Hepatic Insulin Clearance Is Closely Related to Metabolic Syndrome Components

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OBJECTIVE—Insulin clearance is decreased in type 2 diabetes mellitus (T2DM) for unknown reasons. Subjects with metabolic syndrome are hyperinsulinemic and have an increased risk of T2DM. We aimed to investigate the relationship between hepatic insulin clearance (HIC) and different components of metabolic syndrome and tested the hypothesis that HIC may predict the risk of metabolic syndrome.

RESEARCH DESIGN AND METHODS—Individuals without diabetes from the Metabolic Syndrome Berlin Brandenburg (MeSyBePo) study (800 subjects with the baseline examination and 189 subjects from the MeSyBePo recall study) underwent an oral glucose tolerance test (OGTT) with assessment of insulin secretion (insulin secretion rate [ISR]) and insulin sensitivity. Two indices of HIC were calculated.

RESULTS—Both HIC indices showed lower values in subjects with metabolic syndrome ($P < 0.001$) at baseline. HIC indices correlate inversely with waist circumference, diastolic blood pressure, fasting glucose, triglycerides, and OGTT-derived insulin secretion index. During a mean follow-up of 5.1 ± 0.9 years, 47 individuals developed metabolic syndrome and 33 subjects progressed to impaired glucose metabolism. Both indices of HIC showed a trend of an association with increased risk of metabolic syndrome ($HIC_{C\text{-peptide}}$ odds ratio 1.13 [95% CI 0.97–1.31], $P = 0.12$, and HIC_{ISR} 1.38 [0.88–2.17], $P = 0.16$) and impaired glucose metabolism ($HIC_{C\text{-peptide}}$ 1.12 [0.92–1.36], $P = 0.26$, and HIC_{ISR} 1.31 [0.74–2.33] $P = 0.36$), although point estimates reached no statistical significance.

CONCLUSIONS—HIC was associated with different components of metabolic syndrome and markers of insulin secretion and insulin sensitivity. Decreased HIC may represent a novel pathophysiological mechanism of the metabolic syndrome, which may be used additionally for early identification of high-risk subjects.

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The clustering of metabolic and physiological abnormalities such as insulin resistance, hyperinsulinemia, hyperglycemia, arterial hypertension, and dyslipidemia in subjects with increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases has been described as "insulin resistance" syndrome or "metabolic syndrome" (1,2). More recently, several new components have been proposed as belonging to the metabolic syndrome, including microalbuminuria, hyperuricemia, markers of systemic inflammation, fibrinolytic and coagulation abnormalities (3), and increased liver enzymes (4). In his original description, Reaven (1) considered the development of hyperinsulinemia as a compensative phenomenon in response to insulin resistance to be the core and fundamental sign of metabolic syndrome. Growing evidence suggests that hyperinsulinemia in the insulin-resistant state reflects two pathophysiological processes: increase in insulin secretion and decrease in hepatic insulin clearance (HIC) (5,6). In subjects with different stages of glucose tolerance (6–8), HIC measured during the hyperinsulinemic-euglycemic clamp is decreased and independently determines fasting serum insulin concentrations. Moreover, the postprandial increase in circulating insulin is closely dependent on changes in hepatic HIC (9–11).

Young subjects with elevated risk of T2DM (12), overweight children (13,14), insulin-resistant subjects (8), and subjects with hypertension (6), polycystic ovary syndrome (15), and nonalcoholic fatty liver disease (16) all show decreased HIC. Mechanisms underlying this phenomenon are not completely defined, although it has been suggested that the genetic background (17,18), metabolic factors such as hyperglycemia (19), and increased free fatty acid (20) may contribute to altered HIC.

Only a few previous studies have focused on potential associations of HIC with components of the metabolic syndrome (4,8). Here, we examined systematically the relationship between HIC and different components of metabolic syndrome and tested the hypothesis that HIC may predict the risk of metabolic syndrome.

RESEARCH DESIGN AND METHODS

—The study protocol was approved by the ethics committee of Potsdam University, Potsdam, Germany. An informed written consent was obtained from all participants. Participants were selected from the ongoing German Metabolic Syndrome Berlin Potsdam (MeSyBePo) study that currently includes ~2,500 individuals with different states of glucose tolerance. Details of baseline

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phenotyping have previously been described (17), and all individuals with at least 3 years of follow-up time were recruited to repeat phenotyping (21). The baseline examination of participants included anthropometric measurements, blood sampling, a 75-g oral glucose tolerance test (OGTT) for 120 min, which was performed after overnight fast of 10 hours, and a personal interview on lifestyle habits and medical history. For the current study, we examined a consecutive series of 800 subjects (subjects with metabolic syndrome, n = 325; subjects without metabolic syndrome, n = 475) at baseline and 189 subjects with follow-up data (incident metabolic syndrome, n = 47; incident impaired glucose metabolism [IGM], n = 33). All subjects had no history of diabetes, cardiovascular diseases, malignant disease, liver or chronic kidney failure, or inflammatory diseases at baseline visit. The metabolic syndrome was diagnosed according to Harmonizing Criteria of the Metabolic Syndrome (22). Samples for insulin and C-peptide measurements were drawn at 0, 30, 60, 90, and 120 min of the OGTT.

Biochemical analyses

All venous blood samples were immediately centrifuged and frozen at −70°C until analysis. Capillary blood glucose concentrations were measured using the glucose oxidase method on a Super GL (Dr. Müller, Freital, Germany). HbA_{1c} was measured using a Hi-Auto A1C HA-8140 system (Menarini Diagnostics, Berlin, Germany). Serum triglycerides, total cholesterol, and HDL cholesterol were measured by standard enzymatic assays, and LDL cholesterol was calculated from these data (certified laboratory for clinical chemistry). Serum insulin and C-peptide were measured using commercial ELISAs (insulin ELISA and C-peptide ELISA; Mercodia, Uppsala, Sweden).

Calculations and statistical analyses

Data are presented as mean ± SD. Based on the OGTT data, we calculated the insulin secretion rate (ISR) using the two-compartment model of C-peptide kinetics (23). The $HIC_{C\text{-}peptide}$ was determined as a ratio of the incremental areas under the curve (AUC) of OGTT ($AUC_{C\text{-}peptide\ 0–120\ min}$/$AUC_{insulin\ 0–120\ min}$) (12,14,24). In addition, we calculated HIC_{ISR} as a ratio of the incremental area under the ISR curve ($AUC_{ISR\ 0–120\ min}$) to the incremental area under the peripheral insulin concentration curve ($AUC_{insulin\ 0–120\ min}$) (12). The OGTT-derived $HIC_{C\text{-}peptide}$ was strong correlated with metabolic insulin clearance determined in hyperinsulinemic-euglycemic clamp experiments in our previous study (17). Insulin sensitivity was quantified from the OGTT by Gutt index (Gutt $ISI_{0,120}$) (25). Insulin response to glucose in the OGTT was estimated by calculation of 1st-phase insulin secretion index: $1{,}283 + (1.829 \times Ins_{30\ min}$ [pmol]) − ($138.7 \times$ blood $glucose_{30\ min}$ [mmol]) + ($3.772 \times Ins_{0\ min}$ [pmol]), where Ins is insulin (26). The difference between groups was calculated by one-way ANOVA. The linear relationships between HIC and anthropometric as well as metabolic markers were calculated using Pearson correlation. To investigate the shape of the associations between both indices of HIC and 1st-phase insulin secretion, we used restricted cubic spline regressions (27) with knots at the 5th, 50th, and 95th percentiles. These models were compared with linear regression models. The effect and the term for nonlinearity of the restricted cubic spline regression were statistically tested. Binary logistic regression was used for the calculation of odds ratios (ORs). The power (the probability of avoiding a type II error) for the estimation of the ORs of HIC on metabolic syndrome was calculated with SAS Power and Sample Size 3.12. The nominal significance level was 0.05. The statistical analyses were performed with SPSS 18 (SPSS, Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC).

RESULTS—At baseline, 325 of the participants fulfilled the criteria for metabolic syndrome (Table 1). These subjects had higher BMI, waist circumference, triglycerides, fasting glucose, and systolic and diastolic blood pressure, as well as surrogate markers of 1st-phase insulin secretion, and were more insulin resistant compared with subjects without metabolic syndrome. OGTT-derived indices of HIC were markedly lower in subjects with metabolic syndrome ($HIC_{C\text{-}peptide}$ 6.7 ± 2.6 vs. 5.5 ± 2.3 arbitrary units [AU], $P < 0.001$, and HIC_{ISR} 2.2 ± 0.8 vs. 1.9 ± 0.8 pmol/min, respectively) and remained significant after adjustment for BMI and age. Moreover, subjects with normal glucose tolerance (NGT) and metabolic syndrome had decreased HIC compared with subjects without metabolic syndrome ($HIC_{C\text{-}peptide}$ 5.90 ± 2.54 vs. 6.73 ± 2.60 AU, $P < 0.05$, and HIC_{ISR} 2.09 ± 0.86 vs. 2.21 ± 0.84 pmol/min, $P < 0.05$, respectively) (Table 1).

Both HIC indices correlated significantly with each other (r = 0.94, $P < 0.001$). Positive linear correlation of HIC indices with Gutt $ISI_{0,120}$ was observed in subjects with metabolic syndrome (r = 0.44, $P < 0.001$, for $HIC_{C\text{-}peptide}$ and r = 0.50, $P < 0.001$, for HIC_{ISR}) and in subjects without metabolic syndrome (r = 0.34, $P < 0.001$, for $HIC_{C\text{-}peptide}$ and r = 0.39, $P < 0.001$, for HIC_{ISR}). Moreover, an inverse relationship was found between HIC and 1st-phase insulin secretion index (r^2 = 0.23, $P < 0.001$, for $HIC_{C\text{-}peptide}$ and r^2 = 0.15, $P < 0.001$, for HIC_{ISR}) in the analysis of the general cohort. To investigate the mechanism by which insulin secretion interacts with HIC, we tested the relationship between these variables separately in subjects with and without metabolic syndrome (Fig. 1). We found close nonlinear relationships between HIC and 1st-phase insulin secretion only in the subjects with metabolic syndrome (r^2 = 0.26, P_{nonlin} (P value for nonlinear model) <0.007, for $HIC_{C\text{-}peptide}$) (Fig. 1*B*)—not in subjects without metabolic syndrome (r^2 = 0.16, $P_{effect} < 0.001$, and r^2 = 0.16, P_{nonlin} = 0.24, for $HIC_{C\text{-}peptide}$ and r^2 = 0.09, $P_{effect} < 0.001$, and r^2 = 0.09, P_{nonlin} = 0.63, for HIC_{ISR}) (Fig. 1*A*, *C*, and *D*). Again, the results remained significant after adjustment for waist circumference, age, and sex.

An inverse correlation between different parameters of metabolic syndrome such as waist circumference, diastolic blood pressure, fasting glucose, and triglycerides was observed in the entire cohort (Table 2). In contrast, plasma HDL cholesterol correlated positively with HIC (r = 0.11, P = 0.003, for $HIC_{C\text{-}peptide}$ and r = 0.11, P = 0.002, for HIC_{ISR}).

In the next step, we analyzed the relation between HIC and incident metabolic syndrome. We observed no statistically significant difference in either index of HIC between subjects with incident metabolic syndrome and subjects without metabolic syndrome ($HIC_{C\text{-}peptide}$ 7.01 ± 3.05 vs. 6.23 ± 2.13 AU, P = 0.11, and HIC_{ISR} 2.32 ± 0.98 vs. 2.09 ± 0.73 pmol/min, P = 0.15, respectively). Logistic regression analysis indicates a trend that HIC independently predicted the risk of developing the metabolic syndrome ($HIC_{C\text{-}peptide}$ OR 1.13 [95% CI 0.97–1.31], P = 0.12, and HIC_{ISR} 1.38 [0.88–2.17], P = 0.16) (crude model). Additional adjustment for age, sex, waist circumference, index of 1st phase of insulin secretion, and time of follow-up ($HIC_{C\text{-}peptide}$ OR 1.13 [95% CI 0.96–1.32],

Table 1—*Clinical characteristics of the study population*

Parameter	Subjects with MS at baseline[a]			Subjects without MS at baseline				
	Subjects with NGT	Subjects with IGT and IFG	All	All	P[b]	Subjects with MS at follow-up	Subjects without MS at follow-up	P[c]
N (male/female)	120 (40/80)	205 (53/152)	325 (93/232)	475 (119/356)		47 (14/33)	69 (17/52)	
Age (years)	53.9 ± 10.8	57.4 ± 11.1†	56.1 ± 11.1	51.9 ± 12.7	**<0.001**	55.9 ± 10.4	53.1 ± 11.3	0.177
BMI (kg/m^2)	32.1 ± 4.5	31.6 ± 5.5	31.8 ± 5.1	27.5 ± 5.0†	**<0.001**	29.1 ± 4.6	28.5 ± 4.8	0.527
Waist circumference (cm)	103.4 ± 11.6	101.0 ± 12.7	101.9 ± 12.3	89.4 ± 13.4†	**<0.001**	93.2 ± 11.1	91.5 ± 13.8	0.484
Total cholesterol (mmol/L)*	5.5 ± 1.1	5.6 ± 1.1	5.6 ± 1.1	5.4 ± 1.0	0.124	5.7 ± 1.0	5.3 ± 0.9	**0.021**
HDL cholesterol (mmol/L)*	1.2 ± 0.3	1.3 ± 0.3†	1.3 ± 0.3	1.5 ± 0.3†	**<0.001**	1.5 ± 0.3	1.5 ± 0.3	0.967
Triglyceride (mmol/L)*	2.1 ± 0.9	1.8 ± 0.9†	1.9 ± 0.9	1.1 ± 0.5†	**<0.001**	1.2 ± 0.5	1.0 ± 0.5	0.094
Systolic blood pressure (mmHg)**	131.4 ± 15.1	132.1 ± 16.2	131.8 ± 15.7	117.1 ± 13.1†	**<0.001**	119.3 ± 12.4	118.0 ± 13.5	0.635
Diastolic blood pressure (mmHg)**	83.5 ± 8.7	81.2 ± 8.8	82.1 ± 8.8	74.2 ± 8.1†	**<0.001**	74.8 ± 8.7	75.5 ± 8.2	0.688
Fasting glucose (mmol/L)	4.9 ± 0.5	5.3 ± 0.5†	5.2 ± 0.5	4.9 ± 0.5	**<0.001**	5.0 ± 0.4	4.9 ± 0.6	0.173
Glucose 120 min	6.2 ± 0.9	8.5 ± 1.2†	7.6 ± 1.5	6.5 ± 1.3	**<0.001**	6.9 ± 1.7	6.9 ± 1.5	0.810
Fasting insulin (pmol/L)	66.0 ± 43.0	64.2 ± 37.5	64.9 ± 39.6	42.1 ± 25.6†	**<0.001**	45.4 ± 22.0	41.4 ± 20.0	0.315
1st-phase insulin secretion	1177 ± 654	901 ± 503†	1003 ± 578	810 ± 422†	**<0.001**	778 ± 446	808 ± 410	0.710
$HIC_{C\text{-}peptide}$ (AU)	5.90 ± 2.54	5.27 ± 2.19†	5.50 ± 2.34	6.73 ± 2.60†	**<0.001**	7.01 ± 3.05	6.23 ± 2.13	0.110
HIC_{ISR} (pmol/min)	2.09 ± 0.86	1.77 ± 0.71†	1.89 ± 0.78	2.21 ± 0.84†	**<0.001**	2.32 ± 0.98	2.09 ± 0.73	0.153
Gutt $ISI_{0,120}$, OGTT (mg · L^2/ mmol · mU · min)	80.6 ± 19.4	58.0 ± 17.0†	66.4 ± 20.9	91.9 ± 36.7	**<0.001**	81.7 ± 23.2	83.1 ± 25.9	0.764

Data are means ± SD unless otherwise indicated. The studied cohort includes NGT or impaired fasting glucose/impaired glucose tolerance subjects with complete insulin and C-peptide data from 2-h OGTT and BMI ≤50 kg/m^2 and not treated with antidiabetes drugs. All values obtained from subjects after an overnight fast without beverage intake. *P* values: the comparison by one-way ANOVA. Boldface data indicate *P* values < 0.05. MS, metabolic syndrome. [a]Defined by Harmonized Metabolic Syndrome criteria (22). [b]Subjects without MS vs. subjects with MS at baseline. [c]Subjects without MS vs. subjects with MS at follow-up examination. †P < 0.05 compared with NGT subjects with MS. *Subjects not treated with lipid-lowering drugs (444 subjects without MS at baseline/288 subjects with MS at baseline/66 subjects without MS at follow-up/42 subjects with MS at follow-up). **Subjects not treated with antihypertension drugs (386 subjects without MS at baseline/193 subjects with MS at baseline/60 subjects without MS at follow-up/38 subjects with MS at follow-up).

P = 0.14, and HIC_{ISR}1.41 [0.87–2.29], *P* = 0.16), which slightly attenuated results, but HIC still remained an independent predictor of future metabolic syndrome (Fig. 2*A–B*).

In addition, HIC_{ISR} showed a trend for association with increased risk of IGM incidents after adjustment for age, sex, waist circumference, time of follow-up, and 1st-phase of insulin secretion ($HIC_{C\text{-}peptide}$ OR 1.12 [95% CI 0.92–1.36], *P* = 0.26, and HIC_{ISR} 1.31 [0.74–2.33], *P* = 0.36), although point estimates reached no statistical significance. Additional adjustment for waist-to-hip ratio, diastolic blood pressure, HDL cholesterol, triglycerides, and baseline fasting and 2-h glucose again modified results, but point estimates remained comparable with the crude analysis for incident metabolic syndrome and incident IGM (data not shown). The power (the probability of avoiding a type II error) for the estimation of the ORs of HIC on metabolic syndrome was 0.30 and 0.32 for $HIC_{C\text{-}peptide}$ and HIC_{ISR}, respectively.

CONCLUSIONS—Decreased HIC is an early phenotypical marker of disturbances in insulin metabolism and was observed in various disorders associated with metabolic syndrome and T2DM (6,13–16,28). However, most studies were not designed to test the hypothesis that insulin clearance is strongly associated with existing metabolic syndrome and may predict this condition. In this large-cohort prospective study, we found an association between two OGTT-derived indices of HIC and different components of metabolic syndrome and a trend indicating their possible association with an increased risk of incident metabolic syndrome and IGM. Moreover, we observed an inverse nonlinear correlation between HIC and 1st-phase insulin secretion index in subjects with metabolic syndrome and a positive linear correlation between HIC and OGTT-derived index of insulin sensitivity for the general MeSyBePo cohort.

In our study, we identified highly significant correlations between OGTT-derived HIC indices and different components of metabolic syndrome, in agreement with previous results from other studies (4,6,13). The imbalance of hepatic insulin metabolism appears to be a first change in the development of weight gain–related insulin resistance (29). Conversely, weight loss increases HIC in both humans (29) and animals (30). In accordance with this, our study subjects with NGT and metabolic syndrome had lower HIC compared with subjects without metabolic syndrome, suggesting that impairment of insulin clearance may occur before the development of disturbances in glucose metabolism. Moreover, we found a trend for the association between two OGTT-derived indices of HIC and increased risk of incident metabolic syndrome and IGM, although point estimates reached no statistical significance. The OGTT-derived HIC was strongly correlated with metabolic insulin clearance, as determined in hyperinsulinemic-euglycemic clamp experiments in our previous study (17), and

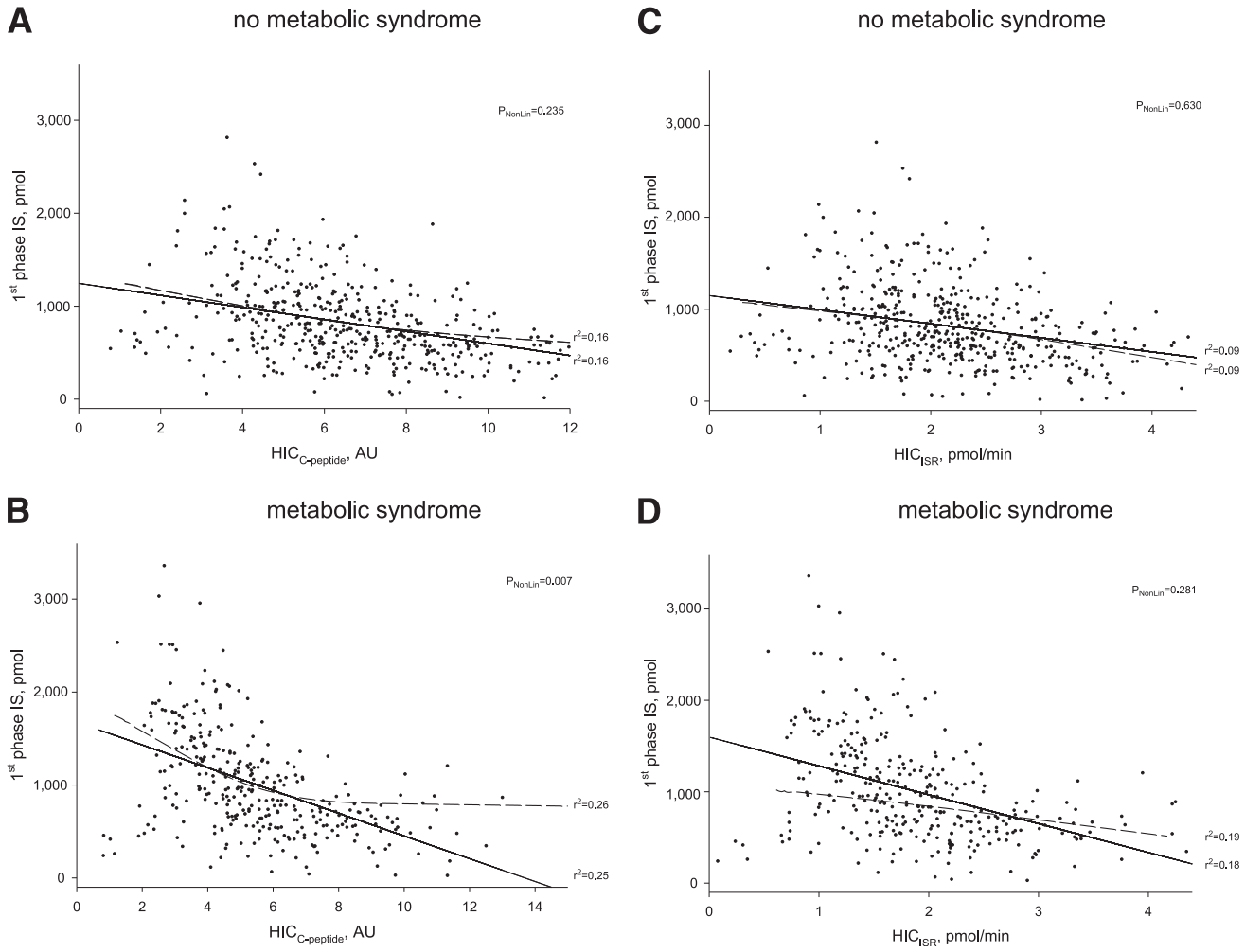

Figure 1—*Relationship between HIC estimated as HIC_{ISR}* (C *and* D) *and $HIC_{C\text{-}peptide}$* (A *and* B) *and OGTT-derived indices of insulin secretion (1st-phase insulin secretion index [IS] [26]) in the entire cohort* (n = *800; subjects with metabolic syndrome,* n = *325; subjects without metabolic syndrome,* n = *475).* R^2 *was calculated for linear and nonlinear restricted cubic spline regression models.*

may be helpful for the identification of subjects with high risk of metabolic syndrome, even in the absence of other signs of IGM.

Reduced hepatic insulin elimination may intensify insulin resistance via chronic elevations of circulating fasting and postprandial insulin concentrations (20,31,32). The Gutt insulin sensitivity index, calculated as a ratio of postloading glucose disposal to the mean of fasting and 2-h postinsulin concentrations, has been suggested as the best predictor of T2DM after 5–8 years of follow-up (33). Our data showed a significant and positive correlation between the Gutt insulin sensitivity index and HIC, supporting complete capture of other important domains of T2DM in this index (32). In accordance with previously published data (11,34–36), we observed an inverse relationship between insulin secretion and HIC, potentially representing a physiological mechanism by which insulin secretion may regulate HIC. Thus, decreased HIC in subjects with metabolic syndrome may not compensate for lower insulin sensitivity but, rather, represent an additional element of insulin disturbance, possibly directly dependent on changes in insulin secretion. We can

Table 2—*Relationship between indexes of HIC and markers of metabolic syndrome*

	$HIC_{C\text{-}peptide}$		HIC_{ISR}	
Parameter	*r*	*P*	*r*	*P*
Waist circumference	−0.28	<0.001	−0.11	0.001
Plasma triglycerides*	−0.17	<0.001	−0.17	<0.001
HDL cholesterol*	0.11	0.003	0.11	0.002
Systolic blood pressure**	−0.08	0.062	−0.08	0.058
Diastolic blood pressure**	−0.12	0.005	−0.12	0.003
Fasting glucose	−0.13	<0.001	−0.13	<0.001

The studied cohort includes NGT or impaired fasting glucose/impaired glucose tolerance subjects with complete insulin and C-peptide data from 2-h OGTT and BMI ≤50 kg/m^2 and not treated with antidiabetes drugs (*n* = 800; 475 subjects without metabolic syndrome/325 subjects with metabolic syndrome). All data except waist circumference were adjusted for age, sex, and BMI; waist circumference was adjusted for age and sex. *Subjects not treated with lipid-lowering drugs (*n* = 732). **Subjects not treated with antihypertension drugs (*n* = 579).

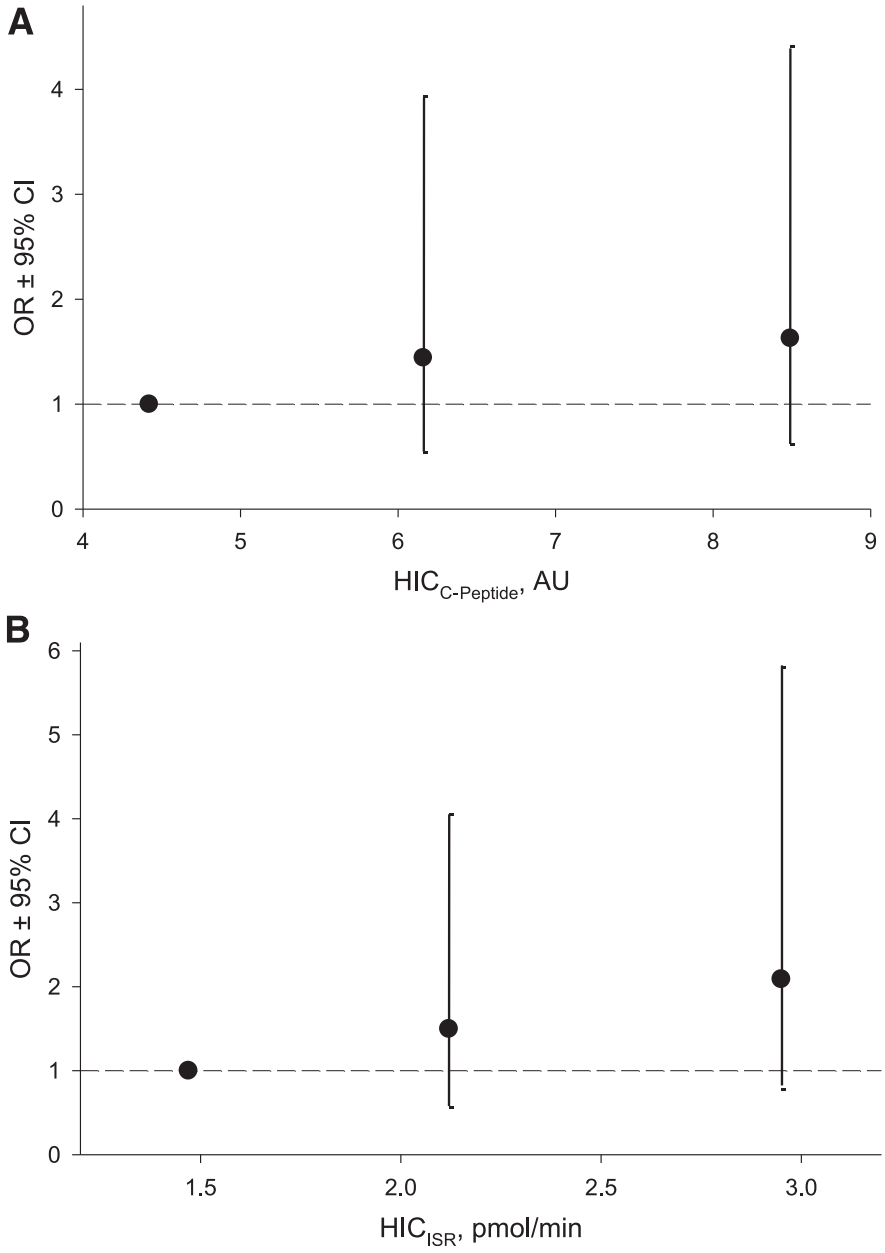

Figure 2—*Risk of subsequent metabolic syndrome according to the respective median of ascending tertiles of two HIC indices.* A: *HIC calculated by C-peptide values.* B: *HIC calculated with use of ISR. Adjustment for age, sex, body weight, waist circumference, 1st-phase insulin secretion, and follow-up time. Error bars represent 95% CIs. The horizontal line at 1.0 represents the reference line. Participants were divided into tertiles, according to HIC values. Tertile cut points were determined from the combined group of case and control subjects.*

speculate that the decrease in the HIC may also be an important mechanism in the case of insulin secretion–stimulating diets like diets with a high glycemic index and the phenomenon of soft drink–induced metabolic syndrome being associated with nonalcoholic steatohepatitis (37). On the other hand, based on the epidemiological character of our study, we cannot entirely rule out the fact that HIC may simply cluster with metabolic syndrome without necessarily belonging to the syndrome as one of the defining components.

However, mechanisms leading to the alteration of insulin degradation in humans are complex and not understood in detail (31). The insulin-degrading enzyme (IDE) is thought to be a major enzyme responsible for insulin degradation (31). All insulin-sensitive cells contain IDE and remove and degrade insulin. However, the liver is the main site of insulin clearance, removing ~75% during the first portal passage (31,36). Hyperglycemia downregulates the insulin-induced IDE activity in the liver cell model (19) and in this way may provoke the known decrease of IDE activity in T2DM (31). On the other hand, insulin clearance is a highly heritable trait (8), and polymorphisms in the IDE gene are associated with increased T2DM risk and decreased OGTT-derived HIC in nondiabetic subjects (17).

We observed a close correlation between HIC and HDL cholesterol, a marker of liver fat metabolism. HIC correlated inversely with liver fat content and hepatic glucose production in diabetic and nondiabetic subjects (16). Taken together, decreased HIC is possibly the earliest marker of hepatic insulin resistance and is directly linked to insulin action in the liver with consequent effects on the hepatic lipid metabolism and liver inflammation.

Limitations of our study need to be mentioned. We measured HIC indirectly in two ways, based on previously reported techniques of insulin clearance calculation (12,17). Although direct assessment of portal concentration of hormones in human subjects has been established (36), this is not a practicable method for the use in large cohorts. In addition, the power to detect more moderate changes of HIC in our prospective study population is likely to be insufficient, and doing so would require the investigation of considerably larger prospective cohorts.

In conclusion, we found decreased HIC in middle-aged subjects with metabolic syndrome. The decrease of HIC showed a trend for association with a risk of incident metabolic syndrome and incident impaired glucose homeostasis independent of obesity and age. Both indices of HIC significantly correlated with different components of metabolic syndrome. Thus, OGTT-derived indices of HIC may be helpful for the identification of people with high risk of metabolic syndrome.

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O.P., W.B., T.B., F.I., and M.M. contributed to the conception and design of the project, contributed to discussion, collected and analyzed data, and drafted, reviewed, and edited the manuscript. J.S., M.O.W., and M.O. contributed to the conception and design of the project, researched data, contributed to discussion, and reviewed and edited the manuscript. A.F.H.P. and N.R. contributed to the conception and design of the project, contributed to discussion, collected and analyzed data, and drafted, reviewed, and edited the manuscript. O.P., W.B., and N.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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