Differential Postprandial Lipoprotein Responses in Type 2 Diabetic Men with and without Clinical Evidence of a Former Myocardial Infarction

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Abstract

Postprandial lipemia plays an important role in the development of coronary heart disease through an elevation of triglyceride-rich lipoproteins. In type 2 diabetic male subjects, our aim was to compare postprandial lipemia in a high-risk population with former myocardial infarction (MI) with that of a lower risk population free of clinically detectable heart disease. 32 male type 2 diabetic subjects were included in the study. We matched 17 cases with a verified history of MI with 15 controls according to age, BMI, HbA1c, diabetes duration, smoking, and treatment of diabetes. Ongoing metformin, insulin, or lipid lowering pharmacological treatment were exclusion criteria. After a maximal exercise tolerance test and echocardiography, the subjects underwent a hyperinsulinemic, euglycemic clamp and a vitamin A fat loading test. Plasma triglyceride levels in the case group were significantly higher after 360 minutes (4.6 ± 3.1 vs. 2.8 ± 1.8 mmol/l, p = 0.04) and 480 minutes (3.6 ± 2.2 vs. 2.4 ± 2.4 mmol/l, p = 0.03), as was the incremental Area Under the Curve (iAUC) for the whole period (560 ± 452 vs. 297 ± 214 mmol×480min./l; p = 0.048). In addition, the retinyl palmitate responses in the chylomicron-fraction from the case group were significantly higher (iAUC 311,502 ± 194,933 vs. 187,004 ± 102,928 ng×480min./ml; p = 0.035). Type 2 diabetic males with prior MI had higher postprandial triglyceride-rich lipoprotein responses than those without MI, indicating that high responses may be a marker for a high-risk population.

Keywords: lipoproteins · myocardial infarction · postprandial period · triglycerides · type 2 diabetes

Introduction

The increased risk of cardiovascular disease, e.g. coronary artery disease (CAD), in type 2 diabetes is well recognized [1]. The 2- to 4-fold increased morbidity and mortality to cardiovascular disease in diabetes [1, 2] is associated with both diabetes-specific risk factors [3] and increased frequency of conventional risk factors for cardiovascular disease [4]. The absolute and relative mortality risks are greater once myocardial infarction (MI) has occurred [5, 6]. The prognosis of coronary heart disease in type 2 diabetic subjects without previous myocardial infarction may be comparable to the prognosis in non-diabetic subjects with prior myocardial infarction [5, 6], although this has recently been contested [7].

The diabetic dyslipidemia that is characterized by hypertriglyceridemia, low HDL-cholesterol and the ac-
cumulation of remnant and small dense LDL particles is one of the major risk factors contributing to cardiovascular disease in type 2 diabetes [8]. Plasma lipids and lipoproteins are generally measured in the fasting state, but in Western societies, most of our lives are spent in the postprandial state. In 1979, Zilversmit [9] put forward the hypothesis describing atherosclerosis as a postprandial phenomenon. Subsequent studies in non-diabetic subjects have confirmed that patients with angiographically verified CAD versus subjects without CAD have increased postprandial levels of triglyceride and intestinally-derived triglyceride-rich lipoproteins (TRL) (chylomicrons and their remnants) [10-14]. Little information exists on postprandial lipemia in type 2 diabetes with and without CAD. Syvanne et al. [15] were unable to distinguish type 2 diabetic patients with and without CAD on the magnitude of postprandial lipemia after an oral fat load. In a cross-sectional angiographic study in type 2 diabetes, the same group found delayed clearance of both hepatic and intestinal lipoproteins, however, without revealing any difference between a group with severe CAD and a group with mild CAD [16]. We hypothesize that diabetic men with a prior myocardial infarction (MI) have a more severe form of lipid metabolic derangement than men without MI, a feature per se may contribute to the susceptibility to CAD. The present study was performed to compare postprandial lipemia in two matched groups of type 2 diabetic men with and without a verified previous MI.

Subjects and Methods

Subjects

Thirty-four type 2 diabetic men were recruited from the outpatients’ clinics at Aarhus University Hospital. They were all characterized as having type 2 diabetes according to the criteria given by WHO 1985 [17]. Cases had recovered from a myocardial infarction diagnosed on the basis of medical history, activities of cardiac enzymes (S-troponin T (TNT) or creatine kinase – myocardial band (CK-MB)), and/or appearance of Q waves and changes in ST or T segments on the electrocardiogram (ECG). Controls had no prior history of MI, negative maximal stress exercise ECG tests, and echocardiograms showing no sign of prior MI. Criteria of inclusion were: Caucasian origin; diabetes treated only with diet, Acarbose and/or sulfonylurea. Subjects with alcohol abuse or treated with lipid-lowering drugs were excluded. None of the patients had known diabetic complications except for background retinopathy and microalbuminuria.

One case subject withdrew his informed consent after the first visit and one control subject was excluded due to a positive stress exercise ECG. The two study groups subsequently contained 17 cases and 15 controls. Case and control subjects were matched according to age, Body Mass Index (BMI), glycated hemoglobin (HbA1c), diabetes duration, smoking, and treatment of diabetes. Seven case and two control subjects took ACE-antagonists. Seven case subjects took β-blockers. Seventeen case and two control subjects took acetylsalicylic acid. Five case and one control subject took calcium antagonists and loop diuretics. They took the prescribed medicine throughout the study and kept an unchanged dose of medicine. Usual morning medication was postponed until the test was completed.

The study was conducted in accordance with the Declaration of Helsinki, was approved by the local ethics committee, and all subjects gave their written informed consent before entering the study.

Study design

Subjects attended three study days. A standard ECG, a maximal stress exercise test, as well as an echocardiography, were performed at day one. At study day two, fasting and postprandial responses were measured after a fat-rich meal. On study day three, a euglycemic hyperinsulinemic clamp and a 24-hour ambulatory blood pressure measurement were carried out.

Methods

One experienced investigator performed all the echocardiographic examinations with a 2.5 MHz transducer and standard clinical ultrasound equipment. The investigator was unaware of patient history. The left ventricle ejection fraction was calculated by the method of Teichholz et al. [18] and given as the mean of 3 to 4 readings from M-mode echocardiograms. Further, a 9-segment wall motion index of the left ventricle was recorded in 2D-mode [19, 20]. A conventional 12-lead ECG was obtained, as well as a maximum exercise tolerance test. A standard protocol with an initial workload of 25 watts (W) and incremental increase in workload with 25 W every two minutes was used [21].

For three days preceding the oral vitamin A fat loading test, subjects ingested a high-carbohydrate diet provided by the dietitian. Food amounts corresponded
to individual energy requirements [22]. Subjects fasted overnight from 22:00. Morning medication was postponed until after the test. On arrival, an indwelling catheter was inserted into an antecubital vein. The test meal was ingested at 08:00. The meal consisted of 150 ml non-caloric soup, 100 g salted butter (20 % water), 25 g sliced raw leek, and 94 g white bread. Total energy content was 1027 kcal with 77 E% fat, 20 E% carbohydrate, and 3 E% protein. Total fat amounted to 86.6 g (54.3 g saturated fat (SAFA), 21.9 g monounsaturated fat (MUFA), and 4.4 g polyunsaturated fat (PUFA)). Carbohydrate content was 51 g and protein 8 g. The meal contained 220 mg of cholesterol. The meal was ingested within 10 minutes and was served with 250 ml tap water. With the first spoonful of soup, the subjects took a standard dose of vitamin A (30 mg, 100,000 IU) in tablet form (Medic Team, Birkeroed, Denmark) as a means of quantifying lipoproteins of intestinal origin, i.e. chylomicrons and chylomicron remnants [23]. Ingestion of vitamin A causes retinyl ester labeling of chylomicrons [24]. Blood was sampled for measurements in plasma of glucose, insulin, free fatty acids (FFA), total cholesterol, triacylglycerol (TG), retinyl palmitate (RP), GLP-1, and GIP at preplanned intervals for 8 hours. EDTA-samples were instantly put into ice in a closed box. Plasma was then immediately separated by centrifugation at 2300 × g for 10 minutes at 4°C and kept frozen at −80°C until analyzed or further subdivided by ultracentrifugation.

To separate lipoproteins, the EDTA plasma samples were subjected to a single ultracentrifugation step to divide the samples into chylomicron-rich and chylomicron-poor fractions according to the method previously described in detail [25]. Ambulatory blood pressure was measured by SpaceLabs model 90207 (Redmond, Washington, USA) [26]. Urine was collected for 24 hours.

An indwelling venous catheter for blood sampling was placed in the back of the left hand, which was heated in order to approximate arterialized blood values [27] and a hyperinsulinemic, euglycemic clamp was performed as described by DeFronzo [28]. The M-value (the rate of glucose infusion per kilo body weight during steady state [28]) was calculated from the glucose utilization during the 30 minutes steady state period. Statistical analysis

The number of participants needed to obtain sufficient statistical power (i.e., > 0.8) was calculated a priori. Results are presented as cases versus controls (mean ± SD) with the exception of postprandial responses. Mean ± Standard Error of the Mean (SEM) as error bars is used here for clarity of presentation. When the data was consistent with the hypothesis of normality an unpaired t-test was used for statistical analysis; otherwise the Mann-Whitney Rank Sum Test was used. The number of individuals in contingency tables was analyzed by a Fisher Exact Test. Incremental areas under the curve (iAUC) correlating best to responses [38] were calculated using the trapezoidal rule from Matthews et al. [39]. One-way ANOVA (repeated measures) was applied to the responses of the subjects to the meal test. Statistical differences were then located using the Student-Newman-Keuls multiple comparisons test. Statistical analysis was done using SigmaStat for Windows version 2.03 (SPSS Inc.
Chicago, Illinois, USA). P < 0.05 was considered statistically significant.

Results

Clinical characteristics

The clinical characteristics of the study groups are summarized in Table 1. Subjects were matched according to age, weight, BMI, HbA1c, smoking, and known diabetes duration for which we found no statistical differences. Insulin sensitivity measured by the hyperinsulinemic, euglycemic clamp did not differ significantly. Blood pressure was lower in the MI group, but the difference was not statistically significant.

Table 1. Characteristics of the study groups

| Parameter (dimension) | MI group (n = 17) | Control (n = 15) | p   |
|-----------------------|------------------|-----------------|-----|
| Age (yr)              | 64.80 ± 8.30     | 62.50 ± 8.50    | 0.45|
| Weight (kg)           | 93.30 ± 12.10    | 93.10 ± 13.40   | 0.97|
| BMI (kg/m²)           | 30.60 ± 4.10     | 29.90 ± 4.90    | 0.65|
| HbA1c (%)             | 7.55 ± 0.01      | 7.51 ± 0.02     | 0.69|
| Smoking (n)           | 7                | 6               | 0.77|
| Diabetes duration (yr)| 5.20 ± 4.00      | 3.50 ± 2.60     | 0.16|
| Insulin sensitivity   | 3.60 ± 1.80      | 4.90 ± 3.20     | 0.40|
| Total cholesterol     | 5.52 ± 1.23      | 5.27 ± 0.73     | 0.49|
| HDL-cholesterol       | 0.95 ± 0.29      | 1.11 ± 0.24     | 0.10|
| LDL-cholesterol       | 3.51 ± 1.05      | 3.39 ± 0.57     | 0.48|
| Triglycerides         | 2.35 ± 1.07      | 1.80 ± 1.28     | 0.06|
| Free fatty acids      | 0.72 ± 0.20      | 0.70 ± 0.22     | 0.78|
| Albuminuria (mg/24h)  | 77.00 ± 108.00   | 30.00 ± 44.00   | 0.06|
| 24-h systolic BP      | 131.90 ± 17.20   | 136.70 ± 15.80  | 0.42|
| 24-h diastolic BP     | 78.10 ± 10.30    | 83.50 ± 11.10   | 0.16|

Legend: Data are means ± SD. MI: former myocardial infarction, n: number of patients, BP: blood pressure. p-values represent matching impact.

Echocardiography and exercise stress ECG showed a clear distinction between the two groups. Cardiac characteristics of the study groups are summarized in Table 2. Oxygen uptake is expressed in multiples of resting energy requirements (METs). In the MI group, eight subjects had suffered a Q-wave MI and nine subjects a non-Q-wave MI from 4 months to 18 years (mean 5 years) previously. During the stress test, eight subjects developed significant ST-segment depression and three subjects developed angina, one without significant ST-segment depression. In the control group, one subject had a pathological Q-wave, but with no history and with no sequelae of MI to be found in echocardiography and stress ECG. No one in the control group developed angina or significant ST-segment depression. No significant differences in apolipoprotein E isoforms were found.

Urinary excretion of albumin differed significantly with 154 ± 334 vs. 30 ± 44 mg/24h (p = 0.04), but with the exclusion of one extreme outlier from the MI group, excretion of albumin only tended to be significant with 77 ± 108 vs. 30 ± 44 mg/24h (p = 0.06).

Lipids and lipoproteins (Figure 1)

Fasting cholesterol values are summarized in Table 1. Fasting free fatty acids did not differ. FFA responses differed only at a single point at 60 minutes (0.55 ± 0.09 vs. 0.42 ± 0.16 mmol/l (p = 0.02)). Fasting lipid and lipoprotein levels showed no significant difference. Although fasting triglycerides tended to differ, it did not reach statistical significance: 2.35 ± 1.07 vs. 1.80 ± 1.28 mmol/l (p = 0.06). Plasma triglyceride levels in the case group were significantly higher after 360 minutes (4.6 ± 3.1 vs. 2.8 ± 1.8 mmol/l (p = 0.04)) and 480 minutes (3.6 ± 2.2 vs. 2.4 ± 2.4 mmol/l (p = 0.03)), as were the iAUC for the whole period (559.9 ± 452.0 vs. 296.6 ± 214.4 mmol×480min/l (p = 0.048)).

In the supernatant fraction, triglyceride eight-hour response (iAUC) did not reach a statistically significant difference (408.5 ± 326.9 vs. 262.4 ± 173.2 mmol×840min/l (p = 0.22)), nor did triglyceride eight-hour response in the infranatant fraction (26.6 ± 30.5 mmol×840min/l (p = 0.865)). Enrichment of the supernatant fraction with retinyl palmitate demonstrated a significantly higher response in the case group with an iAUC of 314,798 ± 200,837 vs. 187,004 ± 102,928 ng×480min/ml (p = 0.035). No significant
difference was found in the infranatant fraction with an iAUC of 93,678 ± 51,102 vs. 77,132 ± 30,263 ng×480min/ml (p = 0.396).

Table 2. Cardiac characteristics of the study groups

| Parameter                  | MI group (n = 17) | Control (n = 15) | p     |
|---------------------------|-------------------|------------------|-------|
| Wall Motion Index         | 1.60 ± 0.20       | 1.90 ± 0.10      | < 0.001|
| Ejection fraction         | 0.52 ± 0.09       | 0.61 ± 0.09      | 0.006 |
| Fractional shortening     | 0.26 ± 0.05       | 0.32 ± 0.05      | 0.002 |
| Diastolic volume (ml)     | 175.90 ± 57.40    | 127.10 ± 37.00   | 0.001 |
| End systolic volume (ml)  | 88.00 ± 43.50     | 52.20 ± 23.70    | < 0.001|
| Exercise time (min)       | 8.80 ± 2.20       | 12.30 ± 3.60     | 0.002 |
| Maximal exercise capacity (W) | 105.90 ± 26.60 | 151.70 ± 44.80   | < 0.001|
| Heart rate of expected (%) | 84.50 ± 11.70     | 97.70 ± 14.40    | 0.008 |
| Oxygen uptake (METS)      | 4.90 ± 1.00       | 6.90 ± 1.90      | < 0.001|

Legend: Data are means ± SD. METS: multiples of resting energy requirements.

Glucose and hormones (Figure 2)

No significant differences between the two groups were found in eight-hour responses measured as incremental area under the curve (iAUC) for glucose (p = 0.20) and insulin (p = 0.33). The insulin response presented a single significant difference at 240 min: 152.5 ± 63.3 vs. 100.8 ± 56.7 mmol/l (p = 0.02). No significant differences in iAUC for GIP (32,318 ± 13,226 vs. 29,478 ± 8,504 pmol×480min./l (p = 0.48)) and GLP-1 (7,559 ± 3,642 vs. 8,882 ± 6,831 pmol×480min./l (p = 0.49)) were found in 8-h responses.

Discussion

The present study demonstrated that type 2 diabetic men with prior MI had significantly higher responses of plasma triglycerides and retinyl palmitate-labeled lipoproteins of intestinal origin in the CM-rich fraction to a fat rich meal than a matched group without prior MI. These results contrast with the studies of Syvanne et al. [15] and Mero et al. [16], indicating that abnormal metabolism of postprandial lipoproteins in patients with type 2 diabetes has no relationship to CAD.

Our study corroborates previous investigations in non-diabetic subjects with CAD exhibiting enhanced postprandial lipemia [10-14]. Furthermore, type 2 diabetic patients have raised levels of postprandial remnant lipoproteins compared to non-diabetic subjects [15, 16, 40]. A long residence time of TG-rich remnant particles in circulation has been demonstrated in type 2 diabetic subjects [15, 41], in which total AUC was highly correlated to fasting TG, whereas iAUC was correlated to the postprandial TG responses [38]. The postprandial TG-rich lipoprotein metabolism is closely coupled with LDL and HDL metabolism. The long residence time of remnant particles results in an increased exchange of the core lipid cholesterol ester for TG between the TG-rich lipoprotein particles and LDL, and HDL cholesterol mediated by cholesteryl ester transfer protein (CETP). The process enriches LDL and HDL with TG, and hydrolysis by hepatic lipase results in smaller, denser LDL and HDL particles. This pattern further increases the risk of CAD in type 2 diabetes [15]. The major postprandial lipoprotein is the apo B48-containing chylomicron (CM) particle. Specific binding sites on the human monocyte/macrophage have recently been discovered [42], which suggests the existence of a mechanism that may explain the atherogenicity of these particles.

Syvanne et al. [15] and Mero et al. [16] found no apparent associations between CAD and postprandial lipemia in type 2 diabetic subjects. Syvanne et al. [15] suggested that the excessive alimentary lipemia in type 2 diabetic patients is to an equal extent present in individuals with and without CAD documented by coronary angiography showing at least 50% stenosis in one or more major coronary branches. The study of Mero et al. [16] corroborated these results showing that type 2 diabetic patients with mild and severe CAD verified angiographically have similar concentrations of postprandial apo B-48 and apo B-100-containing particles.

Various reasons for the contrasting results between their studies and ours may be provided e.g. by differences in a) our populations b) severity of CAD, c) diets and meal testing, d) medication, e) degree of matching of the control and case groups.

The subjects in Syvanne’s study [15] and ours were comparable regarding fasting glucose, HbA1c, apo E phenotype, and fasting cholesterol levels (total, LDL, and HDL). However, our subjects were about one de-
Age is known to be an independent risk factor for MI [44] and both fasting triglycerides and LDL-cholesterol increase with age, based on elevated VLDL apo B-100 secretion and delayed LDL apo B-100 clearance [45]. Our case group might also have had more severe CAD with verified MI, which was not demonstrated for their CAD subjects [15, 16]. Haffner et al. [5] have shown that the seven-year incidence rates of MI in Finnish type 2 diabetic subjects with and without prior MI at baseline were 45.0 % and 20.2 %, respectively. If angiography or thallium scintigraphy had been carried out in our study, the possibility of a different degree of CAD would have been further clarified.

Surprisingly, Syvanne [15] found a tendency towards lower average fasting triglycerides in the DM+CAD+ group than in the DM+CAD- group (1.88 versus 2.17 mmol/l, NS) even though fasting HDL-cholesterol implied an inverse relationship (1.08 versus 1.24 mmol/l, NS) quite comparable to our results. This could reflect that their case group might have changed diet according to cardio protective recommendations. Besides a 12-hour fast, Syvanne and Mero did not standardize dietary differences between the two groups. We provided a high-carbohydrate diet for three days preceding the meal test based on the findings that type 2 diabetic subjects then have only a very modest day-to-day variation in insulin sensitivity [46]. The fat loads were sufficient [47] and comparable providing 86.6 g fat in our regime, 78 g fat in the study of Syvanne [15], and about 50 g fat per surface square meter in Mero’s study [16].

The effects of unselective β-blockers on total cholesterol or LDL-cholesterol are negligible while triglyceride levels may be increased (10 to 40 %) and HDL-cholesterol levels decreased (5 to 20 %) [48]. β1-selectivity is associated with a more neutral effect i.e. in a group of type 2 diabetic subjects metoprolol did not significantly change fasting metabolic variables [49]. Metoprolol treatment has been shown to enhance fast-

Figure 1. Eight-hour responses of P-triglyceride (A), free fatty acids (B), retinyl palmitate in the supernatant fraction (C), and retinylpalmitate in the infranatant fraction (D). Data are means ± SEM. Black circles = MI group; White circles = control group. * p < 0.05.
ing and postprandial triglyceridemia in middle-aged non-diabetic men but did not significantly influence the postprandial responses of CM and CM remnants [50]. Most patients in the study of Syvanne [15] with CAD took \(\beta\)-blockers and several patients without CAD took metformin, which presumably should have exaggerated postprandial differences. In our study, seven out of 17 case patients took \(\beta\)-blockers (Metoprolol), whereas metformin treatment was an exclusion criterion. A further reason for the contrasting results could be that their case and control groups were not too well matched [15, 16]. Independent of triglycerides, smoking is a strong predictor of postprandial lipemia [51] with substantially increased RP and apolipoprotein B-48 responses. Thus, smoking was not a matching criterion of Syvanne et al. [15]. In our study, as well as in the study of Mero et al. [16], no significant difference in smoking status was found. Fifty percent of the control group in the study of Mero [16] received insulin versus 22% of the case group (p = 0.060). In our study, insulin therapy was an exclusion criterion. It should also be noted that the glycemic control in the control group of Mero et al. was significantly worse than in the CAD group (mean HbA1c 8.4 versus 7.4 %, p = 0.007). In our study, cases and controls had similar HbA1c and the M-values were not statistically different. Furthermore, duration of diabetes was significantly longer (11 years versus 7 years, p = 0.04) in Mero’s control group [16], which also had gender skewness with 50% females versus a nearly all male case group (p = 0.013), which both tend to reduce a possible difference. The metabolic control of type 2 diabetes and the duration of diabetes are important predictors of CAD in elderly subjects [52].

The responses of the duodenal incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) showed no statistical difference between the MI and non-MI groups. GLP-1, which has an insulinotropic effect and is known to inhibit gastric emptying, is being investigated as a possible treatment of hyperglycemia in type 2 diabetes. A possible con-

![Graph](image-url)
connection between the types of ingested fat in a test meal, the resulting postprandial triglyceridemia and the postprandial levels of incretins has been demonstrated earlier in healthy subjects [25] and in type 2 diabetic subjects [53].

Microalbuminuria is a risk factor for cardiovascular events. Our study corroborates the finding that the risk of cardiovascular events, e.g. MI, increases with the degree of albumin excretion [43] and that screening for albuminuria identifies people at high risk for CV events. In the 1998 WHO definition of the metabolic syndrome, microalbuminuria was included as one of four criteria together with dyslipidemia, central obesity and hypertension in subjects with insulin resistance, impaired glucose tolerance, or type 2 diabetes. In vitro and in vivo data support the notion that dyslipidemia contributes to glomerular and interstitial injury of the renal parenchyma. In turn, progressive renal disease may lead, at early stages, to compositional changes in lipoproteins that result in an atherogenic profile [54].

The small sample size of our study does not allow meaningful statistical stratification related to the presence/absence of risk markers such as hypertension, microalbuminuria or baseline triglyceride levels. Precaution regarding the results of our study with a limited number of participants should be exercised. Larger-scale, prospective long-term studies in type 2 diabetic subjects are needed to clarify whether a deranged postprandial lipid profile plays an important role for the susceptibility of CAD in type 2 diabetes.

In conclusion, excessive postprandial responses of total triglycerides and retinyl palmitate-labeled lipoproteins in the CM-rich fraction were observed in type 2 diabetic men with, rather than without, prior MI suggesting a reduced postprandial clearance and/or increased production. Given the atherogenicity of these changes, our results stress the importance of an aggressive therapeutical approach towards type 2 diabetic males with CAD. Larger-scale prospective longitudinal studies to evaluate markers of postprandial lipid metabolism related to hard endpoints in type 2 diabetic subjects are needed. The presence of excessive postprandial lipemia in type 2 diabetic subjects may be a marker of a high-risk population prone to experience atherosclerotic events.

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