The Role of Markers of Low-Grade Inflammation for the Early Time Course of Glycemic Control, Glucose Disappearance Rate, and β-Cell Function in Recently Diagnosed Type 1 and Type 2 Diabetes

*Katharina S. Weber,[1,2] Bettina Nowotny,[1,2] Klaus Strassburger,[2,3] Giovanni Pacini,[4] Karsten Müssig,[1,2,5] Julia Szendroedi,[1,2,5] Christian Herder,[1,2] and Michael Roden,[1,2,5] for the GDS Group**

Diabetes Care 2015;38:1758–1767 | DOI: 10.2337/dc15-0169

OBJECTIVE

Inflammatory processes are involved in the progression of insulin resistance and β-cell dysfunction in individuals with prediabetes and contribute to the development of diabetes. We hypothesized that higher levels of biomarkers of low-grade inflammation are associated with the early progression of recently diagnosed diabetes.

RESEARCH DESIGN AND METHODS

Within the prospective German Diabetes Study, patients with recently diagnosed type 1 (*n* = 42) and type 2 (*n* = 94) diabetes underwent detailed metabolic characterization within the first year after diagnosis and 2 years thereafter. Associations between changes in markers of low-grade inflammation with changes in glycemic control, β-cell function, and glucose disappearance rate were assessed using multivariable linear regression analysis. Associations were adjusted for age, sex, BMI, smoking status, and 2-year changes in BMI, smoking status, and glucose-lowering medication.

RESULTS

Patients with type 1 and type 2 diabetes exhibited good glucometabolic control at baseline (mean HbA_{1c} 7.08 ± 1.58% [54 ± 17 mmol/mol] and 6.43 ± 0.98% [47 ± 11 mmol/mol], respectively) and 2 years thereafter (mean HbA_{1c} 7.03 ± 1.20% [53 ± 13 mmol/mol] and 6.62 ± 1.14% [49 ± 13], respectively). Two-year increases of high-sensitivity C-reactive protein, soluble E-selectin (sE-selectin), and soluble intercellular adhesion molecule-1 in type 2 diabetes and of IL-18 in type 1 diabetes were associated with 2-year increases of HbA_{1c}. Additionally, 2-year increases of sE-selectin were associated with 2-year decreases of prehepatic β-cell function in type 2 diabetes (all $P < 0.05$).

CONCLUSIONS

These data indicate that with the clinical onset of diabetes, low-grade inflammation relates to worsening of glycemia and that endothelial activation may contribute to decreasing β-cell function.

[1]Institute for Clinical Diabetology, German Diabetes Center at Heinrich Heine University, Leibniz Institute for Diabetes Research, Düsseldorf, Germany
[2]German Center for Diabetes Research, Partner Düsseldorf, Düsseldorf, Germany
[3]Institute for Biometrics and Epidemiology, German Diabetes Center at Heinrich Heine University, Leibniz Institute for Diabetes Research, Düsseldorf, Germany
[4]Metabolic Unit, Institute of Biomedical Engineering, National Research Council, Padua, Italy
[5]Department of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Corresponding author: Michael Roden, michael.roden@ddz.uni-duesseldorf.de.

Received 23 January 2015 and accepted 27 May 2015.

Clinical trial reg. no. NCT01055093, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0169/-/DC1.

C.H. and M.R. contributed equally to this work.

**A full list of German Diabetes Study (GDS) Group members can be found in the APPENDIX.*

Hyperglycemia is the primary diagnostic criterion of diabetes. The most abundant types of diabetes, type 1 and type 2, differ in etiology (1) but share the common feature of impaired β-cell function before the onset of the disease (2,3). β-Cell function generally declines rapidly in type 1 diabetes due to progressive autoimmune destruction (4), whereas it deteriorates more slowly before type 2 diabetes (3). Genome-wide association studies have emphasized the role of impaired β-cell function for type 2 diabetes (5). Nevertheless, chronic insulin resistance is considered more important in triggering type 2 diabetes (6). Of note, data also suggest an accelerating role of insulin resistance for type 1 diabetes (7).

Inflammatory processes can contribute to both insulin resistance and β-cell dysfunction. In type 2 diabetes, most studies have focused on low-grade inflammation as a trigger for insulin resistance. However, data also link inflammation and β-cell function in type 2 diabetes (8). In type 1 diabetes, inflammatory processes appear more relevant because of their β-cell toxicity rather than their impact on insulin resistance (9). Given the importance of insulin resistance and β-cell function for near-normoglycemic control, whether circulating inflammation-related biomarkers indeed associate with insulin resistance and β-cell function during the progression of type 1 and type 2 diabetes is relevant. Associations between biomarkers of low-grade inflammation and diabetes status, insulin resistance, and β-cell function have been analyzed in cross-sectional studies (10,11). In addition, prospective studies have examined the role of acute phase proteins, cytokines, chemokines, and biomarkers of endothelial function in the context of incident diabetes, mostly type 2 diabetes (12–14). In contrast, data on the impact of inflammation-related biomarkers on changes of insulin resistance and β-cell function in the early course of the disease are scarce (15).

It is conceivable that inflammatory processes affect insulin sensitivity and β-cell function not only before but also after the clinical diagnosis of type 1 and type 2 diabetes. Thus, this study aimed to investigate the associations of 2-year changes of markers of low-grade inflammation with 2-year changes of glycemic control, β-cell function, and glucose disappearance rate in patients with recently diagnosed type 1 or type 2 diabetes. We hypothesized that higher levels of biomarkers of low-grade inflammation are associated with the early progression of recently diagnosed diabetes and aimed to describe the impact of changes in the levels of biomarkers of low-grade inflammation on early changes of glycemic control, β-cell function, and glucose disappearance rate in both type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The German Diabetes Study (GDS) is a prospective observational study investigating the natural history of recent-onset diabetes and the development of diabetes-associated complications to improve risk assessment and targeted treatment of patients with diabetes (16,17). The primary outcome measure of the GDS is the change in insulin sensitivity; secondary outcome measures are change of insulin secretion and incidence of diabetes-related complications. The study is performed according to the Declaration of Helsinki and is approved by the ethics committee of Heinrich Heine University Düsseldorf. All patients give written informed consent before inclusion into the study. The study was started in September 2005 and still includes new patients, aiming for 2,000 in total. For this substudy, all patients were included for whom baseline and 2-year follow-up data were available. For this group, 200 baseline examinations were conducted between September 2005 and December 2008 and follow-up examinations between November 2007 and October 2011. Baseline inclusion criteria were age between 18 and 69 years and known diabetes duration $<$12 months. Exclusion criteria were diabetes owing to secondary diseases, pregnancy, acute infections, immunosuppressive therapy, evidence of congestive heart failure, kidney diseases, liver diseases, symptomatic peripheral arterial disease, psychiatric or addictive diseases, history of malignancies, or participation in pharmacological intervention studies. Patients with previous gestational diabetes mellitus with type 2 diabetes after postpartum normalization of glucose tolerance are not excluded from this study. Patients are referred to the German Diabetes Center by their local general practitioner or by specialized outpatient units or recruited by advertisement. If necessary, diabetes diagnosis is confirmed by records of plasma glucose $\geq$7.0 mmol/L at fasting or $\geq$11.1 mmol/L at 120 min of a standardized 75-g oral glucose tolerance test in accordance with American Diabetes Association guidelines (1). Type 1 diabetes is defined by the presence of autoantibodies, classic symptoms, and/or ketoacidosis at onset of disease.

Experimental Design

Patients underwent detailed metabolic phenotyping at baseline and 2-year follow-up examination after fasting overnight ($\geq$8 h) and after having stopped oral glucose-lowering medication for 3 days. Patients on insulin treatment administered their last insulin dose in the evening before the first examination day. On the first day, patients underwent anthropometric examinations, fasting blood analyses, and glucagon stimulation testing. A structured interview covering medical history, family history of chronic diseases, and socioeconomic status was conducted. This was followed by an intravenous glucose tolerance test (IVGTT) on the next day.

Anthropometry

BMI was calculated from body weight and height recorded using a calibrated scale with stadiometer (seca 674; Hamburg, Germany) without wearing shoes and in light underwear to the nearest 0.5 kg and 0.1 cm, respectively.

Glucagon Stimulation Test

A catheter was inserted into an antecubital vein, and a fasting blood sample was drawn. At 0 min, a bolus of 1 mg glucagon (GlucaGen; Novo Nordisk, Mainz, Germany) was injected intravenously within 60 s. At 6 min, a second blood sample was obtained (18). The ratio between C-peptide concentrations at 6 min and 0 min was calculated to assess glucagon-stimulated C-peptide secretion capacity.

IVGTT

The protocol of the IVGTT has been previously described (19). The acute C-peptide glucose-dependent response (ACPRG) was calculated as the average of C-peptide concentrations between 2 and 10 min following glucose injection. This value is an extension to the C-peptide of the acute insulin response introduced by Kahn et al. (20). It represents the β-cell direct secretory response to glucose stimulation. Glucose-

stimulated total incremental area under the curve (AUC) for C-peptide ($iAUC_{CP}$) was calculated using the trapezoidal rule subtracting the basal area from the AUC. β-Cell function was also characterized by calculating the incremental prehepatic β-cell function (iBCF) based on modeling analysis of C-peptide to assess prehepatic insulin secretion (21). Glucose disappearance rate is a measure of intravenous glucose tolerance and represents the net glucose elimination rate after glucose injection. It was calculated as the slope for the interval 6–40 min after glucose injection using log-transformed glucose values (22).

Laboratory Measurements

Supplementary Table 1 provides detailed information with respect to biospecimen type, storage, freeze-thaw cycles, intra- and interassay coefficients of variation, and measurement ranges for all analytes (HbA_{1c}, glucose, C-peptide, lipids, high-sensitivity C-reactive protein [hsCRP], IL-6, IL-18, soluble E-selectin [sE-selectin], soluble intercellular adhesion molecule-1 [sICAM-1], and autoantibodies). For all parameters, blood samples at baseline and follow-up were taken using the same tubes and tube additives. Immune mediator measurements of samples from baseline and follow-up were done for all samples at the same time, using the same instruments and methods.

Statistical Analyses

Results are presented as mean ± SD for normally distributed data and median (25th; 75th percentiles) for nonnormally distributed data. Differences between baseline and 2-year follow-up were assessed using paired Student *t* test for normally distributed continuous variables, Wilcoxon signed rank test for nonnormally distributed continuous variables, McNemar test for paired samples for categorical variables with two characteristics, and Bowker test of symmetry for categorical variables with more than two characteristics.

Multivariable linear regression models were used to analyze the associations between 2-year changes (2-year follow-up divided by baseline) of markers of inflammation (independent variable) with 2-year changes of glycemic control, β-cell function, and glucose disappearance rate (dependent variable). Glucagon-stimulated C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, iBCF, hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 were not normally distributed and, thus, were entered into the models as ln-transformed variables. In the basic model (model 1), the value of the respective measure of glucose metabolism at baseline, the concentration of the marker of low-grade inflammation at baseline, age at baseline, sex, and diabetes type were considered as covariables potentially affecting the associations. A second model (model 2) was additionally adjusted for BMI at baseline, change of BMI, change of the type of glucose-lowering medication, smoking status at baseline, and change of smoking status. The fit of the full models was checked for normality using Q-Q plots. Residuals were checked for homoscedasticity. Scatter plots of the predicted value with the dependent variable were evaluated. Additionally, R^2 values and *P* values of the *F* statistic were calculated for each model (Supplementary Tables 2 and 3). Regression coefficients (β) should be interpreted as follows: A doubling of the ratio of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 between baseline and 2-year follow-up associates with an absolute change of HbA_{1c} and glucose disappearance rate within the first 2 years by β, and a doubling of the ratio of 2-year follow-up/baseline values of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 associates with a percent change of C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, and iBCF within the first 2 years by β. Post hoc power calculations and patient numbers needed to detect changes were conducted as described in the Supplementary Data (Supplementary Tables 4–7).

Additionally, four sensitivity analyses were conducted. First, glucose disappearance rate was added as a potential confounder to model 2 for those models with indices of insulin secretion as a dependent variable. Second, β-values of patients with type 1 and type 2 diabetes were tested for differences as described (23). Third, only patients without glucose-lowering medications at baseline and follow-up were included in linear regression models (Supplementary Tables 8 and 9). Fourth, disease status of bronchial asthma and chronic obstructive pulmonary disease (COPD) at baseline (presence of the disease within the past 12 months) and follow-up (presence of the disease within the past 24 months) were added as potential confounders to model 2. $P < 0.05$ were considered statistically significant. All statistical analyses were carried out using SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 137 individuals with type 1 and type 2 diabetes participated in the baseline and 2-year follow-up examinations. Follow-up time was 2.1 ± 0.1 years. The response rate for the follow-up was 68.5% (Fig. 1 and Supplementary Fig. 1). Patients with type 2 diabetes who were lost to follow-up were younger and had shorter known diabetes duration compared with those who participated in both examinations. Patients with type 1 diabetes who quit study participation did not differ from those who continued (Supplementary Table 10). Type 1 diabetes was present in 31% of the study population (Table 1). At baseline, all patients with type 2 diabetes were autoantibody negative. Of the patients with type 1 diabetes, 15% were autoantibody negative, 36% had one autoantibody, and 49% expressed two autoantibodies. Patients exhibited good glucometabolic control. Between baseline and 2-year follow-up, glucagon-stimulated C-peptide secretion and sE-selectin increased, whereas ACPRG and $iAUC_{CP}$ decreased in patients with type 2 diabetes. In type 1 diabetes, BMI and sICAM-1 increased, whereas ACPRG, $iAUC_{CP}$, and glucose disappearance rate decreased within the first 2 years after diabetes diagnosis (Table 1).

Markers of Low-Grade Inflammation and Glycemic Control, Insulin Secretion, and Glucose Disappearance Rate in Patients With Type 2 Diabetes

In patients with type 2 diabetes, increases of serum concentrations of hsCRP, sE-selectin, and sICAM-1 (per doubling of the ratio of 2-year follow-up/baseline values) within the first 2 years after diagnosis was associated with absolute increases of HbA_{1c} by 0.46%, 0.90%, and 1.69%, respectively (model 2, all $P < 0.01$). No association was observed between changes of IL-6 or IL-18 and changes of HbA_{1c}. Additionally, 2-year changes of sE-selectin were associated with a relative decrease of iBCF of 34.87% (model 2). The associations between 2-year changes of sE-selectin and sICAM-1 with

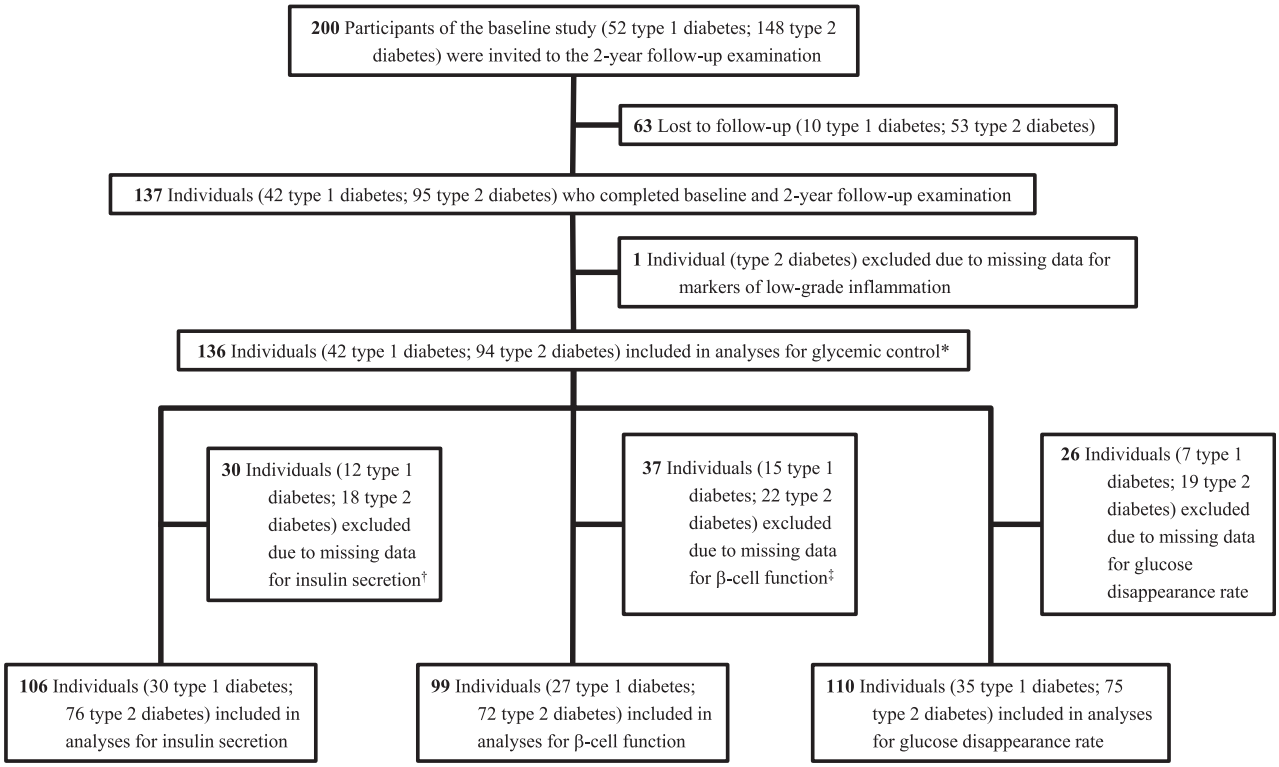

Figure 1—Flow diagram showing the number of patients included in the analyses for IL-6, IL-18, sE-selectin, and sICAM-1 from those enrolled in the GDS. *HbA_{1c}. †C-peptide secretion from glucagon stimulation testing, ACPRG, and glucose-stimulated total $iAUC_{CP}$. ‡iBCF. Patients lost to follow-up were deceased, seriously ill, not to be contacted, no longer interested in or lacking time for study participation, or declined without giving a reason.

HbA_{1c} and of sE-selectin with iBCF were not explained by serum concentrations of triglycerides, HDL cholesterol, or LDL cholesterol at baseline (data not shown). Associations between changes of hsCRP and sE-selectin with changes of C-peptide secretion capacity from glucagon stimulation testing lost significance after adjustment (model 2). Associations between changes of IL-6 and changes of $iAUC_{CP}$ as well as between sICAM-1 and ACPRG were only significant in the fully adjusted model (model 2). There was no evidence for associations between changes of serum concentrations of biomarkers of low-grade inflammation and changes of glucose disappearance rate (Table 2 and Supplementary Table 2).

Markers of Low-Grade Inflammation and Glycemic Control, Insulin Secretion, and Glucose Disappearance Rate in Patients With Type 1 Diabetes

In patients with type 1 diabetes, increases of serum concentrations of IL-18 (per doubling of the ratio of 2-year follow-up/baseline values) within the first 2 years after diagnosis associated with absolute increases of HbA_{1c} by 1.18% after multiple adjustment (model 2). Associations between changes of sE-selectin with changes of C-peptide secretion capacity from glucagon stimulation testing lost significance after adjustment for confounders (model 2). There was no evidence that changes of biomarkers of subclinical inflammation associated with changes of ACPRG, $iAUC_{CP}$, iBCF, or glucose disappearance rate in patients with type 1 diabetes (Table 3 and Supplementary Table 3).

Sensitivity Analyses

Results virtually did not change when we also adjusted the data for glucose disappearance rate (data not shown). COPD and bronchial asthma were present in ≤5% of patients with the only exception being of asthma in 10% and 12% of patients with type 1 diabetes at baseline and follow-up, respectively (Table 1). Because both diseases are important determinants of inflammatory status, we included disease status at baseline and follow-up as potential confounding factors to linear regression models. Again, results were virtually unchanged (data not shown).

Because associations between changes of markers of low-grade inflammation with glycemic control, β-cell function, and glucose disappearance rate might already differ between type 1 and type 2 diabetes during early disease progression, we also tested β-values for differences between diabetes types. The association between 2-year changes of sE-selectin and C-peptide secretion capacity from glucagon stimulation testing was different between diabetes types (type 1 diabetes $\beta = 46.10$, type 2 diabetes $\beta = -13.29$, $P = 0.007$ [model 1]). There was no indication for any other statistically significant difference between diabetes types.

We also repeated regression analyses with only patients with type 2 diabetes who had no glucose-lowering medication at baseline and follow-up. Of the associations that were significant in the main analysis, the association between changes of hsCRP and sICAM-1 with changes of HbA_{1c} remained significant. In the subgroup of patients without glucose-lowering medication, additional associations were found between changes of IL-6 with changes of HbA_{1c} and changes of hsCRP with changes of iBCF. Associations were attenuated and lost significance in this subgroup between sE-selectin and HbA_{1c} as well as iBCF (Supplementary Tables 8 and 9).

Table 1—Patient characteristics

	Type 2 diabetes			Type 1 diabetes		
Variable	Baseline	After 2 years	Δ	Baseline	After 2 years	Δ
Basic characteristics						
n (% male)	94 (71)	—	—	42 (55)	—	—
Duration since diagnosis of diabetes (days)	167 ± 110	—	—	177 ± 109	—	—
Age (years)	54 ± 10	—	—	35 ± 12	—	—
BMI (kg/m^2)	31.5 ± 5.8	31.7 ± 5.5	0.2 ± 1.7	24.8 ± 4.0	26.1 ± 3.8	**1.3 ± 1.5****
Current smoking status						
Yes	20 (21)	24 (26)	—	8 (19)	10 (24)	—
No	74 (79)	70 (74)	—	34 (81)	32 (76)	—
COPD within the past 12 (baseline) or 24 (follow-up) months*						
Yes	4 (4)	5 (5)	—	1 (2)	1 (2)	—
No	89 (96)	88 (95)	—	41 (98)	41 (98)	—
Bronchial asthma within the past 12 (baseline) or 24 (follow-up) months*						
Yes	1 (1)	2 (2)	—	4 (10)	5 (12)	—
No	92 (99)	91 (98)	—	38 (90)	37 (88)	—
Change of the type of glucose-lowering medication						
Intensified	—	—	11 (12)	—	—	3 (7)
Unchanged	—	—	78 (83)	—	—	37 (88)
Reduced	—	—	5 (5)	—	—	2 (5)
No glucose-lowering medication	52 (55)	45 (48)	—	5 (12)	5 (12)	—
Only oral glucose-lowering medication	35 (37)	44 (47)	—	5 (12)	4 (10)	—
Only insulin therapy	5 (5)	3 (3)	—	31 (74)	32 (76)	—
Oral glucose-lowering medication and insulin therapy	2 (2)	2 (2)	—	1 (2)	1 (2)	—
Glycemic control						
HbA_{1c} (%)	6.43 ± 0.98	6.62 ± 1.14	0.20 ± 1.09	7.08 ± 1.58	7.03 ± 1.20	0.05 ± 1.68
HbA_{1c} (mmol/mol)	47 ± 11	49 ± 13	2.2 ± 12	54 ± 17	53 ± 13	0.5 ± 18.4
Measures of insulin secretion						
Ratio of C-peptide secretion (6 min/0 min) from glucagon stimulation test†	1.86 (1.62; 2.19)	2.14 (1.85; 2.43)	**0.24 (−0.13; 0.50)****	1.76 (1.57; 2.03)	1.68 (1.37; 2.14)	−0.05 (−0.36; 0.32)
ACPRG (ng/mL)†	3.50 (2.85; 4.60)	3.30 (2.40; 4.50)	**0.00 (−0.80; 0.40)¶**	1.25 (0.80; 2.20)	0.65 (0.20; 1.20)	**−0.60 (−1.00; −0.40)****
$iAUC_{CP}$ (pmol/L)†	351.2 (275.8; 477.2)	312.4 (202.4; 469.0)	**−38.8 (−133.9; 60.9)¶**	82.4 (34.4; 148.6)	44.4 (12.1; 116.8)	**−25.8 (−65.2; −0.3)#**
iBCF‡	86.9 (64.2; 118.2)	91.8 (63.0; 126.8)	0.5 (−25.6; 26.2)	18.4 (18.4; 45.5)	11.1 (3.2; 27.7)	−7.9 (−18.8; 0.7)
Measure of intravenous glucose tolerance						
Glucose disappearance rate (%/min)§	0.80 ± 0.34	0.74 ± 0.25	−0.07 ± 0.36	0.62 ± 0.28	0.48 ± 0.31	**−0.14 ± 0.28#**
Markers of low-grade inflammation						
hsCRP (mg/L)\\	2.30 (1.50; 5.60)	2.25 (1.40; 4.60)	0.00 (−1.50; 0.70)	1.05 (0.70; 1.70)	1.40 (1.10; 2.60)	0.20 (−0.30; 1.20)
IL-6 (pg/mL)*	1.98 (1.38; 2.55)	1.88 (1.30; 2.51)	−0.16 (−0.69; 0.56)	0.98 (0.75; 1.54)	0.96 (0.73; 1.30)	−0.04 (−0.51; 0.27)
IL-18 (pg/mL)	295.5 (230.3; 427.0)	314.0 (234.7; 434.5)	3.6 (−47.3; 62.8)	280.8 (183.8; 373.2)	242.5 (199.3; 320.1)	−27.9 (−85.6; 34.3)
sE-selectin (ng/mL)*	37.6 (27.4; 53.9)	39.6 (30.5; 54.9)	**2.6 (−1.6; 7.6)****	35.9 (28.5; 44.2)	37.9 (29.6; 44.3.3)	1.3 (−1.8; 4.5)
sICAM-1 (ng/mL)*	232.1 (197.3; 292.1)	241.0 (211.5; 288.1)	4.8 (−11.8; 27.3)	205.7 (171.9; 242.7)	223.8 (189.4; 271.3)	**13.9 (−7.1; 36.4)#**

Data are *n* (%), mean ± SD, or median (25th; 75th percentile). Statistical analysis used paired Student *t* test for normally distributed variables, Wilcoxon signed rank test for nonnormally distributed variables, McNemar test for paired samples for categorical variables with two characteristics, and Bowker test of symmetry for categorical variables with more than two characteristics to test for differences between baseline and after 2 years. Boldface indicates significant differences ($P < 0.05$). Δ, values after 2 years − baseline values. *Data only available for 93 with type 2 diabetes and 30 with type 1 diabetes. †Data only available for 76 with type 2 diabetes and 27 with type 1 diabetes. ‡Data only available for 72 with type 2 diabetes and 35 with type 1 diabetes. §Data only available for 75 with type 2 diabetes and 38 with type 1 diabetes. \\Data only available for 74 patients with type 2 diabetes. ¶$P < 0.05$. #$P < 0.01$. **$P < 0.001$.

Table 2—Associations between changes of markers of low-grade inflammation and changes of glycemic control, insulin secretion, and glucose disappearance rate within the first 2 years after diabetes diagnosis in patients with type 2 diabetes

	hsCRP		IL-6		IL-18		sE-selectin		sICAM-1	
Variable/model	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Glycemic control										
HbA_{1c}*										
Model 1		**0.001**		0.087		0.112		**0.001**		**<0.001**
%	**0.46 (0.20; 0.71)**		0.27 (−0.04; 0.57)		0.38 (−0.09; 0.86)		**0.88 (0.39; 1.37)**		**1.78 (1.03; 2.52)**	
mmol/mol	**5.0 (2.2; 7.8)**		3.0 (−0.4; 6.2)		4.2 (−1.0; 9.4)		**9.6 (4.3; 15.0)**		**19.5 (11.3; 24.6)**	
Model 2		**0.002**		0.232		0.186		**0.001**		**<0.001**
%	**0.46 (0.18; 0.74)**		0.20 (−0.13; 0.53)		0.34 (−0.17; 0.85)		**0.90 (0.38; 1.42)**		**1.69 (0.88; 2.51)**	
mmol/mol	**5.0 (2.0; 8.1)**		2.2 (−1.4; 5.8)		3.7 (−1.9; 9.3)		**9.8 (4.2; 15.5)**		**18.5 (9.6; 27.4)**	
Indices of insulin secretion										
C-peptide secretion capacity†										
Model 1	**−6.22 (−10.94; −1.24)**	**0.016**	−6.48 (−12.73; 0.22)	0.057	−1.80 (−11.55; 9.03)	0.730	**−13.29 (−23.97; −1.11)**	**0.034**	−11.64 (−27.15; 7.18)	0.205
Model 2	−2.90 (−7.75; 2.22)	0.255	−2.18 (−8.72; 4.83)	0.527	−1.16 (−10.53; 9.19)	0.815	−8.40 (−19.44; 4.14)	0.177	−5.98 (−22.03; 13.38)	0.513
ACPRG†										
Model 1	−1.38 (−8.31; 6.07)	0.703	1.37 (−6.46; 9.86)	0.737	2.29 (−9.39; 15.48)	0.710	1.48 (−13.27; 18.74)	0.852	−17.97 (−34.39; 2.56)	0.081
Model 2	−0.83 (−8.62; 7.62)	0.838	0.60 (−8.18; 10.21)	0.897	2.11 (−10.41; 16.38)	0.751	−1.36 (−17.13; 17.41)	0.876	**−21.61 (−38.51; −0.05)**	**0.0496**
$iAUC_{CP}$†										
Model 1	−3.85 (−16.38; 10.57)	0.576	16.43 (−1.90; 38.18)	0.081	−10.01 (−30.64; 16.76)	0.422	−13.70 (−38.05; 20.21)	0.378	−27.91 (−55.93; 17.94)	0.189
Model 2	−3.17 (−17.26; 13.30)	0.681	**21.16 (0.03; 46.76)**	**0.0495**	−11.12 (−32.93; 17.76)	0.406	−18.92 (−44.00; 17.40)	0.262	−29.45 (−59.09; 21.67)	0.205
iBCF†										
Model 1	−8.70 (−20.29; 4.57)	0.184	10.41 (−6.38; 30.20)	0.235	−13.61 (−32.43; 10.47)	0.239	**−30.88 (−50.63; −3.24)**	**0.032**	−29.33 (−55.60; 12.49)	0.141
Model 2	−7.62 (−20.16; 6.89)	0.279	14.55 (−4.60; 37.53)	0.143	−16.87 (−36.18; 8.29)	0.167	**−34.87 (−54.81; −6.13)**	**0.022**	−30.94 (−58.42; 14.71)	0.150
Measure of intravenous glucose tolerance										
Glucose disappearance rate*										
Model 1	0.01 (−0.06; 0.08)	0.810	0.00 (−0.08; 0.08)	0.905	0.03 (−0.09; 0.15)	0.611	0.01 (−0.13; 0.14)	0.923	−0.08 (−0.29; 0.13)	0.431
Model 2	0.02 (−0.05; 0.10)	0.526	0.01 (−0.08; 0.10)	0.827	0.01 (−0.12; 0.13)	0.912	0.01 (−0.13; 0.16)	0.860	−0.07 (−0.30; 0.15)	0.512

Data are regression coefficients (β), 95% CIs, and *P* values from linear regression analyses with hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 as the independent variables and HbA_{1c}, C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, iBCF, and glucose disappearance rate as the dependent variables. Model 1 was adjusted for the independent variable at baseline, concentration of the marker of low-grade inflammation at baseline, age at baseline, and sex, and model 2 was additionally adjusted for BMI at baseline, change of BMI, change of the type of glucose-lowering medication, smoking status at baseline, and change of smoking status. C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, iBCF, hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 were entered into the models as ln-transformed variables. Boldface indicates significant associations ($P < 0.05$). C-peptide secretion capacity as ratio of C-peptide 6 min/C-peptide 0 min from glucagon stimulation test. Regression coefficients should be interpreted as follows: *A doubling of the ratio of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 within the first 2 years after diabetes diagnosis associates with an absolute change of HbA_{1c} and glucose disappearance rate within the first 2 years by β. †A doubling of the ratio of 2-year follow-up/baseline values of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 associates with a percent change of C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, and iBCF within the first 2 years by β.

Table 3—Associations between changes of markers of low-grade inflammation and changes of glycemic control, insulin secretion, and glucose disappearance rate within the first 2 years after diabetes diagnosis in patients with type 1 diabetes

	hsCRP		IL-6		IL-18		sE-selectin		sICAM-1	
Variable/model	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Glycemic control										
HbA_{1c}*										
Model 1		0.290		0.421		**0.003**		0.778		0.812
%	0.26 (−0.23; 0.76)		−0.20 (−0.68; 0.29)		**1.14 (0.42; 1.86)**		0.18 (−1.10; 1.46)		0.22 (−1.63; 2.06)	
mmol/mol	2.8 (−2.5; 8.3)		−2.2 (−7.4; 3.2)		**12.5 (4.6; 20.3)**		2.0 (−12.0; 16.0)		2.4 (−17.8; 22.5)	
Model 2		0.299		0.882		**0.003**		0.425		0.675
%	0.31 (−0.29; 0.91)		−0.04 (−0.63; 0.54)		**1.18 (0.43; 1.93)**		0.62 (−0.94; 2.18)		0.43 (−1.64; 2.49)	
mmol/mol	3.4 (−3.2; 9.9)		−0.4 (−6.9; 5.9)		**12.9 (4.7; 21.1)**		6.8 (−10.3; 23.8)		4.7 (−17.9; 27.2)	
Indices of insulin secretion										
C-peptide secretion capacity†										
Model 1	4.88 (−9.36; 21.35)	0.504	1.80 (−14.87; 21.73)	0.838	−2.43 (−20.03; 19.05)	0.801	**46.10 (0.47; 112.46)**	**0.047**	−11.84 (−49.73; 54.60)	0.647
Model 2	4.80 (−11.86; 24.62)	0.571	−3.66 (−22.38; 19.58)	0.721	1.50 (−18.71; 26.74)	0.890	35.43 (−14.07; 113.43)	0.178	13.82 (−45.95; 139.71)	0.719
ACPRG†										
Model 1	−7.26 (−35.93; 34.24)	0.675	−20.57 (−49.72; 25.50)	0.309	−20.72 (−51.76; 30.29)	0.344	−38.64 (−77.88; 70.15)	0.333	−71.08 (−92.27; 8.23)	0.064
Model 2	−4.98 (−36.96; 43.22)	0.793	−27.64 (−59.09; 27.96)	0.249	−14.36 (−50.12; 47.04)	0.554	−41.49 (−82.14; 91.68)	0.355	−44.64 (−91.73; 270.70)	0.522
$iAUC_{CP}$†										
Model 1	11.14 (−39.08; 102.78)	0.718	−30.52 (−67.23; 47.30)	0.327	−23.71 (−65.98; 71.04)	0.496	48.36 (−70.65; 650.04)	0.620	−79.73 (−97.60; 71.48)	0.136
Model 2	30.91 (−32.53; 154.01)	0.398	−47.94 (−80.01; 35.59)	0.169	−3.84 (−64.24; 158.59)	0.935	178.21 (−60.97; 1,883.08)	0.288	6.67 (−95.73; 2,564.91)	0.967
iBCF†										
Model 1	37.69 (−30.89; 174.35)	0.341	−4.69 (−56.16; 107.18)	0.899	−13.24 (−65.01; 115.09)	0.748	56.93 (−68.70; 686.69)	0.567	−72.08 (−96.73; 138.51)	0.230
Model 2	79.12 (−28.94; 351.53)	0.193	−23.22 (−77.52; 162.24)	0.653	−2.37 (−69.39; 211.39)	0.965	199.27 (−61.69; 2,237.79)	0.274	−0.88 (−95.43; 2,050.90)	0.995
Measure of intravenous glucose tolerance										
Glucose disappearance rate*										
Model 1	0.07 (−0.05; 0.20)	0.245	0.09 (−0.05; 0.24)	0.194	−0.11 (−0.33; 0.10)	0.294	−0.23 (−0.56; 0.09)	0.148	−0.01 (−0.48; 0.46)	0.972
Model 2	0.01 (−0.15; 0.17)	0.883	0.14 (−0.01; 0.29)	0.075	−0.16 (−0.38; 0.05)	0.126	−0.19 (−0.54; 0.15)	0.259	0.07 (−0.40; 0.54)	0.766

Data are regression coefficients (β), 95% CIs, and *P* values from linear regression analyses with hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 as the independent variables and HbA_{1c}, C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, iBCF, and glucose disappearance rate as dependent variables. Model 1 was adjusted for the independent variable at baseline, concentration of the marker of low-grade inflammation at baseline, age at baseline, and sex, and model 2 was additionally adjusted for BMI at baseline, change of BMI, change of the type of glucose-lowering medication, smoking status at baseline, and change of smoking status. C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, iBCF, hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 entered the models as ln-transformed variables. Boldface indicates significant associations ($P < 0.05$). C-peptide secretion capacity as ratio of C-peptide 6 min/C-peptide 0 min from glucagon stimulation test. Regression coefficients should be interpreted as follows: *A doubling of the ratio of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 within the first 2 years after diabetes diagnosis associates with an absolute change of HbA_{1c} and glucose disappearance rate within the first 2 years by β. †A doubling of the ratio of 2-year follow-up/baseline values of hsCRP, IL-6, IL-18, sE-selectin, and sICAM-1 within the first 2 years after diabetes diagnosis associates with a percent change of C-peptide secretion capacity, ACPRG, $iAUC_{CP}$, and iBCF within the first 2 years by β.

CONCLUSIONS

This study in recently diagnosed patients with type 1 and type 2 diabetes with overall good metabolic control demonstrates that 2-year increases of hsCRP, sE-selectin, and sICAM-1 in type 2 diabetes and of IL-18 in type 1 diabetes associated with 2-year deterioration in glycemic control (i.e., increases in HbA_{1c}). Furthermore, 2-year increases of sE-selectin were related to 2-year impairment of glucose-stimulated insulin secretion (i.e., decreases of iBCF). These associations were not explained by baseline BMI or concomitant BMI changes.

Associations Between Markers of Low-Grade Inflammation and Glycemic Control

Changes of hsCRP, sE-selectin, and sICAM-1 within the first 2 years after diabetes diagnosis positively associated with 2-year changes of HbA_{1c} in type 2 diabetes. Changes of IL-18 were positively related to changes of HbA_{1c} in type 1 diabetes, extending the current literature of cross-sectional studies (24–28) because the present data provide prospective associations between glycemic control and markers of low-grade inflammation. Additionally, unlike previous investigations in patients with longer diabetes duration (29–31), we included patients with recently diagnosed diabetes.

The present data are in line with cross-sectional studies reporting associations of higher serum concentrations of hsCRP, sE-selectin, and sICAM-1 with higher HbA_{1c} (26,27). The associations were confirmed in prospective studies (15,30,31). However, two of these prospective studies did not focus on recently diagnosed diabetes (30,31). Concerning hsCRP and HbA_{1c}, the one study considered associations between hsCRP at one time point with the average HbA_{1c} during follow-up (31), and another compared average hsCRP during the study period with changes of HbA_{1c} (15). High IL-18 levels were also previously shown to be related to acute hyperglycemia as well as to long-term glycemic control in cross-sectional analyses of healthy people, individuals with impaired glucose tolerance, and patients with type 1 diabetes with a mean duration of 9 years (24,28). Correction of hyperglycemia to normoglycemia in patients with recently diagnosed type 2 diabetes resulted in normalization of increased plasma concentrations of sICAM-1 (25). Furthermore, reductions in hsCRP levels were associated with reductions in HbA_{1c} in patients with type 2 diabetes on structured self-monitoring of blood glucose (29). Both associations (changes of hsCRP and sICAM-1 with changes of HbA_{1c}) could be replicated in the present patients with type 2 diabetes not taking glucose-lowering medications. This indicates that oral glucose-lowering medication or insulin does not appear to affect these relations, whereas associations of sE-selectin and IL-6 with HbA_{1c} seem to be influenced more strongly by glucose-lowering medication.

Associations between markers of low-grade inflammation and HbA_{1c} might be mediated by glucose-induced oxidative stress (26,28) and thereby could contribute to early stages of atherogenesis (25). Additionally, HbA_{1c} has been related to reduced antioxidant trapping capacity in patients with type 2 diabetes (30). However, whether these early changes increase the risk for chronic vascular complications in diabetes remains to be proven (25).

Associations Among Markers of Low-Grade Inflammation, Insulin Secretion, and β-Cell Function

In the present cohort, changes of sE-selectin inversely associated with changes of iBCF in patients with type 2 diabetes. In the subgroup of patients with type 2 diabetes without glucose-lowering medication, this relation was attenuated probably owing to power issues. Additionally, changes of IL-6 associated with changes of iBCF in these patients. The few available data on the association between soluble adhesion molecules and β-cell function are from cross-sectional studies. In healthy men, lipid infusion increases concentrations of circulating adhesion molecules (32). In other studies, sICAM-1 concentrations were also associated with the $AUC_{insulin}$ and with maximal insulin secretion after the ingestion of a lipid-rich meal (33). Circulating concentrations of sE-selectin, but not sICAM-1, were related to $AUC_{insulin}$ in patients with impaired glucose tolerance (34) as well as with fasting insulin concentrations in patients with type 2 diabetes (27). By proposing an association between soluble adhesion molecules, especially sE-selectin, and the early development of insulin secretion and β-cell function in patients with diabetes, the present results provide new insights into a possible link among vascular inflammation, endothelial activation, and decreasing β-cell function. Increased concentrations of soluble adhesion molecules reflecting endothelial activation were previously described in the state of hyperinsulinemia and insulin resistance (34). Because elevated circulating lipid concentrations impair endothelial function (35), we also tested whether serum concentrations of triglycerides, HDL cholesterol, and LDL cholesterol influenced the findings. However, the results indicate that the associations between soluble adhesion molecules with glycemic control and β-cell function were not confounded by serum lipid levels.

Associations Between Markers of Low-Grade Inflammation and Glucose Disappearance Rate

In the present cohort, there was no evidence that changes of biomarkers of low-grade inflammation were associated with changes of glucose disappearance rate, a measure of intravenous glucose tolerance. Therefore, the data differ from previous findings from cross-sectional studies that reported associations between elevated concentrations of hsCRP and insulin resistance in patients with recent-onset type 1 diabetes (15) as well as associations between sE-selectin and insulin resistance in patients with type 2 diabetes (27,36). Relations between sE-selectin and insulin resistance were also observed in healthy individuals and those with impaired glucose tolerance (10,34,37). In contrast, the present data suggest that the biomarkers of low-grade inflammation analyzed in this study do not play a key role in the deterioration of the glucose disappearance rate during the early time course of type 1 and type 2 diabetes. Given positive findings from prospective studies on the associations between these biomarkers and incident diabetes (12–14), we believe that this question merits further studies in larger cohorts.

Differences Between Type 1 and Type 2 Diabetes

Although mechanisms leading to type 1 and type 2 diabetes partially differ (1), the impact of low-grade inflammation on the deterioration of glycemia may be comparable between both diabetes types, as suggested by the present results. Regarding all findings on associations between

biomarkers of low-grade inflammation with HbA_{1c}, insulin secretion, and β-cell function, sensitivity analyses only revealed diabetes-specific patterns for the relation between changes of hsCRP with changes of C-peptide secretion from glucagon stimulation testing. Evidence suggests that biomarkers of inflammation are similar risk factors for diabetes complications (e.g., cardiovascular diseases) in both type 1 and type 2 diabetes (30,31).

Strengths and Limitations

Strengths of this study are the use of prospective data on biomarkers of low-grade inflammation and on the natural history of diabetes. Additionally, the study comprises patients with type 1 and type 2 diabetes with comparable short-term duration of disease and similar glycemic control who also underwent extensive metabolic characterization. We followed the same protocols and standard operating procedures during the baseline and follow-up examinations with respect to blood sampling and biomarker measurement to minimize the impact of any preanalytical, interassay, or biological/environmental variations on the results. Furthermore, the study population is unique regarding patients with type 1 diabetes because we only included those in whom diabetes developed at an age of at least 17 years. On the other hand, this method restricts comparability to childhood and adolescence disease onset and limits the generalizability of the results. This can be exemplified by the 15% of patients with type 1 diabetes who are autoantibody negative at baseline. A rather mild disease progression might be characteristic at least for some of the patients with adult-onset type 1 diabetes in this cohort.

There are also several limitations. First, lack of genetic screening exists for maturity-onset diabetes of the young or for even less frequent rare forms of diabetes. However, according to the SEARCH for Diabetes in Youth cohort, the prevalence for a mutation in one of the three maturity-onset diabetes of the young genes is only 1.2% (38). Second, we obtained the glucose disappearance rate as a measure of intravenous glucose tolerance from the IVGTT, although the hyperinsulinemic-euglycemic clamp is considered the gold standard method for assessment of insulin sensitivity. Third, HbA_{1c} was measured using the Diabetes Control and Complications Trial (DCCT) method instead of the newer World Health Organization–recommended International Federation of Clinical Chemistry and Laboratory Medicine method. Fourth, the good glucometabolic control of the patients might have originated from selection bias (i.e., the higher interest of health-conscious people in clinical study participation); thus, transferability of the findings to the general population of patients with type 1 and type 2 diabetes requires further testing. Fifth, regression models, especially the fully adjusted model (model 2), for type 1 diabetes might be overfitted because of the small sample size. Additionally, when considering multiple testing and applying Bonferroni correction to results from patients with type 1 and type 2 diabetes, only the associations between sICAM-1 and HbA_{1c} in type 2 diabetes remains significant in both models ($P < 0.05/60$). Based on the R^2 values, the strongest relationships were observed for IVGTT-derived C-peptide secretion and β-cell function (ACPRG, $iAUC_{CP}$, iBCF) in patients with type 1 and type 2 diabetes. Weak associations were found for glucose disappearance rate in type 2 diabetes and for HbA_{1c} in type 1 diabetes (Supplementary Tables 2 and 3). We cannot exclude that the weak association for HbA_{1c} might be a result of the variability of the DCCT method. Along with that, the present analyses might be underpowered, again specifically applying to type 1 diabetes, which implies the possibility of type II error. However, for some of the analyses, either associations in the cohort or associations in general appear to be absent when assuming a clinically relevant change of the dependent variable with a doubling of the low-grade inflammation biomarker (both indicated by a patient number >10,000 in Supplementary Tables 4–7). Additionally, no real association instead of type II error is possible if power calculations yield a large number of patients needed to detect significant differences (Supplementary Tables 4 and 5).

Conclusion

Low-grade inflammation may negatively affect glycemic control, first-phase insulin secretion, and β-cell function in the early time course of type 1 and type 2 diabetes. Long-term follow-up of patients with repetitive measurements over time will allow us to examine the extent to which the associations observed in early disease development will influence the progression of diabetes and the occurrence of macro- and microvascular diabetes-related complications at later stages of the disease.

Acknowledgments. The authors appreciate the voluntary contribution of all study participants. They also thank the staff of the Clinical Research Center of the German Diabetes Center (DDZ) for excellent technical assistance and taking care of the patients. The authors further thank Ulrike Partke and Gabi Gornitzka, DDZ, for technical assistance.

Funding. The GDS was initiated and is performed by the DDZ, which is funded by the German Federal Ministry of Health and the Ministry of Innovation, Science, Research and Technology of the State North Rhine-Westphalia. This study was supported in part by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.) and by a grant of the Helmholtz Alliance Imaging and Curing Environmental Metabolic Diseases (ICEMED).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.S.W. researched data and contributed to the statistical analysis and writing and critical review of the manuscript. B.N. researched data and critically reviewed the manuscript. K.S. researched data and contributed to the statistical analysis and critical review of the manuscript. G.P. assessed metabolic parameters by running the mathematical models, interpreted the results, and contributed to the writing and critical review of the manuscript. K.M. and J.S. researched data and contributed to discussion and critical review and editing of the manuscript. C.H. researched data, analyzed the biomarkers of low-grade inflammation, and contributed to the study design, discussion, and critical review and editing of the manuscript. M.R. contributed to the study design, discussion, and critical review and editing of the manuscript. M.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015; the Diabetes Congress of the German Diabetes Association, Berlin, Germany, 13–16 May 2015; and the 58th Symposium of the German Society of Endocrinology, Lübeck, Germany, 18–21 March 2015.

Appendix

GDS Group. M. Roden (speaker), A.E. Buyken, J. Eckel, G. Geerling, H. Al-Hasani, C. Herder, A. Icks, J. Kotzka, O. Kuss, E. Lammert, J. Lundbom, K. Müssig, P. Nowotny, W. Rathmann, J. Szendroedi, D. Ziegler, and their coworkers who are responsible for the design and performance of the GDS.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–S90

2. van Belle TL, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. Physiol Rev 2011;91: 79–118
3. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
4. Daneman D. Type 1 diabetes. Lancet 2006; 367:847–858
5. Herder C, Roden M. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. Eur J Clin Invest 2011;41:679–692
6. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846
7. Ferrannini E, Mari A, Nofrate V, Sosenko JM, Skyler JS; DPT-1 Study Group. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes 2010; 59:679–685
8. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011;11:98–107
9. Donath MY, Størling J, Berchtold LA, Billestrup N, Mandrup-Poulsen T. Cytokines and beta-cell biology: from concept to clinical translation. Endocr Rev 2008;29:334–350
10. Festa A, D'Agostino R Jr., Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102:42–47
11. Müller S, Martin S, Koenig W, et al. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. Diabetologia 2002; 45:805–812
12. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–334
13. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 1999;353:1649–1652
14. Herder C, Baumert J, Thorand B, et al. Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984-2002. Diabetologia 2006;49:921–929
15. Schölin A, Siegbahn A, Lind L, et al.; Diabetes Incidence Study in Sweden group. CRP and IL-6 concentrations are associated with poor glycemic control despite preserved beta-cell function during the first year after diagnosis of type 1 diabetes. Diabetes Metab Res Rev 2004; 20:205–210
16. Menart-Houtermans B, Rütter R, Nowotny B, et al.; German Diabetes Study Group. Leukocyte profiles differ between type 1 and type 2 diabetes and are associated with metabolic phenotypes: results from the German Diabetes Study (GDS). Diabetes Care 2014;37:2326–2333
17. Ziegler D, Papanas N, Zhivov A, et al.; German Diabetes Study (GDS) Group. Early detection of nerve fiber loss by corneal confocal microscopy and skin biopsy in recently diagnosed type 2 diabetes. Diabetes 2014;63: 2454–2463
18. Faber OK, Binder C. C-peptide response to glucagon. A test for the residual beta-cell function in diabetes mellitus. Diabetes 1977;26: 605–610
19. Kahl S, Nowotny B, Piepel S, et al. Estimates of insulin sensitivity from the intravenous-glucose-modified-clamp test depend on suppression of lipolysis in type 2 diabetes: a randomised controlled trial. Diabetologia 2014;57:2094–2102
20. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42:1663–1672
21. Pacini G, Mari A. Methods for clinical assessment of insulin sensitivity and beta-cell function. Best Pract Res Clin Endocrinol Metab 2003;17:305–322
22. Pacini G, Tonolo G, Sambataro M, et al. Insulin sensitivity and glucose effectiveness: minimal model analysis of regular and insulin-modified FSIGT. Am J Physiol 1998;274:E592–E599
23. Paternoster R, Brame R. Using the correct statistical test for the equality of regression coefficients. Criminology 1998;36:859–866
24. Altinova AE, Yetkin I, Akbay E, Bukan N, Arslan M. Serum IL-18 levels in patients with type 1 diabetes: relations to metabolic control and microvascular complications. Cytokine 2008;42:217–221
25. Marfella R, Esposito K, Giunta R, et al. Circulating adhesion molecules in humans: role of hyperglycemia and hyperinsulinemia. Circulation 2000;101:2247–2251
26. King DE, Mainous AG 3rd, Buchanan TA, Pearson WS. C-reactive protein and glycemic control in adults with diabetes. Diabetes Care 2003;26:1535–1539
27. Blüher M, Unger R, Rassoul F, Richter V, Paschke R. Relation between glycaemic control, hyperinsulinaemia and plasma concentrations of soluble adhesion molecules in patients with impaired glucose tolerance or type II diabetes. Diabetologia 2002;45:210–216
28. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–2072
29. Schnell O, Amann-Zalan I, Jelsovsky Z, et al. Changes in A1C levels are significantly associated with changes in levels of the cardiovascular risk biomarker hs-CRP: results from the SteP study. Diabetes Care 2013;36:2084–2089
30. Ryysy L, Yki-Järvinen H. Improvement of glycemic control by 1 year of insulin therapy leads to a sustained decrease in sE-selectin concentrations in type 2 diabetes. Diabetes Care 2001;24:549–554
31. Schaumberg DA, Glynn RJ, Jenkins AJ, et al. Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the Diabetes Control and Complications Trial. Circulation 2005;111:2446–2453
32. Krebs M, Geiger M, Polak K, et al. Increased plasma levels of plasminogen activator inhibitor-1 and soluble vascular cell adhesion molecule after triacylglycerol infusion in man. Thromb Haemost 2003;90:422–428
33. Rubin D, Claas S, Pfeuffer M, Nothnagel M, Foelsch UR, Schrezenmeir J. s-ICAM-1 and s-VCAM-1 in healthy men are strongly associated with traits of the metabolic syndrome, becoming evident in the postprandial response to a lipid-rich meal. Lipids Health Dis 2008;7:32
34. Matsumoto K, Miyake S, Yano M, Ueki Y, Tominaga Y. High serum concentrations of soluble E-selectin in patients with impaired glucose tolerance with hyperinsulinemia. Atherosclerosis 2000;152:415–420
35. Krebs M, Roden M. Molecular mechanisms of lipid-induced insulin resistance in muscle, liver and vasculature. Diabetes Obes Metab 2005;7:621–632
36. Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S. Serum concentrations of soluble adhesion molecules are related to degree of hyperglycemia and insulin resistance in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2002;55:131–138
37. Heliövaara MK, Teppo AM, Karonen SL, Tuominen JA, Ebeling P. Plasma IL-6 concentration is inversely related to insulin sensitivity, and acute-phase proteins associate with glucose and lipid metabolism in healthy subjects. Diabetes Obes Metab 2005;7:729–736
38. Pihoker C, Gilliam LK, Ellard S, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98:4055–4062