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Circulating levels of insulin-like growth factor binding protein–1 in relation to insulin resistance, type 2 diabetes mellitus, and metabolic syndrome (Chennai Urban Rural Epidemiology Study 118)

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ABSTRACT

The objective was to assess the association of insulin-like growth factor binding protein–1 (IGFBP-1) with insulin resistance (IR), type 2 diabetes mellitus (T2DM), and metabolic syndrome (MS) in Asian Indians. Fifty subjects with normal glucose tolerance (NGT) and 50 with T2DM were randomly selected from the Chennai Urban Rural Epidemiology Study. Insulin-like growth factor binding protein–1 was measured by sandwich enzyme-linked immunosorbent assay. Serum insulin was estimated using Dako (Glostrup, Denmark) kits. Insulin resistance was calculated using the homeostasis model assessment. Subjects with T2DM had significantly decreased levels of IGFBP-1 (21.7 ± 3.5 ng/mL) compared with NGT subjects (34.4 ± 7.6 ng/mL, $P < .001$). The IGFBP-1 was significantly lower in NGT subjects with IR as measured by the homeostasis model assessment (25.5 ± 6.5 ng/mL) compared with NGT subjects without IR (40.7 ± 9.5 ng/mL, $P < .001$). On regression analysis, IR showed a significant association with IGFBP-1 even after adjusting for age, sex, body mass index, and glycated hemoglobin ($\beta = -3.714$, $P < .001$). Type 2 diabetes mellitus was significantly associated with IGFBP-1 even after adjusting for age, sex, and body mass index ($\beta = -12.798$, $P < .001$). The IGFBP-1 levels decreased with increasing number of metabolic abnormalities (P for trend $< .001$). Logistic regression analysis showed that IGFBP-1 had a strong negative association with MS even after adjusting for age and sex (odds ratio, 0.942; 95% confidence interval, 0.914-0.971; $P < .001$). Among Asian Indians, lower levels of circulating IGFBP-1 are seen in subjects with IR, T2DM, and MS.

Author contributions: VM conceived, initiated, supervised, conducted, and commented on all drafts of this paper. KG, KV, and SG coordinated the study and monitored all the data entry and work parts of the paper. KG, KV, and SG had full access to the data; and they take full responsibility for the integrity and accuracy of the data.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is caused by a combination of insulin resistance (IR) and insufficient pancreatic insulin secretion [1]. Insulin-like growths (IGFs) and their binding proteins are increasingly recognized as important in understanding the pathogenesis of cardiovascular disease. Low circulating IGF-1 concentrations are associated with worsening glucose tolerance [2]. Activities of IGFs are mediated through 6 different binding proteins, inclusive of insulin-like growth factor binding protein (IGFBP)–1. Low IGFBP-1, particularly coupled with low IGF-I, is associated with increased cardiovascular risk [2]. Free IGF-I and low IGFBP-1 and IGFBP-2 have been associated with greater IR, higher fasting glucose, and higher fasting insulin levels [3] and have also been shown to be associated with greater mortality [4]. Furthermore, recent studies have demonstrated that IGFBP-2, like IGFBP-1, is strongly associated with the metabolic syndrome (MS) [5].

A study of 2 Gujarati Asian Indian populations of similar genetic origin reported that there were significant differences in levels of circulating IGF-I, IGFBP-3, and IGFBP-1 depending on whether people had migrated to the United Kingdom or remained in Gujarat, India [6]. In this article, we report on the association of IGFBP-1 level with IR, T2DM, and MS in urban Asian Indians in south India.

2. Materials and methods

Study subjects were recruited from the Chennai Urban Rural Epidemiology Study (CURES), the study design of which is described elsewhere [7]. For the present study, a total of 100 study subjects were randomly selected using computer-generated numbers from Phase 3 of CURES. This included the following groups: 50 subjects with normal glucose tolerance (NGT) and 50 subjects with T2DM based on the World Health Organization criteria [8]. The inclusion criteria for all groups were as follows: nonsmokers, normal resting 12-lead electrocardiogram result, and absence of angina and myocardial infarction. Institutional ethical committee approval and informed consent were obtained.

3. Anthropometric measurements

Height, weight, and blood pressure were measured using standardized methods [7]. Body mass index (BMI) was calculated as weight (kilograms)/height (square meters).

3.1. Biochemical parameters

Biochemical analyses were done on Hitachi-912 Autoanalyzer (Roche, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Fasting plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and high-density lipoprotein cholesterol (direct method–polyethylene glycol-pretreated enzymes) were measured. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Glycated hemoglobin (HbA_{1c}) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA). Serum insulin concentration was estimated using Dako kits (Dako, Glostrup, Denmark).

3.2. Definitions and diagnostic criteria

Hypertension was diagnosed based on drug treatment of hypertension and/or if the subjects had systolic blood pressure of at least 130 mm Hg and/or diastolic blood pressure of at least 85 mm Hg [9]. Metabolic syndrome was diagnosed based on modified Adult Treatment Panel III guidelines [9]. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR). Subjects whose HOMA-IR values exceeded the 75th percentile of the total population were considered to have IR [10].

3.3. Insulin-like growth factor binding protein–1

Insulin-like growth factor binding protein–1 was measured by sandwich enzyme-linked immunosorbent assay (Diagnostic Systems Laboratories, Webster, TX) in which 2 monoclonal antibodies are directed against separate antigenic determinants on the IGFBP-1 molecule. During incubation, IGFBP-1 in the sample reacts with anti–IGFBP-1 antibodies bound to the microtitration well. After a first incubation and simple washing step, which removes unbound enzyme labeled antibody, the bound conjugate is detected by colorimetry with substrate. Absorbance was read at 450 nm. The intra- and interassay coefficients of variation were 4.6% and 7.6%, respectively.

3.4. Statistical analysis

Student *t* test or 1-way analysis of variance (with Turkey honestly significant difference) was used to compare groups for continuous variables; and χ^2 test or Fisher exact test, as appropriate, was used to compare proportions. Regression analysis was done to determine the association of IGFBP-1 with IR, T2DM, and MS. All analyses were done using Windows-based SPSS statistical package (Version 10.0, Chicago, IL), and P values < .05 were taken as significant.

4. Results

Subjects with T2DM had significantly lower levels of IGFBP-1 (21.7 ± 3.5 ng/mL) compared with NGT group (34.4 ± 7.6 ng/mL; $P < .001$)]. Insulin-like growth factor binding protein–1 was significantly lower in NGT subjects with IR (25.5 ± 6.5 ng/mL) compared with NGT subjects without IR (40.7 ± 9.5 ng/mL; $P < .001$) (Fig. 1).

Linear regression analysis was performed using IGFBP-1 as the dependent variable and IR and T2DM as independent variables to determine the association of IR and T2DM with IGFBP-1 (Table 1). Insulin resistance showed significant association with IGFBP-1 ($\beta = -4.286$, $P < .001$) even after adjusting

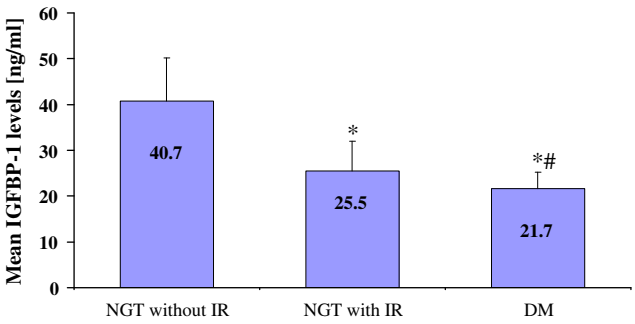

Fig. 1 – Mean IGFBP-1 levels in subjects with IR and T2DM. *P < .001 compared with NGT without IR. #P < .001 compared with NGT with IR.

for age, sex, BMI, and HbA_{1c} ($\beta = -3.714$, $P < .001$). Type 2 diabetes mellitus was significantly associated with IGFBP-1 ($\beta = -13.530$, $P < .001$) and remained statistically significant even after adjusting for age, sex, and BMI ($\beta = -12.798$, $P < .001$).

Mean IGFBP-1 levels were significantly lower in subjects with abdominal obesity ($P < .001$), elevated fasting glucose ($P < .001$), hypertension ($P < .001$), low high-density lipoprotein cholesterol ($P < .001$), and MS ($P < .001$) compared with their respective counterparts without these metabolic abnormalities. Although mean IGFBP-1 levels were lower in subjects with hypertriglyceridemia compared with those without, the difference did not reach statistical significance.

Mean levels of IGFBP-1 progressively decreased with increasing number of components of MS (no metabolic abnormality, 37.8 ± 16.5 ng/mL; 1 metabolic abnormality, 35.4 ± 10.5 ng/mL; 2 metabolic abnormalities, 33.7 ± 8.6 ng/mL; ≥3 metabolic abnormalities, 20 ± 6.5 ng/mL) (P for trend < .001). Logistic regression analysis using MS as dependant variable showed that IGFBP-1 had a significant association with MS (odds ratio, 0.946; 95% confidence interval, 0.919-0.973; $P < .001$) that remained statistically significant even after adjusting for age and sex (odds ratio, 0.942; 95% confidence interval, 0.914-0.971; $P < .001$).

5. Discussion

We report that IGFBP-1 levels are significantly lower in subjects with T2DM and IR as well as in those with MS.

Table 1 – Linear regression analysis using IGFBP-1 as dependent variable and presence of T2DM and IR as independent variable

Parameters	β	P value
IR, independent variable		
IR, unadjusted (HOMA-IR)	−4.286	<.001
Adjusted for age and sex	−4.491	<.001
Adjusted for age, sex, and BMI	−4.001	<.001
Adjusted for age, sex, BMI, and HbA_{1c}	−3.714	<.001
T2DM, independent variable		
T2DM, unadjusted	−13.530	<.001
Adjusted for age and sex	−14.007	<.001
Adjusted for age, sex, and BMI	−12.798	<.001

Low circulating levels of IGFBP-1 are associated with well-known risk factors for cardiovascular disease [2,5,6]. In the present study also, lower IGFBP-1 levels are found to be associated with cardiometabolic risk factors that are consistent with other studies [2,11]. Some studies have addressed the sex differences in cardiovascular risk factors in relation to the IGF system [12]. A recent study reported that women had higher levels of IGFBP-1 than men [13]. However, we did not find any sex differences in IGFBP-1 levels.

There is emerging evidence that IGFBP-1 or the IGF/IGFBP system may be a vital link between hyperinsulinemia/IR and cardiovascular disease [14]. Previous studies have shown that insulin levels are inversely associated with IGFBP-1 levels [15]. Heald et al [11] demonstrated a positive association between IGFBP-1 and insulin sensitivity in a population-based study of European and Pakistani subjects. Other studies have reported an inverse association between HOMA-IR and IGFBP-1 [11,16,17], indicating that a low IGFBP-1 concentration could serve as a marker of IR that is considered to be one of the important links between diabetes and cardiovascular disease. In this respect, this study has yielded interesting information with regard to IR. It was observed that IGFBP-1 levels are decreased in NGT subjects with IR as measured by HOMA-IR compared with NGT subjects without IR.

Liew et al [18] have reported that healthy glucose-tolerant Asian Indian subjects have an adverse combination of relative IR and low fasting IGFBP-1 levels, which may account for their higher risk of developing MS and T2DM. Our results corroborate this finding, as IGFBP-1 had a significant association with T2DM. We observe that subjects with MS had lower levels of IGFBP-1 compared with subjects without MS. It was also observed that IGFBP-1 levels decreased with increasing number of metabolic abnormalities, suggesting a possible dose-response relationship between lower IGFBP-1 levels and metabolic abnormalities. The lack of significant correlations between IGFBP-1 and triglycerides or LDL cholesterol in our study may be due to the small sample size of the study. However, this is consistent with another study that reported a lack of correlation between IGFBP-1 and triglycerides or LDL cholesterol [16].

One of the limitations of this study is the small sample size. Secondly, because of its cross-sectional nature, this study cannot establish a cause-effect relationship. The strength of the study is that it is a population-based study in Asian Indians in whom such data are not available.

In conclusion, this study reports that, among Asian Indians, low levels of circulating IGFBP-1 are seen with IR, T2DM, and MS.

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Conflict of Interest

Nil.

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