Elevated Levels of the Anti-Inflammatory Interleukin-1 Receptor Antagonist Precede the Onset of Type 2 Diabetes

The Whitehall II Study

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OBJECTIVE — Interleukin-1 receptor antagonist (IL-1Ra), a natural inhibitor of interleukin-1β, has been shown to improve β-cell function and glycemic control in patients with type 2 diabetes. The aim of this study was to investigate whether baseline systemic levels of IL-1Ra are associated with incident type 2 diabetes during more than 10 years of follow-up.

RESEARCH DESIGN AND METHODS — We measured serum IL-1Ra concentrations in a nested case-control study (181 case and 376 age-, sex-, and BMI-matched normoglycemic control subjects) within the Whitehall II cohort (U.K.).

RESULTS — IL-1Ra concentrations were higher in case subjects ($P = 0.0006$) and associated with incident type 2 diabetes (odds ratio for a 1-SD increase of IL-1Ra 1.48 [95% CI 1.21–1.80]). This association remained significant after adjustment for multiple potential confounders but was attenuated by adjusting for 2-h glucose.

CONCLUSIONS — Our findings indicate that individuals who will develop type 2 diabetes are characterized by a complex immune activation that also includes upregulation of the anti-inflammatory cytokine IL-1Ra.

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Systemic concentrations of several acute-phase proteins, cytokines, and chemokines are elevated in individuals who will subsequently develop type 2 diabetes compared with those in individuals who remain disease free (1–3). Immune mediators such as interleukin-6 and monocyte chemoattractant protein-1 have been shown to interfere with insulin signaling in fat, liver, and muscle cells (1,4), whereas, in particular, the proinflammatory cytokine interleukin-1β inhibits β-cell function and promotes β-cell apoptosis (5). Therefore, low-grade inflammation may contribute to diabetes development both by inducing insulin resistance and reducing insulin secretion.

The importance of interleukin-1β and interleukin-1 receptor antagonist (IL-1Ra) was emphasized by a randomized, double-blind, clinical trial; IL-1Ra improved β-cell function and glycemic control in patients with type 2 diabetes (6). It is thus tempting to speculate that high circulating IL-1Ra concentrations could indicate decreased risk of type 2 diabetes much like increased adiponectin levels are associated with lower incidence of type 2 diabetes (7). Systemic IL-1Ra levels are increased in patients with obesity, impaired glucose tolerance, and the metabolic syndrome in cross-sectional studies (8–10). Longitudinal data on the relationship between IL-1Ra and the risk of type 2 diabetes are not available. Therefore, the aim of the current study was to investigate whether systemic levels of IL-1Ra are associated with incident type 2 diabetes in a nested case-control study within the prospective Whitehall II cohort study.

RESEARCH DESIGN AND METHODS

— We present results from a nested case-control study within the Whitehall II cohort, which was established in 1985 and included 10,308 civil servants age 35–55 years (11). Phase 3 (1991–1994) of the study was the first phase where glucose tolerance was assessed by a 75-g oral glucose tolerance test and is the baseline for the current study ($n = 7,537$). Participants were followed through postal questionnaires at 2.5-year intervals (phases 4–8) and further clinical examinations (including an oral glucose tolerance test) in 1997–1999 (phase 5) and 2003–2004 (phase 7) (12). Individuals without type 2 diabetes at baseline and with incident type 2 diabetes during the follow-up period of 11.5 ± 3.0 years served as case subjects ($n = 181$). The control subjects ($n = 376$), with normal glucose tolerance at baseline and during the follow-up, were frequency matched to case subjects for age (5-year bands), sex, and BMI (5 kg/m^2 bands). Further details on the selection criteria for this nested case-control study and information on the collection of anthropometric, metabolic, socioeconomic, and immunological variables and on statistical analysis are given in an online appendix (available at http://dx.doi.org/10.2337/dc08-1161).

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Table 1—*Association between circulating concentrations of IL-1Ra and incident diabetes*

Model	Covariables	Odds ratio (95% CI)	*P*
1	Age and sex	1.48 (1.21–1.80)	0.0001
2	Age, sex, and waist circumference	1.39 (1.11–1.74)	0.0038
3	Those for model 2 plus cardiovascular risk factors (cholesterol, fasting triglycerides, systolic blood pressure, smoking*, physical activity†, antihypertensive medication, and lipid-lowering medication)	1.34 (1.05–1.72)	0.021
4	Those for model 2 plus socioeconomic status (employment grade‡)	1.39 (1.10–1.75)	0.0059
5	Those for model 2 plus proinflammatory mediators (CRP and IL-6)	1.35 (1.06–1.70)	0.013
6	Those for model 2 plus fasting glycemia (fasting glucose and fasting insulin)	1.39 (1.05–1.86)	0.024
7	Those for model 2 plus 2-h glucose	1.24 (0.91–1.69)	0.17
8	Age, sex, waist circumference, and all covariables from models 3–6	1.43 (1.03–2.00)	0.034
9	Age, sex, waist circumference, and all covariables from models 3–7	1.20 (0.84–1.71)	0.32

Data are odds ratio (95% CI) given for a 1-SD increase of IL-1Ra concentrations unless otherwise indicated. IL-1Ra, triglycerides, C-reactive protein (CRP), interleukin (IL)-6, and insulin entered the models as ln-transformed variables. *Smoking is coded in three classes (never smoked, former smoker, and current smoker). †Physical activity is coded in three classes (none/mild, moderate, and vigorous). ‡Employment grade is coded in six classes running from 1 (highest grade) to 6 (lowest grade).

RESULTS — Characteristics of case and control subjects are shown in Table A1 of the online appendix. The comparison of the included and excluded diabetic case subjects revealed only a few significant differences: selected case subjects were less likely to be women and smokers, were more likely to be ex-smokers, and had a marginally lower BMI. Other comparisons between the two groups were not significant (data not shown). Characteristics of control subjects in our selection mainly reflected the selection criteria (normal glucose tolerance throughout the study and matching for age, sex, and BMI to case subjects): they were slightly older and had a higher BMI, waist circumference, and diastolic blood pressure but lower fasting and 2-h glucose compared with the rest of the cohort who were nondiabetic at baseline and follow-up (data not shown).

IL-1Ra concentrations at baseline were higher in case subjects (median 232.8 pg/ml [25th–75th percentiles 180.7–342.2]) than in control subjects (207.6 pg/ml [159.3–274.8]) (P = 0.0006). A 1-SD increase of IL-1Ra (157.7 pg/ml) was associated with incident type 2 diabetes in models that adjusted for multiple potential confounders, including age, sex, waist circumference, cardiovascular risk factors, socioeconomic status, proinflammatory mediators, and fasting glycemia (Table 1). Further inclusion of BMI had virtually no impact on odds ratio (model 2 plus BMI odds ratio 1.41 [95% CI 1.13–1.77]; P = 0.0027). However, addition of 2-h glucose led to reduced effect sizes and loss of statistical significance (Table 1).

CONCLUSIONS — Elevated levels of IL-1Ra were associated with an increased risk of developing type 2 diabetes in this nested case-control study. We found a slight attenuation of this association when adjusting for waist circumference, which is consistent with IL-1Ra production in adipose tissue (13). It is remarkable that the association was stable to adjustment for a range of further potential confounders, including fasting glucose and insulin. However, adjustment for 2-h glucose attenuated the association. This finding could be interpreted to indicate that increased IL-1Ra levels are a reaction to and not a cause of early postprandial hyperglycemia before the onset of diabetes. Studies with measurements of glycemic markers and IL-1Ra at multiple time points and analysis of their trajectories will be needed to clarify this point.

Our findings expand observations from cross-sectional studies that reported elevated levels of IL-1Ra in the circulation of individuals with obesity and insulin resistance (8–10). Thus, individuals who will develop type 2 diabetes are characterized not only by an upregulation of proinflammatory immune mediators (1–3) but also by the upregulation of at least one anti-inflammatory immune marker. Because animal studies and a recent clinical trial indicated that administration of IL-1Ra attenuates subclinical inflammation, supports β-cell function/insulin secretion, and may also improve insulin sensitivity (6,14), it is tempting to speculate that elevated IL-1Ra levels in individuals at risk of type 2 diabetes may be an attempt to counteract the proinflammatory effects of interleukin-1β and to preserve insulin secretion and insulin sensitivity—an effort that eventually fails. However, our data cannot rule out the alternative interpretation that IL-1Ra has additional metabolic effects beyond the inhibition of interleukin-1β that could lead to insulin resistance and type 2 diabetes.

As a potential limitation of the study, it should be mentioned that point estimates and CIs are derived from nonweighted data from a nested case-control study and, therefore, their statistical inference may be restricted and may not represent the best available estimate within the context of the original cohort. Thus, further studies will be needed to support our hypothesis that individuals with high risk of type 2 diabetes are characterized by the presence of an early compensatory, anti-inflammatory response that precedes the development of the disease. This hypothesis could be tested by the analysis of further, mainly anti-inflammatory immune mediators, such as interleukin-10 or transforming growth factor-β in additional cohorts.

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References

1. Kolb H, Mandrup-Poulsen T: An immune origin of type 2 diabetes? *Diabetologia* 48: 1038–1050, 2005
2. Herder C, Baumert J, Thorand B, Koenig W, de Jager W, Meisinger C, Illig T, Martin S, Kolb H: Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984–2002. *Diabetologia* 49:921–929, 2006
3. Herder C, Klopp N, Baumert J, Müller M, Khuseyinova N, Meisinger C, Martin S, Illig T, Koenig W, Thorand B: Effect of macrophage migration inhibitory factor (MIF) gene variants and MIF serum concentrations on the risk of type 2 diabetes: results from the MONICA/KORA Augsburg Case-Cohort Study, 1984–2002. *Diabetologia* 51:276–284, 2008
4. Sell H, Dietze-Schroeder D, Eckel J: The adipocyte-myocyte axis in insulin resistance. *Trends Endocrinol Metab* 17:416–422, 2006
5. Donath MY, Schumann DM, Faulenbach M, Ellingsgaard H, Perren A, Ehses JA: Islet inflammation in type 2 diabetes: from metabolic stress to therapy. *Diabetes Care* 31 (Suppl. 2):S161–S164, 2008
6. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY: Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N Engl J Med* 356:1517–1526, 2007
7. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57–58, 2002
8. Salmenniemi U, Ruotsalainen E, Pihlajmäki J, Vauhkonen I, Kainulainen S, Punnonen K, Vanninen E, Laakso M: Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. *Circulation* 110:3842–3848, 2004
9. Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet F, Golay A, Dayer JM: IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? *J Clin Endocrinol Metab* 87:1184–1188, 2002
10. Ruotsalainen E, Salmenniemi U, Vauhkonen I, Pihlajmäki J, Punnonen K, Kainulainen S, Laakso M: Changes in inflammatory cytokines are related to impaired glucose tolerance in offspring of type 2 diabetic subjects. *Diabetes Care* 29: 2714–2720, 2006
11. Marmot M, Brunner E: Cohort profile: the Whitehall II study. *Int J Epidemiol* 34:251–256, 2005
12. Kumari M, Head J, Marmot M: Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. *Arch Intern Med* 164: 1873–1880, 2004
13. Juge-Aubry CE, Somm E, Giusti V, Pernin A, Chicheportiche R, Verdumo C, Rohner-Jeanrenaud F, Burger D, Dayer JM, Meier CA: Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes* 52:1104–1110, 2003
14. Sauter NS, Schulthess FT, Galasso R, Castellani LW, Maedler K: The anti-inflammatory cytokine IL-1Ra protects from high-fat diet-induced hyperglycemia. *Endocrinology* 149:2208–2218, 2008