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Impact of the Triglyceride/High-Density Lipoprotein Cholesterol Ratio and the Hypertriglyceremic-Waist Phenotype to Predict the Metabolic Syndrome and Insulin Resistance

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ABSTRACT

Insulin resistance is the underlying mechanism for the metabolic syndrome and associated dyslipidaemia that theoretically implies a practical tool for identifying individuals at risk for cardiovascular disease and type-2-diabetes. Another screening tool is the hypertriglyceremic-waist phenotype (HTW). There is important impact of the ethnic background but a lack of studied European populations for the association of the triglyceride/high-density lipoprotein cholesterol (HDL-C) ratio and insulin resistance. This observational, retrospective study evaluated lipid ratios and the HTW for predicting the metabolic syndrome/insulin resistance in 1932 non-diabetic individuals from Germany in the fasting state and during a glucose tolerance test. The relations of triglyceride/HDL-C, total-cholesterol/HDL-C, and low-density lipoprotein cholesterol/HDL-C with 5 surrogate estimates of insulin resistance/sensitivity and metabolic syndrome were analysed by linear regression analysis and receiver operating characteristics (ROC) in participants with normal (n = 1 333) or impaired fasting glucose (n = 599), also for the impact of gender. Within the lipid ratios, triglyceride/HDL-C had the strongest associations with insulin resistance/sensitivity markers. In the prediction of metabolic syndrome, diagnostic accuracy was good for triglyceride/HDL-C (area under the ROC curve 0.817) with optimal cut-off points (in mg/dl units) of 2.8 for men (80 % sensitivity, 71 % specificity) and 1.9 for women (80 % sensitivity, 75 % specificity) and fair for HTW and HOMA-IR (area under the curve 0.773 and 0.761). These data suggest the triglyceride/HDL-C ratio as a physiologically relevant and practical index for predicting the concomitant presence of metabolic syndrome, insulin resistance and dyslipidaemia for therapeutic and preventive care in apparently healthy European populations.

Introduction

The metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) Expert Panel [1] is widely used as a practical tool for identifying individuals at risk of prevalent diseases such as type 2 diabetes, heart failure, cardiovascular diseases, non-alcoholic fatty-liver disease or cancer [2–6], and for independent prog-

nostic information [7]. By now, insulin resistance has been identified as a common pathway of the underlying pathological mechanisms [8, 9] but the lack of practical quantitative and generally available methods for its diagnosis [10] limits its use for risk prevention and for effective therapeutic strategies [11].

Instead, quantification of serum triglyceride (TG) and cholesterol levels is commonly used to assess cardiovascular risk, especially as an increased plasma concentration of low-density lipoprotein cholesterol (LDL) or fasting TG [1, 12]. Superior predictive value has been attributed to lipoprotein ratios such as total cholesterol/high-density lipoprotein (TC/HDL-C) and LDL-C/HDL-C ratios [13]. The TG/HDL-C ratio, in particular, has emerged as both a marker of insulin resistance [14] in non-diabetic individuals as well as a good predictor for the metabolic syndrome and the development of cardiovascular disease [15]. Accordingly, the TG/HDL-C ratio may allow the physician to identify insulin resistance simultaneously with dyslipidaemia [16, 17] and also monitor the efficacy of evidence-based new dietary therapy for the metabolic syndrome that is independent of weight loss [18, 19]. Concerning an adequate cut-off point for the determination of individuals at risk, however, the published data present the important impact of the ethnic background [20, 21] but lack data from a European population.

Another screening concept, the hypertriglyceremic-waist phenotype (HTW) is based on the presence of hypertriglyceridemia and visceral fat as proxy indicator of cardiovascular risk and determinant of insulin resistance and diabetes. This phenotype has been proposed to be a simpler alternative to the metabolic syndrome [22, 23].

We analysed data at the University Clinic Carl Gustav Carus, Dresden, Germany to evaluate the TG/HDL-C ratio for the prediction of the metabolic syndrome and the impact of this and other screening tools on the underlying insulin resistance/sensitivity as assessed in the fasting state and during a glucose tolerance test. The present analysis aims to define the most suitable marker for the risks of metabolic syndrome among apparently healthy individuals in a fairly large sample size European population addressing also the impact of gender and age.

Subjects and Methods

This observational, retrospective study presents data from 1 932 individuals (> 20 years of age) from the city of Dresden and adjacent areas over a period of 17 years (1996 to 2012). Exclusion criteria were diabetes mellitus, other acute or chronic diseases having a strong impact on life expectancy, and concomitant therapies with drugs known to influence the glucose metabolism. The participants were categorised into 2 groups [24]: normal (NFG) and impaired fasting glucose (IFG). The clinical definition of the metabolic syndrome [1] was ascribed in the presence of ≥ 3 positive findings: waist circumference for men (women) ≥ 102 (≥ 88) cm, fasting plasma glucose ≥ 5.6 mmol/l or known diabetes, triglycerides ≥ 1.7 mmol/l or treatment against dyslipidaemia, HDL-C in men (women) < 1.03 (< 1.30) mmol/l and blood pressure > 130/85 or known hypertension. The 4 subgroups of the hypertriglyceremic-waist phenotype were defined as HTW = men (women) with elevated waist circumference (≥ 90 (≥ 85) cm) and elevated triglycerides (≥ 2,0 (≥ 1,5) mmol/l), elevated waist and normal triglycerides, normal waist and elevated triglycerides and, finally, both normal waist circumference and triglycerides [23]. Other subgroups were created according to gender and age (< 50 vs. ≥ 50 years). The study was approved by the local ethics committee and written informed consent was obtained from all participants according to the guidelines of the institutional review boards for human studies at the Technical University of Dresden.

Medical screening of all individuals included measurements of blood pressure, pulse, waist circumference, weight, and height. Following an overnight fasting (≥ 10 h), blood samples were drawn for assessing fasting lipid and glucometabolic state. Plasma glucose and insulin were measured before and after the ingestion of 75 g glucose at 30-min intervals for 2 h. Insulin resistance was measured as HOMA-IR (glucose * insulin/22.5 in molar units) [25] and insulin sensitivity as Quicki, as 1/[log (fasting insulin, U/ml) + log (fasting glucose, mg/dl)] [26]. Additionally, measures of functional insulin sensitivity/resistance were assessed from a glucose tolerance test as area under the curve (AUC) for the respective insulin responses using a trapezoidal model and Stumvoll index as 0.156 –0.0000459 * insulin120 (pmol/l) – 0.000321 * I0 (pmol/l) – 0.00541 * glucose120 (mmol/l) [27].

Plasma glucose was determined by the hexokinase method (interassay coefficient of variation (CV) 1.5 %) and insulin levels by enzyme immunoassay (BioSource EUROPE, Nivelles, Belgium, (interassay CV 7.5 %). Serum cholesterol and triglyceride levels were determined by enzymatic techniques (Boehringer Mannheim, Mannheim, Germany) and HDL-C after precipitation with dextran sulfate (Boehringer Mannheim). Plasma LDL-C was estimated by the Friedewald formula.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, Ill, USA). The distribution of quantitative data is described by means ± standard deviation if normally distributed and otherwise by median and interquartile range (IQR). Group comparisons of baseline characteristics were performed by student's t-test and ANOVA. Pearson correlation coefficients were calculated between the lipid ratios and the surrogate insulin resistance markers. The coefficient of determination R^2 was calculated to quantify the relation of metabolic syndrome and HTW to HOMA-IR and the TG/HDL ratio. Additionally, a receiver-operating characteristic (ROC) curves analysis was used to estimate the predictive value of the TG/HDL-C ratio or HTW for insulin resistance and for the metabolic syndrome, to determine the sensitivity and specificity of the diagnostic procedure and also the optimal cut-off points. This implied the use of a logistic regression analysis for non-continuous variables. All statistical testing was conducted on two-sided 5 % significance levels.

Results

The demographic, clinical, metabolic characteristics, and prevalences of classification by screening tools of the participants (▶ **Table 1**) demonstrate significantly ($p < 0.001$) higher values in the IFG (n = 599) compared to the NFG group (n = 1 333) with the exception of a lower HDL-C level. The characteristics for the gender related specific subgroups demonstrated the expected differ-

▶ **Table 1** Characteristics of non-diabetic participants.

	Total	NFG	IFG *
Total number (men; women)	1 932 (812; 1 120)	1 333 (505; 828)	599 (307; 292) *
Age (years)	55 ± 15	53 ± 15	59 ± 12 *
BMI (kg/m^2)	27.1 ± 4.6	26.5 ± 4.3	28.6 ± 4.6 *
Waist circumference (cm)	94 ± 13	92 ± 13	98 ± 12 *
SBP (mmHg)	131 ± 17	129 16	137 ± 18 *
DBP (mmHg)	81 ± 11	79 ± 11	84 ± 11 *
Total cholesterol (mmol/l)	5.46 ± 1.06	5.40 ± 1.04	5.60 ± 1.09 *
Triglyceride (mmol/l)	1.17 (0.86–1.68)	1.11 (0.81–1.55)	1.37 (1.02–1.88) *
HDL-C (mmol/l)	1.56 ± 0.43	1.60 ± 0.43	1.46 ± 0.40 *
LDL (mmol/l)	3.35 ± 0.97	3.29 ± 0.96	3.49 ± 0.97 *
Triglyceride/HDL-C (mg/dl units)	1.7 (1.1–2.6)	1.5 (1.0–2.4)	2.1 (1.4–3.3) *
Fasting insulin (pmol/l)	65 (42–93)	59 (38–83)	80 (55–118) *
HOMA IR	2.2 (1.4–3.3)	1.9 (1.2–2.7)	3.1 (2.1–4.5)
Quicki	0.35 ± 0.04	0.35 ± 0.04	0.32 ± 0.02 *
AUC insulin (pmol · min/l)	40 868 (28 695–61 072)	37 973 (27 517–54 690)	48 435 (33 165–74 700)
Stumvoll index	0.08 ± 0.03	0.09 ± 0.02	0.07 ± 0.03 *
Metabolic syndrome (%)	18	8	43 *
HTW (%)	19	17	26 *
Insulin resistance by HOMA-IR > 3 (%)	30	20	52 *
Insulin resistance by TG/HDL-C > 2.8 men, > 1.9 women ± (%)	34	27	51 *

Data are presented as mean ± standard deviation or median (interquartile range)

NFG: Normal fasting glucose; IFG: Impaired fasting glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

*Significant at the level of $p < 0.001$ compared to NFG

ences between men and women with higher risk factors in men (data not shown). HOMA-IR was 2.7 ± 1.7 in men vs. 2.4 ± 1.6 in women ($p < 0.001$) and TG/HDL-C ratio 2.9 ± 2.2 vs. 1.9 ± 1.3 in mg/dl units ($p < 0.001$). HTW was observed in 19 % of men and 21 % of women and the metabolic syndrome in 28 % and 24 %, respectively. The characteristics of participants according to the 4 subgroups of the hypertriglyceremic-waist phenotype (normal, high TG, high waist, HTW) demonstrated an incremental increase in risks, especially from the high waist vs. the HTW subgroup (▶ **Table 2**).

The correlation coefficients for the 3 lipoprotein ratios or the TG level and surrogate markers of insulin resistance/sensitivity (▶ **Table 3**) showed significant and positive relations with HOMA-IR, fasting insulin and AUC insulin and negative relations with the surrogate parameters of insulin sensitivity, Quicki and Stumvoll index, establishing TG/HDL-C as the best marker of insulin resistance/sensitivity. The association of TG/HDL-C with HOMA-IR in the NFG subgroup had a similar correlation coefficient but variance slightly smaller than in IFG (standard error of the estimate = 1.5 vs. 1.8 in mg/dl units). The 19 individuals who may be considered outliers by combining high TG/HDL-C values (≥ 3.5 in mg/dl units) with low HOMA-IR (≤ 1.2) had high TG values (2.8 ± 0.9 mmol/l) associated with low HDL-C (1.1 ± 0.24 mmol/l), insulin (27 ± 8.6 pmol/l), and borderline BMI (26 ± 2.6 kgm^{-2}).

Compared to men, women (▶ **Table 4**) had stronger correlations of the TG/HDL-C ratio with markers of insulin resistance and with the Stumvoll index and an analogue superiority pattern for the other lipid ratios albeit at lower levels of correlation coefficients. The division of the study participants into < 50 years (n = 655) vs. ≥ 50 years (n = 1 277) did not render distinctly different associations between the lipid ratios and markers of insulin resistance/sensitivity in comparison of these age groups (▶ **Table 4**).

The coefficient of determination R^2 showed that determination was stronger between the TG/HDL-C ratio and the metabolic syndrome ($R^2 = 0.346$, $p < 0.001$) or HTW ($R^2 = 0.442$, $p < 0.001$) than between HOMA-IR and the metabolic syndrome ($R^2 = 0.254$, $p < 0.001$) or the HTW phenotype ($R^2 = 0.139$, $p < 0.001$).

Predictive performances were additionally evaluated by ROC curves: The accuracy for the diagnosis of insulin resistance (HOMA-IR > 3) (▶ **Fig. 1a**) was best using the ratio TG/HDL-C and incrementally decreased with HTW, TG, TC/HDL-C and LDL/HDL-C. Notably, the NFG and IFG subgroups demonstrated an analogue pattern of accuracies albeit with distinctly higher values in the NFG group (▶ **Table 5**). Additionally, the potential diagnosis of the metabolic syndrome was assessed by the predictive performance of TG/HDL-C, HOMA-IR and HTW (▶ **Fig. 1b**): diagnostic accuracy was good for the TG/HDL-C ratio and fair for HTW and HOMA-IR

▶ **Table 2** Subgroups of hypertriglyceremic-waist phenotype.

	Normal	High TG	High Waist	HTW
Total number (%)	429 (25)	77 (4)	964 (51)	378 (20)
Men (women)	142 (287)	17 (60)	499 (465)	150 (228)
Age	49 ± 15	52 ± 15	58 ± 14 *,#	56 ± 12 *,¤
BMI (kg/m²)	23 ± 2	24 ± 2	28 ± 4 *,##	30 ± 4 *,##,¤¤
SBP (mmHg)	123 ± 15	130 ± 18	133 ± 16	136 ± 19
Total cholesterol (mmol/l)	5.3 ± 1.1	6.0 ± 1.1 *	5.4 ± 1.0##	5.8 ± 1.1 *,¤¤
HDL-C (mmol/l)	1.76 ± 0.43	1.51 ± 0.39 *	1.56 ± 0.40 *	1.34 ± 0.37 *,#,¤¤
Triglycerides/HDL-C (mg/dl units)	1.0 (0.8–1.5)	3.0 (2.2–4.2) *	1.5 (1.1–2.1) *,##	3.6 (2.6–5.3) *,##,¤¤
Fasting insulin (pmol/l)	48 (32–65)	66 (48–94) *	67 (45–95) *	90 (63–128) *
HOMA IR	1.6 (1.0–2.1)	2.1 (1.6–3.2) *	2.3 (1.5–3.3)	3.1 (2.1–4.5) *,##,¤¤
Quicki	0.37 ± 0.03	0.34 ± 0.03 *	0.35 ± 0.05 *	0.33 ± 0.03 *,#,¤¤
AUC insulin (pmol · min/l)	30 420 (22 624–39 401)	41 535 (30 705–57 191)	41 843(29663 – 63 866) *	57 652 (41 674–85 691) *,#,¤
Stumvoll index	0.10 ± 0.02	0.07 ± 0.04 *	0.08 ± 0.03 *	0.06 ± 0.04 *,#,¤¤
Metabolic syndrome (%)	2	22 *	23 *	64 *,##,¤¤
IFG (%)	15	31	35 *	41 *

Data are presented as mean ± standard deviation or median (interquartile range)

HTW: High waist and high triglycerides; NFG: Normal fasting glucose; SBP = systolic blood pressure

* $p < 0.001$ vs. normal; # $p < 0.05$; ## $p < 0.001$ vs. High TG; ¤ $p < 0.05$; ¤¤ $p < 0.001$ vs. High Waist

(▶ **Table 4**) with the optimal cut-off values (in mg/dl units) 2.12 for TG/HDL-C and 2.18 for HOMA-IR.

The predictive performances of TG/HDL-C for the diagnosis of the metabolic syndrome and for the underlying insulin resistance were analysed separately for men (women): Their AUC was 0.823 (0.852) for the diagnosis of the metabolic syndrome with the optimal cut-off point of 2.8 (1.9) in mg/dl units and 80 % (80 %) sensitivity and 71 % (75 %) specificity. For insulin resistance, AUC was 0.651 (0.737) with the cut-off level of 2.8 (1.9) in mg/dl units, 53 % (60 %) sensitivity and 68 % (75 %) specificity.

Discussion

Given the epidemic of the metabolic syndrome, there is a need to develop simple and inexpensive screening tools that support general physicians in identifying carriers of the risk not only of cardiovascular disease or diabetes but also of non-alcoholic fatty-liver disease, cancer of the colon and arterial hypertension, that are all linked to insulin resistance and the associated hyperinsulinemia of the metabolic syndrome [5, 6, 8, 28]. This is particularly important, because the upstream metabolic syndrome implies a therapeutic potential enabling the natural course and quality of subsequent diseases to be altered: 1) insulin resistance/metabolic syndrome is a consequence of chronic overnutrition and, accordingly, may be cured by weight loss and increased exercise and 2) increasing recent evidence describes effective dietary therapy independent of weight loss by a paradigm change in dietary recommendations that are now based on modified food composition with restricted glycaemic load and increased vegetable, protein and vegetable fat content [18, 19, 29].

By comparing the associations of different screening tools with insulin resistance/sensitivity in a fairly large sample size of non-diabetic German individuals, the present study builds an evidence basis that the TG/HDL-C ratio has good or fair diagnostic accuracy, for simultaneously predicting the metabolic syndrome and the underlying insulin resistance especially with gender-specific cut-off points.

Confirming earlier studies, the present study showed significant positive associations of TG/HDL-C with markers of insulin resistance in NFG and IFG individuals of a German cohort [15, 20] and negative correlations with markers of insulin sensitivity [10, 30]. Altogether, the TG/HDL-C ratio was superior to the ratios TC/HDL-C or LDL/HDL-C and marginally stronger than TG as a marker of insulin resistance (▶ **Fig. 1** left panel), in line with earlier reports on the associations between TG concentrations, TC, LDL-C or their ratios and insulin resistance/sensitivity [30–33]. Patients with primary hyperlipidaemia should be excluded from assessing insulin resistance or the metabolic syndrome by the TG/HDL-C ratio as also suggested by the characteristics of the 19 outliers.

The present NFG and IFG data demonstrated different lipid levels, ratios and associations with insulin resistance/sensitivity: HDL-C had a 9 % decrease from NFG to IFG; LDL and TC levels had a 6 % and 4 % increase, respectively, but fasting serum TG concentration had a 21 % increase. This difference may be due to the higher prevalence of insulin resistance in IFG (52 vs. 20 % in NFG) putting IFG individuals not only at an increased risk of cardiovascular dis-

▶ **Table 3** Significant correlations ($p<0.01$) between lipid ratios and insulin resistance/sensitivity markers among non-diabetic individuals.

Insulin resistance/ sensitivity	Lipid ratio	NFG r	IFG r
HOMA-IR	TG/HDL-C	0.302	0.302
Fasting insulin		0.294	0.309
AUC insulin		0.314	0.305
Stumvoll		–0.255	–0.297
Quicki		–0.219	–0.253
HOMA-IR	TC/HDL-C	0.216	0.206
Fasting insulin		0.201	0.209
AUC insulin		0.226	0.224
Stumvoll		–0.169	–0.196
Quicki		–0.171	–0.178
HOMA-IR	LDL/HDL-C	0.182	0.162
Fasting insulin		0.168	0.164
AUC insulin		0.170	0.170
Stumvoll		–0.162	–0.149
Quicki		–0.144	–0.164
HOMA-IR	TG	0.288	0.264
Fasting insulin		0.278	0.269
AUC insulin		0.311	0.283
Stumvoll		–0.257	–0.273
Quicki		–0.220	–0.226

NFG: Normal fasting glucose; IFG: Impaired fasting glucose; r: Correlation coefficient; TG: Triglyceride; TC: Total cholesterol

ease but also of beta cell dysfunction/failure. The latter complication may be reflected in the 66 % difference in HOMA-IR vs. 36 % difference in insulin serum levels between NFG and IFG groups. In spite of a clinically-relevant degree of insulin resistance, beta cell dysfunction leads to at minimum relatively reduced insulin levels so that their quantitative association to insulin resistance becomes less predictable. This has been demonstrated in men with impaired glucose tolerance [34] and may contribute to the slightly higher variability of the correlation TG/HDL-C with HOMA-IR in the present IFG group and furthermore to the reduced accuracy of predicting insulin resistance in the IFG vs. the NFG group in ROC analysis (▶ **Table 5**). Consequently, insulin levels and, accordingly, HOMA-IR may no longer be accepted as safe measures of insulin resistance in patients with prediabetes.

Considering the insulin-associated methodological problems of non-standardised analysis and reference values [21, 35] as well as the variance of insulin action due to its pulsatile secretion pattern and variable hepatic elimination [10] and finally due to beta cell exhaustion/failure already in prediabetes [34], the common "standard" HOMA-IR for assessing insulin resistance reveals considerable limitations even in non-diabetic individuals. Consequently, the clinical question behind the attempt to diagnose insulin resistance needs to be reconsidered.

Clearly, the point is prevention of subsequent diseases. The NECP has sagaciously declared the metabolic syndrome as the diagnostic tool of choice for all the risks linked by the underlying insulin resistance, such as the development of metabolic, cardiovascular, gastroentero-hepatic diseases, cancer and arterial hypertension [2–6]. The differentiation between the assessment of the upstream metabolic risk by this diagnostic method and the prediction/diagnosis of any downstream disease is important because the triggers for contracting a respective disease are still unknown and may depend on concomitant risk factors: age, gender, genetic disposition, specific nutrition, sedentary life style, inflammation/immune responses, infection, hormonal/cytokine activities, environmental factors etc. Accordingly, each of these downstream diseases is more accurately diagnosed using a specific diagnostic tool that incorporates the respective risk factors compared to using the metabolic syndrome alone [36].

The inherent therapeutic potential for the metabolic syndrome and the high morbidity and mortality associated with the downstream diseases [6, 18], make it essential to give this subject the utmost focus in public health concepts and imply the need of a practical parameter for early diagnosis and quantitative follow up during therapy. Its key problem, the insulin resistance, is difficult to quantify by robust and generally available methods based on measuring insulin levels whereas its metabolic nature almost automatically leads to dyslipidaemia with an elevated TG and reduced HDL-C.

Interestingly, our study could solve the issue of a practical parameter by demonstrating the TG/HDL-C ratio as being a good predictor of the metabolic syndrome and its associated prognostic information [7], followed by HTW as a screening tool, in comparison to the diagnostic performance of HOMA-IR which is less satisfying. This may partly be caused by the NCEP definition of the metabolic syndrome that lists TG and HDL-C levels and waist circumference among the multiple determinants but not HOMA-IR with its many limitations. Nevertheless, taking a pragmatic and practical approach, the TG/HDL-C ratio had the best diagnostic accuracy among all tested screening tools for the prediction of insulin resistance and was followed by HTW.

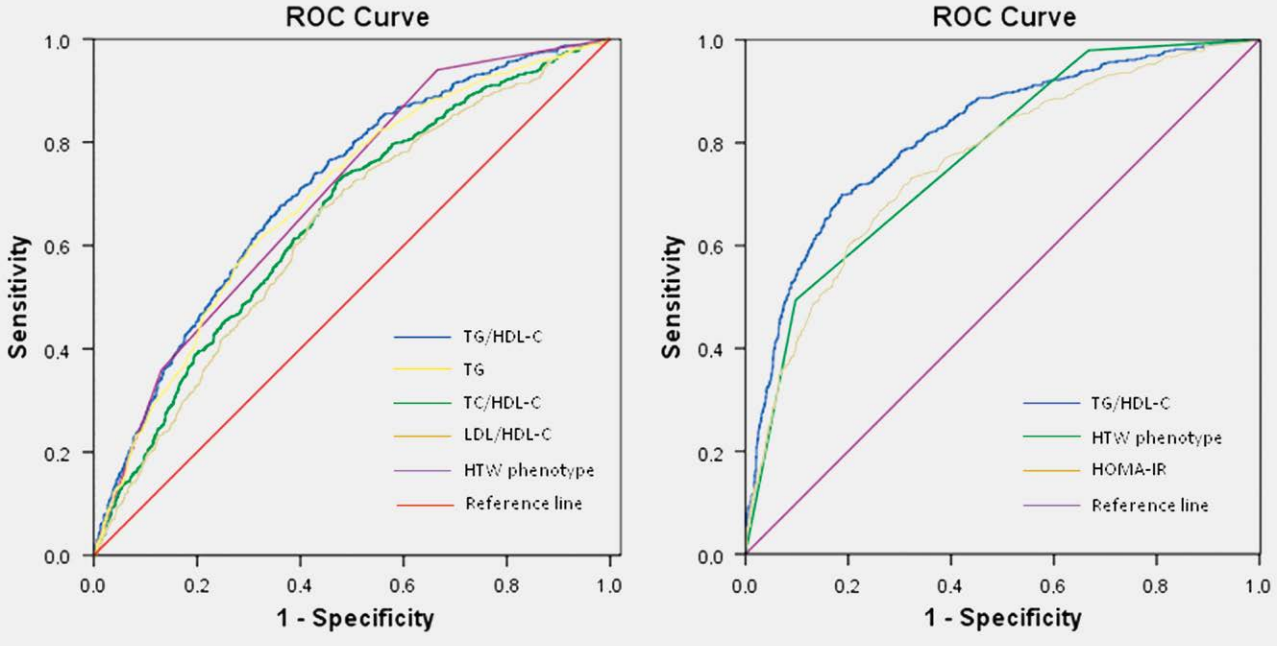
Taking all the insulin associated problems into consideration, the TG/HDL-C ratio appeals as continuous variable that is a physiological, robust, easily-available and accurate marker for the metabolic syndrome and insulin resistance. Of particular interest in this context is its potential to monitor therapeutic efficiency either by medical therapy [17] or by life style modification [16, 37]. This includes dietary approaches for both hypocaloric nutrition as well as for modified macronutrient composition which is not focused on weight loss but, instead, on reduced glycaemic load. The latter, in turn, would improve insulin resistance independently of weight loss so that increased patients' compliance should result in better therapeutic effects [18, 28, 29].

In our study comprising a central European population, the best cut-off point for the TG/HDL-C ratio to predict insulin resistance was 2.2 in mg/dl units. This differs from the respective data for Mexican and white Americans [15] and for a non-Hispanic black population [20]. It confirms that a single cut-off point is not applicable for diverse populations due to differences in race/ethnicity and due to the lack of any between-laboratory standardisation for insulin assays [20, 21].

▶ **Table 4** Impact of age and gender on significant ($p < 0.01$) associations of lipid ratios with insulin resistance/sensitivity markers.

Insulin resistance/sensitivity marker	Lipid ratio	Gender		Age	
		Male r	Female r	<50 years r	>50 years r
HOMA-IR	TG/HDL-C	0.284	0.423	0.361	0.354
Fasting insulin		0.283	0.412	0.354	0.335
AUC insulin		0.310	0.409	0.382	0.324
Stumvoll		−0.305	−0.446	−0.346	−0.322
Quicki		−0.264	−0.277	−0.226	−0.299
HOMA-IR	TC/HDL-C	0.212	0.296	0.280	0.265
Fasting insulin		0.206	0.271	0.251	0.246
AUC insulin		0.238	0.285	0.279	0.248
Stumvoll		−0.234	−0.340	−0.275	−0.239
Quicki		−0.208	−0.210	−0.202	−0.233
HOMA-IR	LDL/HDL-C	0.155	0.261	0.239	0.217
Fasting insulin		0.150	0.236	0.207	0.203
AUC insulin		0.156	0.240	0.217	0.191
Stumvoll		−0.164	−0.292	−0.233	−0.183
Quicki		−0.158	−0.185	−0.180	−0.194

r: Correlation coefficient; TG: Triglyceride; TC: Total cholesterol



▶ **Fig. 1** Left panel: ROC curve for the prediction of insulin resistance (HOMA-IR > 3.0) by the lipoprotein ratios TG/HDL-C, TC/HDL-C, LDL/HDL-C, the HTW phenotype, and TG. Accuracy is given in ▶ **Table 5**. Right panel: ROC curve for the prediction of the metabolic syndrome [1] by the TG/HDL-C ratio, by the HTW phenotype and by HOMA-IR. Accuracy is given in ▶ **Table 5**.

In line with our data, gender differences have recently been shown for the TG/HDL-C ratio [21] and for HOMA-IR cut-off values [35]. For the detection of insulin resistance by TG/HDL-C, higher cut-off levels that were derived as top quartile [21] were recently described in men (women) as: ≥ 3.5 (≥ 2.5) in mg / dl units with a sensitivity of 42 % (44 %) and specificity of 80 % (82 %). Based on the

▶ **Table 5** Accuracy in the prediction of insulin resistance or the metabolic syndrome by receiver operator curve analysis for all participants and NFG and IFG subgroups.

Insulin resistance		**All**	**NFG**	**IFG**
	TG/HDL-C	0.706	0.714	0.646
	TC/HDL-C	0.650	0.643	0.609
	LDL/HDL-C	0.632	0.621	0.600
	HTW	0.696	0.707	0.643
	TG	0.689	0.698	0.629
Metabolic syndrome		**All**	**NFG**	**IFG**
	TG/HDLC-C	0.817	0.897	0.766
	HTW	0.773	0.847	0.724
	HOMA-IR	0.761	0.724	0.680

NFG: Normal fasting glucose; IFG: Impaired fasting glucose

present ROC analysis, we propose a TG/HDL-C ratio of >2.8 (in mg/dl units) in men and >1.9 in women [equivalent to 1.22 and 0.83 in mmol/l units] as optimal cut-off points to identify individuals at risk for the metabolic syndrome and for insulin resistance. These cut-off points have yielded good diagnostic accuracy for the detection of the metabolic syndrome and balanced accuracy for the detection of insulin resistance. Application of these cut-off levels rendered prevalences of insulin resistance and the metabolic syndrome in our European cohort and its subgroups that were in line with earlier epidemiological evidence [38]. They confirm, that 30 % of non-diabetic individuals and 51 % of IFG individuals are at increased cardiometabolic risk including heart failure and, therefore, in need of therapeutic and preventive care.

The strength of the study is that the findings were obtained from a reasonably large central European population that allowed to empirically test differences between the groups in the association of screening tools for the metabolic syndrome with surrogate insulin resistance/sensitivity markers from the fasting state and a glucose tolerance test. However there are some limitations: Fasting insulin level and HOMA-IR are the most commonly-used surrogate measures of insulin resistance, but the gold standard is the direct and time-consuming measurement of insulin resistance by euglycaemic insulin clamp technique. Such a validation would have been beyond the scope of this large observational study and would not have altered the well-known insulin-associated problems. Furthermore, this study demonstrates data from a European population and therefore limits the generalisation of these results for different ethnicities.

Conclusion

In order to identify practical predictors for the metabolic syndrome and the underlying insulin resistance, this study compared lipid ratios and the HTW phenotype in a fairly large sample size of German individuals without diabetes mellitus. The results build an evidence basis that the TG/HDL-C ratio is a reliable determinant, less costly, easily available and physiologically relevant in detecting the metabolic syndrome and insulin resistance in the absence of standardised insulin assays and that the HTW phenotype compares reasonably well as screening tool. The TG/HDL-C ratio may be used as a marker of cardiometabolic risk in routine clinical care. Furthermore, it offers prognostic potential and the chance to control therapeutic efficiency which is the corner stone of individual therapeutic strategies.

Conflicts of interest

The authors declare that they have no conflict of interest.

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