heavy drinkers 0.89-5.29 µmol/l (630-3700 ng/ml) [20]. In Sweden, a concentration of 0.20 µmol/l was initially proposed for the 16:0/18:1 homologue of PEth [21]. Later, in order to increase specificity, the threshold level for alcohol abuse was raised to 0.30 µmol/L (210 ng/mL), while the concentration > 0.05 µmol/L (35 ng/mL) was taken as threshold for social drinkers [22].

A number of studies have shown a dose-dependent relationship between the amount of alcohol consumed according to self-reports and the concentration of PEth in the blood [23,24]. A study involving alcohol-dependent patients treated at the Stockholm Addictions Treatment Center showed that blood concentrations of PEth 16:0/18:1 correlated with the amount of alcohol consumed during the previous two weeks [25]. According to the ratio of the dose of alcohol consumed and the concentration of PEth, several subgroups were distinguished: the subgroup with the concentration of PEth < 0.05 mmol/l corresponded to withdrawal or low-level alcohol consumption (0-25 standard drinks or 0-300 g in the last two weeks); the subgroup with PEth concentration > 0.30 µmol/l corresponded to excessive alcohol consumption (16-106 standard drinks or 192-1270 g of alcohol during the last two weeks). Regression analysis showed that an increase in alcohol consumption by 1.5 standard doses (approximately 20 g of alcohol) per day leads to an increase in the concentration of PEth 16:0/18:1 by 0.10 µmol/l [25].

Accumulated evidence suggests that PEth is a more reliable indicator of alcohol abuse than other biochemical markers. In a study involving individuals undergoing a medical examination referred by an employment agency, PEth was a more sensitive indicator of regular high alcohol consumption compared to carbohydrate transferrin (CDT), Gamma-Glutamine Transferase (GGTP) [26]. Despite the fact that PEth correlated with CDT ($r = 0.63$; $p < 0.0001$), in 22% of cases the test for CDT was negative, while the concentration of PE exceeded 0.30 µmol/l (the cut-off level for alcohol abuse). Sensitivity and specificity for discrimination between withdrawal and moderate alcohol consumption for a cut-off concentration of 0.009 µmol/l (6.3 ng/ml) were 84.4% and 83%, respectively; for a threshold concentration of 0.006 µmol/l (4.2 ng/ml), 100 and 78%, respectively; for a threshold concentration of 0.04 µmol/l (28 ng/ml), 100 and 28%, respectively [26].

In a study involving alcohol-dependent patients undergoing detoxification, it was shown that PEth was the only one of all biochemical markers that was detected in all patients. The threshold level of total PEth of 0.36 µmol/l had a sensitivity of 94.5% and a specificity of 100%. At the same time, the sensitivity and specificity of CDT were 77.1 and 88%, respectively; the sensitivity and specificity of GGTP were 94% and 72%, respectively [27].

In another study, it was found that the average concentration of PEth in the blood of patients with alcohol dependence was 2.47 µmol/l [18]. Discrimination between practicing alcoholics and abstaining from drinking alcohol at a threshold concentration of PEth of 0.36 µmol/l has a sensitivity of 94.5% and a specificity of 100%. PEth concentration statistically significantly correlates with GGTP, CDT and the amount of alcohol consumed during the last 7 days. Sensitivity and specificity for CDT were 77.1% and 88%, respectively; for GGTP, respectively, 94 and 72%. It has also been established that in alcohol-dependent patients, the concentration of PE in the blood correlates with the amount of alcohol consumed during the last month, the number of points according to the AUDIT test, and also with the activity of GGTP [19].

The results of another study showed that in patients suffering from alcohol dependence, the sensitivity of PEth as a biochemical marker was 100%, while the sensitivity of other markers depended on the amount of alcohol consumed [9]. In the low alcohol consumption group, the sensitivity of CDT and GGTP

was approximately 40%; in the intermediate level of alcohol consumption (40-60 g per day), the sensitivity was approximately 60%; in the group consuming 80-120 g of alcohol per day, the sensitivity was 80%; in the group consuming more than 200 grams of alcohol per day, the sensitivity was about 90%. A strong correlation was found between PEth concentration and the amount of alcohol consumed, while the relationship between CDT/GGTP and the amount of alcohol consumed was weaker [9].

One study attempted to establish reference values for PEth 16:1/18:1 and PEth 16:1/18:2 for various levels of alcohol consumption, which was assessed using self-reports as well as the AUDIT-C test [23]. None of the study participants who declared complete abstinence from alcohol consumption had PEth in their blood, which indicates the absence of its endogenous level. In 85 study participants who consumed up to 10 g of alcohol per day during the two weeks preceding the study, PEth 16:0/18:1 was not determined in the blood. At the same time, 9 participants classified as "abusive" had PEth 16:0/18:1 concentrations below 10 ng/mL. In moderate drinkers according to the AUDIT-C test (1-3 points for women and 1-4 points for men), the concentration of PEth 16:0/18:1 was 0-112 ng/ml, and the concentration of PEth 16:0/18: 2 was 0-67 ng/ml. ROC analysis showed that 95% of abstinents and moderate drinkers had a 16:0/18:1 PEth concentration of 0 to 112 ng/mL, but only 36.5% of AUDIT-C heavy drinkers had a 16:0/18 PE concentration :1 > 112 ng/mL. The corresponding threshold for PEth 16:0/18:2 was 67 ng/mL [23].

Analysis of the blood of patients undergoing inpatient treatment for alcohol dependence showed that in 60% of cases of positive testing, the concentration of PEth exceeded 0.7 µmol/l, which corresponds to the threshold for excessive drinking. PE was found to be a more sensitive biochemical marker of relapse during remission than CDT, as it detects lower levels of alcohol consumption. At the same time, a correlation was found between the content of PEth and CDT ($r = 0.62$; $p < 0.001$) [24].

In one study, young people aged 18-30 years were divided into subgroups according to the level of alcohol consumption: abstinents, moderate drinkers and heavy drinkers [17]. It turned out that in all abstinents the result of the test for the content of PE was negative. The concentration of PEth in abusers was higher than in abstinents and moderate drinkers. There were no differences in the content of PEth between abstinents and moderate drinkers. The results of the AUDIT test correlated with the concentration of PEth in the group of moderate drinkers ($r = 0.75$; $p < 0.001$) and the group of heavy drinkers ($r = 0.74$; $p < 0.001$). The concentration of PEth correlated with the amount of alcohol consumed during the week, as well as with the number of standard doses of alcohol drunk during the last month. In patients of the intensive care unit, the concentration of PEth positively correlated with the results of the AUDIT test, regardless of gender and age. The threshold concentration of PEth for alcohol abuse was > 250 ng/ml, and for heavy drinking > 400 ng/ml [17].

A study of blood received by the laboratory from narcological clinics and forensic medical examination bureaus for the routine detection of biochemical markers of alcohol consumption showed that in more than half of the samples, the concentration of PEth exceeded the threshold value for heavy drinking (> 0.3 µmol/l) [15]. At the same time, the concentration of PEth did not correlate with the content of ethyl glucuronide (EG), which indicates the independence of these indicators. Therefore, these biochemical markers provide complementary information: PEth indicates chronic alcohol consumption, while EG indicates recent alcohol consumption. If the concentration of PE < 0.05 µmol/l, and EG is not detected, it heavily suggests the abstinence from alcohol. The concentration of PEth exceeding 0.05 µmol/l with a positive test for the content of EG may indicate episodic alcohol consumption. If the concentration of PE indicates alcohol abuse, EG can be used to discriminate between the period of heavy drinking and the period of abstinence from alcohol [15].

The results of a cross-sectional study, which involved patients with acute pathology who were hospitalized in clinics in Oslo and Moscow, showed that in Norwegian patients, whose AUDIT-QF score was less than 6, the concentration of PEth was less than 0, 5 µmol/l and increased as the number of points increased [28]. A trend towards an increase in the concentration of PEth with an increase in the number of points according to the test was also noted in Russian patients. In both populations, a statistically significant relationship was found between the concentration of PEth and the number of points according to the test, as well as the dose of alcohol drunk during the last week. The threshold concentration of PEth for discrimination between safe and harmful alcohol consumption (> 5 points for men and > 4 points for women) in Norwegian and Russian patients was 0.128 and 0.270 µmol/L, respectively. When using a weekly dose of > 350 g as a criterion for harmful alcohol consumption, the threshold concentration of PEth in discrimination between safe and harmful alcohol consumption in Norwegian and Russian patients was 0.327 and 0.396 µmol/L, respectively. Compared to Norwegian women, Russian women had lower scores on the test with a higher level of excessive drinking, which may be due to the low reliability of Russian women's self-reports [28].

Thus, the available data indicate the advantage of PEth over other biochemical markers in the detection of chronic alcohol abuse, since it has greater sensitivity and specificity. Unlike most indirect markers used in the

diagnosis of chronic alcohol abuse, the concentration of PEth in blood does not depend on gender, age, and the presence of concomitant diseases. In addition, the concentration of PEth is independent of exposure to alcohol in the home. The disadvantage of using PEth in routine clinical practice is the methodological complexity of its determination. Currently, various methods have been developed for the quantitative detection of PEth, which make it possible to detect both its total amount and its individual homologues at low concentrations. The most sensitive method for identifying and quantifying individual PEth homologues is High-Performance Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS).

A systematic review of the current knowledge indicates a significant variability in the reference threshold of PEth concentration to discriminate between different levels of alcohol consumption, which complicates its use as a biochemical marker of alcohol abuse. Variability in the reference threshold concentration of PEth may be due to various unaccounted variables, such as individual differences in the rate of its formation (determined by phospholipase D activity) and elimination of PEth, the possibility of formation of PEth in vitro, differences in the analytical methods used and detected homologues, consumption pattern, reliability of self-reports alcohol consumption.

In conclusion, the accumulated data allow us to consider the detection of PEth in the blood as a promising marker of episodic alcohol consumption in large doses, as well as chronic alcohol intoxication/ alcohol dependence. An urgent task for further research is to study the sensitivity, specificity, threshold values of PEth in various modes of alcohol abuse, as well as depending on gender, age and comorbidity.

References

1. Razvodovsky YE (2001) The role of general practitioners in addiction prevention. Medical news 11: 29-32.
2. Razvodovsky YE (2019) Biological markers of alcoholism: current state and prospects for use. Scientific forum. Siberia 5: 79-81.
3. Plavinsky SL, Kuznetsova OYu, Degtyareva LN, Barinova AN, Boyarsky SG (2013) Laboratory markers of alcohol abuse in general medical practice. Russian family doctor 17: 10-15.
4. Adler D (2013) The Difficulty of using a Biological Marker for Alcohol Use: A Recent Historical Overview. Sound Neuroscience: An Undergraduate Neuroscience Journal 1: 1-8.
5. Alatalo P, Koivisto H, Puukka K, Hietala J, Antilla P, et al. (2009) Biomarkers of liver status in heavy drinkers, moderate drinkers and abstainers. Alcohol Alcohol 44: 199-203.
6. Andresen-Streichert H, Müller A, Glahn A, Skopp G, Sterneck M (2018) Alcohol biomarkers in clinical and forensic contexts. Dtsch Arztebl Int 115: 309-315.
7. Bearer CF, Bailey SM, Hoek JB (2010) Advancing Alcohol Biomarkers Research. Alcohol Clin Exp Res 34: 941-945.
8. Freeman WM, Vrana KE (2010) Future prospects for biomarkers of alcohol consumption and alcohol-induced disorders. Alcohol Clin Exp Res 34: 946-954.
9. Helander A (2003) Biological markers in alcoholism. J Neural Transm Suppl 15-32.
10. Jastrzębska I, Zwolak A, Szczyrek M, Wawryniuk A, Skrzydło-Radomańska B, et al. (2016) Biomarkers of alcohol misuse: recent advances and future prospects. Prz Gastroenterol 11: 78-89.
11. Liangpunsakul S, Lai X, Ross RA, Zhangsheng Yu, Modlik E, et al. (2015) Novel serum biomarkers for detection of excessive alcohol use. Alcohol Clin Exp Res 39: 556-565.
12. Neumann T, Spies C (1998) Use of biomarkers for alcohol use disorders in clinical practice. 2003 Society for the study of addiction to alcohol and other drugs. Addiction 81-91.
13. Peterson K (2005) Biomarkers for alcohol use and abuse – a summary. Alcohol Res Health 30-37.
14. Skrzydło-Radomańska B, Daniluk J (2016) Biomarkers of alcohol misuse: recent advances and future prospects. Gastroenterology Rev 11: 78-89.
15. Waszkiewicz N, Konarzewska B, Waszkiewicz M, Popławska R, Dariusz Szajda S, et al. (2010) Biomarkers of alcohol abuse. Part I. Traditional biomarkers and their interpretation. Psychiatr Pol 44: 127-136.
16. Hashimoto E, Riederer PF, Hesselbrock VM, Hesselbrock MN, Mann K, et al. (2013) Consensus paper of the WFSBP task force on biological markers: Biological markers for alcoholism. World J Biol Psychiatry 14: 549-564.
17. Aradottir S, Asanovska G, Gjerss S, Hansson P, Alling C (2006) Phosphatidylethanol concentrations in blood are correlated to reported alcohol intake in alcoholdependent patients. Alcohol Alcohol 431-437.
18. Cabarcos P, Álvarez I, Tabernero MJ, Bermejo AM (2015) Determination of direct alcohol markers: a review. Anal Bioanal Chem 4907-4925.
19. Das SK, Nayak P, Vasudevan DM (2003) Biochemical markers for alcohol consumption. Indian J Clin Biochem 18: 111-118.
20. Hartmann S (2017) Phosphatidylethanol as a sensitive and specific biomarker-comparison with gamma-glutamyl transpeptidase, mean corpuscular volume and carbohydrate-deficient transferrin. Addict Biol 81-84.
21. Litten R, Bradley A, Moss H (2010) Alcohol biomarkers in applied settings: recent advances and future research opportunities. Alcohol Clin Exp Res 34: 955-967.
22. Nanau RM, Neuman MG (2015) Biomolecules and Biomarkers Used in Diagnosis of Alcohol Drinking and in Monitoring Therapeutic Interventions. Biomolecules 5: 1339-1385.
23. Niemelä O (2016) Biomarker-Based Approaches for Assessing Alcohol Use Disorders. Int J Environ Res Public Health 13: 166.
24. Stewart S, Law TL, Randall PK, Newman R (2010) Phosphatidylethanol and alcohol consumption in reproductive age women. Alcohol Clin Exp Res 34: 488-492.
25. Tavakoli HR, Hull M, Okasinski M (2011) Review of current clinical biomarkers for the detection of alcohol dependence. Innov Clin Neurosci 8: 26-33.
26. Wurst FM, Alling C, Aradottir S, Pragst F, Allen JP, et al. (2005) Emerging biomarkers: new directions and clinical applications. Alcohol Clinic Exp Res 29: 465-473.

27. Wurst FM, Thon N, Aradottir S, Hartmann S, Wiesbeck GA, et al. (2010) Phosphatidylethanol: normalization during detoxification, gender aspects and correlation with other biomarkers and self-reports. Addict Biol 15: 88-95.

28. Jorgenrud B, Kabashi S, Nadezgdin A, Bryun E, Koshkina E, et al. (2021) The association between alcohol biomarker phosphatidylethanol and self-reported alcohol consumption among Russian and Noewegian medical patients. Alcohol Alcohol 56: 726-736.