Biomarkers of subclinical inflammation and increases in glycaemia, insulin resistance and beta-cell function in non-diabetic individuals: the Whitehall II study

Christian Herder^{1,2}, Kristine Færch³, Maren Carstensen-Kirberg^{1,2}, Gordon D Lowe⁴, Rita Haapakoski⁵, Daniel R Witte^{6,7}, Eric J Brunner⁵, Michael Roden^{1,2,8}, Adam G Tabák^{5,9}, Mika Kivimäki⁵ and Dorte Vistisen³

¹Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany, ²German Center for Diabetes Research, München-Neuherberg, Germany, ³Steno Diabetes Center, Gentofte, Denmark, ⁴Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK, ⁵Department of Epidemiology and Public Health, University College London, London, UK, ⁶Department of Public Health, Aarhus University, Aarhus, Denmark, ⁷Danish Diabetes Academy, Odense, Denmark, ⁸Department of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, and ⁹First Department of Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary

Correspondence should be addressed to C Herder

Email
christian.herder@ddz.uni-duesseldorf.de

Abstract

Objective: Higher systemic levels of pro-inflammatory biomarkers and low adiponectin are associated with increased risk of type 2 diabetes, but their associations with changes in glycaemic deterioration before onset of diabetes are poorly understood. We aimed to study whether inflammation-related biomarkers are associated with 5-year changes in glucose and insulin, HbA1c, insulin sensitivity and beta-cell function before the diagnosis of type 2 diabetes and whether these associations may be bidirectional.

Design and methods: We used multiple repeat measures (17 891 person-examinations from 7683 non-diabetic participants) from the Whitehall II study to assess whether circulating high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL6), IL1 receptor antagonist (IL1Ra) and adiponectin are associated with subsequent changes in glycaemia, insulin, insulin resistance and beta-cell function (based on oral glucose tolerance tests). We examined bidirectionality by testing if parameters of glucose metabolism at baseline are associated with changes in inflammation-related biomarkers.

Results: Higher hsCRP and IL6 were associated with increases in fasting insulin, insulin resistance and, for IL6, with beta-cell function after adjustment for confounders. Higher adiponectin was associated with decreases in fasting glucose, HbA1c, fasting insulin, insulin resistance and beta-cell function. The reverse approach showed that 2-h glucose and insulin sensitivity were associated with changes in IL1Ra. Fasting insulin and insulin resistance showed inverse associations with changes in adiponectin.

Conclusions: Subclinical inflammation is associated with development of increased glycaemia, insulin resistance and beta-cell function in non-diabetic individuals. These findings are consistent with the hypothesis that inflammation-related processes may increase insulin resistance and lead to a compensatory upregulation of beta-cell function.

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Introduction

Biomarkers of subclinical inflammation are associated with incident type 2 diabetes (1, 2), but prospective data on glycaemic deterioration before the onset of diabetes are scarce. Cross-sectional studies suggest differential time courses for changes in biomarkers of subclinical inflammation before type 2 diabetes. Regarding circulating C-reactive protein (CRP), for example, higher levels were observed in prediabetes (i.e., impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)) compared with normal glucose tolerance (NGT), whereas only minor differences in CRP levels were observed between people with prediabetes and type 2 diabetes (3). In contrast, systemic levels of interleukin (IL)-6 or IL18 seemed to be similar in individuals with NGT and prediabetes, but higher in those with type 2 diabetes compared with those with prediabetes (3, 4). Thus, different biomarkers of subclinical inflammation are related to early vs late stages of glycaemic deterioration, but little is known about the underlying pathophysiology (5).

If subclinical inflammation influences early deterioration of glycaemic control, biomarkers of subclinical inflammation should be associated with the development of prediabetes, when individuals with NGT are followed up longitudinally. To date, two small studies have failed to provide evidence for an association of pro-inflammatory cytokines or adiponectin with incident IFG or IGT (6, 7). An alternative approach with higher statistical power is to investigate whether baseline levels of biomarkers of subclinical inflammation are associated with subsequent changes in measures of glucose metabolism (8, 9).

In this study, we adopted the latter approach to examine whether biomarkers of subclinical inflammation are associated with 5-year changes in glucose and insulin levels, HbA_{1c}, insulin sensitivity and beta-cell function before the diagnosis of type 2 diabetes in a large population-based cohort. The study was based on three 5-year observation cycles, which were combined by means of a mixed model (10). As there is evidence for an impact of hyperglycaemia and hyperinsulinaemia on subclinical inflammation and hypoadiponectinaemia (11, 12), we also considered a potentially bidirectional relationship by investigating to what extent markers of glucose metabolism may also be associated with changes in biomarkers of subclinical inflammation.

Subjects and methods

Study participants, procedures and measurements

Participants are from the Whitehall II study, an occupational cohort of 10 308 British civil servants (6896 men and 3412 women aged 35–55 years) of mainly white ethnicity recruited between 1985 and 1988 (phase 1) (13). The UK NHS Health Research Authority London-Harrow Ethics Committee reviewed and approved the study. Written informed consent was obtained from each participant at each examination phase. The study was conducted according to the principles of the Helsinki Declaration. The cohort has been followed at eight subsequent phases, 2.5 years apart. All study phases included a questionnaire, and every second phase (5 years apart) also included a clinical health examination (phases 1, 3, 5, 7 and 9). Phase 3 (1991–1993) was the first phase with an oral glucose tolerance test (OGTT), therefore phase 1 was not used. In the Whitehall II cohort, 8815 participated at phase 3 (1991–1993); 7870 at phase 5 (1997–1999); 6967 at phase 7 (2002–2004) and 6761 at phase 9 (2007–2009) with the same individual participating in several phases. During follow-up, participants were censored if they died, were lost to follow-up or developed diabetes. Anthropometric, demographic, clinical and lifestyle characteristics are summarised in Table 1.

At phases 3, 5, 7 and 9, a standard 2-h 75 g OGTT was performed in the morning after an overnight fast (≥ 8 h of fasting). For around one-third of the examinations, the OGTT was administered in the afternoon after a light fat-free breakfast (≥ 5 h of fasting). These examinations were not considered in this study. Diabetes was diagnosed by the treating physician (outside the study) or during screening by OGTT (as part of the study examination). Screen-detected diabetes was ascertained throughout follow-up by OGTTs administered every 5 years and defined according to the OGTT criteria defined by the World Health Organization (14).

Information on smoking habits (never/ex/current), alcohol consumption (units per week) and physical activity (hours per week of mild, moderate and vigorous physical activity) were collected using a self-administered questionnaire (15).

Plasma glucose, serum insulin, HbA_{1c} and serum lipids were measured as described previously (16, 17). Insulin sensitivity and beta-cell function were estimated based on fasting plasma glucose and serum insulin using the homeostasis model assessment for insulin resistance (HOMA-IR) and beta-cell function (HOMA- β). In addition,

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Table 1 Characteristics of the study population at each study phase. Data are presented as means (s.d.), medians (25th; 75th percentiles) or proportions (95% CI).

Variable	Phase 3 (1991–1993)	Phase 5 (1997–1999)	Phase 7 (2002–2004)	Phase 9 (2007–2009)
<i>n</i>	5310	4310	4498	3773
Men (%)	69.1 (67.8; 70.3)	71.6 (70.3; 73.0)	73.3 (71.9; 74.5)	72.9 (71.4; 74.3)
White ethnicity (%)	90.5 (89.7; 91.3)	91.9 (91.1; 92.7)	92.8 (92.0; 93.5)	93.1 (92.2; 93.8)
Age (years)	49.4 (6.0)	55.1 (5.9)	60.6 (5.9)	65.4 (5.9)
BMI (kg/m ²)	25.3 (3.7)	26.1 (3.9)	26.6 (4.2)	26.6 (4.3)
Waist circumference (cm)	85.7 (11.6)	90.5 (11.6)	93.3 (11.9)	94.4 (11.9)
Total cholesterol (mmol/L)	6.5 (1.2)	5.9 (1.1)	5.8 (1.0)	5.3 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.4)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)
LDL cholesterol (mmol/L)	4.4 (1.0)	3.9 (0.9)	3.6 (0.9)	3.2 (1.0)
Triacylglycerols (mmol/L)	1.5 (1.1)	1.3 (0.9)	1.3 (0.9)	1.2 (0.7)
Systolic blood pressure (mmHg)	120.4 (13.6)	122.2 (16.3)	127.7 (16.8)	125.3 (15.9)
Diastolic blood pressure (mmHg)	79.7 (9.5)	77.3 (10.4)	74.5 (10.5)	71.5 (10.0)
Fasting plasma glucose (mmol/L)	5.3 (0.7)	5.2 (0.7)	5.3 (0.8)	5.2 (0.6)
2-h plasma glucose (mmol/L)	5.3 (1.9)	5.9 (1.8)	6.3 (1.9)	6.4 (1.9)
HbA _{1c} (%)	–	–	5.3 (0.5)	5.6 (0.4)
HbA _{1c} (mmol/mol)	–	–	39.1 (5.9)	43.8 (5.3)
Fasting serum insulin (pmol/L)	5.7 (3.7; 8.9)	7.0 (4.9; 10.2)	7.0 (4.7; 10.7)	6.6 (4.3; 10.2)
2-h serum insulin (pmol/L)	33.0 (18.5; 56.5)	32.6 (19.8; 53.2)	37.8 (23.3; 63.7)	41.3 (25.6; 69.1)
HOMA-IR	1.3 (0.8; 2.1)	1.6 (1.1; 2.4)	1.6 (1.1; 2.6)	1.5 (1.0; 2.4)
HOMA-β	67.1 (44.4; 100.8)	92.0 (65.1; 131.3)	80.0 (55.2; 118.9)	82.2 (55.7; 120)
ISI _{0,120}	40.7 (31.5; 53.3)	38.1 (29.8; 48.9)	34.4 (26.4; 44.5)	33.6 (25.5; 43.6)
hsCRP (mg/dL)	0.9 (0.4; 1.8)	1.0 (0.5; 2.0)	1.2 (0.6; 2.4)	–
IL6 (pg/mL)	1.4 (1.0; 2.0)	1.4 (1.0; 2.0)	1.7 (1.2; 2.4)	–
IL1Ra (ng/mL)*	0.2 (0.2; 0.3)	0.3 (0.3; 0.4)	0.3 (0.3; 0.4)	0.3 (0.3; 0.4)
Adiponectin (μg/mL)*	8.7 (6.4; 12.4)	8.6 (6.2; 12.2)	8.3 (6.0; 11.7)	8.5 (5.6; 13.4)
Family history of diabetes (%)	11.2 (10.4; 12.1)	10.3 (9.4; 11.3)	10.0 (9.1; 10.9)	9.6 (8.7; 10.6)
Current smoker (%)	13.7 (12.8; 14.7)	10.4 (9.5; 11.3)	8.4 (7.6; 9.3)	5.7 (5.0; 6.5)
Moderate-to-vigorous exercise (h/week)	2.0 (1.0; 5.0)	11.5 (4.5; 20.0)	12.0 (4.5; 20.5)	–
Alcohol intake (units/week)	6.0 (2.0; 14.0)	10.0 (3.0; 20.0)	9.0 (3.0; 18.0)	7.0 (2.0; 16.0)
Antihypertensive treatment (%)	7.3 (6.6; 8.0)	11.3 (10.3; 12.2)	22.2 (21; 23.4)	33.0 (31.5; 34.5)
Lipid-lowering treatment (%)	0.8 (0.6; 1.1)	2.8 (2.4; 3.4)	10.0 (9.2; 11.0)	29.1 (27.6; 30.6)

*Subsample (*n* = 2636).

whole-body insulin sensitivity was assessed using the insulin sensitivity index (ISI_{0,120}) based on fasting and 2-h values of glucose and insulin (18).

High-sensitivity CRP (hsCRP) was measured using a high-sensitivity immunonephelometric assay, IL6 was measured using a high-sensitivity ELISA assay, IL1 receptor antagonist (IL1Ra) and total adiponectin were measured with Quantikine ELISA kits (R&D Systems) in a diabetes case-cohort sample (19, 20).

Statistical analysis

Statistical analyses were performed in R, version 3.1.3 (The R Foundation for Statistical Computing) and SAS, version 9.2 (SAS Institute, Cary, NC, USA). In the main analysis, the following outcomes were studied: fasting plasma glucose, 2-h plasma glucose, HbA_{1c}, fasting and 2-h serum insulin, HOMA-IR, HOMA-β and ISI_{0,120}. We excluded 10 529 (36.5%) person-examinations for which the

participant had been fasting for <8 h (OGTTs administered in the afternoon). Outcomes with a skewed distribution (fasting and 2-h insulin, HOMA-IR, HOMA-β and ISI_{0,120}) were log-transformed before analysis.

The following biomarkers of subclinical inflammation were included as exposures: high-sensitivity (hs)CRP, IL6, IL1 receptor antagonist (IL1Ra) and adiponectin (all log₂ transformed before analysis). As adiponectin and IL1Ra were measured only in a case-cohort subsample nested within the Whitehall II study (19, 20), analyses were restricted to the subcohort with these measurements. We excluded 412 (2.3%) person-examinations with hsCRP >10 mg/L as indicator of acute infections.

Up to a total of 17 891 person-examinations for 7683 non-diabetic participants were analysed (8303 person-examinations for 2965 participants in the subcohort). We studied the associations of baseline levels of inflammation-related biomarkers and 5-year follow-up levels of the

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Table 2 Effects (with 95% CI) of doubling in the inflammatory marker at baseline on 5-year changes in glycaemia, insulin, insulin sensitivity and beta-cell function.

Outcome	Model	hsCRP			IL6		
		n	Estimate	P	n	Estimate	P
Fasting glucose (mmol/L)	1	6716	0.02 (0.01; 0.03)	<0.001	6525	0.02 (0.00; 0.04)	0.027
	2	6716	0.01 (0.00; 0.02)	0.044	6525	0.01 (−0.01; 0.03)	0.336
	3	6716	0.01 (0.00; 0.02)	0.139	6525	0.00 (−0.02; 0.02)	0.778
	4	6716	0.01 (0.00; 0.02)	0.208	6525	0.00 (−0.02; 0.02)	0.968
2-h glucose (mmol/L)	1	6033	0.08 (0.05; 0.10)	<0.001	6029	0.08 (0.03; 0.13)	0.003
	2	6033	0.04 (0.01; 0.07)	0.004	6029	0.03 (−0.02; 0.08)	0.292
	3	6033	0.03 (0.00; 0.06)	0.028	6029	0.01 (−0.04; 0.07)	0.661
	4	6033	0.03 (0.00; 0.06)	0.044	6029	0.01 (−0.05; 0.06)	0.806
HbA _{1c} (mmol/mol)	1	2535	0.06 (−0.05; 0.16)	0.285	2363	−0.11 (−0.31; 0.08)	0.263
	2	2535	0.02 (−0.09; 0.14)	0.712	2363	−0.16 (−0.36; 0.04)	0.120
	3	2535	0.01 (−0.11; 0.12)	0.904	2363	−0.17 (−0.38; 0.04)	0.107
	4	2535	−0.01 (−0.12; 0.11)	0.874	2363	−0.22 (−0.42; −0.02)	0.033
Fasting insulin (% diff.)	1	6186	2.5 (1.7; 3.3)	<0.001	6177	4.8 (3.2; 6.4)	<0.001
	2	6186	1.4 (0.6; 2.3)	0.001	6177	3.4 (1.8; 5.0)	<0.001
	3	6186	1.1 (0.3; 2.0)	0.010	6177	2.7 (1.2; 4.4)	<0.001
	4	6186	0.9 (0.1; 1.7)	0.024	6177	2.2 (0.7; 3.7)	0.003
2-h insulin (% diff.)	1	5951	2.4 (1.3; 3.5)	<0.001	5946	2.5 (0.4; 4.8)	0.021
	2	5951	1.7 (0.5; 3.0)	0.005	5946	1.5 (−0.7; 3.8)	0.188
	3	5951	1.4 (0.2; 2.6)	0.028	5946	0.9 (−1.4; 3.2)	0.457
	4	5951	1.2 (0.0; 2.4)	0.057	5946	0.5 (−1.7; 2.7)	0.681
HOMA-IR (% diff.)	1	6168	2.7 (1.8; 3.6)	<0.001	6159	5.0 (3.3; 6.7)	<0.001
	2	6168	1.5 (0.6; 2.5)	0.001	6159	3.5 (1.8; 5.2)	<0.001
	3	6168	1.2 (0.3; 2.2)	0.010	6159	2.7 (1.0; 4.5)	0.002
	4	6168	1.0 (0.1; 1.9)	0.025	6159	2.2 (0.6; 3.8)	0.008
HOMA-β (% diff.)	1	6164	2.1 (1.3; 2.9)	<0.001	6155	4.3 (2.7; 5.8)	<0.001
	2	6164	1.1 (0.3; 2.0)	0.009	6155	3.0 (1.5; 4.6)	<0.001
	3	6164	1.0 (0.1; 1.8)	0.031	6155	2.6 (1.0; 4.2)	0.001
	4	6164	0.8 (0.0; 1.6)	0.064	6155	2.2 (0.7; 3.8)	0.005
ISI _{0,120} (% diff.)	1	5800	−1.6 (−2.2; −1.0)	<0.001	5793	−1.9 (−3.1; −0.8)	<0.001
	2	5800	−1.0 (−1.6; −0.3)	0.003	5793	−1.0 (−2.2; 0.2)	0.090
	3	5800	−0.8 (−1.4; −0.1)	0.022	5793	−0.6 (−1.8; 0.6)	0.320
	4	5800	−0.7 (−1.3; 0.0)	0.046	5793	−0.4 (−1.6; 0.8)	0.519

different outcomes, including the baseline level of the outcome as a covariate. The main analysis is based on all available data after the aforementioned exclusions and provides effect estimates per doubling in baseline levels of the respective biomarker. In addition, we used the subset of the population for whom all four biomarkers were available at the same time points to calculate regression coefficients that were standardised per 1-SD difference in the log of the biomarker to allow direct comparisons of effect sizes between the exposure variables.

All analyses were adjusted for age, sex, study phase and baseline value of the outcome studied (model 1). We further adjusted the analyses for other variables in a successive manner: model 2, further adjustment for baseline BMI; model 3, further adjustment for baseline lifestyle factors (smoking, physical activity and alcohol intake) and lipids (triacylglycerols, HDL-C and LDL-C); model 4, further adjustment for a 5-year change in BMI after baseline.

To compare the estimated associations across models 1–4 for a given outcome and exposure, we used

IL1Ra			Adiponectin		
<i>n</i>	Estimate	<i>P</i>	<i>n</i>	Estimate	<i>P</i>
3651	0.05 (0.02; 0.08)	0.004	3651	-0.05 (-0.08; -0.02)	<0.001
3651	0.03 (-0.01; 0.06)	0.132	3651	-0.04 (-0.07; -0.01)	0.003
3651	0.02 (-0.02; 0.05)	0.353	3651	-0.04 (-0.07; -0.01)	0.020
3651	0.01 (-0.03; 0.05)	0.591	3651	-0.04 (-0.07; -0.01)	0.011
3479	0.11 (0.01; 0.20)	0.027	3479	-0.13 (-0.21; -0.05)	0.001
3479	0.00 (-0.10; 0.10)	0.998	3479	-0.09 (-0.17; -0.01)	0.035
3479	-0.03 (-0.14; 0.07)	0.509	3479	-0.07 (-0.16; 0.02)	0.135
3479	-0.05 (-0.16; 0.05)	0.309	3479	-0.07 (-0.16; 0.02)	0.109
1190	-0.01 (-0.42; 0.40)	0.961	1190	-0.53 (-0.88; -0.18)	0.003
1190	-0.10 (-0.55; 0.34)	0.648	1190	-0.52 (-0.88; -0.16)	0.005
1190	-0.23 (-0.69; 0.23)	0.325	1190	-0.45 (-0.84; -0.06)	0.026
1190	-0.28 (-0.73; 0.18)	0.238	1190	-0.44 (-0.83; -0.05)	0.028
3617	7.2 (4.3; 10.2)	<0.001	3617	-5.6 (-7.8; -3.3)	<0.001
3617	4.9 (1.9; 7.9)	0.001	3617	-4.8 (-7.0; -2.6)	<0.001
3617	4.0 (1.0; 7.1)	0.009	3617	-4.1 (-6.5; -1.7)	0.001
3617	2.4 (-0.4; 5.3)	0.094	3617	-4.6 (-6.8; -2.3)	<0.001
3428	4.0 (0.0; 8.1)	0.050	3428	-5.1 (-8.2; -1.8)	0.002
3428	2.0 (-2.2; 6.4)	0.349	3428	-4.4 (-7.6; -1.1)	0.010
3428	1.0 (-3.3; 5.4)	0.667	3428	-3.8 (-7.2; -0.2)	0.038
3428	-0.6 (-4.7; 3.7)	0.791	3428	-4.0 (-7.4; -0.6)	0.024
3612	7.9 (4.7; 11.1)	<0.001	3612	-6.2 (-8.6; -3.8)	<0.001
3612	5.3 (2.1; 8.7)	0.001	3612	-5.4 (-7.8; -3.0)	<0.001
3612	4.3 (1.0; 7.7)	0.010	3612	-4.6 (-7.2; -2.0)	<0.001
3612	2.6 (-0.5; 5.7)	0.096	3612	-5.2 (-7.5; -2.7)	<0.001
3611	5.3 (2.5; 8.2)	<0.001	3611	-3.9 (-6.1; -1.7)	<0.001
3611	3.7 (0.8; 6.7)	0.012	3611	-3.3 (-5.5; -1.0)	0.005
3611	3.2 (0.2; 6.3)	0.036	3611	-2.7 (-5.0; -0.2)	0.032
3611	2.0 (-0.8; 5.0)	0.163	3611	-3.0 (-5.3; -0.7)	0.012
3419	-2.5 (-4.5; -0.5)	0.015	3419	2.9 (1.1; 4.7)	0.002
3419	-0.6 (-2.8; 1.6)	0.596	3419	2.1 (0.3; 4.0)	0.023
3419	0.0 (-2.2; 2.4)	0.970	3419	1.8 (-0.2; 3.7)	0.075
3419	0.9 (-1.4; 3.1)	0.457	3419	1.9 (0.0; 3.9)	0.049

n, number of person-examinations used in the particular analysis. *P*, *P* value for the test of the effect being equal to zero. Values in bold indicate significant associations after adjustment for multiple testing (128 tests) with the method of Benjamini and Hochberg.

Model 1: Adjusted for baseline age, sex, study phase and baseline value of the outcome; Model 2: Further adjustment for baseline BMI; Model 3: Further adjustment for baseline smoking, physical activity, alcohol intake, triacylglycerols, HDL-C and LDL-C; Model 4: Further adjustment for 5-year change in BMI after baseline.

a complete case approach, limiting the analyses to data with complete information on all covariates in model 4. Except for HbA_{1c}, which was only measured at phases 7 and 9, the same individual may contribute to more than one observation to the analyses. To account for the likely correlation of repeated measurements within the same participant, we used mixed-effects models with a random intercept and a random slope for time. For HbA_{1c}, a standard linear model was used. In a sensitivity analysis, we further tested whether the associations

were changed when using waist circumference instead of BMI.

In the reverse approach, we interchanged exposures and outcomes and studied the associations of the baseline levels of glycaemia, insulin, insulin sensitivity and beta-cell function with 5-year changes in inflammation-related biomarkers. These analyses were performed using the same methods and models as described previously.

A two-sided 5% level of significance was adjusted for multiple testing with the method of Benjamini

and Hochberg (21). This method controls the false discovery rate and is considered more powerful than the more simple Bonferroni adjustment of the error rate, because the risk of false negative results is lower with the Benjamini–Hochberg method.

Results

Associations between biomarkers of inflammation at baseline and 5-year changes in glycaemia, insulin, insulin sensitivity and beta-cell function

Higher systemic concentrations of hsCRP, IL6 and IL1Ra were associated with higher changes in fasting and 2-h glucose and fasting and 2-h insulin, but not HbA_{1c}, whereas adiponectin was inversely associated with all these five outcomes (Table 2, model 1). After adjustment for baseline BMI, lipids, lifestyle factors and change in BMI, the positive associations of hsCRP and IL6 with fasting insulin and the inverse associations between adiponectin and fasting glucose, HbA_{1c} and fasting insulin remained significant (Table 2, models 2–4).

High baseline levels of hsCRP, IL6 and IL1Ra were also associated with increases in insulin resistance (i.e., increase in HOMA-IR and decrease in ISI_{0,120}) and beta-cell function, whereas baseline adiponectin showed inverse associations (Table 2, model 1). Effect sizes were attenuated by adjustment for the aforementioned covariables, but the associations of hsCRP, IL6 and adiponectin with changes in HOMA-IR and the associations of IL6 and adiponectin with HOMA- β remained significant in the final model (model 4). Associations with ISI_{0,120} lost statistical significance after adjustment.

To compare effect sizes between biomarkers of inflammation as exposure variables, we standardised our estimates per 1 population SD of 1 Log unit of the concentrations of the four biomarkers of subclinical inflammation (Fig. 1 and Supplementary Tables 1 and 2, see section on supplementary data given at the end of this article). Effect sizes were similar for hsCRP, IL6 and IL1Ra, but of larger magnitude (and in the opposite direction) for adiponectin.

We substituted BMI with waist circumference in a sensitivity analysis. In general, this changed the effect estimates in Table 2 by <10% (data not shown). Some effect estimates showed greater changes ($\geq 10\%$), but these were only observed for non-significant associations.

Associations of glycaemia, insulin, insulin sensitivity and beta-cell function at baseline with 5-year changes in biomarkers of inflammation

When interchanging exposures and outcomes, we observed fewer significant associations (Fig. 2). None of the measures of glycaemia was associated with changes in hsCRP, IL6, IL1Ra or adiponectin when further adjusting for 5-year change in BMI after baseline (fully adjusted model), except an inverse association between 2-h glucose and IL1Ra (Supplementary Tables 3 and 4). Fasting insulin and HOMA-IR showed inverse associations with changes in adiponectin in the fully adjusted models, but neither insulin levels nor HOMA-IR were related to changes in hsCRP, IL6 or IL1Ra (Supplementary Tables 3 and 4). High baseline levels of ISI_{0,120} were positively associated with increases in IL1Ra (Supplementary Tables 3 and 4).

Figure 1

Effect of one population standard deviation difference in the Log of the immune marker at baseline (hsCRP, IL6, IL1Ra and adiponectin) on subsequent 5-year changes in markers of glucose regulation. The associations are adjusted for baseline age, sex, study phase, BMI, smoking, physical activity, alcohol intake, triacylglycerols, HDL-C and LDL-C and baseline value of the outcome.

Discussion

This study examined the temporal relationship between biomarkers of subclinical inflammation and changes in glucose metabolism before the diagnosis of type 2 diabetes using repeat data. Baseline levels of hsCRP and IL6 were positively associated with subsequent increases in fasting insulin, HOMA-IR and beta-cell function, whereas adiponectin was inversely associated with future changes in fasting glucose, HbA_{1c}, fasting insulin, HOMA-IR and beta-cell function. In the reverse analysis, baseline fasting insulin and HOMA-IR were associated with decreases in adiponectin, whereas 2-h glucose and ISI_{0,120} showed associations with changes in IL1Ra.

Subclinical inflammation and glycaemia

Serum hsCRP, IL6 and IL1Ra were associated with 5-year increases in fasting and 2-h glucose in age- and sex-adjusted models, but further adjustment attenuated these associations to non-significance, with BMI being the most important confounder. In contrast, adiponectin levels showed an independent inverse association with fasting glucose, but not with 2-h glucose. These data are novel and may point towards a specific role of adiponectin in the early deterioration of glycaemia.

Fasting glucose levels are mainly determined by hepatic glucose production, whereas increased 2-h glucose

mainly reflects peripheral glucose uptake (22). Adiponectin receptors (ADIPOR)-1 and 2 are expressed on both hepatocytes and skeletal muscle cells with ADIPOR2 being the predominant receptor in the liver and ADIPOR1 being the predominant receptor in skeletal muscle (23). Therefore, it can be speculated that ADIPOR2-mediated signalling and downstream effects on peroxisome proliferator-activated receptor- α and regulation of glucose uptake, fatty acid oxidation, oxidative stress and inflammation may mediate the observed association between adiponectin and deterioration of fasting glycaemia in our study. Importantly, chronically decreased adiponectin levels are indicators of adipose tissue dysfunction and not only related to increased risk of type 2 diabetes but also related to diabetic complications (1, 2, 24, 25).

With respect to HbA_{1c}, we observed an inverse association between adiponectin and increases in HbA_{1c}, but no associations among the other three biomarkers. Based on the findings for fasting glucose, associations may have been expected for all four biomarkers at least for the age- and sex-adjusted model. However, this discrepancy may be because glucose levels are only weak determinants of HbA_{1c} in non-diabetic individuals (26). Furthermore, the sample size for the HbA_{1c} analysis was smaller than that for other glycaemic traits. Our data are only partly in line with previous observations in the KORA study showing a positive association between hsCRP and 7-year changes in HbA_{1c}, but no association between adiponectin and HbA_{1c} (9). There are no obvious differences in baseline characteristics between the two studies, so the relevance of subclinical inflammation for HbA_{1c} levels in non-diabetic individuals merits further studies.

Subclinical inflammation and insulin resistance

Our study revealed consistent associations between all four biomarkers and fasting insulin and HOMA-IR, although the associations of IL1Ra were not independent of 5-year changes in BMI. In contrast, for 2-h insulin and ISI_{0,120}, which were based on post-load measures, associations with hsCRP, IL6 and adiponectin were only found in the initial regression models, but not after full adjustment.

So far, only one previous study used a comparable design and found that high hsCRP levels were associated with increases in HOMA-IR in a young non-diabetic population (8). Thus, the use of a more comprehensive assessment of subclinical inflammation and dynamic measures of insulin resistance represents an extension of the current literature. Our observations for changes in fasting insulin and HOMA-IR complemented and

Figure 2

Effect of a difference in baseline glycaemia, insulin sensitivity or beta-cell function on subsequent 5-year changes in immune markers (hsCRP, IL6, IL1Ra and adiponectin). The associations are adjusted for baseline age, sex, study phase, BMI, smoking, physical activity, alcohol intake, triacylglycerols, HDL-C and LDL-C and baseline value of the outcome.

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corroborated our findings for fasting glucose and pointed towards an association between subclinical inflammation and hepatic rather than peripheral insulin resistance in non-diabetic individuals. Associations were weaker for changes in IL1Ra. IL1Ra levels are considered as indicators of IL1 β -mediated processes. IL1 β has been demonstrated to induce insulin resistance in hepatocytes (27). Therefore, an association between IL1Ra and hepatic insulin resistance is plausible.

Subclinical inflammation and beta-cell function

This is apparently the first study to show that higher hsCRP, IL6 and IL1Ra and lower adiponectin at baseline are associated with 5-year increases in beta-cell function assessed in the fasting state. After full adjustment, high IL6 levels and low adiponectin levels remained associated with increases in fasting beta-cell function.

Although an increase in beta-cell function does not seem intuitively related to an increased risk of type 2 diabetes, our findings have to be seen in context of the aforementioned associations with worsening fasting glycaemia and increased insulin resistance. The associations of IL6 and adiponectin with increases in beta-cell function were most likely a consequence of their associations with increased insulin resistance. In other words, increases in HOMA-IR in our non-diabetic study sample may reflect a compensatory upregulation of insulin secretion in response to decreases in insulin action, which was still sufficient to maintain glucose levels.

However, our data are also in line with the alternative hypothesis that biomarkers of subclinical inflammation have a direct impact on beta-cell function. IL6 has been reported to stimulate insulin secretion through an incretin-mediated mechanism in experimental models of diabetes (28). The interpretation of our findings regarding beta-cell function would have been facilitated by the investigation of associations between subclinical inflammation and changes in the disposition index. Unfortunately, the assessment of dynamic beta-cell function is not possible with the available data in the Whitehall II cohort.

Bidirectionality in temporal associations between subclinical inflammation and markers of glucose metabolism

Our study is unique because our design allowed us to assess the potential bidirectionality in the associations of subclinical inflammation and glucose metabolism. Reversing our initial analysis led to two main results.

First, fasting insulin and HOMA-IR were associated with decreases in adiponectin. Secondly, 2-h glucose showed inverse and ISI_{0,120} showed direct associations with changes in IL1Ra.

It has been proposed that hypoadiponectinaemia in obesity and type 2 diabetes may be a consequence rather than a cause of insulin resistance (12). The regulation of adiponectin is still poorly understood in humans, so we cannot draw firm conclusions. However, the results are consistent with our previous observations of continuous and faster decrease in adiponectin levels preceding the development of type 2 diabetes compared with healthy adults (20). Our study suggests that adiponectin and insulin resistance are linked in a bidirectional way with potential deleterious consequences for the regulation of glucose metabolism.

The associations between 2-h glucose, ISI_{0,120} and changes in IL1Ra point towards a potential link between peripheral insulin action and regulation of IL1Ra. Such a link is plausible as the release of both IL1 β and IL1Ra after exercise is part of normal skeletal muscle physiology (29). However, it is unclear how impairments in muscle insulin sensitivity could influence circulating levels of both proteins.

From a pathophysiological point of view, any bidirectionality in the relationship between subclinical inflammation and insulin resistance could reflect a positive feedback loop, potentially fuelling a vicious cycle resulting in progressive worsening of glycaemic control. Our finding of a limited degree of bidirectionality consequently argues in favour of a deleterious impact of hypoadiponectinaemia and subclinical inflammation on the development of dysglycaemia.

Strengths and limitations

Strengths of our study are its large sample size and the analysis of quantitative traits entailing a larger statistical power than the analysis of a dichotomous outcome (e.g., prediabetes). Other strengths are the use of multiple measures of glucose metabolism reflecting different pathophysiological aspects and the availability of repeat data from up to four study phases, which allowed us to assess potential bidirectional relationships. Moreover, we adjusted for baseline BMI and its 5-year changes and thus demonstrated that associations were not solely mediated by obesity.

One limitation is the observational design that provides evidence for temporal, but not for causal relationships. Moreover, HOMA-IR and ISI_{0,120} correlate only moderately well with the euglycaemic-hyperinsulinaemic clamp (30),

but clamp measurements were not available. Thus, our assessment of insulin resistance was less precise than the gold standard, and we had to rely on indirect estimates to compare hepatic vs peripheral insulin resistance. HOMA- β can only be used to estimate fasting beta-cell function, and our study did not include dynamic assessments of beta-cell function. This limits the precision of the measurement, and we could not examine beta-cell function relative to insulin sensitivity using the disposition index. We used a complete case approach in our analyses. The fraction of missingness of hsCRP and IL6 in the cohort was around 5% and between 10 and 15% for IL1Ra and adiponectin in the subcohort. Therefore, and because we are studying associations, the effect of any potential non-randomness of the missing data for biomarkers of subclinical inflammation is considered negligible.

A final limitation of our study is the selection of four biomarkers, which left out others that also merit further research. We focused on hsCRP, IL6, IL1Ra and adiponectin as pro- and anti-inflammatory biomarkers because of their well-established associations with incident type 2 diabetes in prospective studies (1, 2, 31). Based on experimental data and other epidemiological studies, cytokines such as IL1 β (32, 33, 34), tumour necrosis factor (TNF)- α (35, 36) and transforming growth factor (TGF)- β (37, 38) and chemokines such as monocyte chemoattractant protein-1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2) (39, 40) undoubtedly represent interesting candidates because of their impact on insulin sensitivity and/or beta-cell function. However, circulating levels of IL1 β are below the limit of detection for a large proportion of individuals in population-based studies with currently available assays, and experimental data on TNF α and insulin resistance do not appear to be translated into an association between circulating levels of this protein and risk of type 2 diabetes in cohort studies (41, 42). Data on most other inflammation-related biomarkers and incident type 2 diabetes are based on only one or very few cohorts, so that further studies on their relevance both for early deterioration of glucose metabolism and for the manifestation of type 2 diabetes would be important.

Conclusion

Our study demonstrates multiple associations between baseline levels of biomarkers of subclinical inflammation and subsequent 5-year changes in glycaemia, insulin resistance and beta-cell function in a large population-based cohort of non-diabetic individuals. These findings are consistent with the hypothesis that subclinical

inflammation may increase hepatic insulin resistance and thereby upregulate beta-cell function. We observed less consistent evidence for bidirectionality in these temporal relationships, suggesting that low-grade inflammation precedes insulin resistance rather than vice versa.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0528>.

Declaration of interest

D Vistisen and K Færch are employed by Steno Diabetes Center, a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. Steno Diabetes Center receives part of its core funding from unrestricted grants from the Novo Nordisk Foundation and Novo Nordisk A/S. M Kivimäki reports grants from the Medical Research Council (K013351), the British Heart Foundation (RG/13/2/30098) and the US National Institutes of Health (R01 HL036310, R01AG013196), during the conduct of the study. All other authors declare that there is no duality of interest associated with their contribution to this manuscript. The funders of the study had no role in study design, data collection, analysis, interpretation or writing of the report.

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Authors' contribution statement

C Herder, K Færch, E J Brunner, A G Tabak, M Kivimäki and D Vistisen contributed to the study concept and design. C Herder, M Carstensen-Kirberg, G D Lowe, R Haapakoski, D R Witte, E J Brunner, M Roden, A G Tabak and M Kivimäki contributed the data. C Herder, K Færch and D Vistisen planned the statistical analysis. D Vistisen conducted the statistical analysis. C Herder and D Vistisen drafted the paper. All authors contributed to, critically revised and approved the final version of the manuscript.

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