Medical sciences / Sciences médicales

Fructose-induced increase in ethanol metabolism and the risk of Syndrome X in man

Ugochukwu E. Uzuegbu, Innocent Onyesom *

Department of Medical Biochemistry, Delta State University, Abraka, Nigeria

Abstract

Syndrome X is biochemically characterized by impaired glucose tolerance, hypertriacylglycerolemia, altered HDL-cholesterol content and high blood pressure. In different isolated studies, alcohol and fructose have been observed to increase the risk of Syndrome X. However, several reports have recognized the potential of fructose in stimulating the elimination of alcohol from the bloodstream, but the effects of such an anti-intoxicating property of fructose on the biochemical features of Syndrome X have remained scarce. Thus, in this study, oral fructose was used to increase the metabolism of alcohol and the associated changes in blood glucose, triacylglycerol, lipoprotein cholesterol and blood pressure were measured and used to classify subjects into the Syndrome X risk category. One gram of fructose/kg body weight was used to 'treat' the intoxication caused by 1.0 g (20%) ethanol/kg body weight administered to forty-five consenting male subjects in apparently good health. The subjects were light alcohol drinkers (<20 g/day) between the ages of 25 and 35 years. Results show that the administered dose of fructose significantly ($P < 0.05$) reduced the duration of alcohol intoxication by 30.7%, and accelerated the elimination (metabolism) of alcohol from bloodstream by 44.7% ($P < 0.05$). However, ethanol + fructose, increased the number of subjects with impaired glucose and triacylglycerol (TAG) levels to 13 (29%) and 43 (96%) from 8 (18%) and 37 (82%) induced by the ethanol dose alone. The TAG number is the summation of those with borderline high and high concentrations. Oral fructose-induced stimulation of alcohol oxidation from bloodstream also has the potential of increasing the risk of Syndrome X. Ways of curbing the metabolic syndrome associated with oral fructose should be explored, if its anti-intoxicating property and use is to be recognized and promoted. ***To cite this article: U.E. Uzuegbu, I. Onyesom, C. R. Biologies 332 (2009).***

© 2009 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

Keywords: Triacylglycerol; Glucose; Syndrome X; Ethanol

1. Introduction

Syndrome X, also known as insulin resistance, is a metabolic syndrome, biochemically characterized by impaired glucose tolerance, hypertriacylglyc- erolemia, altered HDL-cholesterol and high blood pressure [1]. Insulin resistance has been linked to the macronutrient content in the diet, and in the past, diets high in saturated fats [2] and fructose [3] have been shown to induce insulin resistance. In addition, alcohol consumption has been reported to induce the metabolic features of Syndrome X in isolated studies [4–6].

* Corresponding author.
  E-mail address: onyesominno@yahoo.co.uk (I. Onyesom).

However, oral fructose has been demonstrated to stimulate the elimination of alcohol from the bloodstream [7,8].

However, information on the effects of such a stimulation on the biochemical features of Syndrome X among Nigerians has remained scarce. In this study, oral fructose was used to activate the removal of alcohol from the bloodstream and changes in serum glucose, serum triacylglycerol and blood pressure – the biochemical features of Syndrome X, were then monitored by standard analytical procedures and used to determine the risk of Syndrome X among the subjects.

2. Materials and methods

Subjects: Forty-five consenting, light drinkers (<20 g ethanol/day) in apparent good health were selected after interview. The mean $\pm$SD body weight and age of the subjects were 72 ± 7 kg (range: 65–80 kg) and 30 ± 5 years (range: 25–35 years). The subjects were all males from Delta State, Nigeria. They did not smoke cigarettes, and had no medical history of alcohol and/or drug abuse.

Methods: The volunteers were gathered in a research laboratory after about 2 hours of having eaten same type of light lunch at midday. Details of what they ate were noted, to allow duplication on later occasions. The timing of the lunch is important since the condition of the stomach, full or empty [9,10] and the time of the day, morning, afternoon or evening [11] have been reported to affect alcohol absorption, distribution and bioavailability. Only males were used because the changing hormones and their plasma levels that characterize the menstrual cycle have been observed to alter the elimination of alcohol from bloodstream of females [8,12]. This alteration may likely cause alcohol oxidokinetic data and the elimination pattern to be inconsistent among females.

The participants were then weighed and separated into three (control, ethanol, and ethanol + fructose) groups. The control subjects were given 1.0 g fruit juice/kg body weight, and the ethanol group received 1.0 g ethanol/kg body weight after diluting to 20% with fruit juice. The ethanol + fructose group drank the same amount of ethanol, but in addition, they took 1.0 g fructose/kg body weight dissolved in water, after 20 min of administering the ethanol single dose. The subjects were asked to consume the juice or ethanol, as the case may be, within 10 min. The alcohol dosing regimen was based on the experience of earlier reports [7]. The participants in each group were then rotated round the other remaining two tests every fortnight, so that each volunteer completed the three tests. This cross-over design is important in order to minimize any intra individual factor that may likely influence the result outcome of a particular group.

Collection of blood samples: Blood alcohol level (BAL) was determined [13] every 30 min post alcohol consumption time for 5 h using 0.5 ml of whole blood obtained from a cannula fixed to a vein in the forearm.

Blood alcohol-time curve for each subject was plotted on a graph of BAL (%) against post alcohol consumption time (h). The mean alcohol oxidokinetic parameters (peak blood alcohol level [BAL], time taken to attain peak BAL, time taken to attain zero BAL, and blood ethanol elimination rate – BEER) were then determined from individual curves and recorded. The oxidokinetic data arising from individual records were pooled and mean $\pm$ SD value was obtained and presented.

Serum glucose and triacylglycerol (TAG) were determined by the glucose oxidase method [14] and end-point colorimetric method [15] respectively, using serum samples collected at 0 and 15 h post alcohol consumption time. Blood pressure (BP) was measured *parri pasu* using digital aneroid sphygmomanometer (ACCOSSON MERCURY, CE 0120) as previously described [16]. The serum glucose, TAG and BP values obtained were then used to classify individual subject into risk categories as recommended. Based on fasting glucose levels, subjects were classified as having normal glucose (<100 mg/dL) or impaired fasting glucose (100–125 mg/dL) [17]. Triacylglycerol levels were categorized as normal (<150 mg/dL); borderline high (150–199 mg/dL); or high ($\geqslant200$ mg/dL) [18]. Blood pressure was classified according to current guidelines [19] as normal (systolic <120 and diastolic <80 mmHg), prehypertension (systolic 120–139 or diastolic 80–89 mmHg), and stage I hypertension (systolic 140–145 or diastolic 90–99 mmHg). When systolic and diastolic pressures fell into different categories, the higher category was selected for classification.

Statistics: Student t-test was used to compare the alcohol oxidokinetic values obtained by ethanol alone with that obtained by ethanol + fructose consumption. Significant difference was established at $P < 0.05$.

3. Results

The results obtained from the investigation are shown in Tables 1 and 2. Table 1 is the records obtained from the measurements of blood alcohol parameters, and Table 2 indicates the classification of subjects into risk categories based on experimentally derived data.

Table 1

Records of the blood alcohol parameters.

Blood alcohol parameter	Ethanol	Ethanol + fructose	%Difference
Peak blood alcohol level, BAL (mM)	20.6 ± 0.8	15.8 ± 0.7	-23.3[a]
Time to attain peak BAL (min)	49.3 ± 11.5	38.2 ± 9.2	-22.5
Time to reach zero BAL (min)	583 ± 46	403 ± 51	-30.7[a]
Blood ethanol elimination rate, BEER (mg/kg/h)	103 ± 8	149 ± 18	44.7[a]

[a] $P < 0.05$. Values are expressed as Mean $\pm$ SD of $n = 45$ subjects.

Table 2

Classification of subjects into risk categories based on experimentally derived data.

Postconsumption time (h)	Control		Ethanol		Ethanol + Fructose	
	0	15	0	15	0	15
Glucose						
Normal	45(100)	45(100)	45(100)	37(82)	45(100)	32(71)[a]
Impaired (increased)	–	–		8(18)	–	13(29)[a]
Triacylglycerol (TAG)						
Normal	45(100)	45(100)	45(100)	8(18)	45(100)	2(4)[a]
Borderline high	–	–		22(49)	–	35(78)[a]
High	–	–		15(33)	–	8(18)[a]
Blood pressure						
Normal	45(100)	45(100)	45(100)	26(58)	45(100)	32(71)[a]
Prehypertension	–	–		16(35)	–	11(25)[a]
Hypertension stage 1	–	–		3(7)	–	2(4)
Hypertension stage 2	–	–		–	–	–

Values in parenthesis are percentage expressions for the subjects' distribution. Control: 1.0 g fruit juice/kg; Ethanol: 1.0 g (20%) ethanol/kg; and Ethanol + Fructose: 1.0 g (20%) ethanol + 1.0 g fructose/kg. Basal (0 h) values for fasting glucose and TAG obtained from the participants are 84 ± 7 mg/dL and 102 ± 1 mg/dL, respectively.

[a] Significantly different when compared with the effect of ethanol alone ($P < 0.05$).

Table 1 shows that oral fructose at a dose of 1 g/kg significantly ($P < 0.05$) reduced the total duration of intoxication, that is, the time taken to reach zero BAL by 30.7%. BEER was increased ($P < 0.05$) by 44.7% in the presence of fructose. Fructose administration, also significant ($P < 0.05$) reduced the peak BAL by 23.3%. Fructose possibly shortens the intoxication time by probably reducing the level of alcohol in blood and facilitating its removal from bloodstream.

It can be observed from Table 2 that ethanol (1.0 g [20%]/kg) consumption impaired (increased) glucose levels in about 18% of the subjects after about 15 h of consumption. The dose also increased serum triacylglycerol (TAG) to borderline high and high in 49% and 33% of the subjects, respectively. Ethanol + fructose co-administration (1.0 g [20%] ethanol + 1.0 g fructose/kg) impaired serum glucose in 29% of the subjects. The co-administration impaired serum TAG in 96% (borderline high: 78% and high: 18%) of the participants 35% and 7% of the subjects became prehypertensive and hypertensive (stage 1) following ethanol consumption but ethanol + fructose altered these values to 25% and 4%. Apart from blood pressure, ethanol + fructose

co-administration further increased the percentages induced by ethanol alone.

4. Discussion

This study further verifies that oral fructose at a dose of 1.0 g/kg body wt when used to 'treat' alcohol intoxication (as judged by the peak blood alcohol level attained [7,9]) induced by 1.0 g ethanol/kg body wt is capable of enhancing the elimination of alcohol from the bloodstream by 44.7% in normal male individuals in apparent good health. The ability of fructose to enhance ethanol elimination from the blood stream was first recognized by Stuhlfauth and Neumaier [20], and since then, several studies [7,8,21] have confirmed the original observation. This observation may be due to the diversion in the metabolism of fructose when alcohol is present. It has been demonstrated that fructose metabolism in the liver generates NAD^+ which facilitates alcohol oxidation [22].

In addition, ethanol and fructose co-administration further increased the number of subjects who had impaired serum glucose and TAG levels. This indicates

that the metabolism of fructose especially in the presence of ethanol exacerbates the biochemical features of Syndrome X. The use of fructose to 'treat' alcohol intoxication may increase the risk of developing Syndrome X.

The basis for this observed increase in risk may be because fructose, unlike glucose, does not stimulate insulin secretion from the pancreatic β-cells [23], and this has been shown to reduce the activity of insulin in regulating energy homeostasis [24]. Energy imbalance, remotely induced by fructose has been reported to cause insulin resistance and glucose intolerance [25]. The inability of fructose to stimulate insulin is likely due to the low concentration of fructose transporter – GLUT-5 in β-cells [23]. Compromised GLUT-5 abundance and activity has been observed to cause marked insulin resistance [26], and this implies a possible role of GLUT-5 receptors in the pathology of the metabolic syndrome.

Insulin is also known to regulate lipid synthesis and secretion, and controls hepatic sterol regulatory element binding protein (SREBP) expression which is the transcription factor responsible for regulating fatty acid biosynthesis [27]. Fructose consumption causes an increase in circulating non-esterified fatty acids (NEFA), and this has been shown to reduce insulin sensitivity [28]. Increased NEFA in the liver also leads to alterations in β-cell function [29]. If NEFA are not removed from tissues, there is increased energy and free fatty acid (FFA) flux that leads to increased secretion of triacylglycerol (TAG). Feeding rats fructose stimulated fatty acid synthesis and created a 56% increase in TAG secretion rate and an 86% increase in plasma TAG, and in their control – glucose fed rats. Kazumi et al. [30] observed that glucose did not affect induction of fatty acid synthesis, nor did it stimulate TAG production and its removal. Hallfrisch, et al. [31] have demonstrated that in humans, TAG concentration increases as the amount of fructose taken also increased. Insulin resistance has also been correlated with intracellular TAG stores, which are involved in lipotoxicity and β-cell failure [32]. Because insulin resistance and reduced insulin binding have been reported in hypertriacylglycerolemic patients, these may be part of the mechanisms by which fructose diets promote insulin resistance.

However, there is growing evidence that the insulin resistance state which develops upon fructose feeding may also be associated with hepatic VLDL secretion, and this secretion has been shown to cause less protection to lipid peroxidation [33].

The outcome of this study shows that fructose used to 'treat' alcohol intoxication also has the potential of inducing insulin resistance as evidenced by the changes in serum glucose and TAG. Development of Syndrome X may be a side effect of fructose therapy in the management of alcohol intoxication and associated disorders. Therefore, if fructose must be promoted as a sobering agent, ways of eliminating the metabolic side effects should be explored.

References

[1] H. Basciano, L. Federico, K. Adeli, Fructose, insulin resistance, and metabolic dyslipidemia, Nutr. Metab. 2 (2005) 5–19.

[2] H. Mehnert, Sugar substitutes in the diabetic diet, Int. Z. Vitam. Ernhrungsforsch. Beih. 15 (1976) 295–324.

[3] M.C. Moore, A.D. Cherrington, S.L. Mann, S.N. Davis, Acute fructose administration decreases the glycemic response to an oral glucose tolerance test in normal adults, J. Clin. Endocrinol. Metabl. 85 (2000) 4515–4519.

[4] A.A.-B. Badawy, A review of the effect of alcohol on carbohydrate metabolism, Brit. J. Alcohol. Alcoholism. 12 (1977) 120–136.

[5] A.M. Hodge, G.K. Dowse, V.R. Collins, P.Z. Zimmet, Abnormal glucose tolerance and alcohol consumption in three population at high risk of non-insulin dependent diabetes mellitus, Am. J. Epidemiol. 137 (1993) 178–198.

[6] V. Rakic, I.B. Puddey, V. Burke, S.B. Dimitt, L.J. Berlin, Influence of pattern of alcohol intake on blood pressure in regular drinkers: a controlled trial, J. Hypertens. 16 (2) (1998) 165–174.

[7] P.A.M. Berman, I. Baumgarten, D.L. Viljoen, Effect of oral fructose on ethanol elimination from the bloodstream, South Afr. J. Sci. 99 (Jan/Feb) (2003) 47–50.

[8] I. Onyesom, E.O. Anosike, Oral fructose-induced changes in blood ethanol oxidokinetic data among healthy Nigerians, Southeast Asian J. Trop. Med. Publ. Health 35 (2) (2004) 476–480.

[9] A.W. Jones, K.A. Jonsson, Food-induced lowering of blood ethanol profiles and increased rate of elimination immediately after meal, J. Forensic Sci. 39 (4) (1994) 1084–1093.

[10] J. Rogers, J. Smith, G.A. Starmer, J.B. Whitfield, Differing effects of carbohydrates, fat and protein on the rate of ethanol metabolism, Alcohol Alcoholism 22 (1987) 343–353.

[11] T.J. Peters, V.R. Preedy, Metabolic consequences of alcohol ingestion, Novartis Found. Symp. 216 (1998) 19–24.

[12] B.M. Jones, M.K. Jones, Alcohol effects in women during the menstrual cycle, Ann. NY Acad. Sci. 273 (1976) 576–587.

[13] T.H. Busher, H. Redetzki, Enzyme determination of blood alcohol, Klin. Wochensch. 29 (1951) 615–616.

[14] P. Trinder, Quantitative determination of triglycerides using GPO-PAP method, Ann. Clin. Biochem. 6 (1969) 24–27.

[15] R.L. Searcy, Diagnostic Biochemistry, McGraw-Hill, New York, 1961.

[16] L.B. Moreira, F.D. Fuchs, R.S. Moraes, M. Bredemeier, B. Duncan, Alcohol intake and blood pressure: the importance of time elapsed since last drink, J. Hypertens. 16 (2) (1998) 175–180.

[17] American Diabetic Association, ADA: Diagnosis and classification of diabetes mellitus, Diabetes Care 27 (2004) S5–10.

[18] National Cholesterol Education Programme, NCEP, Executive summary of the third report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA 285 (2001) 2486–2497.

[19] A.V. Chobanian, G.L. Bakris, H.R. Black, et al., The seventh report of the Joint National Committee on Prevention, Detection,

Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report, JAMA 289 (2003) 2560–2571.

[20] K. Stuhlfauth, H. Neumaier, Die Wirkung der Laevulose auf Alcoholintoxikationen, Med. Klin. 49 (1951) 591.

[21] D. Mascord, J. Smith, G.A. Starmer, J.B. Whitfield, Effects of increasing the rate of alcohol metabolism on plasma acetate concentration, Alcohol Alcoholism 27 (1992) 25–28.

[22] R. Scholz, H. Nohl, Mechanism of the stimulatory effect of fructose on ethanol oxidation in perfused rat liver, Eur. J. Biochem. 63 (1976) 449–458.

[23] A.M. Grant, M.R. Christie, S.J. Ashcroft, Insulin release from human pancreatic islets *in vitro*, Diabetologia 19 (1980) 114–117.

[24] D.L. Curry, Effects of mannose and fructose on the synthesis and secretion of insulin, Pancreas. 4 (1989) 2–9.

[25] P.A. Mayes, Intermediary metabolism of fructose, Am. J. Clin. Nutr. 58 (1993) 7545–7655.

[26] G.J. Litherland, E. Hajduch, G.W. Gould, H.S. Hundal, Fructose transport and metabolism in adipose tissue of Zucker rats: diminished GLUT 5 activity during obesity and insulin resistance, Mol. Cell. Biochem. 261 (2004) 23–33.

[27] M.K. Bennett, J.M. Lopex, H.B. Sanchez, T.F. Qsborne, Sterol regulation of fatty acid synthase promoter. Coordinate feedback regulation of two major lipid pathways, J. Biol. Chem. 270 (1995) 25578–25583.

[28] S. Reiser, J. Hallfrisch, Insulin sensitivity and adipose tissue weight of rats fed starch or sucrose diets *ad libitum* or in meals, J. Nutr. 107 (1977) 147–155.

[29] A.W. Thorburn, L.H. Storlien, A.B. Jenkins, S. Khouri, E.W. Kraegen, Fructose-induced *in vivo* insulin resistance and elevated plasma triglyceride levels in rat, Am. J. Clin. Nutr. 49 (1989) 1155–1163.

[30] T. Kazumi, H. Odaka, T. Hozumi, Y. Ishida, N. Amano, G. Yoshino, Effects of dietary fructose or glucose on triglyceride production and lipogenic enzyme activities in the liver of Wistar fatty rats, an animal model of NIDDM, Endocr. J. 44 (1997) 239–245.

[31] J. Hallfrisch, S. Reiser, E.S. Prather, Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose, Am. J. Clin. Nutr. 37 (1983) 740–748.

[32] O. Ziegler, D. Quilliot, B. Guerci, P. Drouin, Macronutirents, fat mass, fatty acid flux and insulin sensitivity, Diabetes Metab. 27 (2001) 261–270.

[33] T. Noguchi, T. Tanaka, Insulin resistance in obesity and its molecular control, Obes Res. 3 (Suppl 2) (1995) 1955–1985.