Increased Carbohydrate Deficient Transferrin: Whisky or Candy ?

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All authors provided critical comments and contributed to review the manuscript.

Carbohydrate deficient transferrin (CDT) is a serum biomarker specific of heavy alcohol consumption. This refers to glycoforms of transferrin characterized by a reduced degree of glycosylation. Excessive alcohol consumption increases these glycoforms [1]. 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 drunk driving or in high-risk occupations. While lower sensitivity of CDT in some conditions is well known, false positives causes are scarcely described.

CASES REPORT:

A 33-year-old man was referred for increased CDT performed for 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 (Table 1). Further biochemical testing (western blot) for congenital disorders of glycosylation (CDG) revealed abnormal protein weight for transferrin, alpha1 anti trypsin, haptoglobin, and orosomucoid, prompting to diagnose CDG or secondary CDG. In depth interview revealed pronounced digestive intolerance to sugar from early childhood, with strong aversion to candy and peculiar diet habits. The diet 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 drunk driving, CDT (2.6%) remained increased despite alcohol withdrawal for eight 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.

DISCUSSION:

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 described (Table 1). Congenital disorders of glycosylation (CDG) by altering glycosylation of proteins may lead to increased CDT [2].

HFI is a secondary CDG defined by reduced aldolase B activity due to *ALDOB* gene variants, the main enzyme of fructose metabolism [3,4]. 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 (F1P), leading to the competitive inhibition of phosphomannose isomerase and thus alteration of N-glycosylation (Figure 1) [4]. The onset of symptoms (nausea, bloating and vomiting) and metabolic disorders (hypoglycaemia, hyperlactataemia, hypophosphataemia, hyperuricaemia, hypermagnesaemia) are strongly correlated with fructose or sucrose introduction in diet [5]. Higher amount 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 paediatric literature, with CDT even being used to monitor compliance [6].

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

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Figure 1. Pathogenesis and metabolic changes in HFI.

F1P : fructose 1 phosphate.

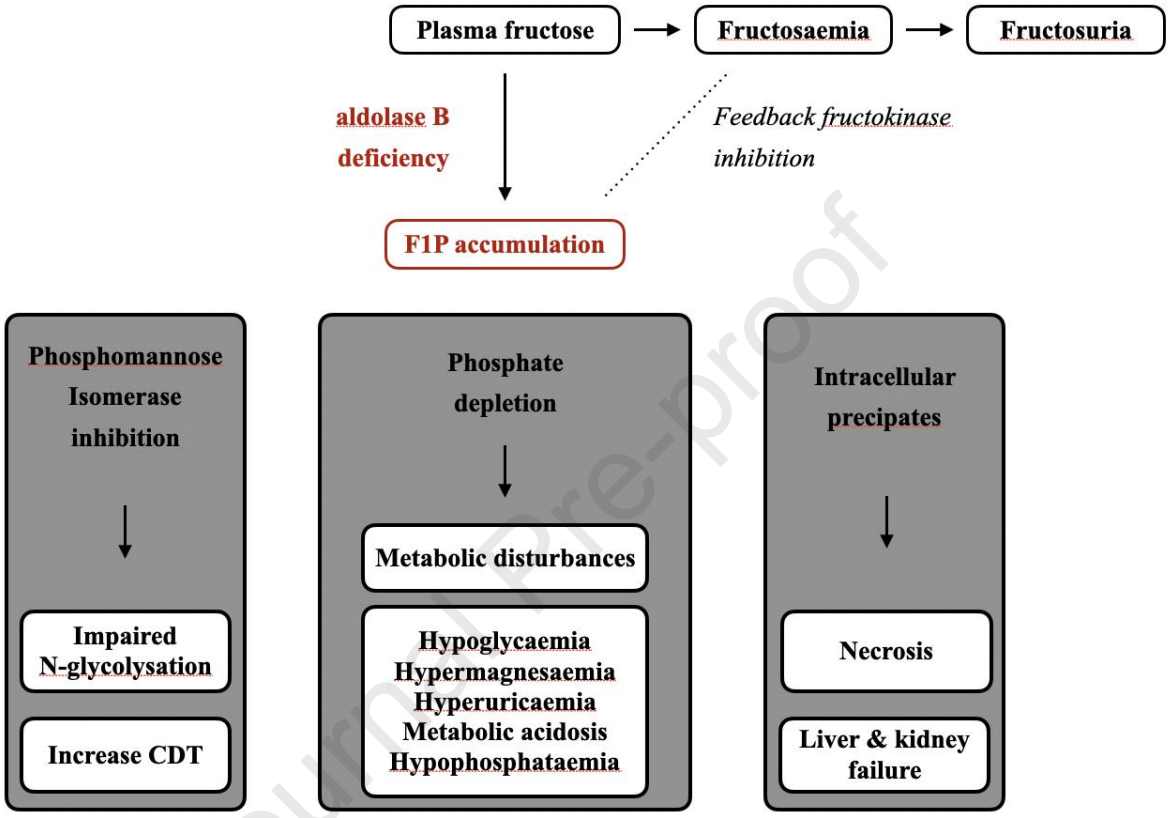
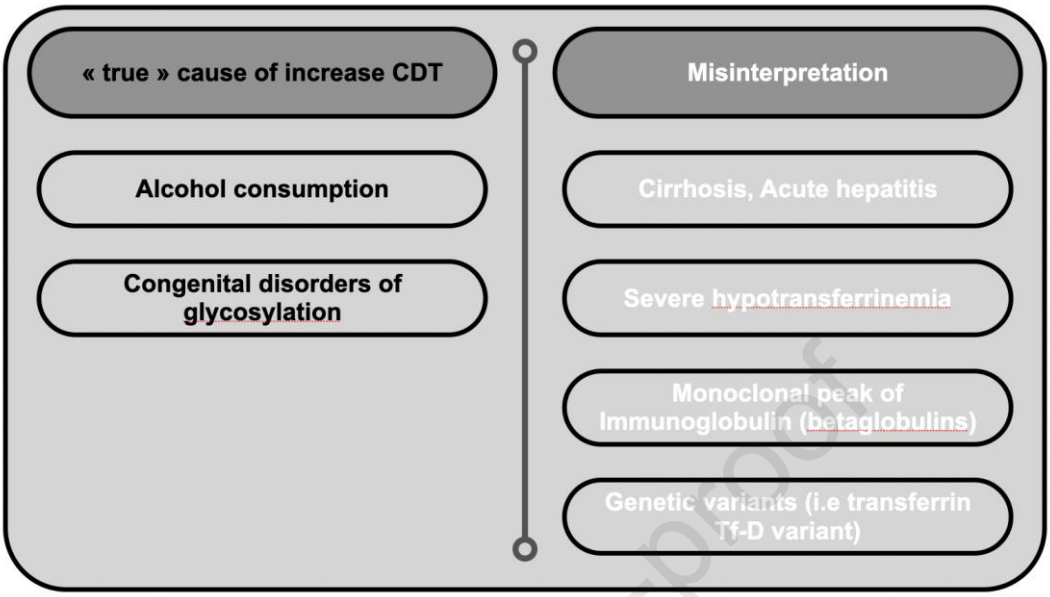


Table 1.



Comprehensive causes of CDT increase.