PROLONGED ORAL GLUCOSE TOLERANCE TEST IN NON-DIABETIC PATIENTS WITH ETHANOL POISONING

L.Sorodoc[1], C. Lionte[1], V. Sorodoc[1], O.R.Petriș[2], C. Badiu[3]

[1] Department of Internal Medicine, [2] Department of Nursing,"Gr.T.Popa" University of Medicine and Pharmacy Iași, Medical Clinic, "Sf.Ioan" Emergency Clinic Hospital Iași, [3]"C.I Parhon" Institute of Endocrinology, Bucharest, Romania

Abstract

Background. Alcohol ingestion can induce either a hypoglycemia or a hyperglycemia, in patients with acute and chronic ethanol poisoning, unknown with diabetes mellitus.

Aim. The aim of this study was to evaluate whether 5 hours prolonged oral glucose tolerance test (5h-OGTT) is useful in evaluating the abnormalities of glucose metabolism in acute and chronic ethanol poisoning, in comparison with standard methods (fasting blood glucose - FBG, and/or 2h-OGTT).

Methods. 497 consecutive patients were enrolled in a 34 months cross sectional study. In all cases, glucose tolerance was assessed by a 75-g oral glucose tolerance, OGTT 2 hours, prolonged to 5 hours. The relationship between clinical and biochemical variables of ethanol poisoning (liver status, lipid profile, metabolic syndrome) and glucose tolerance was investigated. Risk factors for hypoglycemia in ethanol poisoning were identified.

Results. 349 subjects presented acute ethanol poisoning, and 148 subjects had chronic ethanol poisoning. 254 patients (51.10%) had documented alcoholic liver disease (ALD - clinical, biochemical and imagistic criteria). Glucose metabolism abnormalities were recorded in 143 subjects with chronic ethanol poisoning and ALD (96.63%), and in 207 cases with acute alcohol poisoning (59.31%). 371 patients (74.65%) showed normal FBG, diabetes mellitus (DM) was diagnosed in 54 subjects (10.86%), impaired glucose tolerance (IGT) in 43 subjects (8.65%), delayed hypoglycemia in 172 subjects (34.60%) and normal glucose tolerance (NGT) in 147 subjects (29.57%) using OGTT and ADA diagnosis criteria. Hypoglycemia was recorded in more than two thirds of acutely poisoned patients, when alcohol level was 0.5-1.5 g/L. Impaired glucose tolerance (IGT) were recorded in half of patients with blood ethanol levels > 2.5 g/L.

Conclusions. OGTT 2 hours and OGTT 5 hours revealed the same number of patients with diabetes mellitus. Frequent co morbidities in patients with ethanol poisoning influence the prolonged OGTT and revealed .especially delayed hypoglycemia, and IGT, as an indicator of alcoholic liver disease (ALD).

Key words: ethanol, glucose metabolism, OGTT.

*Correspondence to: Laurentiu Sorodoc, MD, "Sf. Ioan" Emergency Hospital, 2 Gen Berthelot 700483, Iasi, Romania, Phone: +40722776247, fax: +40232216518, E-mail: laurentiusorodoc@yahoo.com

Acta Endocrinologica (Buc), vol. V, no. 1, p. 61-73, 2009

INTRODUCTION

Ethanol is the most widely used recreational drug in western industrialized countries. There is a large body of medical literature examining the effect of alcohol on carbohydrate metabolism in healthy, nondiabetic individuals, as well as in diabetics (1-3). Alcohol ingestion can induce either a hyperglycemia, or a hypoglycemia. The hyperglycemiant effect appears when there are enough quantities of glycogen in the liver and is directly related with the amount of alcohol ingested (4). Alcohol may improve insulin sensitivity when consumed in small amounts. At higher levels of intake, alcohol may interfere with insulin mediated glucose disposal, causing insulin resistance (5). Alcohol consumption, which has a large prevalence in general population, represents one of the most frequent causes of hypoglycemia. This can occur not only in chronic alcoholics, but also in occasional consumers (4). Alcohol dehydrogenase and aldehyde dehydrogenase metabolize alcohol to acetaldehyde and subsequently to acetic acid in the mitochondria. This process leads to the reduction of nicotinamide adenine dinucleotide ($NAD^{+)}$ to NADH, with resulting increase in the ratio of NADH/ NAD+, which supports a possible mechanism for the inhibition of hepatic gluconeogenesis (HGN) and corroborates the occurrence of alcohol-induced hypoglycemia, especially in malnourished individuals where renal and hepatic glycogen stores are compromised (6). Retrospective studies of acute hypoglycemia in adults requiring hospital admission identified prevalence of alcohol induced - hypoglycemia to be between 7.01% - 17.64% patients (7, 8). The aim of this study was to assess the relevance of a 5-hours prolonged OGTT in evaluation of the glucose metabolism disturbances in patients with acute and chronic ethanol poisoning, as compared with standard methods, such as FBG and 2h-OGTT. Thus, this category of patients who address to a large group of medical specialties (internal medicine, endocrinology, gastroenterology, emergency medicine, family medicine, psychiatry) can be better managed.

PATIENTS AND METHODS

This cross sectional study included 497 consecutive patients with acute and chronic ethanol poisoning, who were admitted in Medical Clinic of "Sf.Ioan" Emergency Clinic Hospital Iasi January 2006 till October 2008 and agreed to enrol in this study. The study was in accordance with the ethical standards of the Helsinki Declaration (9), and the institutional ethics committee approved it. The data are presented according with 2008 update of requirements for manuscripts submitted to biomedical journals (10).

Methods

All patients diagnosed with acute or chronic ethanol poisoning, in which we obtained an informed consent (from the patient or from next-of-kin in the situation

of comatose patient) were included in the study. Exclusion criteria were represented by: diagnosis of DM, present history of cancer, renal disease, and liver disease (other than ALD). We excluded patients presenting with hypoglycemia secondary to other aetiology, as well as subjects treated with beta-blockers, salicylates, thiazides, or cholesterol lowering medications. The patients were divided into 3 groups: subjects with acute ethanol poisoning requiring hospital admission: group 1, patients with drunkenness requiring assistance only in the Emergency Room (ER) for up to 24 h — group 2, and patients with chronic ethanol poisoning admitted for a medical condition — group 3. On admission of each patient, in clinic or ER, a 20-ml blood sample was immediately drawn. Blood ethanol level (BEL), blood glucose level (BGL), liver function tests (Alanine transaminase — ALT, Aspartate transaminase — AST, Alkaline phosphatase — ALP, Total bilirubin — TBIL, Direct bilirubin, Gamma glutamyl transpeptidase — GGT, Coagulation tests, Lactate dehydrogenase — LDH, albumin, total protein and electrophoresis), and toxicological screen (Barbiturates, Benzodiazepines, Phenothiazines, Amphetamines, Analgesics, Antidepressants, Narcotics and Drug abuse screen) were determined by standard laboratory techniques. At the same time, information was recorded for each patient regarding age, sex, weight, mental state, level of consciousness, elapsed time since last consumption of food, and usual alcoholic beverage, assessed using CAGE questionnaire (11). Evaluation of alcohol units ingestion was performed. In all these patients we performed the next day after admission the 75 g OGTT, in accordance with the WHO criteria, prolonged to 5-

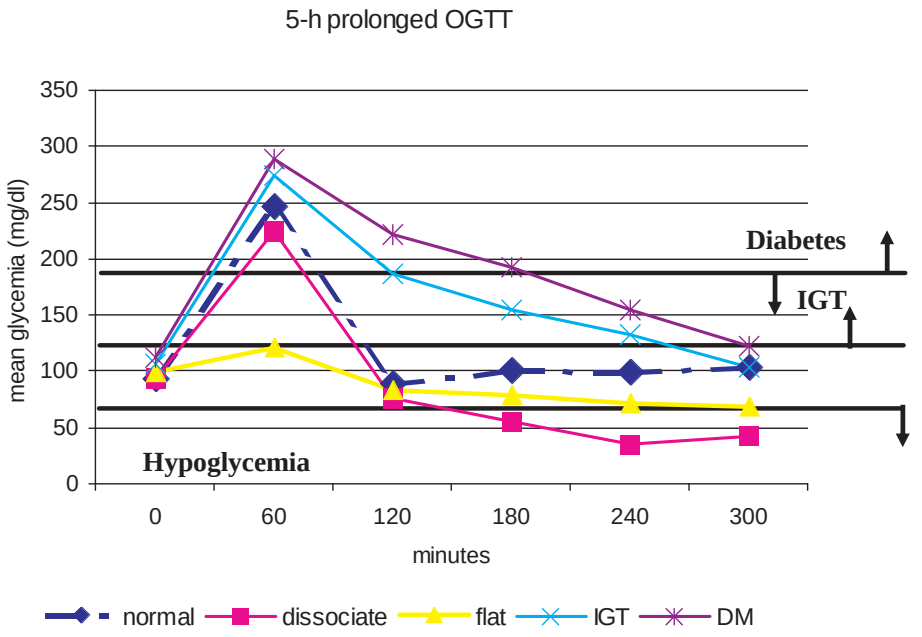

Figure 1. Types of OGTT curves recorded in the study.

h (12, 13). The blood samples were obtained at baseline and every 60 minutes thereafter for 5 h. The subjects remained supine in bed throughout the testing to avoid confounding effects of physical activity on blood glucose. Before data analysis, a glucose concentration ≤ 70 mg/dL was defined as hypoglycemia (14).

We classified the curves obtained after 5-h prolonged OGTT (Fig.1) into:
- Normal curve: fasting plasma glucose (FPG) < 100 mg/dL, 120 minutes post-glucose load < 140 mg/dL (15);
- Dissociate curve (with delayed hypoglycemia or hypoglycemic curve): FPG < 100 mg/dl, 60 minutes post-glucose load > 180 mg/dL, 120, 180, or 240 minutes post-glucose load < 50 mg/dL (4);
- Flat curve: maximum plasma glucose after glucose load is below 120 mg/dL (4);
- IGT curve: plasma glucose 120 minutes post-glucose load is 140 —199 mg/dL (15);
- Diabetic curve: plasma glucose 120 minutes post-glucose load is ≥ 200 mg/dL (15).

Abdominal ultrasonography and computer tomography were used to assess liver steatosis, and endoscopic examinations were performed during routine medical practices to evaluate the presence of esophageal varices and portal hypertensive gastropathy in patients with liver cirrhosis.

Statistical analysis

All continuous variables were expressed as mean ± standard deviation. Comparison of characteristics at baseline between groups was performed by Student's *t*-test (for mean values and percentages) or the chi-square test (to compare frequencies). P-values less than 0.05 were considered statistically significant.

RESULTS

We analysed within a 34 months period a number of 497 consecutive subjects admitted in our clinic with acute and/or chronic ethanol poisoning. 314 of these were men (63.17%) and 183 (36.83%) were women.

They were divided into 3 groups as follows: 167 subjects (aged 37.46 ± 13.44 years) had acute ethanol poisoning requiring hospital admission, 182 patients (aged 38.08 ± 12.77 years) were assisted only in ER for drunkenness, and 148 patients (aged 47.67 ± 12.71 years) had chronic alcoholism, being admitted for diverse other medical conditions (Table 1).

Group 1 was composed of 77.84% men and 22.16% women. 42 patients (12.03%) with acute ethanol poisoning (groups 1 and 2) associated poisoning with another drug or toxin. Majority of the drugs associated were CNS depressants, and the toxins (other than ethanol) involved were pesticides and caustics. 49 acutely intoxicated patients (14.04%) had a history of psychiatric illness. Acute ethanol poisoning (according to literature classification) was mild in 18% patients, moderate in 22%, and severe (ethanol coma) in 60% cases from group 1 (4). BEL was 0.5—1.5 g/L in 22.55% cases, 1.5—2.5 g/L in 25.36% cases, and over 2.5 g/L in 52.09% patients; BEL correlated well with severity of clinical form of ethanol poisoning.

Table 1. Characteristics of the study groups.

Parameter	Group 1	Group 2	Group 3 (n)
Total patients (M/W)	167 (130/37)	182 (117/65)	148 (96/52)
BMI (kg/m^2)	30.5 ± 3.9	30.8 ± 3.5	31.6 ± 3.7
Markers for ALD (n / %)	57 / 34.13	49 / 26.92	148 / 100
Admission BGL (% - p)			
Normal	62 - 0.04*	48 - 0.006&	90
Hypoglycemia	12 - 0.02*	27	0 - 0.03&
Hyperglycemia	26	25 - NS&	10 - 0.05*
FBG (% - p)			
Normal	55.17 - 0.007*	80.17 - NS&	90
IFG	44.83	19.83 - 0.001#	10 - 0.0000*
5-h OGTT curve (% - p)			
Normal	31.73 - 0.0003*	48.9 - 0.0006&	3.37
Hypoglycemic	30.54 - 0.014*	26.37 - 0.029&	63.51
Flat	13.77	11.53 - NS*	10. 81 - NS&
IGT	13.77	7.14 - 0.003*	4.72 - 0,001&
Diabetic	10.19 - 0.007*	6.04 - 0.003&	17.56

M - men; W - women; n - number of patients; NS - p value statistically non-significant;
* comparison between group 1 and 3
# comparison between group 1 and 2
& comparison between group 2 and 3.

Glycemia on admission, FBG and types of curves obtained after 5-h prolonged OGTT started at 7 a.m. the next day after admission were interpreted in accordance with criteria accepted today (Table 2) and the results are presented in Table 1.

Group 2 was composed of 64.28% men and 35.72% women. Their co-morbidities included: traumatic disorders — 47.17% cases, medical disorders — 52.73%.

Table 2. Diagnostic values of glycemia (14, 15)

Category	Fasting plasma glucose (FPG)	OGTT
Normal	< 100 mg/dL (5.6 mmol/l)	2-h post load glucose < 140 mg/dl (7.8 mmol/L)
Hypoglycemia	≤ 70 mg/dL (3.9 mmol/l).	-
Impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)	100-125 mg/dL (5.6-6.9 mmol/L)	2-h post load glucose 140-199 mg/dL (7.8-11.1 mmol/L)
Diabetes (provisional diagnosis)	≥ 126 mg/dL (7.0 mmol/L)	2-h post load glucose ≥ 200 mg/dL (11.1 mmol/L)

BEL was 0.5-1.5 g/L in 67.27% patients, and 1.5-2.5 g/L in 32.73% cases. All patients in this group had a mild/moderate form of ethanol poisoning. Glycemia on arrival in ER, FBG and prolonged OGTT performed the next day are presented in Table 1.

Group 3 consisted of 64.86% men, and 35.14% women. All these patients had ALD, as follows: hepatic steatosis 23%, chronic alcoholic hepatitis 45%, compensated liver cirrhosis 32% patients.

Ultrasound - measured hepatic left lobe volume in obese patients (BMI - 31.6 ± 3.7 kg/m^2 in this group) was 433 ± 215 mL (range 46-1019 mL). Liver cytolysis was present in 67% patients (SGOT 101 ± 17 IU/L). Markers of chronic ethanol intake were present in all patients (GGT 135 ± 23 IU/L, MCV 102 ± 4.12), and all of them recognized a history of chronic drinking, confirmed by CAGE questionnaire. The results of BGL obtained on admission of group 3 (which in this group was in fact FBG), and results of 5-h OGTT are presented in Table 1. In this group hypoglycemia was elicited after prolonged OGTT.

Analysis of BGL showed that hyperglycemia in women of group 2 assisted in ER (50%) was significantly higher, compared with women in group 1 (18.18%, p 0.03), and group 3 (10.13% p=0.02). Men of group 1 had significantly more normal 5-h OGTT (34.29%) as compared with men of group 3 (0%, p =0.02). Age distribution analysis on group 1 showed a higher percentage of normal BGL in patients aged between 30-60 years (13.86%), compared with those below 30 years old (6.8%, p=0.03). Hypoglycemia was recorded more frequently in patients < 30 years old (5.82%), compared with those between 30-60 years (1.81%, p 0.03). Into group 2, hypoglycemia was more frequenthly in patients aged 30-60 years (14.46%), compared with patients < 30 years old (1.85%, p=0.007). In group 3, normal BGL was recorded significantly more in patients aged 30-60 years (44.6%), and above 60 years old (45.4%), compared with those aged < 30 years old (0%, p=0.01).

Analysis of patients in all three groups showed that normal 5h-OGTT appeared to be more frequent in patients aged 30-60 years (40.74%) as compared with patients < 30 years old (15.38%, p 0.01), and those > 60 years old (7.69%, p 0.01). IGT was significantly higher in patients aged > 60 years old (21.74%) as compared with patients aged below 30 years (2.04%, p=0.03).

The correlation of BEL with BGL (in groups 1 and 2) showed that when BEL is 0.5-1.5 g/L, hypoglycemia appeared more frequently (69.03%) as compared with normal glycemia (14.69%, p= 0.0003) and hyperglycemia (16.28%, p=0.008), majority of them being fasting alcoholic hypoglycemia. Relative time from last meal was 22 ± 2 hours in these patients. When BEL is 1.5 — 2.5 g/L, there were significantly increased abnormal values of glycemia: hyperglycemia (46.51%) significantly higher than normal BGL (10.99%, p=0.0005), and hypoglycemia (42.5%) significantly higher than normal BGL (10.99%, p=0.0001).

Analysis of BEL correlated with types of OGTT curves showed that when BEL is higher than 2.5 g/L, there were more frequent IGT curves (50%) as compared with normal curves (18.18%, p=0.02), diabetic curves (11.1%, p=0.02),

flat curves (15%, p=0.03), and dissociate curves (5.7%, p=0.005).

Analysing glycemia in all three groups, in relation to chronic alcoholism, we find that hypoglycemia is more frequent in patients with chronic ethanol poisoning — 207 (79.92%), compared with normal BGL — 26 patients (10.04%, p=0.0001), and hyperglycemia — 26 patients (10%, p=0.0001). Dissociated curves (delayed hypoglycemia) in 5h-prolonged OGTT were significantly more frequent in chronic alcoholics — 105 patients (40.5%) as compared with normal curves — 59 patients (22.77%, p=0.04).

All three groups associated obesity (BMI>30 kg/m^2). Analysis of all 3 groups of patients showed that, based on 5 h prolonged-OGTT, DM was diagnosed in 54 subjects (10.86%), IGT in 43 subjects (8.65%), and delayed hypoglycemia in 172 subjects (34.60%). 147 subjects (29.57%) had normal glucose tolerance. Glucose metabolism abnormalities were recorded in 143 subjects with chronic ethanol poisoning and ALD (96.63%), and in 207 cases with acute alcohol poisoning (59.31%), of which 106 (51.2%) had markers for ALD.

DISCUSSION

In our study, patients with a mild form of acute ethanol poisoning had significantly more hypoglycemia on arrival, compared with normal blood glucose levels or hyperglycemia, because the majority of them had an elapsed time from last meal of 22 ± 2 hours, which probably determined a depletion of glycogen stores.

Blood glucose homeostasis depends on several factors, especially exogenous intake, variations of its utilization, and in the situation of ethanol consumption (sometimes referred to as "alcohol"), on the effect of ethanol on gluconeogenesis (4).

In a healthy-appearing patient, the first cause of a hypoglycemic disorder is ethanol (16). Brown and Harvey described alcohol induced-hypoglycemia for the first time, in 1941 (17). Since then, frequent clinical reports document the association of alcohol ingestion with dysglycemia, both in nondiabetics and in patients with diabetes (18-23).

In a fasted state, where both renal and hepatic glycogen stores are limited, the gluconeogenetic capacity within these organs is elevated, making it the primary mode to maintain blood glucose concentrations (4). Once glycogen stores are depleted, hypoglycemia may develop because ethanol impairs gluconeogenesis. Larger alcohol intake with longer than 24 hours duration of fasting are associated with a greater degree of hypoglycemia (20, 21).

The mechanism of ethanol — induced alteration in blood glucose concentration is complex, but reasonable well understood (23-25). If hepatic glycogen stores are adequate, the combination of alcohol-induced glycogenolysis and decreased glucose uptake into muscles result in an elevation in blood glucose concentration. For example, administration of 150 ml whisky to human subjects results in an increase of glycemia in 30-60 minutes. The concentration of blood glucose then decreases more

rapidly than in control subjects not receiving alcohol (26, 27). A moderate dose of alcohol (0.5 g/kg body weight) significantly impaired glucose tolerance in normal subjects. Consumption of larger doses of alcohol (266 to 513 ml, consumed over 1 to 3 days) resulted in glucose intolerance in both normal and diabetic subjects (28).

In our study, subjects acutely poisoned with ethanol had hyperglycemia recorded on admission in 90 of 349 patients (25.78%).

In these patients (groups 1 and 2), types of OGTT curves recorded 24 h after

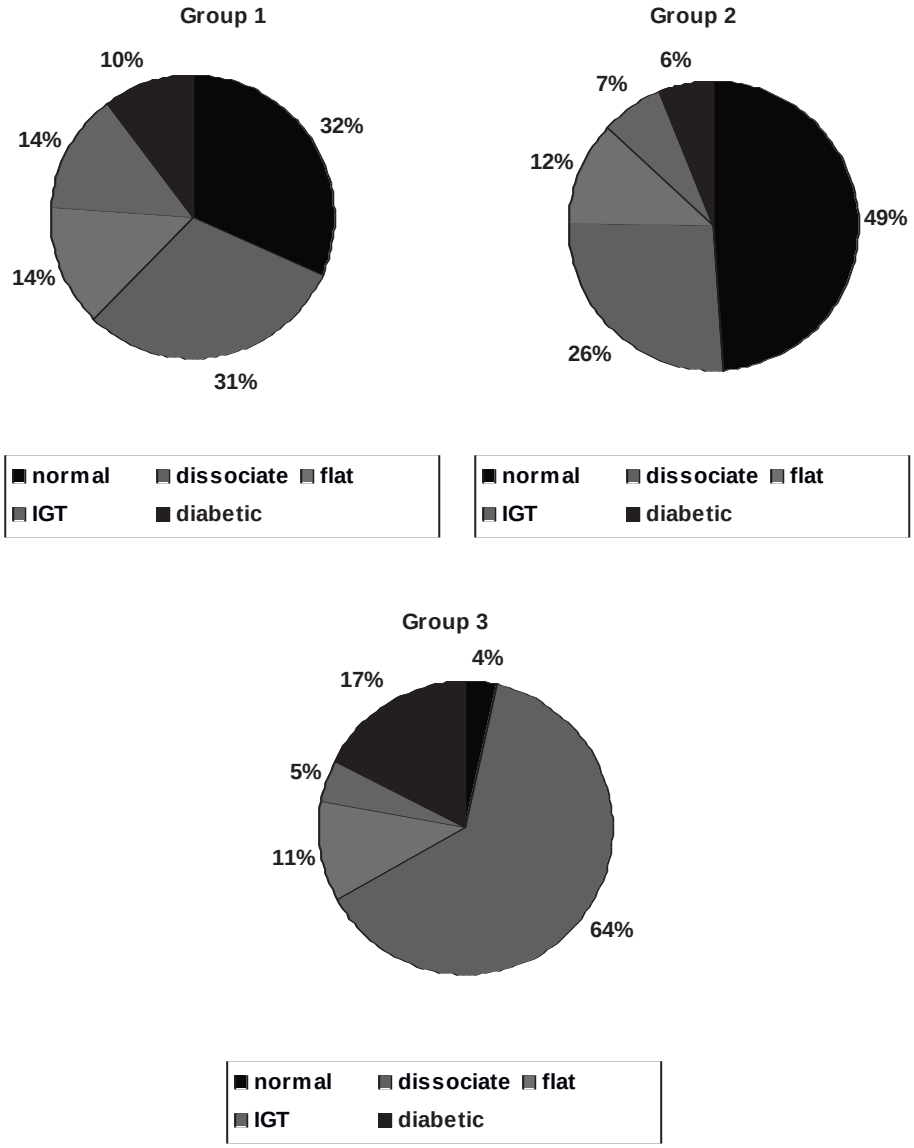

Fig.2. Comparison of 5-h OGTT curves obtained in study groups.

admission (when BEL decreased in all patients < 0.01 g/L) demonstrate that hypoglycemia occurred in 26 — 31% subjects (Fig.2). Hypoglycemia can occur even after alcohol is no longer detectable in the blood if glycogen stores are not replenished (20).

When we analysed BGL correlated with BEL, we find that at BEL 0.5-1.5 g/L, hypoglycemia appeared significantly more than normal BGL, or hyperglycemia in over two thirds of patients. Moderate ethanol consumption induces several metabolic changes in glucose, and lipid metabolism. These changes all take place without a significant effect of ethanol on ß-cell secretion. This implies that ethanol does not cause significant modification in ß-cell function.

However, the presence of reduced plasma insulin concentration during experimental conditions would support the hypothesis that ethanol might increase insulin clearance (29, 30). The mechanism of reactive alcohol-induced hypoglycemia is secondary to hyperstimulation of insulin (twice normal values) when BEL is 0.5-1 g/L. Levels < 0.5 g/L have no effect, and levels > 1 g/L can induce even inhibition of insulin secretion (4). This biphasic effect of ethanol on blood glucose concentration reflects initial stimulation of glycogenolysis and subsequent impairment of gluconeogenesis from lactate by alcohol (2, 25).

It is well known that acute alcohol consumption inhibits HGN. Chronic ethanol ingestion also determines a decrement in gluconeogenic capacity, which results in a greater susceptibility for alcohol-induced hypoglycemia, giving the fact that some alcoholics tend to reduce their food intake and/or consume diets low in carbohydrates (4, 6, 25). Our study finds prevalence of hypoglycemia to be significantly higher than normal BGL or hyperglycemia in chronic alcoholics. In adults, hypoglycemia typically occurs in chronic alcoholic patients with a history of poor dietary intake (31). In chronic alcoholics, because of the NADH excess, gluconeogenesis from lactic acid and alanine is blocked, which could also explain their predisposition to hypoglycemia, especially when glycogen stores are depleted (4).

As it is shown in Fig. 2, majority of patients of group 3, with ALD and chronic ethanol poisoning, had abnormal OGTT curves. Flat curve represents the expression of a hyperinsulinism, which is frequent in the initial stages of diabetes mellitus (pre-diabetes, latent diabetes, or chemical diabetes), and in metabolic syndrome, being a physiological manifestation only in children. The abnormal curves recorded are the expression of carbohydrate metabolism disturbances encountered in ALD, as well as in other chronic liver diseases (27, 29).

BMI was elevated in all 3 groups. In obesity, the secretome (adipokines, cytokines, free fatty acids and other lipid moieties) of fatty tissue is amplified, which through its autocrine, paracrine actions in fat tissue and systemic effects especially in the liver leads to an altered metabolic state with insulin resistance (IR). IR leads to hyperglycemia and reactive hyperinsulinemia, which stimulates lipid-accumulating processes and impairs hepatic lipid metabolism. IR enhances free fatty acid delivery to liver from the adipose tissue storage due to uninhibited lipolysis. These changes result in hepatic abnormal fat accumulation, which may initiate the

hepatic IR and further aggravate the altered metabolic state of whole body (32). IR can explain the metabolic status of these cases and deserves attention. In addition, liver steatosis might impact glycogen production and glucose release. This could also contribute to the pattern of OGTT curves recorded, especially in group 3.

Dissociate curves recorded in 5h-prolonged OGTT are elements that can be missed when OGTT is performed as recommended by WHO (fasting, 60 and 120 minute post load glucose determinations). They are particularly significant, because they are the expression of profound anomalies, as is the alteration of liver glucose production, secondary to collapse of glycogen stores and/or hepatic enzymes, expressed by this delayed hypoglycemia, 3-4 hours after glucose load. Both flat and dissociate curves on 5-h prolonged OGTT show a hyperinsulinism responsible for hypoglycemia, in the presence of an affected liver, feature which is relatively frequent, but ignored. Alcohol itself has anti-insulin effects mediated by at least 2 mechanisms. First, it is the direct aggression on beta-islet cells with appearance in time of chronic calcified pancreatitis and pancreatic amyloidosis. The second mechanism is represented by increase in catecholamine concentration (which has a demonstrated hyperglycemiant effect), secondary to adrenal medulla hypersecretion, synaptic norepinephrine reuptake inhibition, and catecholamine degradation inhibition (4, 27, 29).

These extremely complex biochemical anomalies explain the variety of glucose metabolism changes in ALD from hypoglycemia to impaired glucose tolerance and diabetes. In patients with ALD from our study, hypoglycemia outlined by 5 hours prolonged OGTT could be the expression either of insulin excess, failed to be metabolised by an altered liver, or of glycogen hepatic stores depletion and incapacity of gluconeogenesis to contribute to glucose homeostasis by utilization of non-glucidic substrates, gluconeogenesis enzymes being affected by chronic alcohol intake.

In advanced stages of ALD, with liver cirrhosis and liver failure, even in patients known with diabetes, hypoglycemia can occur, being an expression of profound and irreversible hepatocellular damage (4, 29). Impaired glucose tolerance, diagnosed after OGTT in 5% patients with chronic ethanol poisoning suggests decreased insulin activity, mainly secondary to insulin secretion alteration as an effect of direct aggression of ethanol on beta islet cells. Ignoring this stage leads to failure of pancreatic function, and diabetes onset. A decline in HGN capacity from three carbon precursors as a result of chronic ethanol consumption could elevate the risk of alcohol-induced hypoglycemia, while an increase in HGN capacity (especially in patients with alcohol-induced liver cirrhosis) might lead to an earlier onset for glucose intolerance (6).

It has been reported that excessive alcohol consumption increases the risk of type 2 diabetes (33). Excessive ethanol consumption also causes hyperlipidemia, diabetes and hypertension, constituting alcohol-related syndrome. These morbid conditions are secondary to mechanisms that are apparently independent from obesity, and are peculiar to ethanol consumption, such as shifts in the redox-state, abnormalities of the sympathetic nervous system, changes of hormonal secretions such as the renin-

angiotensin-aldosterone system and cortisol production, damage to the pancreas (34).

In our study, women with drunkenness had significantly more frequent hyperglycemia on arrival in ER, while men had no statistically difference when we analysed BGL. On the other hand, men had significantly more normal OGTT, when they are acutely poisoned with ethanol.

There are differences in the liver's response to both an acute and chronic consumption of ethanol in men *vs* women. There are sex differences in the location and quantity of hepatic ADH and in the first-pass metabolism of ethanol, the latter of which can give rise to higher BEL in women as compared to men despite an equivalent consumption of ethanol (6, 35). Men tend to have a higher gastric ADH activity compared to women, who has a higher hepatic ADH activity (35). Also, women demonstrate a higher BEL as compared to men, even when the alcohol ingestion per body weight is equivalent (36). The fact that men have higher gastric ADH activities, as Lieber demonstrated in 2000, results in a greater first-pass metabolism of alcohol compared to women and substantiates the higher BEL observed in females (37). Also, there are differences in counter-regulatory response to hypoglycemia in alcoholic men compared to alcoholic women, who are more vulnerable for ethanol-induced hypoglycemia (6, 37).

Analysis on age distribution of 5h-prolonged OGTT curves showed that normal OGTT curves are lower in subjects > 60 years old as compared with patients < 60 years old. Also, IGT was significantly higher in patients > 60 years old as compared with younger subjects (< 30 years old). Studies involving nondiabetic individuals have shown that elderly nondiabetic subjects exhibit deterioration in glucose tolerance after ethanol administration compared with younger men. Orally ingested ethanol has direct effects on hepatic glucose production, which may exacerbate or attenuate the tendency to hypoglycemia. Fatty acids play a critical role in glucose homeostasis during ethanol ingestion (1). Alcohol-induced suppression of nonesterified fatty acids prevents the normal lipolytic response to catecholamines during hypoglycemia (38).

Although 371 patients (74.65%) had normal FBG, using 5 h prolonged-OGTT, we were able to diagnose DM in 54 subjects (10.86%), impaired glucose tolerance (IGT) in 43 subjects (8.65%), delayed hypoglycemia in 172 subjects (34.60%) and normal glucose tolerance (NGT) in 147 subjects (29.57%). We consider that glucose metabolism abnormalities outlined by 5 hours prolonged OGTT in our patients is an argument to use this test in all patients with acute or chronic ethanol poisoning, especially in those with ALD, in addition to standard methods.

In **conclusion**, in our series of 497 patients, acute and chronic ethanol poisoning is more frequent in middle-aged men as compared to women. Both blood glucose levels (BGL) on arrival, and prolonged OGTT curves were correlated with blood ethanol levels (BEL). Hypoglycemia was recorded in more than two thirds of acutely poisoned patients, when alcohol level was 0.5-1.5 g/L. Impaired glucose tolerance (IGT) were recorded in half of patients with BEL > 2.5 g/L. We demonstrated abnormal OGTT response in chronic alcoholics, especially delayed hypoglycemia, and IGT, as an indicator of alcoholic liver disease (ALD).

References

1. Van de Wiel A. Diabetes mellitus and alcohol. Diabetes Metab Res Rev. 2004;20(4):263-267.
2. Lionte C., Hurjui J. Study of hypoglycemia in acute ethanol poisoning. Rev Med Chir Soc Med Nat Iasi 2003; 107(Supl. 1): 277-281.
3. Lionte C., Hurjui J. Relationship between blood alcohol level and alcohol-induced hypoglycemia. Rev Med Chir Soc Med Nat Iasi 2003; 107(Supl. 2): 135-140.
4. Lionte C. Hypoglycemias in medical and toxicological practice. Iasi: Ed. Junimea, Esculap Collection, 2004.
5. Parrott MA. Substance abuse and diabetes. In: Raz I, Skyler JS, Shafrir E, eds. Diabetes. From research to diagnosis and treatment. London: Informa Health Care, 2002: 70.
6. Sumida KD, Hill JM, Matveyenko AV. Sex differences in hepatic gluconeogenic capacity after chronic alcohol consumption. Clinical Medicine & Research 2007; 5(3): 193-202.
7. Bartlett D. Confusion, somnolence, seizures, tachycardia? Question drug-induced hypoglycemia. J Emerg Nurs. 2005;31(2):206-208.
8. Lionte C, Șorodoc L, Laba V. Toxic-induced hypoglycemia in clinical practice. Rom J Intern Med 2004; 42(2): 447-455.
9. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA, 2000; 284: 3043-3045.
10. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (Updated October 2008).
11. Ewing JA. Detecting Alcoholism: The CAGE Questionnaire. JAMA, 1984; 252: 1905-1907.
12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. Diabet Med 1998; 15:539-553.
13. Belfiore F, Mogensen CE. New concepts in diabetes and its treatment. Basel (Switzerland): Karger Publishers, 2000:17.
14. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005; 28: 1245-1249.
15. American Diabetes Association. Position Statement: Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2006; 29(Supl.1): S43-S48.
16. Service FJ. Hypoglycemic disorders. N Engl J Med 1995; 332(17): 1144-1152.
17. Brown TM, Harvey AM. Spontaneous hypoglycemia in “smoke” drinkers. JAMA 1941;117: 12-15.
18. Kolacinski Z, Rusiñski P. Biological and toxic effects of ethanol: diagnostics and treatment of acute poisonings. Przegl Lek. 2003; 60(4):204-209.
19. Wilson E, Waring WS. Severe hypotension and hypothermia caused by acute ethanol toxicity. Emerg Med J. 2007;24(2):e7.
20. Jain H, Beriwal S, Singh S. Alcohol induced ketoacidosis, severe hypoglycemia and irreversible encephalopathy. Med Sci Monit. 2002;8(11): CS77-79.
21. Lionte C, Șorodoc L, Laba V. Alcohol-induced hypoglycemias in medical practice. Ther Pharmacol Clin Toxicol 2004; VIII (4): 80-86.
22. Ngatchu T, Sangwaiya A, Dabiri A, Dhar A, McNeil I, Arnold JD. Alcoholic ketoacidosis with multiple

complications: a case report. Emerg Med J 2007; 24: 776-777.
23. Kadono M, Hasegawa G, Shigeta M, Nakazawa A, Ueda M, Fukui M, Yoshikawa T, Nakamura N. Joint effect of alcohol and usual sleep duration on the risk of dysglycemia. Sleep 2007; 30(10): 1341-1347.
24. Lionte C, Șorodoc L, Hurjui J. Alcoholic liver disease and hypoglycemia. Rev Med Chir Soc Med Nat Iasi 2004; 108(Supl.1): 276-280.
25. Lionte C, Șorodoc L, Laba V, Hurjui J. The effect of ethanol on glycemia in acute and chronic poisoning. Curierul Medical 2005; 1(283): 21-27.
26. Freinkel N, Arky RA. Effects of alcohol on carbohydrate metabolism in man. Psychosom 1966; 28: 551.
27. Lionte C, Șorodoc L, Simionescu V. Glucoregulation changes in alcoholic liver disease. Medicina Interna (New Series) 2005; II (1): 61-68.
28. Patel DG. Effects of ethanol on carbohydrate metabolism and implications for the aging alcoholic. Alcohol Health & Research World. 1989. (Accessed 31 Jan, 2009, at site http://findarticles.com/p/articles/mi_m0847/is_n3_v13/ai_8193276)
29. Lionte C, Șorodoc L, Șorodoc V, Petriș O.R. Glucose metabolism changes in chronic liver disease. Rev Med Chir Soc Med Nat Iasi 2006; 119 (Supl. 1): 387-390.
30. Avogaro A, Watanabe RM., Gottardo L, de Kreutzenberg S, Tiengo A, Pacini G. Glucose Tolerance during Moderate Alcohol Intake: Insights on Insulin Action from Glucose/Lactate Dynamics. J Clin Endocrinol Metab 2002; 87(3): 1233-1238.
31. Lieber C.S. Relationships between nutrition, alcohol use, and liver disease. Alcohol Res Health. 2003; 27(3):220-231.
32. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol. 2007; 13(26):3540-3553.
33. Wannamethee SG, Camargo CA Jr, Manson JE, Willett WC, Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med 2003; 163: 1329-1336.
34. Yokoyama H, Hiroshi H, Ohgo H, Hibi T, Saito I. Effects of excessive ethanol consumption on the diagnosis of the metabolic syndrome using its clinical diagnostic criteria. Intern Med 2007; 46(17): 1345-1352.
35. Baraona E, Abittan CS, Dohmen K, Moretti M, Pozzato G, Chayes ZW, Schaefer C, Lieber CS. Gender differences in pharmacokinetics of alcohol. Alcohol Clin Exp Res 2001; 25: 502-507.
36. Li TK, Beard JD, Orr WE, Kwo PY, Ramchandani VA, Thomasson HR. Variation in ethanol pharmacokinetics and perceived gender and ethnic differences in alcohol elimination. Alcohol Clin Exp Res. 2000; 24(4):415-416.
37. Lieber CS. Ethnic and gender differences in ethanol metabolism. Alcohol Clin Exp Res 2000; 24: 417-418.
38. Kerr D, Cheyne E, Thomas P, Sherwin R. Influence of acute alcohol ingestion on the hormonal responses to modest hypoglycaemia in patients with Type 1 diabetes. Diabet Med. 2007; 24(3): 312-316.