

Plasma Interleukin-10 Concentration Is Positively Related to Insulin Sensitivity in Young Healthy Individuals

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There is evidence linking insulin resistance with low-grade chronic inflammation (1). Proinflammatory cytokines, such as tumor necrosis factor- α and interleukin (IL)-6, might impair insulin action (2,3). Little is known about associations between insulin action and anti-inflammatory cytokines. IL-10 is a cytokine with potent anti-inflammatory properties (4). Recent studies provided evidence that IL-10 might exert some beneficial metabolic effects (5–7). So far, no data are available regarding an association between circulating IL-10 and insulin action in humans. The aim of the present study was to examine the relationship between plasma IL-10 concentration and whole-body insulin sensitivity in apparently healthy humans.

RESEARCH DESIGN AND METHODS

A total of 93 subjects, 55 men and 38 women, participated in the present study. All participants had no cardiovascular disease, hypertension, morbid obesity (BMI >40 kg/m²), infections, or any other serious medical problems. The mean age of the study group was 28.13 ± 8.37 years and the mean BMI 26.06 ± 4.79 kg/m². Subjects underwent an oral glucose tolerance test and all had normal glucose tolerance according to World Health Organization criteria (fasting and postload glucose 5.04 ± 0.56 and 4.91 ± 1.29 mmol/l, respectively).

All subjects were nonsmokers and were not taking any anti-inflammatory drugs (within previous 3 months) or drugs known to affect carbohydrate and lipid metabolism. All analyses were performed after an overnight fast. The study protocol was approved by the ethics committee of Medical University of Bialystok, Poland. All subjects gave written informed consent before entering the study.

Anthropometric and biochemical measurements were performed as previously described (8–11). Insulin sensitivity was evaluated by euglycemic-hyperinsulinemic clamp technique according to DeFronzo et al. (12), as described previously (8–11). The rate of whole-body glucose uptake (*M* value) was calculated as the mean glucose infusion rate from 80 to 120 min, corrected for glucose space and normalized per kilogram of fat-free mass.

Plasma IL-10 concentration was measured with a human high-sensitivity immunoassay (Quantikine HS; R&D Systems, Minneapolis, MN) with the detection limit of the method <0.5 pg/ml. The intra- and interassay coefficients of variation (CVs) were below 9.6 and 15.7%, respectively. Serum C-reactive protein (CRP) was estimated with a high-sensitive (hs) enzyme-linked immunosorbent assay kit (hs-CRP; Euroimmun, Luebeck, Germany) with the detection

limit of 0.8 ng/ml and with both intra- and interassay CVs $<7.8\%$.

The statistics were performed with the STATISTICA 5.0 program (StatSoft, Krakow, Poland). IL-10 concentrations were not normally distributed. Relationships between IL-10 and other variables were assessed with Spearman's rank *R* analysis and multiple regression analysis. The level of significance was accepted at $P < 0.05$.

RESULTS— The median (quartile) plasma IL-10 concentration was 0.7 pg/ml (0.6–1.0). The mean *M* value was 50.33 ± 18.51 $\mu\text{mol} \cdot \text{kg fat-free mass}^{-1} \cdot \text{min}^{-1}$. Fasting and postload insulin were 73.08 ± 37.58 and 228.54 ± 182.99 pmol/l, respectively. Total cholesterol was 4.90 ± 0.90 mmol/l, triglycerides 1.19 ± 0.71 mmol/l, and HDL cholesterol 1.35 ± 0.33 mmol/l. The median (quartile) serum hs-CRP concentration was 0.90 mg/l (0.50–2.30).

IL-10 was related positively to insulin sensitivity ($r = 0.37$, $P = 0.00023$) (Fig. 1) and HDL cholesterol ($r = 0.21$, $P = 0.039$) and negatively to fasting and postload insulin ($r = -0.31$, $P = 0.0026$ and $r = -0.24$, $P = 0.02$, respectively) and plasma triglycerides ($r = -0.22$, $P = 0.031$).

Multiple regression analysis revealed that the correlation between IL-10 and insulin sensitivity remained significant after adjustment for age, sex, BMI, fasting and postload glucose and insulin, total and HDL cholesterol, triglycerides, and hs-CRP (all adjusted β -values between 0.19 and 0.25, all $P < 0.05$).

CONCLUSIONS— In the present study, we demonstrated a significant positive association between circulating IL-10 levels and whole-body insulin sensitivity. IL-10 was also associated with other variables closely linked to insulin sensitivity, such as fasting and postload insulin concentrations, HDL cholesterol, and triglyceride levels. Our results are in agreement with previous studies linking low IL-10 production with type 2 diabe-

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Abbreviations: CRP, C-reactive protein; IL, interleukin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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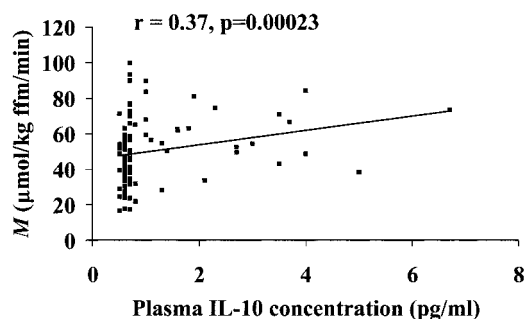


Figure 1—Correlation between IL-10 and insulin sensitivity in the entire study group (n = 93).

tes in an elderly population (5) and low IL-10 levels with metabolic syndrome within the subgroups of lean and obese women (6). Our data indicate that the previous findings might be explained, at least in part, by a direct association between IL-10 and insulin action.

An important limitation of the present study is that it does not reveal any causality. However, on the basis of previous findings, one might hypothesize that the correlation between IL-10 and insulin sensitivity might reflect insulin-sensitizing properties of this cytokine. Treatment with IL-10 normalized disturbances of whole-body glucose metabolism induced by IL-6 or lipid infusion in mice (7). Most likely, IL-10 exerts a beneficial metabolic effect through modulation of intramuscular fatty acid–derived metabolites and through inhibition of proinflammatory cytokine secretion and action (7,13). Our data provide the first evidence linking IL-10 with insulin action in physiological conditions in humans.

Values of IL-10 reported in our study are lower than those reported previously for subjects with metabolic syndrome (6) or acute coronary events (14). It is possible that in such situations IL-10 levels rise to counteract increased proinflammatory activity. Therefore, the correlation between IL-10 and insulin sensitivity, which we demonstrated in young and apparently healthy individuals, may not necessarily be present if different groups of subjects are analyzed.

In conclusion, this is the first time, to our knowledge, that a positive correlation

has been demonstrated between IL-10 concentration and whole-body insulin action. Our data suggest that anti-inflammatory mechanisms might play a protective role against the development of insulin resistance in apparently healthy humans.

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