# Association Between Serum IGF-1 and Diabetes Among U.S. Adults

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**OBJECTIVE** — Serum insulin-like growth factor (IGF)-1 may have a role in the maintenance of glucose homeostasis. We examined the association between serum IGF-1 and diabetes in a representative sample of U.S. adults.

**RESEARCH DESIGN AND METHODS** — Third National Health and Nutrition Examination Survey (NHANES III) participants aged ≥18 years ($n$ = 5,511) were the subjects of the study. The main outcome was the presence of diabetes ($n$ = 387).

**RESULTS** — Lower serum IGF-1 levels were positively associated with diabetes after adjusting for age, sex, race/ethnicity, education, smoking, alcohol intake, BMI, hypertension, glomerular filtration rate, and serum cholesterol. Compared with quartile 4 of IGF-1 (referent), the odds ratio (OR) of diabetes associated with quartile 1 was OR 2.16 (95% CI 1.24–3.76); $P$-trend = 0.002. However, the observed association between IGF-1 and diabetes was present only in those <65 years of age (OR = 3.05; $P$-trend = 0.006) and disappeared in those ≥65 years of age (OR = 0.51; $P$-trend = 0.18); $P$-interaction = 0.0056.

**CONCLUSIONS** — Low IGF-1 levels are associated with diabetes among young subjects.

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Insulin-like growth factor (IGF)-1 is involved in the regulation of growth and cellular proliferation in the human body (1,2). IGF-1 is similar in structure to insulin. Reduced IGF-1 levels have been proposed to have a role in diabetes (3–5). The two previous studies on IGF-1 and diabetes were restricted to elderly populations (6) or had limited sample size (7). There also is some inconsistency in the findings of the two studies: one study (7) found a positive association with decreasing IGF-1, while the other study (6) did not find an association. Therefore, this study examined the independent association between IGF-1 and diabetes in a representative sample of U.S. adults.

## RESEARCH DESIGN AND METHODS

— We used data from the Third National Health and Nutrition Examination Survey (NHANES III) (8–11), which included a probability sample of the U.S. population. We examined subjects ≥18 years of age randomly assigned to the morning exam after an overnight fast. Serum IGF-1 was measured in 6,059 participants. Subjects were excluded that had cardiovascular disease ($n$ = 400) and missing data ($n$ = 148) on covariates included in the multivariable model. This resulted in 5,511 participants, 387 of whom had diabetes.

Diabetes was defined as serum glucose ≥126 mg/dl (if fasting ≥8 h), a serum glucose ≥200 mg/dl (if fasting <8 h), history of diabetes diagnosis, or current use of oral hypoglycemics or insulin. IGF-1 measurement has been previously described (10).

We hypothesized that low IGF-1 levels are associated with diabetes. The odds ratio (OR) of diabetes for IGF-1 was calculated by taking the highest IGF-1 quartile as the referent using multivariable logistic regression models. Sample weights for the complex survey design were applied for all analyses using SAS and SUDAAN software.

## RESULTS

— Decreasing levels of IGF-1 were positively associated with diabetes in the multivariable-adjusted model (Table 1). In a subgroup analysis by age, decreasing levels of serum IGF-1 were positively associated with diabetes in those aged <65 years ($P$-trend = 0.008); the association disappeared in those aged ≥65 years ($P$-trend = 0.19).

In a supplementary analysis to examine if the association between IGF-1 and diabetes was explained by inflammation, we additionally adjusted for high-sensitivity C-reactive protein levels. The results were unaltered. In a second supplementary analysis, we examined the IGF-1 and diabetes association after additionally adjusting for IGF binding protein (IGFBP)-3 levels. Compared with quartile 4 (referent) of IGF-1, the OR of diabetes was 1.57 (95% CI 0.81–3.02) for quartile 3; 2.79 (1.68–4.63) for quartile 2; and 3.83 (1.98–7.39) for quartile 1; $P$-trend < 0.0001. In a third supplementary analysis, we examined the independent association between IGFBP-3 and diabetes after adjusting for variables in the multivariable model and, additionally, IGF-1 levels. Compared with quartile 1 (referent) of IGFBP-3, the OR of diabetes was 0.85 (0.54–1.36) for quartile 2; 1.08 (0.51–2.30) for quartile 3; and 2.50 (1.27–4.93) for quartile 4; $P$-trend = 0.01. In a fourth supplementary analysis, we examined the IGF-diabetes association by sex. Decreasing levels of serum IGF-1 were associated with diabetes in both men and women; $P$-interaction for cross-product sex × IGF-1 term = 0.3431. In a final supplementary analysis, we examined the IGF-diabetes association according to the two main categories of diabetes definition: past history/self-reported diabetes and elevated fasting glucose. For self-reported diabetes, compared with quartile 4 (referent) of IGF-1, the OR of self-reported diabetes was 1.43 (0.46–4.44) for quartile 3; 1.29 (0.50–3.31) for quartile 2; and 3.28 (1.11–9.66) for quartile 1; $P$-trend = 0.06. For diabetes defined based on blood glucose levels, compared with quartile 4 (referent) of

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**Table 1—*Association between serum IGF-1 levels and diabetes***

| | Serum IGF-1 quartiles | | | | |
|---|---|---|---|---|---|
| | Highest quartile (>322 ng/ml) | Third quartile (248–322 ng/ml) | Second quartile (186–247 ng/ml) | Lowest quartile (<186 ng/ml) | *P*-trend |
| Whole cohort ($n$ = 5,511) | | | | | |
| Number at risk (cases) | 1,377 (47) | 1,378 (78) | 1,378 (105) | 1,378 (157) | |
| Age, sex-adjusted OR (95% CI) | 1 (referent) | 1.69 (0.94–3.04) | 2.71 (1.77–4.17) | 3.16 (1.81–5.51) | <0.0001 |
| Multivariable-adjusted OR (95% CI)† | 1 (referent) | 1.33 (0.69–2.53) | 2.02 (1.28–3.19) | 2.16 (1.24–3.76) | 0.002 |
| Age <65 years | | | | | |
| Number at risk (cases) | 1,316 (30) | 1,211 (49) | 1,086 (71) | 886 (94) | |
| Age, sex-adjusted OR (95% CI) | 1 (referent) | 1.91 (0.91–4.01) | 3.61 (1.96–6.66) | 4.54 (1.89–10.93) | 0.0003 |
| Multivariable-adjusted OR (95% CI)† | 1 (referent) | 1.54 (0.70–3.38) | 2.63 (1.40–4.95) | 3.05 (1.31–7.08) | 0.006 |
| Age >65 years | | | | | |
| Number at risk (cases) | 61 (17) | 167 (29) | 292 (34) | 492 (63) | |
| Age, sex-adjusted OR (95% CI) | 1 (referent) | 0.52 (0.23–1.15) | 0.42 (0.23–0.78) | 0.47 (0.24–0.90) | 0.11 |
| Multivariable-adjusted OR (95% CI)† | 1 (referent) | 0.55 (0.20–1.52) | 0.55 (0.20–1.52) | 0.51 (0.24–1.06) | 0.18 |

†Adjusted for age (years), gender, race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), education categories (<high school, high school, >high school), smoking (never, former, current), alcohol intake (never, former, current), BMI (normal, overweight, obese), hypertension (absent, present), estimated glomerular filtration rate (ml/min per 1.73 $m^2$), and total cholesterol (mg/dl). *P*-interaction for cross-product age × IGF-1 quartile variable was 0.0056.

IGF-1, the OR of diabetes was 1.86 (0.79–4.36) for quartile 3; 3.77 (1.83–7.76) for quartile 2; and 5.59 (2.09–15.00) for quartile 4; *P*-trend < 0.0001.

**CONCLUSIONS** — In a representative sample of U.S. adults without clinical cardiovascular disease, we found low levels of serum IGF-1 to be positively associated with diabetes. When we examined the association between serum IGF-1 and diabetes by age, low serum IGF-1 was positively associated with diabetes only in subjects <65 years of age and not in those ≥65 years of age. Our results contribute to the existing literature (6,7) by suggesting that low IGF-1 may be a predictor of diabetes only in younger subjects. However, the cross-sectional nature of our study precludes conclusions regarding the temporal nature of the association between IGF-1 and diabetes.

Sandhu et al. (7) reported a positive association between low IGF-1 levels and glucose intolerance/diabetes in a sample of 615 subjects 45–65 years of age. In contrast, Rajpatak et al. (6) recently did not find an independent association between IGF-1 and diabetes among 922 subjects ≥65 years of age from the Cardiovascular Health Study. It has been shown that growth hormone and IGF-1 levels decline with age. Therefore, if IGF-1 has an independent role in glucose homeostasis, it is possible that this effect is less pronounced in older individuals.

In the current study, we had an adequate sample size to examine the association between IGF-1 and diabetes separately among younger and older subjects. We found that the association between low IGF-1 and diabetes was strongly present among subjects who were <65 years of age, but the association disappeared in those ≥65 years of age. Therefore, this clarifies the seeming inconsistency in previous literature (6,7) by suggesting that the difference in the age groups of subjects examined in those studies may be a reason for their difference in findings. However, the robustness of our findings of an interaction by age in the IGF-diabetes association should be interpreted with caution and needs to be confirmed in future larger studies with follow-up data.

IGFBP-3 may inhibit the bioactivity of IGF-1 by sequestering IGF-1 into a circulating reservoir, thereby reducing the free-circulating fraction of IGF-1 (12). In the current study, adjusting for IGFBP-3 levels in the multivariable model accentuated the association between IGF-1 and diabetes, suggesting that the observed association is mainly due to the effect of IGFBP-independent free fraction of IGF-1. We also found that IGFBP levels were positively associated with diabetes, even after additionally adjusting for serum IGF-1 levels, suggesting that IGFBP may have IGF-1–independent effects (13). In conclusion, lower IGF-1 levels were positively associated with diabetes in younger subjects.

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