



## Increased carbohydrate deficient transferrin: Whisky or candy?

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# Increased carbohydrate deficient transferrin: Whisky or candy?



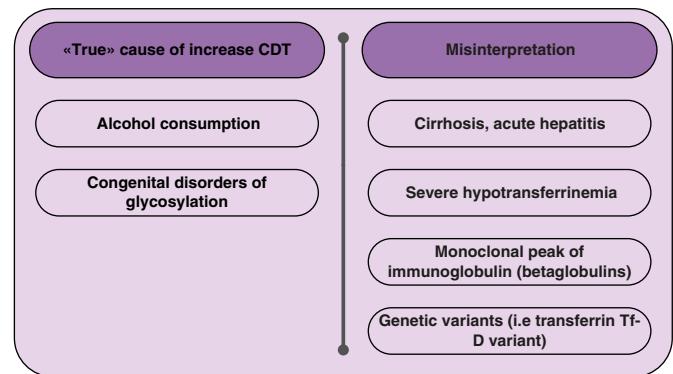
## To the Editor:

Carbohydrate deficient transferrin (CDT) is a serum biomarker specific for heavy alcohol consumption. This refers to glycoforms of transferrin characterized by a reduced degree of glycosylation. Excessive alcohol consumption increases these glycoforms.<sup>1</sup> Therefore, CDT is used as a surrogate marker of chronic alcohol consumption and in some countries for the renewal of driving licenses after being arrested for drink driving or for re-entry into high-risk occupations. While lower sensitivity of CDT in some conditions is well known, false positives are scarcely described.

A 33-year-old man was referred for increased CDT measured as part of occupational screening (train driver). He has no personal or family history and denies alcohol consumption for several months. There was no clinical sign of chronic liver disease. Repeat testing confirmed increased CDT (6.8%, N <1.7%) with normal hepatic tests. Further biochemical testing (western blot) for congenital disorders of glycosylation (CDG) revealed abnormal protein weight for transferrin, alpha-1 antitrypsin, haptoglobin, and orosomucoid, prompting a diagnosis of CDG or secondary CDG. An in-depth interview revealed pronounced digestive intolerance to sugar from early childhood, with strong aversion to candy and peculiar dietary habits. The dietary pattern was highly suggestive of hereditary fructose intolerance (HFI).

A 31-year-old patient was referred for persistently increased CDT. After losing his driving license for drink driving, CDT (2.6%) remained increased despite alcohol withdrawal for 8 months. Clinical examination found no sign of chronic liver disease. Liver tests and abdominal ultrasound were normal. History revealed that one sister also had unexplained increased CDT (4%) without alcohol consumption. Furthermore, the patient described digestive intolerance, for himself and for his two sisters, during early childhood when dietary diversification was initiated. He had no history of tooth decay and dislikes candy. Genetic testing confirmed the diagnosis of HFI in both patients by showing p.Ala150Pro homozygosity in the *ALDOB* gene.

Although CDT is a reliable marker of chronic alcohol misuse, many conditions impair its interpretation. Most of them are related to lower sensitivity like female sex, higher body mass index, and chronic liver disease. Increased CDT without alcohol consumption is less well described (Fig. 1). By altering glycosylation of proteins, CDG may lead to increased CDT.<sup>2</sup>



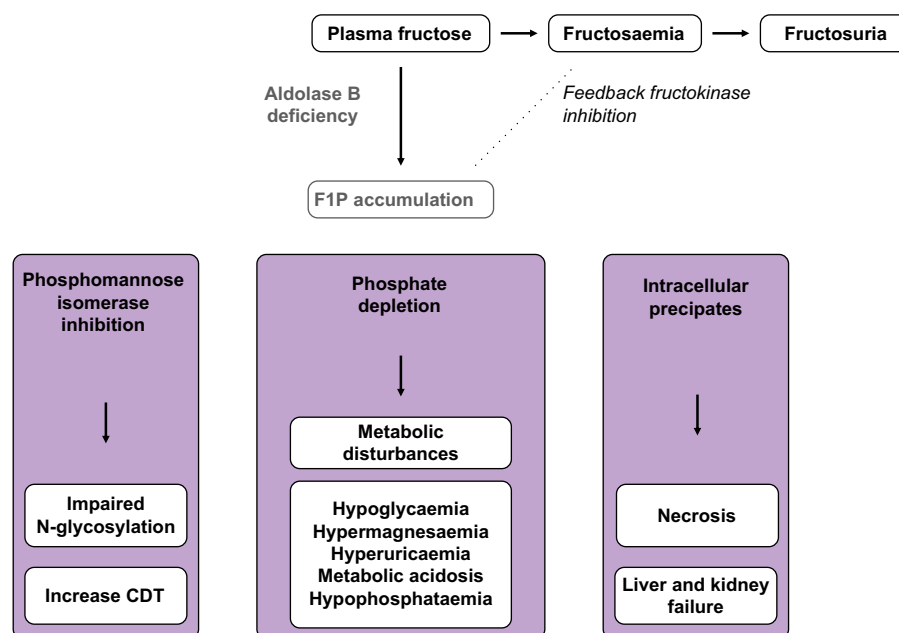
**Fig. 1. Comprehensive causes of CDT increase.** CDT, carbohydrate deficient transferrin.

HFI is a secondary CDG defined by reduced aldolase B activity due to *ALDOB* gene variants, the main enzyme of fructose metabolism.<sup>3,4</sup> It is usually diagnosed in early childhood, when foods containing fructose are introduced during weaning. Fructose uptake results in a rapid increase in fructose 1 phosphate, leading to the competitive inhibition of phosphomannose isomerase and thus altering N-glycosylation (Fig. 2).<sup>4</sup> The onset of symptoms (nausea, bloating and vomiting) and metabolic disorders (hypoglycaemia, hyperlactataemia, hypophosphataemia, hyperuricaemia, hypermagnesaemia) are strongly correlated with the introduction of fructose or sucrose to the diet.<sup>5</sup> Higher amounts of fructose may lead to acute lethargy, convulsions and/or progressive coma. However, due to variable penetrance, residual enzymatic activity, and “spontaneous” adoption of an appropriate diet by the children’s family, diagnosis may be overlooked.

Treatment is based on dietary restriction of fructose, sucrose and sorbitol. Although untreated HFI can induce long-term renal and hepatic impairment, adequate treatment before onset of organ failure grants normal quality of life and life expectancy. Increased CDT in HFI is well described in the paediatric literature, with CDT even being used to monitor compliance.<sup>6</sup>

This cause of altered transferrin glycosylation is not that uncommon and should be investigated when facing unexplained high CDT. Moreover, the strong aversion to candy and specific food intolerance makes it easy to screen for if adequately assessed along with alcohol consumption.

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**Fig. 2. Pathogenesis and metabolic changes in HFI.** CDT, carbohydrate deficient transferrin; F1P, fructose 1 phosphate; HFI, hereditary fructose intolerance.

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### Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

BG and EBJ wrote the manuscript, BG designed the figures. AB and SVB performed the genetic analysis of the patients. All authors provided critical comments and contributed to review the manuscript.

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2022.100494>.

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*Author names in bold designate shared co-first authorship*

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