Clinical Biochemistry xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Blood alcohol levels after standardized intake of alcohol are related to measured blood phosphate levels

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ARTICLE INFO

Keywords:
Phosphate
Alcohol metabolism
Gastric alcohol dehydrogenase
Alcohol dehydrogenase

ABSTRACT

The role of blood phosphate in alcohol metabolism has not been studied. In this explorative experimental study, the relationship between blood phosphate levels and metabolism of alcohol was investigated. Twenty young male volunteers were given alcohol relative to body weight to make them reach a theoretical blood alcohol concentration (BAC) of 0.12%. Ten measurements of BAC were taken across the time from intake, to peak and total elimination. The results indicated that individuals with high blood phosphate levels achieved a lower BAC maximum than those with low blood phosphate levels. The difference between the highest and lowest maximum BAC was as much as 30–40% and correlated negatively to physiological blood phosphate levels. The results suggest that phosphate plays a role in prehepatic, possibly gastric, alcohol metabolism. The Alcohol Dehydrogenase enzyme 7 (ADH7) is represented in the upper gastrointestinal tract and may be the enzyme responsible for this variation in the blood alcohol concentration reached.

1. Introduction

The study of alcohol use and alcohol use disorders (AUD) is of major importance for public health. There is substantial evidence that variation in alcohol pharmacokinetics affect individuals' risk of AUD. This implicates alcohol-metabolizing enzymes in the risk for AUD and other alcohol-related diseases [1].

After ingestion, alcohol (ethanol) is rapidly absorbed, mostly from the small intestine, but with some absorption from the stomach and the colon. Once in the blood stream it is rapidly distributed, mostly in the water phase, to all body tissues including the central nervous system. Alcohol is mostly eliminated by hepatic metabolism into acetaldehyde and further to acetate. However, before absorption, there is also oxidation of ethanol in the gastric ventricle by ADH [2], of unknown importance and mostly in men [3]. The isomer of ADH mostly expressed in the gastric tract is ADH7 [4,5]. Its importance is illustrated by the fact that genetic variation in the enzyme predicts risk of AUD [6].

The average human body contains approximately 700 g of phosphate, bound to bone or in teeth (85%) or intracellularly bound (14%). Only 1% is found extracellularly. Peripheral blood phosphate is regulated by parathyroid hormone (PTH), vitamin D and fibroblast growth factor 23 (FGF23) [7]. Level of blood phosphate varies with diet, time of day, season, gender, age and genetics [8]. Phosphate is essential for several metabolic processes, like freeing oxygen from hemoglobin, making glucose lipid soluble for transport into cells and in adenosine triphosphate (ATP). Low serum blood phosphate gives symptoms of exhaustion. Adult males usually have a blood level of phosphate of 0.75–1.65 mmol/l, declining with age. Low levels of phosphate are seen in alcohol withdrawal [9], possibly related to renal dysfunction [10] or reduced phosphate uptake [11].

The aim of this study was to investigate any role of phosphate in the metabolism of alcohol. In a study of 20 volunteers drinking to a

Abbreviations: ADH, alcohol dehydrogenase; ALAT, alanine aminotransferase; ATP, adenosine triphosphate; AUC, area under the curve; AUD, alcohol use disorder; AUDIT, alcohol use disorder identification test; BAC, blood alcohol concentration; BMI, body mass index; CDT, carbo deficient transferrin; CRP, c-reactive protein; FGF23, Fibroblast growth factor 23; γGT, Gamma-glutamyl transferase; GI, gastrointestinal; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PEth, phosphatidyl ethanol; PTH, parathyroid hormone; SPSS, statistical package for the social sciences.

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https://doi.org/10.1016/j.clinbiochem.2022.08.006
Received 10 April 2022; Received in revised form 14 July 2022; Accepted 10 August 2022
Available online 13 August 2022

Table 1
Pearson's r correlations between basic blood phosphate and several measured basic parameters (including routine biochemistry), alcohol use parameters and blood alcohol measures from the clinical study as measured by Pearson's R (p-value).

Basic parameters			Alcohol use parameters			Experimental alcohol parameters		
Variable	Pearson's R	p-value	variable	Pearson's R	p-value	variable	Pearson's R	p-value
Age	−0.375	0.103	AUDIT	−0.324	0.175	BAC baseline	ND[A]	
BMI	0.160	0.501				BAC 1.0 h	**−0.548**	**0.012**
			MCV	0.093	0.695	BAC 1.5 h	−0.418	0.067
Hemoglobin	−0.235	0.318	MCH	−0.021	0.929	BAC 2.0 h	−0.433	0.056
Glucose	−0.288	0.219	ALAT	−0.134	0.573	BAC 3.5 h	**−0.489**	**0.029**
Sodium	−0.072	0.852	γGT	0.087	0.716	BAC 5.0 h	**−0.468**	**0.037**
Potassium	0.184	0.637	CDT	−0.018	0.939	BAC 6.5 h	−0.423	0.063
Creatinine	−0.184	0.428				BAC 8.0 h	−0.407	0.075
CRP	0.046	0.846				BAC 10.0 h	−0.275	0.240
Cortisol	−0.064	0.790				BAC 12.0 h	ND[A]	
						Elimination rate	0.024	0.921
						BAC AUC 0–2 h	**−0.498**	**0.025**
						BAC AUC 0–12 h	**−0.482**	**0.032**

Bold figures represent statistically significant relationships $p < 0.005$.
[A] ND = non-detectable BAC levels.

relatively high blood alcohol concentration (BAC) we measured BACs to find out if their baseline serum phosphate level was related to alcohol metabolism.

2. Materials and methods

2.1. Study participants

Twenty healthy volunteers were recruited through an open advertisement in the University College of Norwegian Correctional Service, training prison officers. Inclusion criteria were male gender, age 20–45 years, and Caucasian origin who admitted having experiences of high dose alcohol drinking sometime in the past. Exclusion criteria were significant medical illness, alcohol or other substance use disorders, and metabolic disorders.

Volunteers interested in participating were invited to be screened for AUD as well as physical and psychological health. Basic information was recorded, and basic biochemical parameters were determined by venous blood drawn after an overnight fast. AUD screening was carried out using the Alcohol Use Disorder Identification Test (AUDIT) [12]. All individuals scored below 15 in the AUDIT scale, consistent with being non-dependent on alcohol. This was confirmed by measuring serum carbohydrate deficient transferrin (CDT) value at baseline which was <1.7% in all participants.

2.2. Practical implementation of the experimental study

Participants arrived on location at 07:00 in the morning following overnight fast. Baseline blood samples were taken 15 min after arrival and a light breakfast was served. After thirty minutes participants were served oral ethanol (vodka 38% by volume) in a dose of 4.28 mL/kg which they drank over a period of 30 min aiming at a peak BAC of 0.12% (SD 0.028), equivalent to 0.03 mmol/L (SD 0.01). Participants were allowed standard meals and indoor activities throughout the experiment.

2.3. Measured variables

We recorded age and body mass index (BMI). Routine biochemical measurements had been taken on all participants 10 days prior to the experiment day at approximately 2:00p.m. to determine eligibility and to assess baseline values. These tests included general biomedical measurements of blood hemoglobin, glucose level, sodium, potassium, C-reactive protein (CRP), cortisol and phosphate. We also took biomedical measurements thought to be related to alcohol use, such as; mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), alanine aminotransferase enzyme (ALAT), gammaglutamyl transferase (γGT), and CDT.

BACs were measured 10 times during the experimental study. We calculated the time vs BAC area under the curve (AUC) both for the whole period (BAC AUC 0–12 h; %*h) and for the 2 first hours (BAC AUC 0–2 h; %*h). We also used BAC values from the descending part of the alcohol curve (3.5–6.5 h after alcohol intake) to calculate BAC elimination rate (%/h).

2.4. Statistical analyses

The statistical analysis was performed using IBM SPSS Statistics for Windows version 22 (IBM Corp., Armonk, NY). Correlations between blood phosphate and other variables were investigated by Pearson's R. Exact p-values are given.

2.5. Ethics

The study protocol was approved by the Norwegian Regional Ethics Committee (REK case ref. 2013/1563). Written informed consent was obtained, but participants could withdraw this consent at any time during the study. They received a bank transfer amounting to 2000 Norwegian Kroner (approximately €220) per day in compensation for the time used and were reimbursed their taxi fare home. All were insured as part of the project leader's membership of the Norwegian Drug Liability Association (ref. 5041916/1).

3. Results

Table 1 illustrates (by Pearson's R and p-values) no significant relationships between blood phosphate levels and age, BMI, hemoglobin, glucose, sodium, potassium, creatinine, CRP, and cortisol, or the potentially alcohol-related measures of AUDIT, MCV, MCH, ALAT, γGT and CDT. Blood phosphate levels were, however, related to BAC at all the first 6 time points, albeit only marginally for BAC at 1.5, 2, 6.5, and 8 h. The highest correlation was found for BAC at the first time point, i.e., at 1 h (Pearson's r −0.548, p = 0.012). Suggesting an approximately 30–40% higher BAC at 1 h in those with low blood phosphate levels (e.g., around 1.05 μmol/L) compared to those with higher blood phosphate levels (e.g., around 1.65 μmol/L). These findings were reflected in a statistically significant negative correlation between phosphate levels and BAC AUC 0–2 h and 0–12 h. This is further illustrated in Fig. 1 (one panel for each AUC). We observed no relationship between the different levels of blood phosphate and variations in alcohol elimination rate.

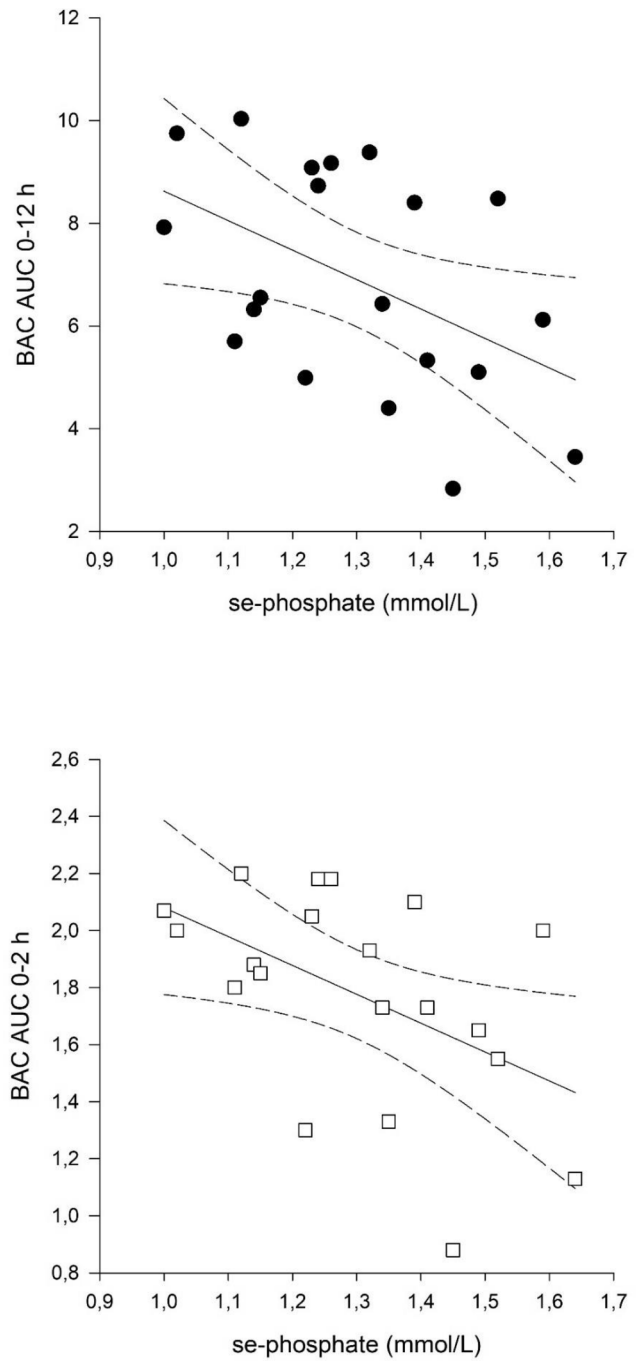

Fig. 1. Correlations between BAC AUC and serum phosphate concentrations at basic time. BAC AUC 0–12 h with filled black circles and BAC AUC 0–2 h with open squares.

4. Discussion

We report a significant negative relationship between blood phosphate levels and BACs after a weight-adjusted amount of alcohol. This was reflected in many of the successive BAC measurements, but mostly in the relationship between blood phosphate and the BAC area under the curve. The highest correlation was found for the BAC at 1 h after alcohol intake, the first alcohol measurement. There was no relationship between phosphate levels and alcohol elimination rate and no relationship to other commonly investigated biochemical measures, even those related to alcohol intake in the clinical setting.

The lower BAC AUC in high phosphate subjects seemed to be due to effects in the first period after alcohol intake. We observed a lower peak BAC, but as no difference in elimination rate, pointing to the activity in gastric ADH, more specifically the isoenzyme ADH7 which is most expressed in the upper GI tract [2,4]. There were only males included in this study and gastric ADH has been shown to be a factor mostly in males [3,13]. We have found no other human studies in this area, but a recent study in a mouse model found no difference in peak BAC related to blood phosphate level [14].

Studies have shown that first pass metabolism can eliminate more than 1/3 of the alcohol before it reaches systemic circulation [13]. In our study the observed difference in BAC AUC between high and low blood phosphate subjects was as much as 30–40%. It is unclear why phosphate levels should be related to the activity of gastric ADH, influencing the relationship between ingested alcohol and BAC, but our findings indicate that the lower BAC_{max} was not related to the hepatic metabolism and elimination rate. Gastric ADH activity seems to increase with progressive, but moderate, drinking [15]. Studies in AUD patients show that gastric metabolism may be substantially decreased in severe AUD [2]. Is this yet another pointer towards a relationship between phosphate levels and ADH7?

Limitations to our study include not having used phosphatidylethanol (PEth) as a specific marker of alcohol use and not including information on other factors involved in phosphate regulation, such as PTH, vitamin D and even FGF23. The inclusion of female participants could have shed light on gender differences. Lastly, this small study must be viewed as hypothesis generating rather than conclusive.

4.1. Consequences

On the basis of these findings, we hypothesize that the gastric metabolism of alcohol is related to blood phosphate levels, possibly through its effect on ADH7. Higher blood phosphate levels may produce higher gastric metabolism of alcohol and leave the individual with less alcohol to absorb and a lower BAC. Further studies should include a more detailed and targeted investigation of this hypothesis with a broader variety of individuals according to gender, age and maybe even genetic polymorphisms of ADH7.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Fürst medical laboratory from Oslo, Norway for analyzing samples at reduced rates and bio-technician Martine Engeset for providing help in gathering the samples. We thank Gudrun Høiseth at Oslo University Hospital for helping us calculate the amount of alcohol to be given. We thank Dr. Sudan P. Neupane for practical support. We thank biostatistician Quirino Puzo at the University of Oslo for help in preliminary statistical calculations for the experimental part of the study.

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