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Commentary

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Can Urinary Ethyl Glucuronide Be Used as a Biomarker of Habitual Alcohol Consumption?

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Alcohol is widely used by humans globally and has had a long and complicated role in human society and health. Excessive use of alcohol causes morbidity and mortality, but the health effects of moderate alcohol use, within recommended guidelines, are diverse and complex. Although alcohol abuse remains a global health issue, most drinkers consume alcohol within recommended limits (≤2 drinks per day for men and ≤1 drink per day for women). The adverse effects of heavy drinking are well established, but the role of moderate alcohol consumption is more complex and associations go in both directions. A large number of observational studies suggest that moderate drinking appears to increase the risk of colon and breast cancer, as well as hemorrhagic stroke, but these risks are more than counterbalanced by the boost in cardiovascular health, including protection against type 2 diabetes, coronary heart disease, and ischemic stroke (1, 2).

The majority of studies evaluating the role of alcohol intake and long-term health are observational studies. Evaluation of the health effects of alcohol in such studies is challenging due to nonlinear dose–response associations, changes of intake due to health conditions, and the fact that most studies rely on self-reported intakes. Self-reported intakes are associated with measurement errors that may result in inaccurate intake estimations that could affect the interpretation of the results. For example, underreporting of alcohol consumption is common (3).

To overcome these problem, there is a need for objective markers of alcohol intake that can be easily assessed in large-scale studies and that can be used as complement to self-reported intakes to strengthen the analysis. Several indirect biomarkers of excessive alcohol intake have been used to indicate consumption (acute and chronic) as well as alcohol-induced organ damage. For example, γ-glutamyltransferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are markers traditionally linked with hazardous drinking. However, their utility as diagnostic tools for alcohol abuse or as ranking tools reflecting long-term, habitual alcohol consumption along the entire intake range from nondrinkers to vigorous drinkers is greatly hampered due to variable results in different populations and low sensitivity and specificity (4).

In recent years, several putative biochemical markers with considerable potential for more accurate reflection of alcohol use and abuse compared with the traditional markers have been suggested. These markers often represent degradation products or their adducts, including acetaldehyde, hemoglobin-bound acetaldehyde, and molecules derived from alcohol metabolism or synthesized in the presence of alcohol, such as fatty acid ethyl esters and phosphatidylethanol, respectively (4). They all have limitations with regard to the time window under which they reflect intake and the dose of alcohol needed to give an accurate readout. Moreover, for many of them, rapid and cheap analytical methods that allow fast and accurate determination at a low cost are lacking. As a result, large-scale observational studies using objective measures of alcohol intake are lacking.

In this issue of the Journal, van de Luitgaarden et al. (5) report an interesting and excellent study that evaluated for the first time the performance of ethyl glucuronide (EtG) as a marker for habitual alcohol consumption compared with self-reports and other biomarkers in the general population. EtG is a metabolite conjugate of ethanol formed in low amounts primarily in the liver through catalysis by UDP-glucuronosyltransferase. EtG has been used as a marker of recent alcohol intake due to a longer detection window than that for ethanol per se. EtG is present in blood for up to 36 h and in urine for 3–5 d with heavy consumption (4). EtG has proven useful for detecting drinking relapses in alcoholism treatment programs, but it has not previously been investigated as a biomarker of habitual alcohol intake in a large population study.

Van de Luitgaarden et al. (5) measured EtG concentrations in 24 urine samples from 6211 subjects in the Dutch Prevention of Renal and Vascular End-Stage Disease cohort that included men and women aged 28–74 y. Habitual alcohol consumption was assessed by questionnaire in the categories no/almost never, 1–4 units/mo, 2–7 units/wk, 1–3 units/d, and ≥43 units/d.

The large study size allowed the authors to provide estimates of the sensitivity, specificity, positive and negative predictive value, and proportions of agreement between reported consumption and EtG both for the entire cohort and across different intake strata as defined by different cutoff values (<100 ng/mL, ≥100 ng/mL, and, in a secondary analysis, 500 ng/mL). In accordance with previous studies, a cutoff value of ≥100 ng/mL was used to reflect intentional alcohol consumption; studies

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Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EtG, ethyl glucuronide; GGT, γ-glutamyltransferase; MCV, mean corpuscular volume.

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have shown positive results after <10 g/d, which corresponds to 1 typical serving of alcohol. The authors also compared EtG to indirect measures of alcohol exposure, including plasma HDL cholesterol concentration, erythrocyte mean corpuscular volume (MCV), AST, ALT, and GGT.

Van de Luitgaarden et al. (5) found that 52% of the study participants tested positive for intentional alcohol intake (EtG ≥100 ng/mL), and cross-tabulation with self-reported intakes showed that 92% of the participants who reported no alcohol intake also had <100 ng/mL EtG in their urine. Approximately 34% of the participants with self-reported alcohol intake had discordant EtG concentrations below cutoff. The sensitivity of EtG was modest at 66%. Importantly, but unfortunately, the sensitivity differed widely across the self-reported intakes, ranging from 30% to 93% across the 4 intake categories (1–4 units/mo, 2–7 units/wk, 1–3 units/d, and ≥4 units/d). The positive predictive value was 96%, and the negative predictive value was 47%. The authors found a clear positive association between reported alcohol intake and EtG in urine. They also found positive associations between EtG and plasma HDL cholesterol, MCV, and GGT biomarkers but not with plasma AST and ALT, independently of sex, age, or estimated glomerular filtration rate.

The modest sensitivity of EtG as a biomarker of habitual alcohol intake shown in van de Luitgaarden et al.'s (5) study is not surprising in light of the pharmacokinetics of EtG, showing a relatively short half-life (6). Among individuals with low intake (1–4 units/mo) and even those with moderate intake (2–7 units/wk), the misclassification is therefore expected to be large. This is problematic because it is for the low to moderate intakes in populations that the need for an accurate biomarker is most warranted. The use of repeated samplings may be one way to overcome fluctuations in the intake of alcohol over time and could therefore reduce misclassification. However, repeated 24-h urine samples are rarely available in prospective cohort studies, and the performance of the somewhat more prevalent, but still rare, repeated spot urine samples needs to be investigated.

Because there is no gold standard approach for measuring alcohol intake, van de Luitgaarden et al. (5) used self-reported data to assess the performance of the biomarker. This is currently the best option, but it calls for precaution when interpreting the estimated performance indicators of EtG as a biomarker of habitual alcohol consumption. Furthermore, the authors discussed the selection of the "right" cutoff value for intentional alcohol consumption and their use of 100 ng/mL in light of previous studies and because the use of 500 ng/mL as a cutoff did not alter their conclusions. A higher cutoff will exclude false-positive cases but will lead to lower sensitivity, especially in light to moderate drinkers, so use of a higher cutoff is not recommended given the already modest sensitivity at these intake ranges. Large, randomized controlled trials with controlled alcohol intake would be helpful not only to resolve the remaining controversies about the causal relation between moderate alcohol intake and health outcomes (2) but also to more accurately define the performance indicators of putative biomarkers of alcohol intake.

Van de Luitgaarden et al. (5) concluded that EtG can be used as a measure of habitual alcohol consumption at a group level in epidemiologic research and that the advantage of using an objective biomarker instead of a subjective approach for alcohol consumption is that it is not hampered by recall error or misclassification. Given the modest sensitivity at low to moderate intake, and because the biomarker in fact is likely to generate substantial misclassification at low to moderate intake, further studies in other populations are warranted before self-reported alcohol intake and EtG concentrations can be compared in relation to endpoints in cohort studies. Such studies could preferably be performed in populations in which repeated samples are available. Last, in addition to urine, EtG can also be detected in other body fluids, hair, and body tissues (7). Such matrices, whenever they are available, may have potential to more accurately reflect habitual alcohol consumption, even at low to moderate intakes, and should be further evaluated in larger observational study settings.

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