CLINICAL STUDY

Association of postprandial and fasting triglycerides with traits of the metabolic syndrome in the Metabolic Intervention Cohort Kiel

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Abstract

Objective: Postprandial (pp) lipid metabolism is associated with insulin resistance and type 2 diabetes. In young men, pp triglycerides (TGs) are more strongly associated with traits of metabolic syndrome (MS) than fasting TGs. We established a cohort of middle-aged men selected for traits of MS and pp lipid metabolism to determine if fasting TGs or pp TGs are more closely related to MS.

Research design and methods: A total of 1558 men were characterized for MS. A total of 755 men underwent an oral metabolic tolerance test consisting of a standardized high-fat meal and an oral glucose tolerance test. Blood samples were drawn in the fasting state and hourly until 9 h to determine pp TGs and free fatty acids. Glucose and insulin were analyzed until 5 h pp.

Results: In the overall cohort, 329 subjects (21.1%) had a complete MS based on the Adult Treatment Panel III criteria, and 650 subjects (41.7%) had a complete MS based on the International Diabetes Federation criteria. The association of pp TGs with MS parameters was not stronger than the association of fasting TGs with them. Pp TGs were independently associated with β-cell function.

Conclusions: Pp TGs did not show a higher correlation with MS traits than fasting TGs. This finding is probably due to the high incidence of overweight subjects in this middle-aged cohort.

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Introduction

Truncal obesity, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and precocious atherosclerosis are common metabolic diseases in industrialized countries. Because of the frequent association of these diseases with specific pathophysiological features, their coincidence is characteristic of the metabolic syndrome (MS) phenotype. Each of these disorders is associated with an elevated consumption of saturated fatty acids (1–5).

The importance of the postprandial (pp) triglyceride (TG) metabolism in MS was demonstrated in several studies (6–10). It was shown that common dietary habits caused elevated serum TG levels for most parts of the day due to an elevation in pp TG levels (11). Recent studies have shown excessive pp TG levels and an altered free fatty acid (FFA) metabolism to be early signs of metabolic abnormalities, leading to insulin resistance syndrome in obese subjects with normal fasting TGs and in atherosclerotic subjects without cholesterol abnormalities (12, 13). In young, lean subjects and healthy offspring of diabetics, elevated pp TG levels were associated with insulin resistance, elevated proinsulin levels, increased intra-abdominal fat tissue and elevated pp thermogenesis and catecholamine and cortisol release, all of which are characteristic of MS (14–16). The distribution of pp TG maxima in these subjects followed a bimodal curve, suggesting the existence of a distinct subset of subjects with high pp TGs following a fatty meal and who exhibit the traits of MS (14).

However, the role of pp serum lipid levels in the development of MS still remains to be clarified. In order to elucidate this question, we established a population-based cohort of men who underwent an oral lipid tolerance test and an oral glucose tolerance test (OGTT). Because TG response depends on age and sex, only men in a narrow age span were selected. The objective of the study was to determine the association of pp TGs versus that of fasting TGs with the traits of MS.

Research design and methods

The Metabolic Intervention Cohort Kiel (MICK) study is a long-term, prospective, population-based cohort study of pp parameters and MS, and their association with
the development of type 2 diabetes. The cohort was assembled in Kiel, a city with ~250,000 people which is located on the Baltic Sea in northern Germany. The baseline evaluation was performed between September 2002 and March 2004.

Study population

A total of 1558 male subjects aged 45–65 years were recruited from the general population via the registration register containing all the permanent residents of the city of Kiel. A total of 15355 subjects were randomly contacted by a letter of invitation. A total of 875 subjects were willing to participate in the study, and the final prospective MICK consisted of 755 subjects who participated in the pp study. A total of 125 subjects were excluded on the basis of exclusion criteria. The study population represented the general population of men aged 45–65 years in the study area. The population sample was restricted to a narrow geographical region around Kiel and to an age spectrum of 45–65 years to avoid the known influence of age on TG levels and the prevalence of MS. Subjects with or without components of MS except type 2 diabetes were included in the study. Further exclusion criteria were diseases that impaired nutrient digestion or metabolism, an intake of lipid-lowering drugs or hormones, visceral surgery in the past 3 months, hypo- or hyperthyroidism, chronic renal disease, hepatitis, cholestasis, alcoholism, or cancer. All subjects gave prior written informed consent. The study was approved by the medical ethics committee of the University Clinic of Kiel.

Study design

At inclusion in the study, all participants were instructed by a physician to complete a standardized questionnaire concerning personal and family history, including lifestyle data, such as physical activity, smoking and alcohol consumption, dietary habits, and socio-economic situation. Weight was measured with an electronic scale to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm (Seca GmbH & Co., Hamburg, Germany), after the participants were asked to remove their shoes and jacket. Two kilograms of weight were subtracted for wearing clothes. Body mass index (BMI) was calculated as total body weight (kg) divided by squared height (m²). For waist and hip measurements, participants were asked to roll down their undergarments. Waist circumference was measured with a constant tension tape to the nearest 0.1 cm midway between the lower rib margin and the upper iliac spine, which in most instances was at the level of the umbilicus. Hip circumference was measured at the tip of the trochanter femoris. Waist and hip measurements were taken with the subjects in an upright position while breathing normally. Blood pressure was measured with the subjects in supine position after 5 min of rest with the cuff of a sphygmomanometer (Boso, Jungingen, Germany) at the same level as the heart. The subjects were instructed to take their usual medication during the test. Subjects were classified as hypertensive if they were being treated with antihypertensive medications or if their systolic/diastolic blood pressure (SBP/DBP) was ≥130/85 mmHg.

The health status of all the participants was further assessed by blood cell count and plasma levels of creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase (GGT), alkaline phosphatase, cholinesterase, and C-reactive protein.

Blood samples for glucose determination were stored in fluoride-containing tubes. Serum tubes were used to determine insulin and TG levels.

Oral glucose tolerance test

A 75-g OGTT was performed following a 12-h overnight fast, and after dietary advice had been given to ensure a carbohydrate intake of >150 g/day over the previous 3 days. Blood samples for glucose and insulin were taken before and 30, 60, 120, 180, and 240 min after the glucose load.

Glucose tolerance was classified according to the WHO criteria (17) as follows:

i) Normal glucose tolerance (NGT) – fasting glucose <110 mg/dl and postload glucose <140 mg/dl

ii) Impaired glucose tolerance (IGT) – fasting glucose ≥110 and <126 mg/dl (repeated on a second day) and postload glucose 140–200 mg/dl

iii) Diabetes – fasting glucose ≥126 mg/dl and/or postload glucose ≥200 mg/dl.

Oral metabolic tolerance test

Participants visited the department after a 12-h overnight fast for a minimum of 3 days after the OGTT. An i.v. catheter equipped with disposable obturators was inserted into a forearm vein, and a fasting blood sample was obtained. A liquid lipid load with standardized ingredients (oral metabolic tolerance test, OMTT) was administered. The composition of the test load was standardized to avoid variations in gastric emptying due to the stomach’s differential handling of solid and liquid phases when digesting natural foods. The subjects drank 500 ml of the OMTT meal containing the following ingredients: 30 g of protein (11.9% of calories), 75 g of carbohydrate (29.6% of calories; 93% of sucrose and 7% of lactose), 58 g of fat (51.6% of calories; 65% of saturated fatty acids and 35% of unsaturated fatty acids), 10 g of alcohol (6.9% of calories), 600 mg of cholesterol, and 30 000 IU of retinyl palmitate. The total energy content was 1017 kcal (4.255 kJ). The test meal was drunk within 10 min after the fasting blood was drawn.
Blood withdrawal was repeated at 30 min, 1, 2, 3, 4, 5, 6, 7, 8, and 9 h after ingestion of OMTT meal. Blood samples were kept on ice for a maximum of 1 h until centrifugation. Subjects were allowed to walk or sit, as they wished, but they were not allowed to eat or exercise during the test. Drinking of water ad libitum was permitted.

**Laboratory parameters**

Serum and plasma were separated from whole blood by centrifugation (6 °C, 10 min. 3000 g). Serum and plasma were aliquoted and stored at −20 and −80 °C.

Serum TGs and plasma glucose, serum cholesterol, and high-density lipoprotein cholesterol were determined using enzymatic methods with a Konelab 20i analyzer (KONE, Espoo, Finland). Plasma insulin was measured by RIA (Adaltis, Bologna, Italy). All samples were measured in duplicate.

**Statistical analyses**

Mean and SD, as well as the median and the interquartile range were used for describing the parameter distributions. The 0–9-h area under curve (AUC) was calculated by the trapezoidal method. Spearman’s correlation coefficient was used to determine correlation between continuous parameters. Correlation coefficients were tested for equality by using a χ² test after applying Fisher’s Z transformation (18).

Multiple linear regression analysis was performed to model the influence of the studied variables on two homeostasis model assessment (HOMA) levels. This approach was employed despite slight deviations of the HOMA levels from normality due to the robustness of the linear model. A P value <0.05 was considered statistically significant. Insulin resistance was estimated by applying the HOMA of insulin resistance (HOMA-IR) (19, 20). Insulin resistance index (HOMA-IR) was calculated with the formula: fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5. Pp HOMA-IR was determined using the AUC of insulin and glucose concentrations (HOMA-IR) as described previously (21). β-cell function (HOMA-β-cell) was calculated with the formula: 20 × fasting insulin (µU/ml)/fasting glucose (mmol/l) − 3.5.

Model selection was done by stepwise forward and backward selections. Statistical analysis was performed with SPSS version 14.01 (SPSS Inc., Chicago, IL, USA) and R version 2.2.1 (22).

**Results**

**Subjects characteristics**

A total of 755 subjects participated in the pp cohort study. A total of 714 participants underwent both OGTT and OMTT, 11 underwent OGTT but not OMTT for various reasons (refused to participate and intake of exclusion medication), and 742 underwent OMTT. In total, 18% of the subjects reported type 2 diabetes in at least one parent. In total, 17.6% of the subjects were smokers, 72.5% of the subjects were overweight (BMI ≥ 25.0 kg/m²), and the mean BMI was 27.4 kg/m². Subjects fulfilled a mean four of the IDF criteria for MS according to IDF: mean waist circumference was 100.3 ± 12.2 cm; mean DBP was

**Table 1** Mean ± s.d. of anthropometric and metabolic parameters of study participants of the postprandial cohort study (n=755) and of subgroups with BMI < 25 and ≥ 25 kg/m².

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>BMI &lt; 25 kg/m²</th>
<th>BMI ≥ 25 kg/m²</th>
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<tr>
<td>n</td>
<td>755</td>
<td>205</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td>Anthropometric parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.0±5.4</td>
<td>59.1±5.6</td>
<td>58.9±5.3</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4±4.1</td>
<td>23.3±1.3</td>
<td>29.0±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>100.3±12.2</td>
<td>89.4±6.6</td>
<td>104.6±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.4±17.9</td>
<td>121.7±15.3</td>
<td>132.3±17.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4±10.7</td>
<td>75.9±9.5</td>
<td>82.1±10.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Fasting parameters</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.9±1.1</td>
<td>5.9±1.0</td>
<td>5.9±1.1</td>
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<td>LDL cholesterol (mmol/l)</td>
<td>3.7±0.8</td>
<td>3.6±0.9</td>
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<td>HDL cholesterol (mmol/l)</td>
<td>1.4±0.4</td>
<td>1.5±0.4</td>
<td>1.3±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting TGs (mmol/l)</td>
<td>1.6±1.1</td>
<td>1.2±0.6</td>
<td>1.8±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.8±0.9</td>
<td>5.5±0.6</td>
<td>5.9±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>14.6±11.4</td>
<td>10.3±7.1</td>
<td>16.3±12.2</td>
<td>&lt;0.001</td>
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<tr>
<td>HOMA-IR (mmol/l×µU/ml per 22.5)</td>
<td>3.7±3.4</td>
<td>2.4±1.7</td>
<td>4.3±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-β-cell (%)</td>
<td>7.2±7.2</td>
<td>10.8±10.6</td>
<td>5.8±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting FFAs (mmol/l)</td>
<td>0.43±0.19</td>
<td>0.40±0.18</td>
<td>0.44±0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>Postprandial parameters (OMTT)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2-h plasma glucose (mmol/l)</td>
<td>6.1±2.5</td>
<td>5.5±1.0</td>
<td>6.3±1.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Pp triglycerides (AUC, mmol h/dl)</td>
<td>19.7±11.0</td>
<td>16.3±8.0</td>
<td>21.3±11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pp FFAs (5 h mmol/l)</td>
<td>0.55±0.21</td>
<td>0.50±0.19</td>
<td>0.57±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pp insulin (AUC, µU h/ml)</td>
<td>204.4±166.0</td>
<td>127.2±62.0</td>
<td>233.7±182.9</td>
<td>&lt;0.001</td>
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</table>

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80.4 ± 10.7 mmHg; mean fasting TGs were 142.5 ± 91.8 mg/dl and mean fasting glucose was 104.8 ± 16.7 mg/dl. Additional baseline characteristics are given in Table 1.

Serum TG responses to the OMTT are shown in Fig. 1A. TG concentrations rose from the baseline to the highest values 3 h after the intake of meal. Concentrations returned to baseline after 9 h. The frequencies of serum TG maxima after ingestion of the OMTT meal are shown in Fig. 2. The intervals were chosen to be the same as in a previous study of normal-weight younger subjects (14). The bimodal distribution shown in that study could not be reproduced in this population. Fasting and pp TGs were not different in subjects with an anamnesis of hereditary type 2 diabetes compared with the subjects without parental diabetes (data not shown). Fasting and pp TGs were lowest in the NGT group with a significant difference compared with IGT (P < 0.001), impaired fasting glucose (IFG; P < 0.001), and T2DM (P < 0.001) groups, followed in an order by the IGT group and the IFG group; they were highest in type 2 diabetic subjects (T2DM). IFG subjects showed significantly higher fasting and pp TGs than IGT subjects (P = 0.03 and P = 0.01 respectively). Further adjustment for age, BMI, and waist circumference did not substantially change the patterns of TGs across glucose impairment categories (data not shown).

Plasma glucose levels quickly rose from the baseline to the highest values 0.5 h after both meals. Glucose levels after OGTT rose steeply and were 28.8% higher than those after OMTT at the maximum (Fig. 1B).
Plasma glucose concentrations 2 h after OMTT were correlated with those 2 h after OGTT ($r = 0.55$), but the relationship was less pronounced than that in former studies ($r = 0.97, 50$ g of carbohydrates, (23)). Values returned to baseline 2–3 h pp, and even fell below the baseline at 3–5 h in both tests, but they were more pronounced after OGTT (Fig. 1B). Plasma insulin showed a higher maximum after OGTT compared with the maximum after OMTT (Fig. 1C), fitting to the glucose maxima.

The prevalence of unknown diabetes in the MICK cohort was 6.5% ($n = 49$). In total, 11.5% of all the participants had IFG ($n = 87$) and 9% had IGT ($n = 68$) according to the WHO criteria (17).

The components of MS were determined by applying the criteria of the National Cholesterol Education Program, the Adult Treatment Panel III (ATP III) criteria (24), and the IDF criteria (25). According to the ATP III criteria, 22.9% of the subjects had no component of MS, 32.4% had one component, 23.6% had two components, and 21.1% had three or more components, and thus had a complete MS. Analysis according to the criteria proposed for Europe by the IDF (17) revealed that 11.5% had no component, 19.8% had one component, 27.0% had two components, and 41.7% had a complete MS (Table 2).

### Correlations of fasting and postprandial metabolic parameters

The comparison of correlations between fasting and pp TGs as well as between fasting and pp HOMA-IR disclosed no difference (Table 3).

#### HOMA-IR after OMTT versus HOMA-IR after OGTT

The pp insulin resistance after OMTT (HOMA-IR and AUC) was more closely correlated with fasting glucose than insulin resistance after OGTT (Table 3). In overweight subjects, HOMA-IR after OMTT was more closely correlated with waist circumference and BMI than insulin resistance after OGTT.

### Table 2. Prevalence of signs of the metabolic syndrome in the Metabolic Intervention Cohort Kiel according to the Adult Treatment Panel III (ATP III) (24) and according to the International Diabetes Federation (IDF), 2005 (17); known diabetes was an exclusion criterion of the study; $n=1558$.

<table>
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<tr>
<th></th>
<th>ATP III</th>
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<th>IDF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>No sign</td>
<td>357</td>
<td>22.9</td>
<td>178</td>
<td>11.5</td>
</tr>
<tr>
<td>One sign</td>
<td>506</td>
<td>32.4</td>
<td>307</td>
<td>19.8</td>
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<tr>
<td>Two signs</td>
<td>367</td>
<td>23.6</td>
<td>421</td>
<td>27.0</td>
</tr>
<tr>
<td>$\geq$ Three signs</td>
<td>329</td>
<td>21.1</td>
<td>650</td>
<td>41.7</td>
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Table 4  Regression coefficients ($\beta$ and s.e.m.), corresponding $P$ values (Wald test), and coefficients of determination ($R^2$) of two multiple linear regression models for HOMA after both backward and forward stepwise model selections. The left column lists all the predictors offered to the model selection procedure, while the top row lists the regressed parameter. Forward and backward selections yielded identical models. Only coefficients of predictors that were included in the final model are listed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$ s.e.m.</th>
<th>$P$ value</th>
<th>$\beta$ s.e.m.</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td>Age</td>
<td>NS</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.188 0.019</td>
<td>0.007</td>
<td>−0.165 0.047</td>
<td>0.033</td>
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<tr>
<td>BMI</td>
<td>0.343 0.055</td>
<td>&lt;0.001</td>
<td>−0.208 0.136</td>
<td>0.007</td>
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<tr>
<td>Fasting TGs</td>
<td>0.117 0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Pp TGs</td>
<td>NS</td>
<td>–</td>
<td>−0.085 0.001</td>
<td>0.017</td>
</tr>
</tbody>
</table>

NS, not included in final model after model selection.

Multiple linear regression analysis

Multiple linear regression analysis with both stepwise forward and backward selections revealed that waist circumference and BMI were independently associated with insulin resistance (expressed as HOMA-IR) and with $\beta$-cell function (HOMA-$\beta$-cell) when age and waist circumference were included in the model. The model selection procedure also showed that fasting TGs had an independent effect on insulin resistance, whereas pp TGs were independently associated with $\beta$-cell function (Table 4). Fasting and pp TGs were highly correlated ($r=0.92$). HOMA-IR was explained independently at 34% by BMI, at 19% by waist circumference, and at 12% by fasting TGs. HOMA-$\beta$-cell was explained independently at 21% by BMI, at 17% by waist circumference, and at 9% by pp TGs.

Fasting and pp TGs in glucose tolerance groups

Table 5 shows the fasting and pp TGs according to glucose tolerance status. Subjects with IFG, IGT, and T2DM showed higher fasting and pp TGs than NGT subjects. IFG subjects had higher fasting and pp TGs than IGT subjects (Figure 3).

Discussion

To the best of our knowledge, the MICK study is the largest regional population-based cohort study investing pp metabolism, including a mixed-meal and a plain-glucose load. The dense-blood withdrawal up to 9 h pp after the OMTT allowed an investigation of the kinetics of TG, glucose, and insulin metabolism in more than 750 men from the normal population. To ensure the highest homogeneity among the study subjects, only men aged 45–65 years were included. This sampling also excluded potential bias from metabolism alterations imposed by menopause in middle-aged women. Subjects who were taking statins were excluded from the study to account for the effect of statins on fasting and pp TGs. Although individuals with diabetes were excluded, the prevalence of MS according to NCEP criteria was quite high in the MICK cohort (21.1%). These results are consistent with a recent French study demonstrating a 16% prevalence of MS in men aged 30–64 years (26), considering the lower mean age in that cohort. Data on the US population obtained from the Third National Health and Nutrition Examination Survey, completed in 1994, showed a prevalence of 23.9% in men aged >20 years. The subgroup of 40–74-year-old men had a prevalence of 34.8% according to the ATP III (27). This higher prevalence can be explained by the higher rate of obesity in the US population.

The prevalence of unknown diabetes in our cohort was 6.8%. This rate is in accordance with the results obtained from a Southern German cohort (KORA) in 2000, where the prevalence of unknown diabetes was 9.7% in men aged 55–74 years (28). In another study of the German population, the prevalence of unknown diabetes among subjects at high risk due to a family history, obesity, or dyslipoproteinemia was found to be 15.2% (29).

High TG response as an independent, distinct phenomenon associated with early signs of MS has been described before in young and healthy offspring of type 2 diabetics (14, 30). In these subjects, pp glucose and insulin levels after OMTT showed a stronger correlation with MS parameters than glucose and insulin after OGGT (14). This phenomenon could not be reproduced in the middle-aged cohort presented here.

Table 5  Fasting and postprandial triglycerides according to glucose tolerance status in the Metabolic Intervention Cohort Kiel. All values are expressed as mean ± s.e.m.

<table>
<thead>
<tr>
<th>Glucose tolerance status</th>
<th>Fasting triglycerides (mmol/l)</th>
<th>Pp triglycerides (AUC) (mmol h/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT (n=531)</td>
<td>1.4 ± 0.7</td>
<td>18.1 ± 1.2</td>
</tr>
<tr>
<td>IGT (n=68)</td>
<td>2.0 ± 1.5&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>23.6 ± 13.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IFG (n=87)</td>
<td>2.3 ± 1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.2 ± 17.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2DM (n=49)</td>
<td>2.5 ± 1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.8 ± 11.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Denotes significant differences compared with NGT.

<sup>b</sup>Denotes significant differences compared with IFG.
In overweight subjects, the correlation of pp HOMA-IR after OMTT with waist circumference and BMI was stronger than the correlation of pp HOMA-IR after OGTT with these parameters (Table 3). This phenomenon indicates a stronger correlation of body weight and abdominal fat with insulin resistance after a mixed meal compared with a sole OGTT meal in overweight subjects. The OMTT (fat tolerance test) was designed to detect the premetabolic syndrome earlier than the OGTT, but in this population, it failed to do so because fasting TGs are equally related to insulin resistance. However, in this middle-aged cohort, the pp insulin resistance after OMTT (HOMA-IR and AUC) was more closely correlated with fasting glucose than insulin resistance after OGTT, supporting the importance of assessment by a mixed meal. Furthermore, in overweight subjects, HOMA-IR after OMTT was more closely correlated with waist circumference than insulin resistance after OGTT. This indicates a stronger relationship of insulin resistance after a fatty meal compared with a sole glucose load in higher fat mass.

Recently, we have shown consistently in the MICK that PPARγ A12A subjects, who are known to be protected against type 2 diabetes, have lowered pp insulin levels after OMTT but not after OGTT, a finding favoring the assessment using a mixed meal (31, 32). The bimodal distribution of pp TG levels and the stronger correlation of pp TGs with the traits of MS were not seen in middle-aged subjects. The failure to reproduce this finding is probably due to the high incidence of overweight individuals in this middle-aged population. The higher body fat mass influences the metabolic responses to nutrients and especially pp TG metabolism (9, 33). In subjects with higher fat mass, FFAs mainly determine insulin resistance and VLDL secretion (9, 34). In our sample of middle-aged subjects, these obesity-related changes were probably covering the high TG response that was detected in young and lean subjects. Supporting this hypothesis, pp TGs in the MICK cohort did not show higher correlation with abdominal fat (waist circumference) than fasting values that had been detected in lean subjects (14).

However, in our cohort, the fasting and pp TGs not only were higher in manifest T2DM subjects compared with NGT subjects, but were also higher even in subjects who exhibited early stages of glucose metabolism disturbances (IGT and IFG). This is in contrast to former small studies, which failed to show a difference in pp TGs between NGT and IGT/IFG (35, 36).

The importance of our results is supported by several studies on the risk of an isolated elevation of pp glucose levels in atherosclerosis as an endpoint of MS (37, 38). However, pp TG levels did not have a higher correlation with waist circumference than fasting values, even in the BMI > 25 subgroup. This suggests the existence of a factor other than obesity influencing TG levels in the middle-aged groups. We found the correlation coefficients in the BMI-defined subgroups to be frequently lower than the complete-sample coefficients. This non-homogeneity correlation suggests that the BMI-defined subgroups are distinct groups of individuals showing high intragroup homogeneity and low parameter correlation, but large intergroup differences in parameter values.

Furthermore, our results show that pp TG levels are associated with β-cell function (expressed by
HOMA-β-cell independently of waist circumference and BMI. Waist circumference and BMI themselves were also independent predictors of β-cell function. Fasting TG levels were independently associated with insulin resistance (expressed by HOMA-IR). However, HOMA-IR and HOMA-β-cell were influenced primarily by the independently associated factors, BMI and waist circumference, and only secondarily by fasting and pp TGs. Fasting and pp TG levels showed a very high correlation, and would have been selected as independent predictors in both HOMA models in the absence of the other TG parameters. Thus, the selection of the chosen TG parameters in the HOMA models could be simply a result of chance. However, while we cannot exclude chance as the reason for our observation, the differential selection of HOMA parameters in the models is in accordance with the explanation that β-cell function is known to be impaired by high levels of FFAs (39). Our findings can be explained by long-term exposure to high levels of FFAs, which is associated with prolonged pp hypertriglyceridemia in subjects with abdominal obesity, leading to impaired β-cell function (14). Hanefeld et al. (29) found that subjects with IGT had higher levels of FFAs than subjects with IFG, supporting the hypothesis that pp disturbances result in higher levels of FFAs, with negative effects on β-cell function (38). In the fasting state, hyperinsulinemia leads to low levels of FFAs, and TG levels are not independently associated with insulin secretion. In contrast, high levels of FFAs/TGs occur pp, and they are directly related to insulin secretion, which may induce lipoprotein lipase releasing FFAs from pp TGs. Thus, while we cannot exclude chance as the underlying reason for the observed model selection, the results of the model selection procedure are coherent with previous studies.

This might indicate that pp metabolism has an independent influence on the pathogenesis of MS. It has been demonstrated that pp TG metabolism plays an important role in young subjects and potentially induces a premetabolic state, while this metabolism seems to play a minor role in middle-aged subjects. Still, pp glucose and insulin levels are probably of higher importance than their fasting values in assessing the risk of MS.

Free fatty acids derived from serum TGs are known to increase hepatic glucose production and induce hepatic insulin resistance (40). This explains the strong association of TGs and FFAs with insulin resistance and glucose levels. As described in other cohorts, T2DM subjects showed higher fasting and pp TGs than NGT subjects. Interestingly, the fasting and pp TG concentrations were lower in IGT subjects than in IFG subjects. In contrast to this observation, subjects with IGT in the Atherosclerosis Risk in Communities (ARIC) study showed slightly higher TGs than IFG subjects (41). However, IGT subjects in that study were significantly older than IFG subjects, which may have contributed to the inverse effect (41).

There are two limitations that need to be acknowledged and addressed regarding the present study. The first limitation is that the observations are restricted to an age group with a high prevalence of overweight (72.4%). We assume that the higher fat mass might have influenced the results. The second limitation is that we investigated only men. Since it is known that lipid metabolism is different in (premenopausal) women, we cannot exclude that pp TGs are more closely correlated with MS in women than in men.

In conclusion, in our cohort consisting of middle-aged men with a high prevalence of manifest MS, the OMTT probably gives little additional information for detecting the premetabolic syndrome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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