Accelerated Increase in Serum Interleukin-1 Receptor Antagonist Starts 6 Years Before Diagnosis of Type 2 Diabetes

Whitehall II Prospective Cohort Study

Maren Carstensen,1 Christian Herder,1 Mika Kivimäki,2 Markus Jokela,2 Michael Roden,1,3 Martin J. Shipley,2 Daniel R. Witte,2,4 Eric J. Brunner,2 and Adam G. Tabákov

OBJECTIVE—Although interleukin-1 receptor antagonist (IL-1Ra) treatment is associated with improved β-cell function and glycemic control in patients with type 2 diabetes, its role in the development of type 2 diabetes remains unclear. We used repeated measurements to characterize IL-1Ra trajectories in individuals who developed type 2 diabetes.

RESEARCH DESIGN AND METHODS—This case-cohort study, nested within the Whitehall II cohort, was based on 335 incident type 2 diabetes cases and 2,475 noncases. We measured serum IL-1Ra levels at up to three time points per individual and estimated retrospective trajectories of IL-1Ra before diabetes diagnosis (case subjects) or end of follow-up (control subjects) using multilevel analysis. Models were adjusted for age, sex, and ethnicity.

RESULTS—IL-1Ra levels were already higher in the case than control subjects 13 years before diabetes diagnosis/end of follow-up (mean [95% CI] 302 [290–314] vs. 244 [238–249] pg/ml). In control subjects, IL-1Ra levels showed a modest linear increase throughout the study period. In case subjects, IL-1Ra trajectories were parallel to those in control subjects until 6 years (95% CI 7.5–4.5) before diagnosis and then rose steeply to 399 (379–420) pg/ml at the time of diagnosis (P < 0.0001 for slope difference). Adjustment for BMI and waist circumference as time-varying covariates had little impact on these trajectories.

CONCLUSIONS—We show elevated IL-1Ra levels for 13 years and an accelerated increase during the last 6 years before type 2 diabetes diagnosis, indicating the presence of an anti-inflammatory response that may act to counterbalance the metabolic and immunologic disturbances that precede type 2 diabetes.

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We hypothesize that an accelerated increase in circulating IL-1Ra levels would precede diabetes development by ~5 years before the diagnosis, coinciding with the previously described changes in insulin sensitivity and β-cell function (16). Changes in IL-1Ra would indicate an anti-inflammatory reaction to counterregulate the pro-inflammatory environment and preserve insulin sensitivity and β-cell function.

**RESEARCH DESIGN AND METHODS**

**Study population.** Data are from a nested case-cohort study within the prospective Whitehall II cohort study of 10,308 British civil servants aged 35–55 years at phase 1 (1985–1988). Details regarding study design, baseline characteristics, and source population for the case-cohort study have been described previously (18,19). The study was approved by the University College London Medical School Committee on the Ethics of Human Research and conducted according to the Declaration of Helsinki. Written informed consent was obtained at baseline and renewed at each contact.

Phase 3 (1991–1994), when a 75-g oral glucose tolerance test (OGTT) was administered for the first time, served as baseline for the current study. Participants were followed through postal questionnaires at 2.5-year intervals (phase 4: 1995–1996, phase 6: 2001, phase 8: 2006–2007) and through clinical examinations including an OGTT at phase 5 (1987–1989) and phase 7 (2000–2002). For the case-cohort study, we drew a random sample from the source population of 6,058 men and 2,758 women who had attended the phase 3 examination. We excluded participants with prevalent type 2 diabetes at phase 3 (n = 42), missing follow-up data on diabetes (n = 552), or missing data for key variables (C-reactive protein [CRP]; limited to subjects with CRP <10 mg/L), weight, waist circumference, cholesterol, triglycerides, fasting glucose, fasting insulin) at baseline (n = 2,019) or during follow-up (phases 5 and 7; n = 3,304), leading to a case cohort of 2,810 subjects: 335 subjects with incident type 2 diabetes and 2,475 subjects without incident type 2 diabetes.

**Measurements.** Diabetes was defined as a fasting glucose of 7.0 mmol/L or more, or a 2-h postload glucose of 11.1 mmol/L or more (20). Type 2 diabetes was diagnosed by OGTT (56.4%), self-report (13.1%), or the use of glucose-lowering medication (30.4%).

We measured blood glucose with the glucose oxidase method on a YSI model 2300 STAT PLUS analyzer (phases 5 and 7; mean CV 4.2–9.3%) (16).

Fasting insulin (pmol/L)

|       | Control subjects | Case subjects | P     |
|-------|------------------|---------------|-------|
| n     | 2,475            | 335           |       |
| Age (years) | 49.1 ± 5.8       | 51.0 ± 6.1    | <0.0001 |
| BMI (kg/m²)  | 25.0 ± 3.3       | 27.1 ± 4.2    | <0.0001 |
| Waist circumference (cm) | 83.5 ± 10.8   | 89.2 ± 12.2   | <0.0001 |
| Systolic blood pressure (mmHg) | 119.5 ± 12.7 | 123.8 ± 14.3 | <0.0001 |
| Diastolic blood pressure (mmHg) | 79.3 ± 9.0     | 82.2 ± 9.6    | <0.0001 |
| Fasting blood glucose (mmol/L) | 5.2 ± 0.4      | 5.5 ± 0.5     | <0.0001 |
| 2-h blood glucose (mmol/L) | 5.3 ± 1.4      | 6.7 ± 1.9     | <0.0001 |
| Fasting insulin (pmol/L) | 36.2 ± 28.8    | 61.5 ± 46.4   | <0.0001 |
| Sex, male/female (%) | 73.3/26.7       | 69.9/30.1     | 0.191  |
| Ethnicity, white/nonwhite (%) | 92.9/7.1       | 80.6/19.4     | <0.0001 |

Data are means ± SD or %.

We obtained serum samples from clinical screening (i.e., people who remained diabetes-free) at the start of each of the three different study phases, blood collection, processing, and storage at −80°C followed the same standard operating procedures. All assays were performed consecutively in the same laboratory (German Diabetes Center), and samples from different study phases of the same study participant were always analyzed using the same enzyme-linked immunosorbent assay (ELISA) plate to minimize assay imprecision. Mean intra-assay and inter-assay CVs were 2.6 and 7.9%, respectively. The limit of detection was 14 pm/L. All samples gave values above the limit of detection.

The following variables were included as time-invariant covariates: sex, age at the end of follow-up, and ethnicity (0 = white, 1 = nonwhite). Data for these were derived from phase 3 and phase 1 questionnaires. Given that adipose tissue is a major producer of IL-1Ra (9), BMI and waist circumference (assessed in medical examinations contemporaneously with IL-1Ra measurements) were included as additional covariates and were coded as time-varying covariates.

**Statistical analysis.** Statistical analyses were performed using SPSS 14.0 statistical software (SPSS, Chicago, IL). The participants were divided into case subjects (i.e., individuals who developed type 2 diabetes during the follow-up) and control subjects (i.e., people who remained diabetes-free). Initial analyses compared the characteristics of case and control subjects and tested the differences using t tests and χ² tests. The unadjusted associations between IL-1Ra and potential confounding variables were examined and tested using ANOVA for stratified measures and Spearman rank correlation together with unstandardized regression coefficients (95% CIs) of log(IL-1Ra) for the continuous variables. For subsequent analyses, year 0 of the observation period was the year of diabetes diagnosis for case subjects and a randomly selected time point during follow-up for control subjects to approximate the follow-up time distribution of case subjects. IL-1Ra levels were traced backwards to participants’ first participation in clinical screening (i.e., phase 3, which represents the baseline of the current analysis—a maximum of 13 years previously). Multilevel models were fitted to the data to assess changes in IL-1Ra during these preceding 13 years (21). Of a total of 8,233 serum measurements (964 in case subjects, 7,269 in control subjects), 2,383 measurements after year 0 were excluded and thus the analyses were based on 755 serum samples in case subjects and 5,095 serum samples in control subjects. Data were structured so that measurement times (observations) were nested within subjects, and the standard errors were calculated by taking into account the nonindependence of the observations, that is, that the same individuals contributed to more than one observation in the dataset. We treated observation time as one period (a nonpiecewise approach) for control subjects and as two distinct periods (a piecewise approach) for case subjects.

In the latter approach, we created two time variables: a continuous variable, scaled to take the value zero at the start of the second period, and a dummy variable indicating the period (0 = first period and 1 = second period). We first established the most parsimonious model for each piecewise model and chose the position of the start of the second period (from 0 to 10) that had the lowest information criteria for the final model. We estimated the likelihood-based 95% CI for the position of the start of the second period. The selected model was in close agreement with locally weighted scatter plot smoothers displaying the association graphically (data not shown). All analyses were adjusted for age, sex, ethnicity, and study phase. Additional models included BMI, waist circumference, or insulin as time-varying covariates. To provide figures adjusted for baseline characteristics, trajectories were fitted for a hypothetical population of 72.0% male and 91.2% white at age 62.9 years at the end of follow-up. Statistical significance was inferred at a two-tailed P < 0.05.

**RESULTS**

**Study population.** The comparison of the study participants (n = 2,810) and excluded subjects (n = 6,006) at baseline showed the study participants to be, on average, 1.4 years younger than those excluded, but otherwise revealed only small differences between the groups (supplementary Table 1, available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db09-1199/DC1). Characteristics of case and control subjects at baseline (phase 3) are shown in Table 1. Case subjects (n = 335) were older and more overweight than control subjects (n = 2,475). Case subjects also had higher blood pressure, fasting and 2-h blood glucose, and fasting insulin and were more likely to be nonwhite. Mean follow-up time (± SD) was 8.8 ± 3.4 years.

**Determinants of serum concentrations of IL-1Ra (univariate analyses).** Unadjusted baseline levels of IL-1Ra were higher in case than control subjects (Table 2).
In addition, IL-1Ra levels were higher in women than men. No differences in IL-1Ra were found among ethnic groups. In univariate analyses, IL-1Ra was positively correlated with age, BMI, waist circumference, blood pressure, 2-h glucose, and fasting insulin (Table 3).

**Trajectories of IL-1Ra in case and control subjects.** Multilevel models adjusted for age, sex, and ethnicity showed that serum IL-1Ra levels were already higher in case than control subjects 13 years before diagnosis or end of follow-up. Mean IL-1Ra levels (95% CI) were 302 (290–314) pg/ml in case subjects and 244 (238–249) pg/ml in noncase subjects (Fig. 1A).

From years −13 to −6 (95% CI −4.5 to −7.5), the trajectories of IL-1Ra of case and control subjects were parallel and increased marginally (<1.5 pg/ml per year) over time. An interaction effect among caseness, time period, and time indicated that the IL-1Ra trajectories of case and control subjects began to separate after year −6 (Fig. 1A). From years −6 to 0, IL-1Ra levels in case subjects increased steeply (13–16 pg/ml per year) and reached 399 (379–420) pg/ml at the time of diagnosis, whereas the slope of the IL-1Ra trajectory in the control subjects remained unaltered (P < 0.0001) for the slope difference during the final 6 years; model 1 in Table 4).

Additional adjustment for BMI or waist circumference as time-varying covariates reduced, but did not remove, the differences between case and control subjects (Fig. 1B and C). From years −13 until −6, IL-1Ra levels remained constant in both case and control subjects after adjustment. From years −6 until 0, IL-1Ra levels in case subjects increased steeply (~11–12 pg/ml per year in BMI-adjusted and 9–11 in waist-adjusted models), whereas IL-1Ra levels in control subjects remained unaltered (P < 0.001 for the slope difference during the final 6 years; models 2–3 in Table 4). Adjustment for fasting insulin had hardly any impact on the difference between case and control sub-

**DISCUSSION**

This case-cohort study of a middle-aged metabolically healthy population at baseline has three main findings. First, circulating concentrations of IL-1Ra were elevated in cases of incident type 2 diabetes 13 years in advance of diagnosis compared with individuals who remained diabetes-free. Second, in control subjects, longitudinal changes could be described by a linear trajectory with only a slight increase over time, whereas in case subjects, IL-1Ra increased rapidly starting 6 (95% CI 4.5–7.5) years before diagnosis. Third, changes in obesity explained the slight linear increase in control subjects throughout the observation period and in case subjects up to 6 years before diabetes diagnosis, but did not account for the steep increase in the IL-1Ra trajectory among case subjects in the last 6 years.

Our findings extend current knowledge on the association between inflammation and type 2 diabetes development, as this is the first study to characterize cytokine trajectories before type 2 diabetes. Our previous report on IL-1Ra and incident diabetes in a nested case-control study was limited to a single IL-1Ra measurement at study baseline (phase 3) (15) and therefore did not provide information on the time course of IL-1Ra levels preceding diabetes diagnosis.

Our findings are also novel from a pathophysiological perspective because they support the hypothesis that the pre-diabetic stage is characterized not only by proinflammatory alterations, but also by the presence of an anti-inflammatory response. Several mechanisms could explain the upregulation of IL-1Ra before the diagnosis of type 2 diabetes. The steep increase of IL-1Ra in pre-diabetic individuals occurs within the same time window in which indicators of insulin sensitivity, β-cell function, and glycaemia deteriorate (supplementary Fig. 1). This may indicate that these unfavorable changes in glucose metabolism and the increase of IL-1Ra production are closely connected.

**TABLE 3**

| Spearman r | P  | β (95% CI) | P   |
|------------|----|-----------|-----|
| Age (years) | 0.066 | 0.0005 | 0.007 (0.003–0.011) | 0.0004 |
| BMI (kg/m²) | 0.370 | <0.0001 | 0.070 (0.065–0.076) | <0.0001 |
| Waist circumference (cm) | 0.278 | <0.0001 | 0.016 (0.014–0.018) | <0.0001 |
| Systolic blood pressure (mmHg) | 0.075 | 0.0011 | 0.003 (0.001–0.005) | 0.0005 |
| Diastolic blood pressure (mmHg) | 0.104 | <0.0001 | 0.007 (0.004–0.009) | <0.0001 |
| Fasting blood glucose (mmol/l) | 0.035 | 0.063 | 0.079 (0.030–0.128) | 0.0016 |
| 2-h blood glucose (mmol/l) | 0.210 | <0.0001 | 0.086 (0.071–0.100) | <0.0001 |
| Fasting insulin (mmol/l) | 0.283 | <0.0001 | 0.005 (0.005–0.006) | <0.0001 |
In vitro studies show that both human islets and monocytes respond to high glucose concentrations with an upregulation of IL-1β (22–24), so that increased IL-1Ra concentrations before type 2 diabetes may represent a response to glucose-mediated IL-1β upregulation. The balance between IL-1β and IL-1Ra has been postulated to be a major determinant of the time course and severity of inflammatory diseases (25,26), and it is conceivable that

TABLE 4
Fixed effects for multilevel models of changes over time in log₂(IL-1Ra) serum concentrations before diagnosis of type 2 diabetes or the end of follow-up

| Model  | Time (per year) | Case (incident type 2 diabetes) | Case × time | Case × time × 2nd period | BMI (per kg/m²) | Waist circumference (per cm) |
|--------|----------------|-------------------------------|-------------|--------------------------|----------------|-----------------------------|
| Model 1| 0.004 (0.002)* | 0.31 (0.03)†                 | NS          | 0.052 (0.006)†           | —              | —                           |
| Model 2| NS             | 0.14 (0.03)†                 | NS          | 0.051 (0.006)†           | 0.065 (0.002)† | —                           |
| Model 3| NS             | 0.13 (0.03)†                 | NS          | 0.045 (0.006)†           | —              | 0.025 (0.001)†             |
| Model 4| NS             | 0.28 (0.029)†                | NS          | 0.013 (0.006)*           | —              | —                           |

Data are regression coefficients (SE). Time = continuous variable scaled so that time = 0 at 6 years before diagnosis or the end of follow-up. Case = incident type 2 diabetes case. 2nd period = dummy variable (1 for positive values in the time variable, i.e., later than 6 years before diagnosis or the end of follow-up; 0 for nonpositive values). Trajectories in 335 case subjects with incident type 2 diabetes were compared with those in 2,475 control subjects. Log₂(IL-1Ra) was the outcome variable of the multilevel longitudinal modeling, and data were adjusted for age, sex, ethnicity, and study phase. Only models with the lowest information criteria are shown. *P < 0.05; †P < 0.0001.
the local and/or systemic ratio of these cytokines could also be relevant in the pathogenesis of type 2 diabetes. We could not test this hypothesis here because the physiological concentrations of IL-1β in individuals without severe inflammatory diseases are so low that they are mostly undetectable with currently available assays (23,27). However, it has been suggested that elevation of only IL-1β may not be sufficient to increase risk of type 2 diabetes; instead, increased IL-1β in combination with elevated levels of other proinflammatory cytokines may be required (28), thus limiting the predictive relevance of the IL-1Ra/IL-1β ratio without consideration of other risk factors.

The finding that the difference in trajectories between case and control subjects could not be explained by obesity is important because adipose tissue is a major producer of IL-1Ra (9,29). We replicated strong correlations of IL-1Ra levels with BMI and waist circumference (30–33). However, inclusion of BMI or waist circumference as time-varying covariates had no major effect on the shape of IL-1Ra trajectories, suggesting that the upregulation of IL-1Ra cannot directly be attributed to weight gain. Differences in secretion of leptin, an adipokine strongly upregulated in obesity that can stimulate IL-1β production and lead to increased IL-1Ra release, may be one of the mechanisms involved (34,35).

We did not adjust for glycemia, because our stratifying variable (incident diabetes caseness) already includes fasting and/or postload glucose in its definition, which means that we have already adjusted for glucose values at time 0. Because fasting insulin is not included in the diagnostic criteria, we performed an analysis adjusted for fasting insulin, which substantially attenuated the slope difference between case and control subjects preceding the diagnosis of diabetes. However, a significant acceleration of the slope from years −6 to 0 remains among case subjects, indicating that fasting insulin explains or mediates some, but not all, of the late increase in IL-1Ra. It should be kept in mind that with our study design, we cannot directly establish whether this attenuation is due to confounding, mediation, or shared causation.

Our findings point to the possibility that shape of biomarker trajectories is informative in terms of assessing their predictive value for different time windows. Sequential measurements of cytokines and other biomarkers and the characterization of individual trajectories may improve the estimation of type 2 diabetes risk. Differences in IL-1Ra levels between case and control subjects varied considerably over the lead time such that IL-1Ra may be more useful in predicting short-term diabetes risk, whereas other cytokines may be more strongly associated with long-term risk of type 2 diabetes. To date, attempts to improve diabetes risk prediction in the general population based on biomarker panels measured at a single time point have produced only marginal improvements compared with conventional risk models. It remains to be determined whether it will be possible to improve risk prediction at different pre-diabetic stages in the general population by considering serial biomarker measurements over time.

From a therapeutic point of view, it is noteworthy that recombinant IL-1Ra has been shown to improve metabolic control in patients with type 2 diabetes (13,14). In this light, an upregulation of IL-1Ra may be expected to be protective rather than associated with increased risk. In our study, it appears that the steep increase of IL-1Ra levels by approximately one-third was by far not sufficient to prevent the onset of type 2 diabetes. In the anakinra trial, an improvement of glycemia and β-cell function was accompanied by supraphysiological IL-1Ra peak levels in serum that were >1,000-fold higher in the intervention group than in the placebo group (13).

Our study has some limitations and strengths that should be acknowledged. First, the study design does not enable us to exclude the alternative interpretation that the increase of IL-1Ra before type 2 diabetes contributes to the disease risk and represents a causal factor rather than an anti-inflammatory response. However, data from the anakinra trial (13) as well as preclinical data (12,36) argue strongly against diabetogenic effects of IL-1Ra. Second, we did not determine IL-1β levels and therefore cannot know whether IL-1β increases before type 2 diabetes and whether such an increase precedes the increase in IL-1Ra. In addition, we did not have data from all three study phases for other proinflammatory markers, such as CRP and IL-6, for a comparison of trajectories. We did not adjust for the available CRP or IL-6 levels at baseline, because this adjustment has the capacity to influence only the intercept of the model, not the shape of the trajectories, and therefore would not help to answer the question of temporal sequences. Third, the Whitehall II study is an occupational cohort and as such is not population based. Although the cohort was healthy at recruitment, as in a community-based sample, the cohort overrepresents white, male, and middle-aged individuals. Fourth, due to missing data, approximately two-thirds of the source population at phase 3 was excluded from the present analysis. However, more than 300 incident cases and a total of almost 6,000 measurement points for the trajectories led to sufficient statistical power to detect differences between case and control subjects. In addition, our dropout analysis (supplementary Table 1) indicates that exclusions are unlikely to have affected internal validity.

The study has notable strengths. It is based on a well-phenotyped cohort, and more than half of incident diabetes cases were diagnosed based on the gold standard oral glucose tolerance test. We applied a sophisticated methodology that considered the interrelation among repeated measurements from the same individual at different time points during the follow-up and based our analysis on a large sample, as noted above.

In conclusion, we characterized cytokine trajectories to understand the evolution of the association between IL-1Ra levels in the circulation and type 2 diabetes before the diagnosis of diabetes. IL-1Ra levels showed an accelerated increase during the last 6 years preceding diagnosis. We showed that crude measures of adiposity did not explain the IL-1Ra trajectory, potentially implicating other factors in disease susceptibility. These data support the hypothesis that an anti-inflammatory response counterbalances metabolic and immunologic disturbances preceding type 2 diabetes. Moreover, these results suggest that multiple measurements of inflammation-related and other biomarkers can markedly improve our understanding of the pathogenesis of type 2 diabetes. The clear temporal characterization shown by our data may help define the optimal clinical use of these biomarkers.

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