Letter to the Editor

Biomarkers for harmful alcohol use should be reliable, standardised, and traceable

Only the CDT reference method has been approved by JCTLM and IFCC

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On behalf of the IFCC Working Group CDT (December 2024)

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Dear Editor,

Harmful alcohol consumption is widespread and of major concern. Besides in medical diagnosis and treatment, measurement of overconsumption through biomarkers is often used in forensic and traffic medicine. Traceability and standardisation of biomarkers are required especially in this field, and this is briefly addressed.

None of the modern biomarkers for harmful alcohol use is standardised and traceable yet except carbohydrate-deficient transferrin (CDT). Recently the Joint Committee of Traceability in Laboratory Medicine (JCTLM) has approved the IFCC recognized HPLC reference method for CDT.

Keywords

Carbohydrate deficient transferrin, CDT, Standardisation, Traceability, AUD, Harmful alcohol use, Fitness to drive, DUI

Introduction

Harmful consumption, often called chronic abuse, of alcohol is a major cause of disability and death all over the world. Alcohol consumption resulted in an estimated worldwide 2.6 million deaths (4.7% of all deaths) and 115.9 million DALYs (4.6% of all DALYs) in 2019 [1]. The traditional blood biomarkers for detection and monitoring of excessive alcohol consumption and alcohol use disorder (AUD) include GGT, AST, ALT and MCV. They are still used for this purpose in many countries despite being unsensitive for early detection and also rather unspecific [2]. These biomarkers are called indirect because their increase is based on secondary effects of heavy drinking related to organ or cell damage. Direct biomarkers are products of ethanol metabolism and include PEth, EtG and EtS [3].

Another modern biomarker, carbohydrate-deficient transferrin (CDT), falls somewhat in between the direct and indirect alcohol biomarkers. CDT refers to the disialo glycoform of serum transferrin that is produced in increased levels, in response to prolonged heavy drinking, through action of the ethanol metabolite acetaldehyde [4]. CDT is especially suitable for detecting and monitoring of chronic harmful consumption, not for incidental drinking [5] CDT, which is probably the most studied alcohol biomarker in recent decades, is still relatively unknown and not used in many countries. Even when discussed or reviewed, statements about CDT are repeatedly based on incorrect information and outdated scientific literature [3] using no longer available methods, like a combination of anion exchange chromatography followed by RIA or turbidimetry [6]. The performance of CDT is clearly improved using modern HPLC or CE methods [5].

Alcohol biomarkers are used worldwide as objective measures in medical diagnosis, as well as in forensic tests after driving under influence (DUI) and in fitness-to-drive examinations [7,8]. Especially the latter use implies that the analytical methods used should be reliable, having a high diagnostic accuracy and being standardised and traceable to guarantee a fair judgement about a person's alcohol intake.

A comparison of the diagnostic performance of AUD biomarkers is rather complex and should include the specific time windows, increase and decay kinetics, well defined study populations, analytical and preanalytical interferences, among others [5]. A metrological comparison is preferentially based on ROC curves and a well-chosen study population [5]. In large comparative studies CDT was found favourable to the traditional markers [9,10]. PEth is more sensitive than CDT but depending on the population under study and the consumption level [11,12]. However, this present letter is not about analytical performance, but about the need for standardisation and traceability.

The benefits of standardisation of measurement procedures and having a reference measurement procedure (RMP) are generally acknowledged. To name a few advantages, the improved accuracy and precision of measurement will increase diagnostic accuracy [13]. Method standardisation and uniform cutoffs are also corner stones for developing regulatory guidelines, and important when comparing outcomes of scientific studies. Finally, having an RMP aids in development and improving routine measurement methods.

It is therefore stunning that standardisation of methods is either not discussed at all [14] or incorrectly mentioned even in recent reviews on alcohol biomarkers [3]. The traditional laboratory methods like GGT are standardised by using IFCC procedures [15] but as mentioned before, they lack sufficient specificity.

Although becoming more and more popular, none of the direct alcohol biomarkers like PEth are yet standardised making them vulnerable for dispute in court, especially since the cutoffs are not internationally established [16,17].

It is surprising that the successful IFCC CDT standardisation work [4] is not widely known and implemented. The basis for CDT standardisation was laid by studies performed by the IFCC WG-CDT [4,18,19] starting with a proper selection of the analyte and measurand [18]. Based on an extensive validation study according to ISO15193, an established HPLC method [20] was recognized by the IFCC as the RMP for CDT, to be used for standardisation of all CDT methods on the market [21]. We are now proud to announce that after extensive metrological examinations, the IFCC RMP for CDT was also formally recognized and listed as RMP under database identifier C14RMP1R early 2024 by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) [22]. This is the highest classification available for a reference method.

A distinction has to be made between non-standardised commercial methods and standardised commercial methods since standardisation has not yet been applied to all methods in several countries. Clearly stated, results are only metrologically standardised when measured by the RMP, or by commercial methods that are standardised against the RMP [23]. Standardised results should be expressed as CDT_{IFCC} with an upper level of reference of 1.7% and a cutoff of 2.0% [5,21].

CDT_{IFCC} is currently the only biomarker for alcohol consumption that has an RMP, recognized by both the IFCC and JCTLM, and a set of commercially available commutable reference materials. This means that standardisation is achieved [24]. A patient's CDT_{IFCC} result is traceable to the RMP as required by the JCTLM and the European IVDR 2017/746 regulation.

CDT is also the only FDA approved biomarker in its field and CDT measurement is relatively easy to perform with standard laboratory equipment like HPLC, capillary electrophoresis or immunochemistry / nephelometry.

Summarising, we emphasise the need for traceability and standardisation of biomarkers for harmful alcohol use particularly in forensic and traffic medicine. In addition, we point at the unique status of CDT amongst biomarkers for harmful alcohol use, in fulfilling these demands being JCTLM listed.

Declaration of Conflict of interests

The authors of this article declare that there is no conflict of interest with regard to the content of this manuscript.

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Authorship

All authors have made substantial contributions to all of the following:

The conception of this letter and the publication of underlying studies.

Drafting the article or revising it critically.

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