Association between serum IGF-1 and diabetes mellitus among US adults

Running title: Serum IGF-1 and diabetes mellitus

Srinivas Teppala MD, MPH
Anoop Shankar MD, PhD

1. Department of Community Medicine, West Virginia University School of Medicine, Morgantown, WV 26506

Correspondence to:
Dr. Anoop Shankar,
Email: ashankar@hsc.wvu.edu

Submitted 23 April 2010 and accepted 9 July 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Serum IGF-1 and diabetes mellitus

Background: 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 mellitus in a representative sample of US adults.

Methods: Third National Health and Nutrition Examination Survey participants aged >18 years (n=5,511). Main outcome was the presence of diabetes mellitus (n = 387).

Results: Lower serum IGF-1 levels were positively associated with diabetes mellitus after adjusting for age, sex, race/ethnicity, education, smoking, alcohol intake, body mass index, hypertension, glomerular filtration rate and serum cholesterol. Compared to quartile 4 of IGF-1 (referent), the odds ratio [OR] (95% confidence interval) of diabetes associated with quartile 1 was 2.16 (1.24-3.76); p-trend=0.002. However, the observed association between IGF-1 and diabetes was present only in those <65 years (OR=3.05; p-trend=0.006) and disappeared in those ≥65 years (OR=0.51; p-trend=0.18); p-interaction=0.0056.

Conclusion: Low IGF-1 levels are associated with diabetes mellitus among young subjects.

METHODS

We used data from the Third National Health and Nutrition Examination Survey (NHANES III)8-11 which included a probability sample of the US population. We examined subjects aged ≥18 years randomly assigned to the morning exam after an overnight fast. Serum IGF-1 was measured in 6059 participants. We further excluded subjects with cardiovascular disease (n=400) and missing data (n=148) on covariates included in the multivariable model. This resulted in 5511 participants, 387 of whom had diabetes.

Diabetes was defined as a serum glucose ≥126mg/dl (if fasting ≥8 hours), a serum glucose ≥200 mg/dl (if fasting <8 hours), history of diabetes diagnosis or current use of oral hypoglycemics or insulin. IGF-I measurement has been described before.10 We hypothesized that low IGF-1 levels are associated with diabetes. The odds ratio [(OR) (95% confidence interval (CI)] 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
In Table 1, decreasing levels of IGF-1 were positively associated with diabetes in the multivariable-adjusted model. In a subgroup analysis by age, decreasing levels of serum IGF-1 were positively associated with diabetes in those <65 years (p-trend=0.008); the association disappeared in those ≥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 hsC-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 to quartile 4 (referent) of IGF-1, the OR (95% CI) of diabetes mellitus was 1.57 (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 mellitus after adjusting for variables in the multivariable model and in addition IGF-1 levels. Compared to quartile 1 (referent) of IGFBP-3, the OR (95% CI) of diabetes mellitus 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 gender. Decreasing levels of serum IGF-1 were associated with diabetes in both men and women; p-interaction for cross-product gender x 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 to quartile 4 (referent) of IGF-1, the OR (95% CI) of self-reported diabetes mellitus 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 to quartile 4 (referent) of IGF-1, the OR (95% CI) of diabetes mellitus 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.

DISCUSSION

In a representative sample of US 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 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 reported a positive association between low IGF-1 levels and glucose intolerance/diabetes in a sample of 615 subjects aged 45-65 years. In contrast, recently Rajpatak et al did not find an independent association between IGF-1 and diabetes among 922 subjects aged ≥65 yrs 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 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, but the association
disappeared in those ≥65 years. Thus clarified the seeming inconsistency in previous literature\(^6,\,7\) by suggesting that the difference in age groups of subjects examined in these 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 need to be confirmed in future larger studies with follow-up data.

IGFBP-3 may inhibit the bioactivity of IGF-1 by sequestering IGF-I into a circulating reservoir, thereby reducing the free circulating fraction of IGF-I.\(^12\) 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.

**Author contributors:** All the authors contributed to the intellectual development of this paper. AS had the original idea for the study and is the guarantor. ST wrote the first draft paper and performed the statistical analyses. AS provided critical comments to the manuscript and was involved in revisions.

**ACKNOWLEDGEMENTS**

**Funding:** This study was funded by an American Heart Association National Clinical Research program grant (AS).

**Disclosure:** There are no conflicts of interest related to this manuscript.

**Guarantor statement:** “The guarantor, AS, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.”

**REFERENCES**


Table 1. Association between serum insulin-like growth factor-1 (IGF-1) levels and diabetes mellitus

<table>
<thead>
<tr>
<th>Serum IGF-1 quartiles</th>
<th>Highest quartile (&gt;322 ng/mL)</th>
<th>Third Quartile (248-322 ng/mL)</th>
<th>Second quartile (186-247 ng/mL)</th>
<th>Lowest quartile (&lt;186 ng/mL)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort (n=5511)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (cases)</td>
<td>1377 (47)</td>
<td>1378 (78)</td>
<td>1378 (105)</td>
<td>1378 (157)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, sex-adjusted OR (95% CI)*</td>
<td>1 (referent)</td>
<td>1.69 (0.94-3.04)</td>
<td>2.71 (1.77-4.17)</td>
<td>3.16 (1.81-5.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable-adjusted OR (95% CI)* †</td>
<td>1 (referent)</td>
<td>1.33 (0.69-2.53)</td>
<td>2.02 (1.28-3.19)</td>
<td>2.16 (1.24-3.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (cases)</td>
<td>1316 (30)</td>
<td>1211 (49)</td>
<td>1086 (71)</td>
<td>886 (94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age, sex-adjusted OR (95% CI)*</td>
<td>1 (referent)</td>
<td>1.91 (0.91-4.01)</td>
<td>3.61 (1.96-6.66)</td>
<td>4.54 (1.89-10.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Multivariable-adjusted OR (95% CI)* †</td>
<td>1 (referent)</td>
<td>1.54 (0.70-3.38)</td>
<td>2.63 (1.40-4.95)</td>
<td>3.05 (1.31-7.08)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk (cases)</td>
<td>61 (17)</td>
<td>167 (29)</td>
<td>292 (34)</td>
<td>492 (63)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age, sex-adjusted OR (95% CI)*</td>
<td>1 (referent)</td>
<td>0.52 (0.23-1.15)</td>
<td>0.42 (0.23-0.78)</td>
<td>0.47 (0.24-0.90)</td>
<td>0.11</td>
</tr>
<tr>
<td>Multivariable-adjusted OR (95% CI)* †</td>
<td>1 (referent)</td>
<td>0.55 (0.20-1.52)</td>
<td>0.55 (0.20-1.52)</td>
<td>0.51 (0.24-1.06)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*OR (95% CI): Odds Ratio (95% Confidence Interval)
†Adjusted for age (years), gender, race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (never, former, current), body mass index (normal, overweight, obese), hypertension (absent, present), eGFR ((ml/min/1.73/m2) and total cholesterol (mg/dL). p-interaction for cross-product age x IGF-1 quartile variable was 0.0056.