Carbohydrate Deficient Transferrin: How reliable is it as a Biomarker for Chronic Alcohol Consumption?

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ABSTRACT: Alcohol use disorders are a major cause of a number of health, economic and social challenges for individuals, their families and health care systems worldwide. The inadequate and inaccurate assessment of long-term drinking demeanors is a significant and substantial hindrance to its diagnosis and management. Biomarkers for chronic alcohol consumption are now well established as reliable diagnostic aids but their sensitivity and specificity still need to improve. Therefore, there is a definitive need for the development of more sensitive and specific markers of alcohol abuse and addiction. Biological markers of alcoholism are divided into two cohorts: conventional and circumstantial indices. Lineal markers are detected in some biological fluids including blood and urine. The other matrices encompassing hair, saliva and sweat are not yet internationally accepted and approved, despite some studies seems to be promising for some. Among the conventional biomarkers which are tested for alcohol misuse and abuse are ethanol, ethyl glucuronide and ethyl sulfate. The conventional biomarkers, directly detect the alcohol consumption, with variable degrees of sensitivity and reliability. The circumstantial markers including MCV, γ-GT, transaminase enzymes SGOT (AST) (Serum Glutamate Oxaloacetate Transaminase) & SGPT (ALT) (Serum Glutamate Pyruvate Transaminase) and carbohydrate-deficient transferrin. These biological markers are affected by heavy alcohol consumption for long periods. Objective: Our prime objective of this article is to review the available literature on CDT (Carbohydrate Deficient Transferrin) as a biomarker for chronic alcohol consumption and its role in diagnosing and monitoring alcohol use disorders. We also aim to enrich and add to the scientific debate and knowledge about the manifest reliability of this biomarker.

KEYWORDS: Alcohol use disorders, Biological markers, Laboratory findings, Alcoholism, Transferrin isoforms, CDT

INTRODUCTION

Alcohol use is popular and widespread around the globe. Alcoholism causes a myriad of medical and psychiatric syndromes and complications. For example, alcohol use is a major cause of road traffic accidents. The impact of alcohol abuse is reflected in the biological, psychological, and social domains of our lives. Therefore, there is pressing need for reliable, safe and specific markers for early detection of potential alcohol abuse and follow up of recovering patients. Laboratory testing of alcohol consumption can be of an added value in identifying alcohol ingestion. Yet, the conventional biomarkers, including transaminase enzymes SGOT (AST) (Serum Glutamate Oxaloacetate Transaminase) and SGPT (ALT) (Serum Glutamate Pyruvate Transaminase), Gamma-Glutamyl Transferase (GGT) and (MCV), have mutable and finite sensitivity and specificity.

Discovered in 1976, Carbohydrate-Deficient Transferrin (CDT) was introduced to detect heavy and long-term alcohol abuse. CDT refers to the less sialylated forms of human transferrin: Asialo- and disialo-transferrin (Kent E Vrana et al.-March 25, 2011). It is presumed that alcohol intake of ≥ 50-80 g/day for a period of at least two weeks augments the increase of CDT concentrations. Despite the fact that mechanism of CDT increase still remains poorly understood, a large number of studies suggest and manifest that CDT is a good biomarker for the diagnosis of heavy alcohol consumption, with higher sensitivity and specificity than any of
the other traditional markers. CDT has become a focal point for alcohol abuse research and clinical studies, besides forensic and judicial applications (Peterson, K.-2005, Steven Kipnis-2006).

The novel advances in proteomic technologies have immensely boosted the potential for alcohol abuse biomarker discovery. Quantification of Carbohydrate Deficient Transferrin (CDT) by capillary electrophoresis is used for screening patient serum samples to detect chronic alcohol abuse. Serum transferrin isoforms are separated into five major fractions according to their sialylation level. The human transferrin consists of several isoforms. Each isoform has a different mobility according to its sialic acid content (Isoelectric point between 5.2 and 5.9). The tetrasialo transferrin is the prevalent isoform and represents about 70 to 80% of total transferrin content. Other isoforms that can be revealed are 6-sialo Tf, 5-sialo Tf, 3-sialo Tf, 2-sialo Tf and occasionally 0-sialo Tf. When analysing serum from an alcohol abuser one can find an increase in 2-sialo-Tf and 0-sialo Tf will progressively manifest (Figures 1-4 and Table 1).

**METHODOLOGY**

Literature search and was conducted on the databases of PubMed, Medline and Embase for all articles published using the key words CDT test & chronic alcohol use. A total, of 907 articles, were found, search date 22/02/2018. For the brief description of the different methodologies generally used for detection and quantification of CDT, several laboratory manuals and standard operation procedures were reviewed.

**Carbohydrate Deficient Transferrin**

Transferrin is a carbohydrate-protein that relates and carries Fe ions through the blood. In healthy normal individuals, transferrin has specific sialic acid arrangement through its molecule. The sialic acid component of CDT might range from four to six per molecule. The unique structure of transferrin is disrupted as a result of alcohol consumption due to the impediment of sialic acids bonding to Transferrin, which leads to the presence of inadequate amount of sialic acid in blood and consequently carbohydrate deficient transferrin. Transferrin result is reported as % of total transferrin. A result that exceeds 5%, suggests heavy drinking. The FDA ratified this test in 2001. Prolonged alcohol consumption for two weeks or more will increase the rate of formation of CDT in blood, resulting in a higher percentage value raised CDT blood levels return to normal within fourteen to thirty days after the first day of ceasing intense alcohol intake (SAMSHA).

The levels of CDT in females are always higher than in males, regardless of the any aspect (Allen 2000). Misleading false positive results for CDT testing are seen in many cases and diseases, including, Obstructive liver disease, Post hepatic obstruction, Hepatitis, Liver cirrhosis, Liver Carcinoma, Cardiac insufficiency, Mononucleosis, Renal transplant, Hyperthyroidism, Myotonic dystrophy, Diabetes mellitus, Pancreatitis, Cystic Fibrosis, Low Ferritin, primary biliary cirrhosis, combined kidney and pancreatic transplant, CDG (Carbohydrate Deficient Glycoprotein), congenital glycoprotein metabolism flaw and hereditary variants of transferrin. False negative CDT test result is sometimes seen in females, where further studies are needed to explain the relation of gender to the sensitivity of the test.

The induction or inhibition of sialyl transferase and plasma sialidase may be implicated in the rise of CDT level. Transposition of protein transport during post-translational modification could be a primary mechanism in the decadence of protein metabolism connected with chronic alcohol abuse. Hormonal variations affect sensitivity of CDT. Iron homeostasis and stable equilibrium is
Figure 2: Normal CDT patient result test done on SEBIA Capillary 2 Equipment, by capillary electrophoresis method. Laboratory at the National Rehabilitation Center, Abu Dhabi, United Arab Emirates, 2018

Figure 3: Pathological CDT patient result test done on SEBIA Capillary 2 Equipment, by capillary electrophoresis method. Laboratory at the National Rehabilitation Center, Abu Dhabi, United Arab Emirates, 2018

Figure 4: Abuse check on alcohol abuse test comparison chart
Table 1. Isoelectric point for human transferrin isomers

<table>
<thead>
<tr>
<th>Transferrin Isoform</th>
<th>pI (Isoelectric Point)</th>
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<tbody>
<tr>
<td>0-sialo Transferrin</td>
<td>pH=5.9</td>
</tr>
<tr>
<td>Hexasialo Transferrin</td>
<td>++ + + +</td>
</tr>
<tr>
<td>Pentasialo Transferrin</td>
<td>pH=5.2</td>
</tr>
<tr>
<td>Tetrasialo Transferrin</td>
<td>pH=5.4</td>
</tr>
<tr>
<td>Trisialo Transferrin</td>
<td>pH=5.6</td>
</tr>
<tr>
<td>2-sialo Transferrin</td>
<td>pH=5.7</td>
</tr>
<tr>
<td>Monosialo Transferrin</td>
<td>pH=5.8</td>
</tr>
</tbody>
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Table 2. The assessment of alcohol use utilizing biomarkers

<table>
<thead>
<tr>
<th>Alcohol Concentration (mg%)</th>
<th>Clinical Manifestations</th>
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<tbody>
<tr>
<td>20-99</td>
<td>Loss of muscular coordination</td>
</tr>
<tr>
<td>100-199</td>
<td>Neurological impairment, ataxia, prolonged reaction time, mental impairment, incoordination</td>
</tr>
<tr>
<td>200-299</td>
<td>Nausea, vomiting, ataxia</td>
</tr>
<tr>
<td>300-399</td>
<td>Hypothermia, dysarthria, amnesia, stupor</td>
</tr>
<tr>
<td>400- &gt;</td>
<td>Coma</td>
</tr>
</tbody>
</table>


http://www.nida.nih.gov/about/welcome/MessageBathSalts211.html.


Substance Abuse and Mental Health Services Administration (SAMHSA) https://www.samhsa.gov/


