Ethanol With a Mixed Meal Decreases the Incretin Levels Early Postprandially and Increases Postprandial Lipemia in Type 2 Diabetic Patients

Marian Dalgaard, Claus Thomsen, Birthe M. Rasmussen, Jens J. Holst, and Kjeld Hermansen

Increased postprandial lipemia is a risk marker of cardiovascular disease (CVD). While moderate alcohol drinking is associated with a reduced risk of CVD in nondiabetic and type 2 diabetic patients, it is also known that alcohol increases postprandial triacylglycerol levels. The incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), are important hormones from the gut that enhance nutrient-stimulated insulin secretion. Their responses to a moderate alcohol dose in type 2 diabetes have not previously been studied. We sought to determine how alcohol influences postprandial lipid and incretin levels in patients with type 2 diabetes when taken in combination with a fat-rich mixed meal. Eleven patients with type 2 diabetes ingested on 3 separate days in random order 3 different meals containing: 100 g butter alone or 100 g butter in combination with 40 g alcohol and 50 g carbohydrate, or 100 g butter and 120 g carbohydrate. The meal with alcohol and 50 g carbohydrate was isocaloric to that of 120 g carbohydrate. Triacylglycerol levels were measured after separation by ultracentrifugation into a chylomicron-rich fraction with Svedberg flotation unit values (Sf) > 1,000, and a chylomicron-poor fraction with Sf < 1,000. Supplementation of a fat-rich mixed meal with alcohol in type 2 diabetic subjects suppressed GLP-1 early in the postprandial phase and increased the late triacylglycerol responses compared with the 2 other meals. In the chylomicron-rich fraction, both triacylglycerol and cholesterol were increased by alcohol. No significant differences in high-density lipoprotein (HDL)-cholesterol levels were seen. Isocaloric amounts of carbohydrate and alcohol suppressed equally the postprandial free fatty acid levels, but carbohydrate increased the postprandial glucose, GIP, and insulin levels the most. Early in the postprandial phase, alcohol suppresses the incretin responses and increases the late postprandial triacylglycerol levels in type 2 diabetic patients. Whether this reflects an alcohol-induced suppression of the incretin response, which adds to the alcohol-induced impairment of triacylglycerol clearance in type 2 diabetic patients, remains to be elucidated.

TYPE 2 DIABETES mellitus is a growing health problem in industrialized and developing countries.[1,2] Its mortality derives mainly from cardiovascular disease (CVD), which is several times higher in type 2 diabetic men[3] and women.[4-6] Type 2 diabetes is a central component of the metabolic syndrome, which consists of a cluster of other CVD risk factors, including abdominal obesity, insulin resistance, hypertension, and dyslipidemia with increased triacylglycerol and low high-density lipoprotein (HDL)-cholesterol concentrations.

Treatment of dyslipidemia is often based on measurements of fasting lipid levels. In humans, the postabsorptive phase spans most of the 24 hours of the day. In 1979, Zilversmit[7] suggested that atherogenesis is a postprandial phenomenon, and a positive association between increased and extended postprandial lipemia and clinical atherosclerotic manifestations has been found.[8-11] Elevated fasting triacylglycerol is an important predictor of a greater postprandial increase in triacylglycerol concentrations and a slower rate of chylomicron clearance.[12] Chen et al[13] showed that type 2 diabetic patients display an exaggerated postprandial triacylglycerol response compared with nondiabetic individuals, even when they are carefully matched for fasting plasma triacylglycerol levels. Insulin resistance, diet, current smoking, and alcohol consumption also influence the postprandial lipid response.[14,15] The exaggerated postprandial lipid response seen in type 2 diabetes may be one of the factors responsible for the increased CVD morbidity in this group of patients.

Long-term moderate alcohol consumption is associated with a reduced risk of CVD in patients with and without diabetes,[16-20] however, acute alcohol intake is known to increase postprandial triacylglycerol responses in healthy people.[21-25] The incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), are important hormones from the gut that enhance nutrient-stimulated insulin secretion. This is the so-called incretin effect.

Insulin and GIP stimulate lipoprotein lipase (LPL),[26,27] a central enzyme in hydrolysis of triacylglycerol. In healthy, as well as in type 2 diabetic patients, we have previously seen a possible relationship between the fatty acid composition in the diet and the incretin responses, as well as the triacylglycerol metabolism in the postprandial phase.[28,29] The objective of the present study was to determine how a moderate amount of alcohol changes postprandial lipid and incretin responses in type 2 diabetic patients when taken in combination with a mixed meal versus an isocaloric mixed meal without alcohol or a fat-rich meal without alcohol.

MATERIALS AND METHODS

Subjects

Eleven patients, with diagnosed type 2 diabetes for 4.8 ± 4.0 years, participated in the study. The subjects were selected among outpatients of the Diabetes Clinic at Aarhus University Hospital, Denmark. Included patients were treated with diet or oral antihyperglycemic med-

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Table 1. Clinical Characteristics of the Type 2 Diabetic Patients

Age (yr)	62.8 ± 7.1
BMI (kg/m^2)	28.9 ± 3.2
HbA_{1c} (%)	6.4 ± 0.8
P-cholesterol (mmol/L)	6.1 ± 0.9
P-LDL (mmol/L)	4.0 ± 0.9
P-HDL (mmol/L)	1.4 ± 0.3
P-triacylglycerol (mmol/L)	1.7 ± 0.9

NOTE. Mean ± SD; n = 11; (5 females/6 males).

ication. They continued their regular oral antihyperglycemic medication during the trial except for metformin, which was withdrawn 3 weeks before the test.

Exclusion criteria included treatment with insulin, lipid-lowering medication, nonsteroidal anti-inflammatory drugs (NSAID), and α- and β-blocking agents. Clinical characteristics of the patients (5 females, 6 males) are given in Table 1. All patients were treated with diets, 1 patient with glubyride, 1 with glibenclamide, and 1 with metformin. All were nonsmokers with habitual, moderate alcohol consumption (7 to 21 drinks per week). No patients had clinical signs of neuropathy, and none had more than simplex retinopathy. Participants were fully informed of the experimental nature of the study and gave their written, informed consent to participate. The local ethical committee of Aarhus County approved the protocol.

Study Design

The study was performed on an outpatient basis. The experiments lasted for 8 hours and were performed with a minimum interval of 1 week. The mean duration of the study period was 57 days. For 72 hours preceding each study day, the patients ingested a diet with an energy distribution of 56% carbohydrate, 25% fat, and 19% protein. The dietician prescribed the diets, and the patients were supplied with bread, meat, cheese, and hot dishes. The food amount corresponded to individual energy requirements estimated by the Harris-Benedicts equation with adjustment for activity.[30] The patients were instructed to standardize and minimize their physical activity 3 days before study days. They were not allowed to drink alcohol 24 hours preceding the test. On the test days, following a 12-hour fast, the patients arrived at 7 AM after a minimum of physical activity. A catheter was placed in an antecubital vein, and basal blood samples were drawn 15 minutes after (baseline period). The test meal was ingested within 20 minutes; during the rest of the test day, they rested at the clinic. Blood samples were drawn every 60 minutes from baseline period, ie, t = 0 minute, to t = 240 minutes, and thereafter at t = 360 minutes and t = 480 minutes for analysis of plasma glucose, serum insulin, serum fatty acids, plasma triacylglycerol, cholesterol, GLP-1, and GIP. Plasma was anticoagulated with EDTA and immediately separated by centrifugation at 2,000 × *g* for 20 minutes at 4°C and kept frozen at −20°C until analyzed, except for GIP and GLP-1 samples that were stored at −80°C.

Trial Day Procedures

In a randomized order, the patients received an energy-free soup with 100 g butter (control- meal), control-meal plus 40 g alcohol and 50 g carbohydrate as white bread (alco-meal), or control-meal plus 120 g carbohydrate as white bread (CHO-meal). We have chosen a fixed amount of fat in all the test meals and varied the content of carbohydrate to obtain isocaloric condition between the alco- and the CHO-meals. The composition of the meals is shown in Table 2. The butter contained mainly saturated fatty acids (72% of total fat). The soup was chilled briefly and then butter was added. Sliced, raw leek was added to give taste.

Separation of Chylomicron-Rich and Chylomicron-Poor Plasma Fractions

To separate lipoproteins, the plasma samples were ultracentrifugated once to divide into chylomicron-rich and chylomicron-poor fractions. A 4-mL plasma sample was overlayered with 2 mL of a solution with density of 1,006 g/L in a Quick-seal tube (no. 344619) and was centrifuged in a SW 50.3 Ti fixed-angle rotor (both from Beckman Instruments, Palo Alto, CA) at 25°C for 30 minutes at 26,000 × *g*. Tubes were then sliced in a Beckman-slicer 2 mL from the top and the chylomicron-rich supernatant, with Svedberg flotation unit values > 1,000 was removed and brought to a final volume of 4 mL with saline. The infranatant layer, ie, the chylomicron-poor fraction contains the plasma proteins and remaining lipoprotein. Triacylglycerol and cholesterol concentrations were measured in plasma and in both fractions, whereas HDL cholesterol concentrations were measured only in the chylomicron-poor fraction.

Bioanalysis

Plasma glucose was measured by a glucose oxidase method (coefficient of variation [CV]: 3.8%) (Boehringer, Mannheim, Germany, MPR 3 166 391 Glucose/GOD-PAP Method).[31] Serum insulin concentrations were measured by an enzyme-linked immunosorbent assay method (CV: 1.7%).32 Plasma triacylglycerols, cholesterol, HDL-cholesterol (in the chylomicron-poor fraction only), and serum fatty acids were measured with standard enzymatic colorimetric assays by using commercial kits (Wako Chemicals, Neuss, Germany, code No.994-75409). Total GIP was measured by radioimmunoassay with the antiserum R65, monoiodinated human GIP and human GIP as standards after extraction of the peptide from plasma according a method described previously.[33] The sensitivity and detection limit of the assay is 1 pmol/L. The assay is highly specific for the GIP and does not cross-react with the 8-kd immunoreactive component of unknown nature that cross-reacts in most GIP assays. Plasma concentrations of total GLP-1 were measured as described previously against standards of synthetic GLP-1 7-36 amide (Proglucagon 78-106 amide)[34] by using an antiserum (code no. 89390) that can be used in a final dilution of 1:250 000. This gives the assay a detection limit of 1 pmol/L and has an intra-assay CV < 5% at 20 pmol/L. The antiserum is highly specific for the carboxy terminal of proglucagon 78-107 amide and reacts neither with glycine-extended GLP-1 (proglucagon 78-108) nor with proglucagon 78-106. Thus, it mainly reacts with GLP-1 of intestinal origin. The serum ethanol level was measured by gas chromatography using headspace technique (CV: 1% to 2%).[35]

Statistical Analysis and Calculations

For paired comparisons, 1-way repeated measures of analysis of variance (ANOVA) were used. Whenever data were not normally distributed or passed the Equal Variance Test, the Friedman Repeated Measures Analysis of Variance on Ranks was used. In case of statistical differences between groups, a Student-Newman-Keuls post hoc test was used (SigmaStat version 2.03, BMDP Statistical Software, Berkeley, CA). $P < .05$ was considered statistically significant. The trapezoidal rule was used to calculate the incremental area under the curve

Table 2. Composition of the Three Test Meals

	Control	Alco	CHO
Total energy (kJ)	3,193	4,605	4,603
Fat (E%)	98	69	72
Carbohydrate (E%)	1	4	24
Protein (E%)	1	1	4
Alcohol (E%)	0	26	0

Table 3. Plasma and Serum Concentrations in the Fasted State in Type 2 Diabetic Patients

	Control-Meal	Alco-Meal	CHO-Meal
P-glucose (mmol/L)	7.8 ± 1.5	7.7 ± 1.4	7.7 ± 1.2
S-fatty acids (mmol/L)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
P-triacylglycerols (mmol/L)	1.96 ± 0.90	1.79 ± 0.79	1.77 ± 0.92
S-insulin (pmol/L)	44 ± 24	44 ± 24	52 ± 22
P-GLP-1 (pmol/L)	14 ± 5	11 ± 5	12 ± 5
P-GIP (pmol/L)	12 ± 7	11 ± 6	14 ± 13

NOTE. Mean ± SD; n = 11; (5 females/6 males).

(iAUC). This method of calculation is derived from the summation of the mean plasma concentration for each time period above basal value, multiplied by the number of minutes in the time period. Values below basal value were calculated as null. The iAUC derived expresses both the duration and the magnitude of the plasma responses, while correcting for baseline values.

RESULTS

All subjects completed the study and ingested the test meals without problems. Body weight did not change significantly during the study period, 79 ± 6.7 kg at the start and 78.5 ± 6.2 kg at the end of the study ($P = .3$). The samples from 1 patient were sliced incorrectly after ultracentrifugation and, consequently, only data from 10 patients were used in the calculations of the fractionated lipids.

Plasma Triacylglycerols and Plasma Triacylglycerol-Rich Lipoproteins

Plasma and serum concentrations in the fasted state on the 3 test days are shown in Table 3, no significant differences were observed. As seen in Fig 1, the highest level of postprandial plasma triacylglycerols was 6 to 8 hours after the alco-meal and similar changes are seen in the lipid fractions (Fig 2). The triacylglycerol iAUC (480 minutes) was the highest for the alco-meal, while the control-meal and the CHO-meal did not differ significantly from each other (Table 4).

Plasma Cholesterol Responses

At 6 and 8 hours, a significant increase in the cholesterol level in the chylomicron-rich fraction was seen in response to alcohol (Fig 2). No significant differences between days in the cholesterol responses were found either in plasma, the chylomicron-poor fraction (data not shown), or the HDL-cholesterol levels.

Serum Fatty Acids

Maximal suppression from baseline of serum fatty acids (Fig 1) after the CHO-meal (−0.46 ± 0.16 mmol/L) did not differ

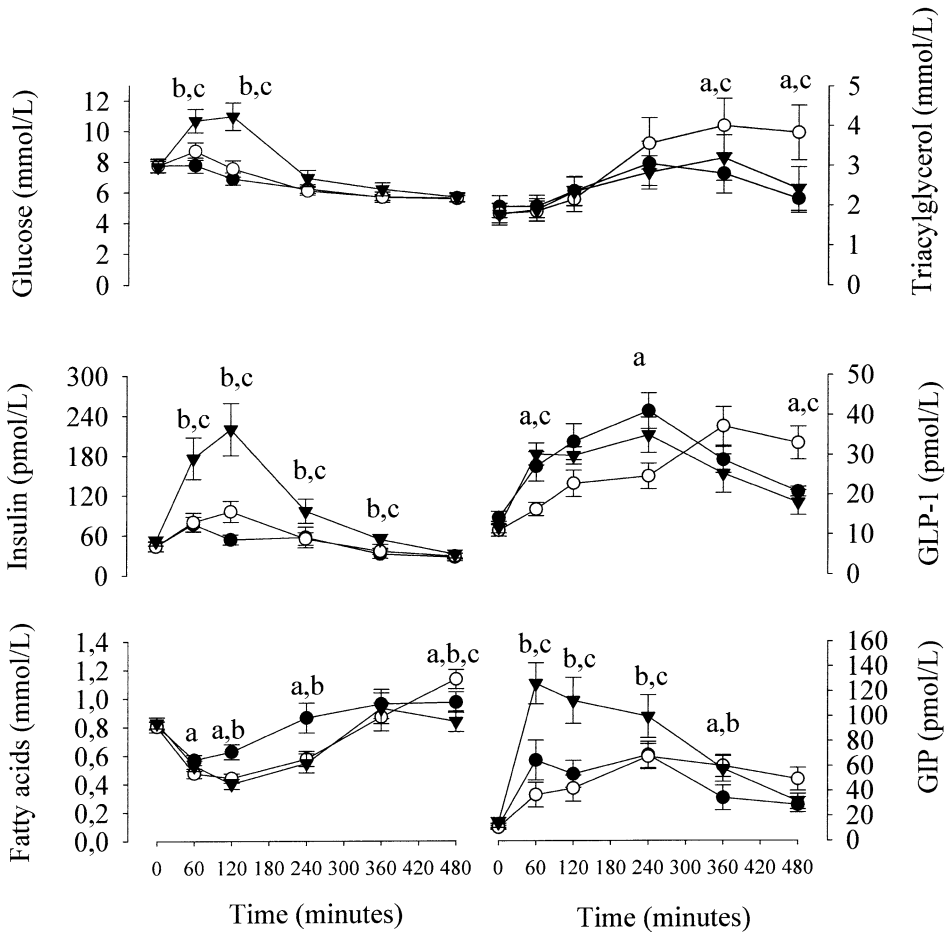

Fig 1. Mean (± SEM) postprandial plasma triacylglycerol, GLP-1, GIP, plasma glucose, serum insulin, and fatty acids in 11 type 2 diabetic patients to a control meal of soup with 100 g butter (●), the control-meal plus 40 g alcohol and 50 g carbohydrate (○), and the control-meal plus 120 g carbohydrate (▼). Significant difference between (●) and (○) is symbolized with a, between (●) and (▼) with b, and between (○) and (▼) with c. Repeated measures ANOVA.

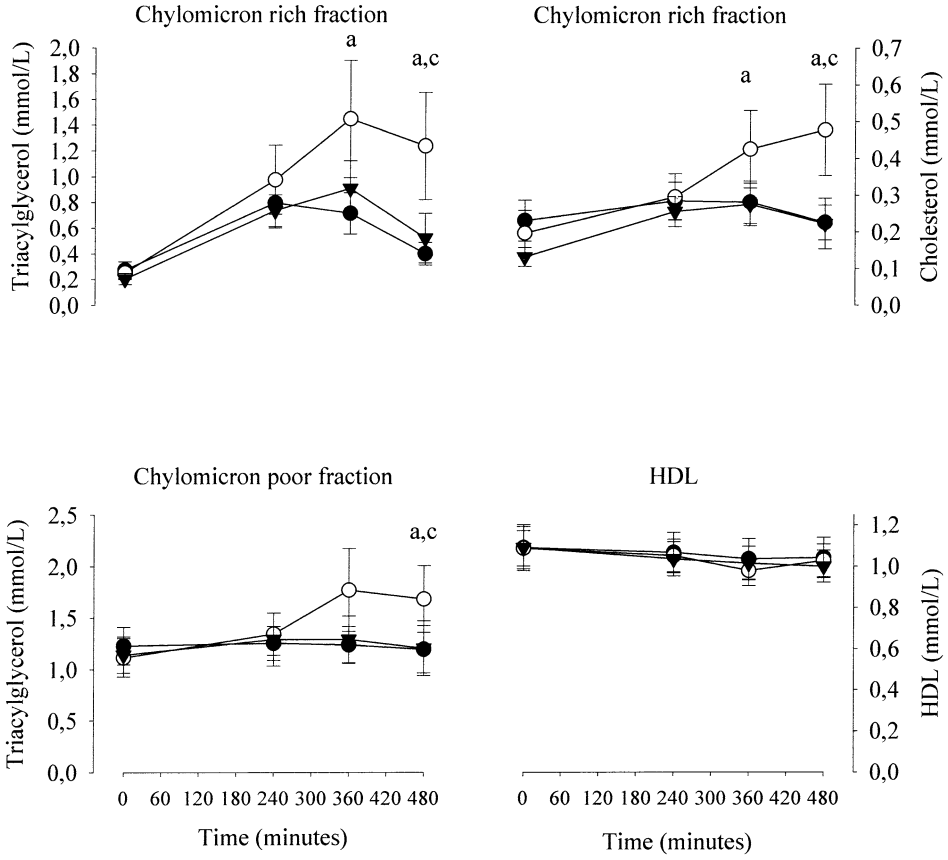

Fig 2. Mean (± SEM) postprandial plasma triacylglycerol responses in the chylomicron (CM)-rich and CM-poor fraction and cholesterol in CM-rich fraction and HDL in the CM-poor fraction in 10 type 2 diabetic patients to a control-meal of soup with 100 g butter (●), the control-meal plus 40 g alcohol and 50 g carbohydrate (○), and the control-meal plus 120 g carbohydrate (▼). Significant difference between (●) and (○) is symbolized with a, between (●) and (▼) with b, and between (○) and (▼) with c. Repeated measures ANOVA.

significantly from the alco-meal (−0.4 ± 0.11 mmol/L). After 8 hours, the level of free fatty acids in response to the alco-meal was significantly elevated compared with the 2 other meals.

GLP-1 and GIP

Table 4 shows the iAUC. The lowest increase in GLP-1 was seen the first 4 hours after alcohol, compared with both the control- and the CHO-meal. As illustrated it Fig 1, the GLP-1 response curve to the alco-meal was subdued after 60 minutes, while it was enhanced above the other test meals at 480 minutes. Despite the differences in carbohydrate content between the control- and the CHO-meal, no statistical differences in GLP-1 responses were observed between the 2 (Fig 1).

The iAUC for GIP was highest in response to the CHO-meal, persisting throughout the entire test. The plasma response curves for GIP (Fig 1) shows an increase from the fasting values in response to all the test meals, the highest levels seen in the CHO-meal and lowest for the control- and alco-meal. Eight hours after the test meals, no significant differences between days were observed for GIP.

Table 4. Incremental Areas Under the Curve in Type 2 Diabetic Patients to Meals of Soup Plus 100 g Butter (Control-Meal) Consumed Alone or Plus Alcohol (40 g) and 50 g Carbohydrate (Alco-Meal) or Carbohydrate (120 g) (CHO-Meal)

	Control-Meal	Alco-Meal	CHO-Meal
Triacylglycerol (mmol/L × 240 min)*	108 (33; 136)	75 (42; 231)	105 (83; 146)
Triacylglycerol (mmol/L × 480 min)	$301^{x} \pm 303$	$614^{x,y} \pm 488$	$397^{y} \pm 255$
GLP-1 (pmol/L × 60 min)	$387^{x} \pm 355$	$161^{x,y} \pm 178$	$551^{y} \pm 262$
GLP-1 (pmol/L × 240 min)	$4{,}162^{x} \pm 2{,}674$	$2{,}236^{x,y} \pm 1{,}322$	$4{,}113^{y} \pm 1{,}753$
GLP-1 (pmol/L × 480 min)	8,116 ± 4,648	7,516 ± 1,675	7,500 ± 3,974
GIP (pmol/L × 60 min)	$1{,}593^{x} \pm 1{,}527$	$783^{y} \pm 918$	$3{,}352^{x,y} \pm 1{,}568$
GIP (pmol/L × 240 min)*	$9{,}180^{x}$ (5,858;14,768)	$6{,}960^{y}$ (3,345;9,930)	$17{,}460^{x,y}$ (14,243;25,095)
GIP (pmol/L × 480 min)*	$13{,}830^{x}$ (12,472;24,968)	$18{,}690^{y}$ (13,733;23,732)	$29{,}640^{x,y}$ (23,693;37,343)
Glucose (mmol/L × 480 min)*	0^{x} (0;17)	93^{x} (32;139)	456^{x} (399;629)
Insulin (pmol/L × 480 min)*	$2{,}520^{x}$ (1,425;8,678)	$8{,}520^{y}$ (4,590;11,910)	$25{,}470^{x,y}$ (17,430;40,905)

NOTE. Mean ± SD; n = 11; (5 females/6 males). Values sharing a common letter in a row (x or y) are significantly different at $P < .05$.
*Values are given as median, (25% and 75% quartile) since the normality test failed.

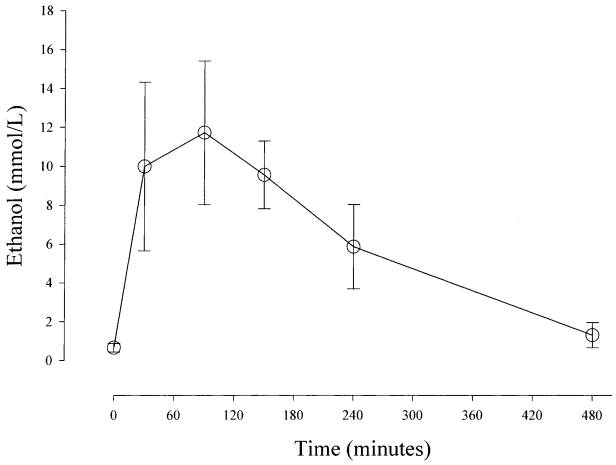

Fig 3. Mean (± SD) postprandial serum levels of ethanol in 11 type 2 diabetic patients in response to a meal with 100 g butter plus 40 g alcohol and 50 g carbohydrate (○).

Plasma Glucose and Serum Insulin

Glucose and insulin concentrations in the fasted state are shown in Table 3; no significant differences between days were observed. The iAUC for glucose and insulin responses were significantly higher after the CHO-meal than after the control- and alco-meal (Table 4).

Serum Ethanol

Serum ethanol concentrations reached a peak value of 11.7 ± 3.7 mmol/L after 90 minutes and returned to basal levels before the end of the 8-hour period as shown in Fig 3.

DISCUSSION

This study shows that 40 g of alcohol in a mixed meal increases the triacylglycerol and cholesterol levels in the chylomicron-rich fraction late in the postprandial period in type 2 diabetic patients. GLP-1 responses are reduced 60 minutes after ingestion of alcohol. The carbohydrate-rich meal induced the highest increase in glucose, insulin, and GIP. Maximal suppressions of fatty acids were alike in the isocaloric CHO- and alco-meal.

Alcohol has been shown to reduce the oxidation of free fatty acids and increases the esterification into triacylglycerol.[36] In healthy men drinking 24 g of alcohol, Siler et al[37] observed that 77% was converted directly to acetate and that the rate of appearance for plasma free fatty acids decreased significantly together with a 47% reduction in fatty acid concentrations. Acetate is known to inhibit lipolysis,[38,39] and a reduction of hepatic LPL in response to 40 g alcohol has previously been shown.[40] In our study, we found 1 to 2 hours after the alco- and CHO-meal a maximal suppression of fatty acids from baseline by 45% and 52%, respectively. It seems that isocaloric amounts of alcohol and carbohydrate suppress fatty acid levels equally, but probably by different mechanisms; alcohol by the previously mentioned ways and carbohydrate via increased levels of glucose and insulin, suppressing fatty acid metabolism.[41] The results shown in Fig 1 indicate that alcohol increases the late postprandial triacylglycerol response, which is very much in line with what is seen in nondiabetic patients.[25]

We did not find any differences in HDL-cholesterol in the chylomicron-poor-fraction between the 3 study days. Some investigators have found transient HDL-cholesterol changes in response to acute alcohol ingestion.[40,42] It occurs that ingestion of a moderate dose of alcohol for some weeks is needed to increase HDL_3-cholesterol and the LPL activity in healthy men.[43]

The potential physiologic role GLP-1 and GIP play in the lipid metabolism is not unambiguous. Villanueva-Penacarrillo et al[44] found that GLP-1 in physiologic levels exerted a lipogenic action in human adipocytes, while Bertin et al[45] did not find any direct effect of GLP-1 in vivo on the lipolysis rate. In type 2 diabetic patients, Toft-Nielsen et al[46] indicate that they did not detect changes in plasma levels of fatty acids or triacylglycerol after subcutaneous infusion of GLP-1 (7-37). Compared with healthy subjects, type 2 diabetic patients seem to have normal or slightly decreased postprandial GIP responses and markedly reduced GLP-1 responses.[47,48] GIP and insulin have been found to stimulate LPL.[27,49] In healthy subjects, Jackson et al[50] found that GIP levels correlated with hepatic LPL activity.

This study suggests that alcohol in combination with a fat-rich mixed meal reduced the initial postprandial GIP and GLP-1 responses. Among several other factors, the reduction of GLP-1 and GIP might participate in the alcohol-induced increase in the postprandial triacylglycerol level in type 2 diabetic patients, eg, due to a lower release of insulin secondary to lower incretin levels. We cannot totally exclude that the lower carbohydrate content in the alco-meal may have contributed to the lower GLP-1 responses compared with the CHO-meal. The conclusion might have been different had a control meal with 100 g butter and 50 g carbohydrate been included in the study. However, it is noteworthy that the alco-meal, despite its 50 g of carbohydrate, also causes a lower GLP-1 response than the control meal (fat without carbohydrate) irrespective that carbohydrate is known to stimulate the GLP-1 secretion (Fig 1 and Table 4). This points to an alcohol-induced suppression of GLP-1. Carbohydrate is a powerful stimulator of GIP secretion. If ethanol did not have any suppressive effect on GIP secretion, we would have expected to find GIP values above the values in the carbohydrate-free control-meal, due to the 50 g carbohydrate in the alco-meal. However, the responses were not statistically significant. Forty gram of ethanol seems, at least, to be able to eradicate the stimulation that 50 g carbohydrate caused on the release of GIP.

This supports our hypothesis that ethanol suppresses or delays the secretion of GIP and GLP-1 early in the postprandial phase.

Differences in rate of absorption could be another explanation for the differences we find. Alcohol is known to influence gastric emptying,[51] and GLP-1 is an inhibitor of gastric emptying and gastric acid secretion.[52,53] We did not measure gastric emptying directly; however, the time courses of serum insulin and fatty acids were similar in control- and alco-meals, so the alcohol in the amounts we gave probably did not delay the gastric emptying.

Our findings contrast with Svartberg et al[54] who found no

impact of ethanol on the GLP-1 responses. The reason for this discrepancy may be caused by the fact that we have studied type 2 diabetic subjects, and the investigation of Svartberg et al was performed in healthy subjects. In addition, they used an intravenous glucose tolerance test that is known to induce lesser stimulation of GLP-1 secretion than oral glucose.[55,56]

In conclusion; supplementation of alcohol to a fat-rich mixed meal in type 2 diabetic subjects increased the late triacylglycerol responses and suppressed or delayed the incretin responses in the postprandial period. Whether this reflects an alcohol-induced suppression of the incretin response, which adds to the alcohol-induced impairment of triacylglycerol clearance in type 2 diabetic patients, remains to be elucidated. Postprandial studies involving long-term intervention with alcohol in type 2 diabetic patients might reveal important insight to how alcohol exerts its cardioprotective effect. Sharret et al[14] found interestingly that regular moderate alcohol drinking is associated with a reduction of the postprandial lipid responses in Caucasian men. Future studies of the acute and chronic effects of alcohol in vivo on the incretin secreting K cells and the L cells might answer some of the questions this study raises.

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