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Research Article

# The Entero-Insular-Axis is retained in Patients with Alcoholic Liver Disease

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## Abstract

The incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted after meals and are involved in the pathogenesis of different metabolic diseases, such as non alcoholic liver disease (NALD). GLP-1 agonists are in addition evaluated for the treatment of NALD. The role of incretins is the pathogenesis of alcoholic liver disease (ALD) is however unclear. We determined the secretion of incretins in patients with alcoholic liver disease after oral glucose administration.

In 23 patients with alcoholic liver disease in the early withdrawn state and 19 control patients serum levels of total GIP, intact GLP-1, insulin and C-peptide were determined after an oral glucose load (75g glucose after an overnight fasting).

In this function test, none of the investigated subjects showed a disturbance of glucose metabolism as indicated by the kinetic of serum glucose. There was a slight tendency for higher insulin resistance and lower insulin sensitivity in alcoholic patients ($p = 0.0064$). GLP-1 and GIP secretion after the oral stimulation was not different between the two groups, despite marked differences in liver function tests.

We conclude that chronic alcohol abuse and alcoholic liver disease is not associated with a disturbed entero-insular axis, which might have influence on treatment options.

**Keywords:** Alcohol Dependence; Glp-1; Gip; Insulin Secretion; Oral Glucose Tolerance Test

## Introduction

Alcohol consumption and abuse is common [1] and in Germany it is estimated that approximately two million people are alcohol dependent [2]. Alcoholic liver disease (ALD) is a major cause of morbidity and mortality in these patients. Approximately 40%-90% of patients with cirrhosis have a history of alcohol abuse and about one third of patients with hepatocellular carcinoma are attributable to alcoholic liver disease [3, 4]. The mechanisms for the development of ALD are multiple. Alcohol itself acts as a potential hepatotoxin with the development of liver disease depending on host factors, such as gender, polymorphism of alcohol-metabolizing enzymes, immunological factors and concomitant diseases like chronic hepatic viral infections, obesity, diabetes and nutritional deficiencies [3].

Steatosis is one of the earliest responses of the liver to alcohol abuse. Triglycerides, phospholipids and cholesterol ester are

accumulated in hepatocytes due to disruption of mitochondrial ß-oxidation of fatty acids [5]. Recent studies have also focused on the direct or indirect regulation of lipid metabolism-associated transcription factors by alcohol exposure leading to hepatic fat accumulation [6].

Non-alcoholic fatty liver disease (NAFLD) and its subgroup steatohepatitis (NASH) are also characterized by hepatic lipid accumulation due to different mechanisms including increased dietary intake, de-novo lipogenesis and influx of free fatty acids. A major risk factor for hepatic fat accumulation is Insulin resistance (IR) [7].

The incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gastrointestinal peptide hormones regulating postprandial insulin release and are shown to be involved in the development of non-alcoholic fatty liver disease and insulin resistance [8]. Both hormones are secreted from neuroendocrine cells (L and K cells) located in the intestinal mucosa [9]. Chronic alcohol consumption has been shown to lead to an increase of the number of Glucagon- and GIP-secreting cells in the duodenal mucosa [10]. In addition, a reduction of the activity of the metabolising enzyme dipeptidyl peptidase-IV (DPP-IV) in serum has been described [11], potentially leading to increased incretin serum levels. These morphological and metabolic changes are seen on the basis of long term alcohol abuse and thus can be assumed to influence glucose metabolism independently of an acute drinking episode.

The aim of the present study was therefore to evaluate incretin and insulin secretion and insulin resistance in patients with alcoholic liver disease by the use of a standardized oral glucose tolerance test.

## Materials and Methods

### Patients

Forty-two subjects participated in this study. Twenty three subjects were alcohol dependent and nineteen abstinent participants served as controls. The alcohol dependent patients were hospitalized in the Medical Department of the St. Elisabeth Hospital, Dorsten, Germany. They participated in the structured withdrawal program of the department. As from admission into the hospital the alcohol dependent patients received Tiapride and Carbamazepine which was tapered of during a 1-week period. There was no evidence of pancreatic dysfunction (clinical, ultrasound, laboratory values) in any of the alcoholic patients, all alcoholic patients in this study had elevated liver enzymes more than twice the normal range (Alanin aminotransferase (ALT), Aspartate aminotransferase (AST) and Gamma glutamyl transpeptidase (yGT)).

All patients received ultrasound examination of the liver with a 3.75 Mhz convex transducer (Elegra, Siemens Medical Systems, Erlangen, Germany). Classification of steatosis was based on the criteria of Saadeh et al. [12]. The severity of echogenicity was graded as follows: grade 0, normal echogenicity; grade 1, slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders; grade 2, moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; grade 3, marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver [12].

Exclusion criteria for controls were alcohol intake, any liver disease with elevated liver function tests and intake of any drug with known influence on glucose homeostasis. All controls had Grade 0 steatosis on ultrasound examination.

The study design was approved by the local ethical committee, and all participants gave informed consent.

### Oral Glucose Tolerance Test

The study was performed three to five days after admission and patients had received a norm caloric diet for at least three days. The same conditions were applied to the control group. After overnight fasting patients were provided with an antecubital vein catheter and given 75g glucose as a 300 ml liquid (Roche, Mannhein, Germany). Blood samples were taken 0, 15, 30, 45, 60, 90 and 120 minutes following oral glucose administration. Samples were collected in chilled tubes containing K-EDTA (Sarstedt, Nümbrecht, Germany) and for GLP-1 determination 50 µL DPP-IV inhibitor (DRG Instruments, Marburg; Germany). After centrifugation at 4° all samples were stored at – 20° C for subsequent assessment of GLP-1, GIP, insulin and c-peptide. Glucose, Hba1c, and baseline liver function tests (Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Gamma glutamyl transpeptidase (yGT)) were determined within four hours.

### Hormones, Glucose, HbA1c and Liver Function Test

Insulin and C-peptide serum levels were analysed by ECLIA technique on a Modular E Analyzer (Roche Diagnostics, Mannheim, Germany). Intact GLP-1 was measured using GLP-1 ELISA (DRG Instruments, Marburg, Germany), according to the instructions of the manufacturer (intra-assay coefficient of variation was below 9%, inter-assay coefficient of variation was below 13%, and the sensitivity was typically 2 pmmol/l). Total GIP serum levels were measured using human GIP ELISA (DRG Instruments, Marburg, Germany), according to the instructions of the manufacturer (intra-assay coefficient of variation was below 8.8%, inter-assay coefficient of variation was below 6.1%, and the sensitivity was typically less than 8.2 pg/mL). Routine laboratory values including blood glucose levels, Hba1c and liver enzymes were measured on an automated clinical chemistry analyser using standard IFCC approved

methods (Dimension EXL, Siemens Diagnostics Healthcare, Erlangen, Germany).

### Insulin resistance

IR was assessed calculating the homeostasis model assessment HOMA2-IR, HOMA-%%B2 and HOMA-%S2 were derived using the HOMA calculator [13].

### Calculations

Mean ± SD or SE are shown throughout. Statistical analysis was calculated by the appropriate test as stated in the text. $P < 0.05$ was considered to indicate statistically significance. Values were compared by the Mann-Whitney U-Test. A P value less than 0.05 were considered significant. XLSTAT (Addinosoft SARL, Paris, France) was used to perform the statistical analyses.

The area under the concentration curves (AUC) for glucose, insulin and c-peptide were calculated with the trapezium method. Hepatic insulin extraction (HIE) represents the proportion of insulin secreted from the ß-cells which is removed by the liver prior to entering the systemic circulation. The equitation used is [1-(AUCinsulin/AUCc-Peptide)].

## Results

### Baseline characteristics

Baseline characteristics are shown in Table 1. While gender distribution, BMI and Hba1c levels were comparable, the patient group was older. Liver enzymes were all significantly elevated in the alcoholic patients.

Degree of hepatic steatosis and liver enzymes in patients with alcoholic liver disease

We diagnosed in 14 patients with alcoholic liver disease hepatic steatosis by ultrasound. Regarding degrees, 8 patients had grade 1, 4 patients' grade 2 and 2 patients grade 3, while in 9 patients steatosis of the liver was absent using ultra sound technique.

Mean ALT levels showed significant variation in the degree of hepatic steatosis ($P < 0.05$), as shown in Table 2. AST and y-GT showed no significant variation with the severity of steatosis (Kruskal-Wallis-Test).

### Fasting plasma glucose, insulin and c-peptide concentrations

No difference was seen between the patients with alcoholic liver disease and the control group regarding fasting levels of glucose, insulin and C-peptide. Moreover, all baseline parameters for glucose metabolism were within the physiological ranges (Table 1).

| | **Controls (n=19)** | **ALD patients (n= 23)** | |
|---|---|---|---|
| Male/Female | 11/8 | 16/7 | n.s. |
| Age (years) | 36.5±9.3 | 47.1±8.9 | $P \leq 0.005$ |
| Mean alcohol intake (g/day) | 0 | 160±105 | $P \leq 0.001$ |
| BMI (kg/m$^2$) | 25.1±4.5 | 24.1±2.8 | n.s. |
| Hba1c (%) | 5.4±0.2 | 5.2±0.2 | n.s. |
| AST (U/L) | 19.3±6.7 | 88.7±61.8 | $P \leq 0.005$ |
| ALT (U/L) | 21.9±11.6 | 67.8±47.5 | $P \leq 0.005$ |
| y-GT (U/L) | 25.2±9.4 | 154.0±169.1 | $P \leq 0.005$ |
| Fasting glucose (mmol/l) | 5.5±0.3 | 5.2±0.2 | n.s. |
| Fasting Insulin (pmol/l) | 65.9±32.8 | 51.1±28.2 | n.s. |
| Fasting c-peptide (nmol/l) | 4.1±2.2 | 5.7±2.9 | n.s. |
| Fasting GLP-1 (pmol/l) | 2.6±1.6 | 3.3±1.7 | n.s. |
| Fasting GIP (pg/ml) | 67.2±35.6 | 60.5±28.0 | n.s. |

Data are expressed as mean ± SD. Differences in baseline characteristics of patients vs. controls are expressed as p-values (Mann-Whitney U test). $P < 0.05$: statistically significant difference; n.s. not significant.

**Table 1.** Baseline characteristics of alcoholic liver disease (ALD) patients and controls.

| **Hepatic steatosis (grade)** | **AST (U/L) n.s.** | **ALT (U/L) $P \leq 0.05$** | **y-GT (U/L) n.s.** |
|---|---|---|---|
| 0 | 75.8±86.3 | 36.8±21.0 | 88.0±47.5 |
| 1 | 99.4±40.0 | 92.8±55.5 | 140.3±84.3 |
| 2 | 75.3±44.0 | 85.0±61.9 | 324.0±377.5 |
| 3 | 131.5±67.2 | 73.5±13.4 | 165.5±78.5 |

Data are expressed as mean ± SD. Kruskal Wallis test was used to compare the means between the degrees of steatosis. $P < 0.05$: statistically significant difference; n.s. not significant.

**Table 2.** Degree of hepatic steatosis (ultra sound criteria) and liver enzymes in patients with alcoholic liver disease (n=23).

### Homeostatic model assessment of insulin sensitivity (HOMA2-%S) and insulin resistance (HOMA2-IR) and hepatic insulin extraction

There was a slight tendency for higher insulin resistance in patients with alcoholic liver disease, the difference was however not significant (12.9±6.3 vs. 9.2±5.0 p = 0.064). The same was shown for insulin sensitivity with lower values in patients with alcoholic liver disease (9.9±5.5 vs. 15.5±10.3 p= 0.064). There was no difference in hepatic insulin extraction between patients with alcoholic liver disease and controls (0.986±0.003 vs. 0.987±0.004 n.s.).

### Fasting levels of incretin hormones

For both incretin hormones (GLP-1 and GIP) there was no statistical difference observed during the fasting state in alcoholics and the control group (Table 1).

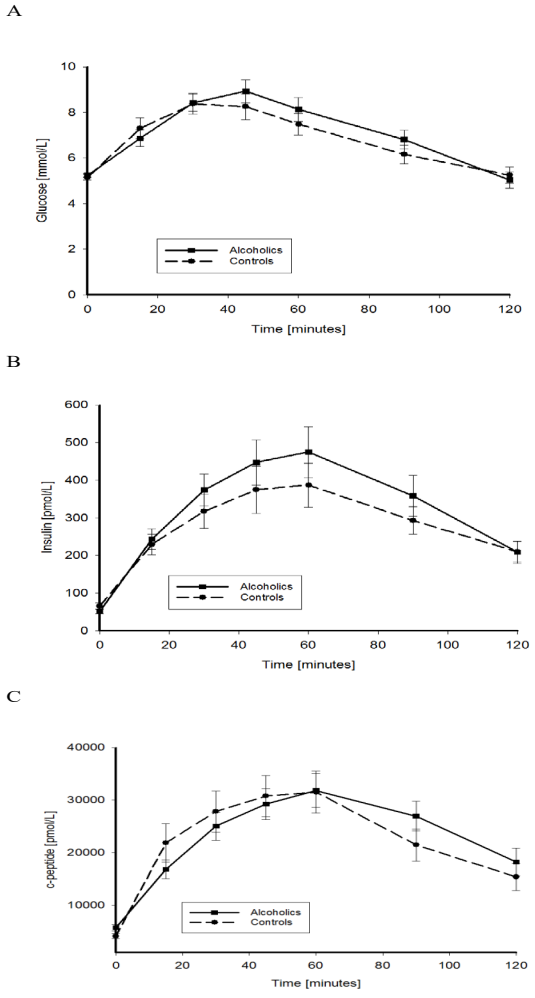


**Figure 1.** Glucose (A), Insulin (B) and C-peptide (C) serum levels during the oral glucose tolerance test (oGTT) (75 g glucose). Means ± SDs are given.

### Glucose, Insulin and C-Peptide levels during the OGTT (Figure 1)

After the ingestion of 75 grams of glucose there was an increase of circulating glucose, insulin and C-peptide, in both groups. The mean 2-h glucose level was similar in both groups (5.0±1.7 mmol/L in the study group vs. 5.3±1.5 mmol/L in controls n.s.) as were the AUC´s (0-120 min) (866±193 mmol x min/L (alcoholic) vs. 829±182mmol x min/L (control)). In addition, the kinetic behaviours of the tested serum levels were equal. Glucose levels peaked after 45 minutes, while insulin and C-peptide peaked after 60 minutes in both groups. Thereafter, glucose values returned to baseline values in both groups, while insulin and c-peptide levels did not return to baseline values during the 120 minutes observation period. Two patients from the alcoholic liver disease group showed glucose level above 7.8 mmol/L after 2 hours but below 11.0 mmol/l, thus being diagnosed as impaired glucose tolerance. In those subjects, AUC´s (0-120 min) for insulin and c-peptide were both in the upper and in the lower normal range.

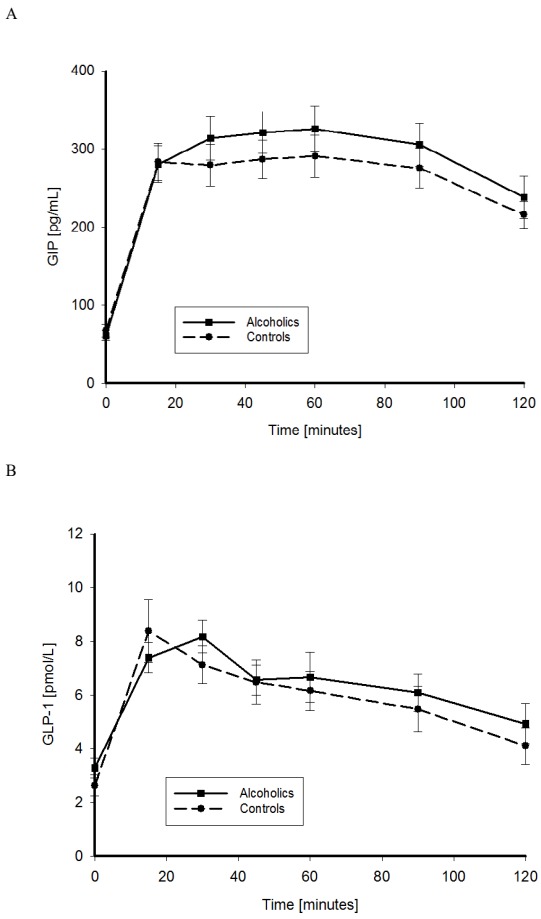


**Figure 2.** Glucose-dependent insulinotropic polypeptide (GIP) (A) and Glucagon-like peptide-1 (GLP-1) (B) secretion during the oral glucose tolerance test (oGTT). GLP-1 and GIP secretion in response to oGTT is not different between patients with alcoholic liver disease and controls. Means ± SDs are given.

**GLP-1 and GIP (Figure 2)**

After oral glucose ingestion, intact GLP-1 and total GIP increased promptly to reach maximum levels after 30 minutes for GLP-1 and 60 minutes for GIP. Thereafter, GLP-1 and GIP gradually declined during the 120 minutes observation period, but did not reach baseline values.

The AUC´s (0-120 min) for GLP-1 were in patients with alcoholic liver disease 785.5±277.7 vs. 713.3 ±338.3 pmol x min/L (n.s.) in controls. The corresponding values for GIP were 33853.2±13365.6 vs. 31267.2±11179.7 pg x min/mL (n.s.) respectively.

## Discussion

We examined the responses kinetics of incretins and insulin after oral glucose tolerance test in alcohol dependent patients with alcoholic liver disease in the early withdrawal state and abstinent control subjects. Despite long term and high daily alcohol abuse, no alterations in incretin and insulin secretion could be observed. There was a tendency towards decreased insulin sensitivity and increased insulin resistance in patients with alcoholic liver disease, but the response curves to an oral glucose tolerance test were similar in both groups, as were the levels of GLP-1 and GIP. Alcoholic liver disease seems therefore not to be associated with disturbances in the entero-insular axis.

Chronic alcohol consumption is associated with alterations in the peptidergic nerve system and endocrine cells involved in peptide secretion in the duodenal mucosa [10]. The observed alterations are however mild and functional data are rare. In one study it was demonstrated that in chronic alcohol consumers insulin and c-peptide secretion was diminished while the incretin effect was unaltered, which might indicate an early beta-cell dysfunction but an intact entero-pancreatic axis [14]. Our data from direct determinations of incretin hormone levels after an oral glucose tolerance test are in accordance with these observations; however we were unable to find a significant alteration in glucose and insulin homeostasis in our patients. A reason might be that carbohydrate intolerance in alcoholics is largely dependent on caloric malnutrition [15-17]. Our patients were however at least for three days on a normocaloric diet with prophylactic thiamine substitution and had a normal BMI indicating absence of significant malnutrition.

A direct effect of the medication of our study patients with Tiapride and Carbamazepine on the investigated parameters cannot completely be ruled out. Incretin hormones are metabolized by the enzyme Dipeptidyl peptidase-IV (DPP-IV). We did not measure DPP-IV activity in our study, but in studies performed with patients suffering from major depression and or schizophrenia, no effect of neuroleptics and or antidepressants on serum DPP-IV activity were detected [18-20], therefore disturbances in incretin metabolism appears unlikely. Furthermore, the incretin kinetics after the oral glucose tolerance test were similar in alcoholic and non-alcoholic subjects, which does not indicates lower serum peptidase activity in our alcohol-dependent patients [11].

Ultrasound is widely used as the first-line diagnostic test in patients with abnormal liver enzymes. In our patients with alcoholic liver disease only ALT showed a significant variation with the degree of hepatic steatosis, however no correlation was found for GGT, AST or HOMA-IR. This is in contrast to findings observed in patients with non-alcoholic steatosis [21] and may underline the different mechanisms involved in the development of hepatic steatosis in alcoholic and non-alcoholic fatty liver disease.

A limitation of our study is, that we did not determine the degree of alcoholic liver disease by histological examination. However, studies performed in alcoholic patients with hepatic histology found alterations in insulin resistance, even in the presence of normal liver histology [22], therefore, we could also expect alterations in glucose metabolism in our patients.

In contrast to alcoholic liver disease, non-alcoholic fatty liver disease is accompanied by several alterations in glucose tolerance, ß-cell function and also in the secretion of the incretin hormone GLP-1 [8]. These pathophysiological findings have led to the evaluation of GLP-1 agonists for the treatment of NAFLD [23]. The GLP-1 related mechanisms (enhanced hepatic fatty acid oxidation, lipid export and insulin sensitivity) decrease liver inflammation and apoptotic liver injuries [24, 25]. And in deed, in a phase 2 randomized controlled trial, GLP-1agonists resolved NASH in a higher (39% of patients) proportion of patients than those given placebo (9% of patients) [26]. There are also data showing that GLP-1 agonists might be useful in the treatment of alcohol related disorders, since they are able to reduce alcohol intake [27]. Whether GLP-1 agonists can also be used for the treatment of alcoholic liver disease can not be concluded from our study, since we detected no alterations in the entero-insular axis in our patients with alcoholic liver disease in the early withdrawal state.

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The authors report no conflicts of interest.

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