Serum IGFBP7 levels associate with insulin resistance and the risk of metabolic syndrome in a Chinese population

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Metabolic syndrome (MetS), one of the major public health concerns, is regarded as the “common soil” of incidence of common chronic diseases and may increase the risk of type 2 diabetes. The predominant underlying mechanism of MetS is insulin resistance (IR). Additionally, previous studies have indicated that IGFBP7 has high affinity of binding with insulin and might induce IR. The objective of this study was to firstly evaluate the associations of serum IGFBP7 levels with IR and MetS with a relatively large sample and population based design. In a population based MetS case-control study, HOMA-IR was used to evaluate the insulin sensitivity and serum IGFBP7 levels were determined with chemiluminescence-linked immunoassay. As a result, the subjects of MetS and IR had higher serum levels of IGFBP7 than control healthy subjects. High serum IGFBP7 levels increased the risk of MetS and IR. Serum IGFBP7 levels were also found to be significantly correlated with metabolic-associated parameters of Waist-to-hip ratio (WHR), HDL and LDL. These findings suggest that serum IGFBP7 levels are associated with IR and MetS, providing new insight into the mechanism of IR and Mets. IGFBP7 may be a potential interventional target for IR and Mets.

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increased the risks of common cancers including colon and rectum, lung, pancreas, liver kidney and female breast.15,16

Insulin-like growth factor binding proteins (IGFBPs) are a family of homogenous proteins and regulate the IGFs signaling pathway by binding with insulin and IGFs.17-18 IGFBP 1-6 have higher ability of binding affinity to IGFs and less to insulin and play important roles on regulating cell growth via the IGFs signaling pathway.19 However, different from the other six IGFBPs, the seventh of IGFBPs, IGFBP7, also known as IGFBP-rP1, MAC25, PSF, TAF, FSTL2 or PGI2-stimulating factor, has weak binding affinity to IGFs and relatively high affinity to insulin.20,21 IGFBP7 is a 30-kDa modular secreted protein with a N-terminal domain, including 11 cysteines, a heparin binding site, a Kazal-type trypsin inhibitor domain and a C-terminal Ig-like type C repeat, involved in multiple pathways mainly in an IGF-independent manner. Previous studies indicated that IGFBP7 expression was associated with tumor development and functions as tumor suppressor gene in cancers such as colon and rectum, breast, thyroid through the regulation of cell proliferation, cell adhesion, apoptosis, cellular senescence and angiogenesis.25-26 IGFBP7 is also involved in TGFβ signal pathway. However, in glioma, IGFBP7 may play as an oncogenic role.27 These studies suggested that IGFBP7 may play different roles in different cancers.

Due to the high affinity to insulin, IGFBP7 may interfere with biological response of insulin, subsequently induces IR and involves in the development of diabetes and cardiovascular diseases. Lopez-Bermejo et al. found increased serum IGFBP7 levels to be associated with IR.22 Kutsukake et al. observed hemodialysis patients with type 2 diabetes had higher serum IGFBP7 levels than the hemodialysis patients without type 2 diabetes.23 Recently, Gu, et al. found newly diagnosed type 2 diabetes had higher levels of IGFBP7 DNA methylation and low IGFBP7 may be associated with IR in type 2 diabetes.24 The findings from these studies indicated serum IGFBP7 might be associated with IR and diabetes. However, the sample sizes in those studies were relatively small and subjects restricted on diabetes patients. No previous study was found on the association of IGFBP7 with prediabetes such as MetS. So far, no convincing evidence was found. In our study, we had determined serum IGFBP7 levels of 1042 MetS patients and 1583 healthy control subjects from a cross-sectional survey on MetS. The objective of this study was to evaluate the associations of serum IGFBP7 with MetS and IR.

Methods

Subjects. A total of 2625 subjects including 1042 MetS patients and 1583 healthy control subjects of Chinese origin were recruited from XiaoShan cross-sectional survey on MetS in Hangzhou, Zhejiang Province, China in 2010. This community-based cluster sampling survey consisted of a questionnaire based epidemiological interview, a health examination and laboratory measurements. All the subjects of this investigation were Han’s Chinese and aged 21 to 75 years old. The case subjects in this study were MetS patients who were diagnosed according to the criteria of Chinese Diabetes Society (CDS). The MetS criteria of CDS includes: when a subject met three or more of the following four components: 1) obesity: Body Mass Index (BMI) ≥ 25 kg/m²; 2) fasting blood glucose (FG) ≥ 6.1 mmol/L or receiving antidiabetic medication; 3) fasting total triglyceride (TG) ≥ 1.7 mmol/L or males’ high density lipoprotein cholesterol (HDL) < 0.9 mmol/L or females’ HDL < 1.0 mmol/L; and 4) blood pressure (BP) ≥ 140/90 mmHg or receiving antihypertensive medication. Healthy control subjects were unrelated individual residents and selected from the subjects with no history of obesity, hyperglycemia, dyslipidemia, hypertension or diabetes mellitus. Participants who had cancer, chronic diseases of the heart, liver, lung or kidney, and other endocrine diseases were excluded. All participants were given and signed the written informed consent form.

Anthropometric measurements. Anthropometric indices, including weight, height, waist circumference (WC), hip circumference (HC) and BP were measured by well-trained investigators, following standard protocols. Height and weight were measured with the participants wearing light clothing and without shoes. WC was measured at the midpoint between the iliac crest and lowest rib. HC was measured at the widest part of the gluteal region with two feet together. BP was measured in a sitting position with a mercury sphygmomanometer after 15 minutes of rest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were reported as the average of three repeat measurements with 30-second rest intervals between measurements. BMI was calculated as the individual’s body weight in kilograms divided by the square of his or her height in meters. Waist to height ratio (WHtR) was calculated as WC in centimeters divided by height in centimeters. Waist-to-hip ratio (WHR) was calculated as HC in centimeters divided by height in centimeters.

Biochemical measurements. After a 12-hour overnight fast, blood samples were drawn to determine the serum levels of total cholesterol (TC), TG, low density lipoprotein cholesterol (LDL), HDL, insulin and FG with a biochemical auto-analyzer (Hitachi 7060, Tokyo, Japan).

Serum IGFBP7 levels were measured by chemiluminescence–linked immunoassay, which incorporated a polyclonal and a monoclonal anti-IGFBP7 antibody (R&D Systems Inc., Abingdon, UK). The decisive coefficient ($R^2$) of the standard curve was 0.9986. The average recovery rate was approximately 106.5%. The sensitivity of the assay was 0.32 ng/L.
categorized into IR and insulin sensitive (IS) with the value of the 75th percentage of HOMA-IR index partial correlation coefficient (rs).

such as age, gender and IR. Correlations between continuous variables were assessed by the spearman was used to compare the frequencies of differences for categorical variables. Odds ratio (OR) and 95%

variables and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test in control subjects as the cut off value.

mean

Basic characteristics of MetS and control subjects. Quantitative data were presented as Table 1.

P75) for TG, HDL, FG, insulin, HOMA-IR. BMI

Statistical analysis. Quantitative data were expressed as means ± standard deviations (SD) for normal distributions, as medians (inter-quartile range) for non-normally distributed variables. Non-normally distributed variables were square-root transformed before analysis. Qualitative data were presented frequencies. Homeostasis model of assessment was used to assess insulin resistance index (HOMA-IR) and calculated as: fasting serum glucose (mmol/L) × fasting serum insulin (μU/ml)/22.5. Subjects were categorized into IR and insulin sensitive (IS) with the value of the 75th percentage of HOMA-IR index in control subjects as the cut off value.

The t-test was used to compare the mean differences between two groups for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test was used to compare the frequencies of differences for categorical variables. Odds ratio (OR) and 95% confident interval (95% CI) was calculated with logistic model adjusted by potential confounding factors such as age, gender and IR. Correlations between continuous variables were assessed by the spearman partial correlation coefficient (r).

All statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was considered to be statistically significant. The study protocol was approved by the Institutional Review Board of School of Public Health, Zhejiang University and methods were carried out in accordance with the approved guidelines.

Results

The basic characteristics of the study population are shown in Table 1. The age (mean ± standard deviation) was 58.1 ± 9.3 years in case subjects and 52.5 ± 10.8 years in healthy controls (P < 0.001). 50.10% of subjects were males in MetS subjects and 47.80% in controls (P = 0.231). Therefore, the following analyses were carried out with adjustment of age and sex. MetS subjects had higher levels of BMI, WC, WHtR, HC, WHR, SBP, DBP, TC, TG, LDL, FG and fasting insulin than controls (all P < 0.001), and lower level of HDL (P < 0.001).

The distributions of serum IGFBP7 levels of the subjects by MetS and IR status are presented in Table 2. The median of serum IGFBP7 level in MetS patients was 45.80 ng/ml, which was significantly higher than that in healthy controls (35.80 ng/ml) (P < 0.001). Serum IGFBP7 levels were categorized into two groups (high and low groups) with the value of the 50th percentage in control subjects (35.80 ng/ml) as the cut off value. High serum IGFBP7 levels (≥35.80 ng/ml) were associated with a significantly increased risk of MetS with the adjusted OR of 2.758 (95% CI = 2.308 – 3.297) (Table 3). After additional adjustment with BMI, association of IGFBP7 with MetS remained significant with the OR of 3.993 (3.037, 5.250).

**Table 1.** Basic characteristics of MetS and control subjects. Quantitative data were presented as mean ± standard deviation for age, BMI, WC, WHtR, HC, WHR, SBP, DBP, TC and LDL, and median (P25, P75) for TG, HDL, FG, insulin, HOMA-IR. BMI = weight/height², WHtR = WC/height, WHR = WC/HC, FG = fasting blood glucose HOMA-IR index = insulin × FG/22.5. *independent t-test. χ² test. rank sum test.
IR status was evaluated with HOMA-IR index and categorized into IR and IS with the value of the 75th percentage of HOMA-IR index in control subjects (0.98) as the cut off value. The median of serum IGFBP7 levels in IR subjects was 40.45 ng/ml, which was significantly higher than that in control subjects (38.25 ng/ml) ($P < 0.001$) (Table 2). High serum IGFBP7 levels (≥35.80 ng/ml) were associated with a significantly increased risk of IR (OR = 1.240, 95% CI = 1.055–1.458) (Table 3). However, the significance with IR was not found after additional adjustment with BMI.

In order to analyze the relationship among these three things (IGFBP7, MetS case/ control status, and IR), we calculated the association of IGFBP7 with MetS modified by HOMA-IR, age, sex, the significance between IGFBP7 and MetS still remained with the OR of 3.497 (95%CI: 2.796-4.375).

Table 4 shows the correlations of serum IGFBP7 levels and metabolic related components. In healthy control subjects, after adjusted by sex and age, serum IGFBP7 levels were found to be negatively correlated with WC (rs = −0.138, $P < 0.001$), WHtR (rs = −0.151, $P < 0.001$), WHR (rs = −0.137, $P < 0.001$), SBP (rs = −0.086, $P = 0.001$), DBP (rs = −0.071, $P = 0.005$), HDL (rs = −0.121, $P < 0.001$), and positively with LDL (rs = 0.157, $P < 0.001$). In MetS subjects the negative correlations were observed between serum IGFBP7 level with WHR (rs = −0.080, $P = 0.012$) and HDL (rs = −0.116, $P < 0.001$), and the positive correlation between serum IGFBP7 level with LDL (rs = 0.157, $P < 0.001$) adjusted by sex and age and WHR (rs = −0.072, $P = 0.023$), HDL (rs = −0.117, $P < 0.001$) and LDL (rs = 0.156, $P < 0.001$) adjusted by age, sex and HOMA-IR.

**Discussion**

In present study, we determined serum IGFBP7 levels in 1042 MetS patients and 1583 healthy control subjects and found that the subjects with MetS and IR had higher levels of serum IGFBP7 than controls. Higher IGFBP7 increased the risk of MetS and IR. Serum IGFBP7 levels were also associated with some metabolic-associated parameters. The findings indicated that increased serum IGFBP7 levels might be one of the mechanisms of IR and MetS.

IGFBP7, also known as IGFBP-related protein 1, is a secreted glycoprotein and widely expressed in various human tissues\(^{20}\), including gastrointestinal tract, brain, lung and prostate. IGFBP7 has been

| Group | N | Median | P25 | P75 | $P$-value* |
|-------|---|--------|-----|-----|------------|
| MetS  |   |        |     |     |            |
| Control | 1575 | 35.80 | 28.70 | 46.40 | <0.001 |
| Case   | 1040 | 45.80 | 36.50 | 59.05 |          |
| HOMA-IR index$^3$ |   |        |     |     |            |
| <0.98 | 1420 | 38.25 | 30.30 | 50.53 | <0.001 |
| ≥0.98 | 1192 | 40.45 | 31.83 | 52.45 |          |

**Table 2.** Serum IGFBP7 levels in the subjects by MetS and IR status. *$P$ values calculated with the Mann-Whitney U test. $^3$categorized by the value of 75th percentage in control group.

| Group | N | IGFBP7-50$^3$ | OR1 (95% CI)$^*$ | OR2 (95% CI)$^*$ |
|-------|---|---------------|-----------------|-----------------|
| MetS  |   | low n (%) | high n (%) | $P$ |   |
| Control | 1575 | 786 (49.9) | 789 (50.1) | <0.001 | 1 | 1 |
| Case   | 1040 | 249 (23.9) | 791 (76.1) | 2.758 (2.308, 3.297) | 3.993 (3.037, 5.250) |
| HOMA-IR$^5$ |   |<0.98 |595 (41.9) |825 (58.1) |0.009 |1 |1 |
| ≥0.98 | 1192 | 438 (36.7) | 754 (63.3) | 1.240 (1.055, 1.458) | 0.951 (0.787, 1.150) |

**Table 3.** Associations of serum IGFBP7 levels with MetS and IR. $^3$categorized with the value (35.80 ng/ml) of 50th percentage in control group; $^*$$P$ value and OR1 (95% CI) were calculated with logistic regression adjusted by sex and age. $^*$OR2 (95% CI) were calculated with logistic regression adjusted by sex, age and BMI.

IR status was evaluated with HOMA-IR index and categorized into IR and IS with the value of the 75th percentage of HOMA-IR index in control subjects (0.98) as the cut off value. The median of serum IGFBP7 levels in IR subjects was 40.45 ng/ml, which was significantly higher than that in control subjects (38.25 ng/ml) ($P < 0.001$) (Table 2). High serum IGFBP7 levels (≥35.80 ng/ml) were associated with a significantly increased risk of IR (OR = 1.240, 95% CI = 1.055–1.458) (Table 3). However, the significance with IR was not found after additional adjustment with BMI.

In order to analyze the relationship among these three things (IGFBP7, MetS case/ control status, and IR), we calculated the association of IGFBP7 with MetS modified by HOMA-IR, age, sex, the significance between IGFBP7 and MetS still remained with the OR of 3.497 (95%CI: 2.796-4.375).

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Bonnet reported that postnatal overgrowth might be related to a dosage effect of the IGFBP7 gene. These findings indicated IGFBP7 might interfere the metabolism of serum lipids and energy. The correlation of WHtR, WHR) irrespectively of adjustment of HOMA-IR. Together with these evidences, these findings represented by a group of interrelated disorders, including central obesity, hypertension, derangement of glucose and lipid metabolism. Our results also indicated that IGFBP7 significantly associated with MetS and its effect on IR might be mediated by obesity. These findings indicated IGFBP7 might interfere the metabolism of serum lipids and energy. Bonnet reported that postnatal overgrowth might be related to a dosage effect of the IGFBP7 gene.

|                  | Control | Case |
|------------------|---------|------|
|                  | $r^2$   | P    | $r^2$ | P    | $r^2$ | P    |
| WC (cm)          | $-0.138$ | $<0.001$ | $-0.103$ | $<0.001$ | $-0.056$ | $0.078$ | $-0.041$ | $>0.10$ |
| WHR             | $-0.151$ | $<0.001$ | $-0.117$ | $<0.001$ | $-0.074$ | $>0.10$ | $-0.059$ | $0.064$ |
| HC (cm)          | $-0.079$ | $0.002$ | $-0.047$ | $0.067$ | $-0.003$ | $>0.10$ | $0.011$ | $>0.10$ |
| WHR             | $-0.137$ | $<0.001$ | $-0.109$ | $<0.001$ | $-0.080$ | $0.012$ | $-0.072$ | $0.023$ |
| BMI (kg/m2)      | $-0.085$ | $0.001$ | $-0.041$ | $>0.10$ | $-0.013$ | $>0.10$ | $0.005$ | $>0.10$ |
| SBP (mmHg)       | $-0.086$ | $0.001$ | $-0.060$ | $0.017$ | $0.050$ | $0.108$ | $0.055$ | $0.080$ |
| DBP (mmHg)       | $-0.071$ | $0.005$ | $-0.051$ | $0.043$ | $0.040$ | $>0.10$ | $0.041$ | $>0.10$ |
| TC (mmol/L)      | $0.011$ | $>0.10$ | $0.024$ | $>0.10$ | $0.050$ | $0.109$ | $0.055$ | $0.078$ |
| TG (mmol/L)*    | $-0.063$ | $0.013$ | $-0.032$ | $>0.10$ | $0.009$ | $>0.10$ | $0.018$ | $>0.10$ |
| HDL (mmol/L)     | $-0.121$ | $<0.001$ | $-0.114$ | $<0.001$ | $-0.116$ | $<0.001$ | $-0.117$ | $<0.001$ |
| LDL (mmol/L)     | $0.164$ | $<0.001$ | $0.157$ | $<0.001$ | $0.157$ | $<0.001$ | $0.156$ | $<0.001$ |
| FGF (mmol/L)**  | $-0.065$ | $0.010$ | $-0.009$ | $>0.10$ | $-0.013$ | $>0.10$ | $0.017$ | $>0.10$ |
| Insulin (µU/ml)  | $-0.127$ | $<0.001$ | $0.009$ | $>0.10$ | $-0.064$ | $0.040$ | $-0.017$ | $>0.10$ |
| HOMA-IR         | $-0.132$ | $<0.001$ | $-0.063$ | $0.044$ |

Table 4. Correlations between serum IGFBP7 levels and metabolic-associated parameters. *Spearman correlation adjusted by sex and age. **Spearman correlation adjusted by sex, age and HOMA-IR.
Further, interactions of IGFBP7 with the IGF system possibly resulted in hyperinsulinemia\textsuperscript{23,37}. More importantly, IR may lie at the heart of the MetS\textsuperscript{38}, differentially contributing to MetS phenotype\textsuperscript{39}. Serum IGFBP7 was also associated with the other metabolic components. The associations of serum IGFBP7 were firstly documented with WHR, HDL and LDL both in the subjects of Mets and control and adjusted by sex, gender or additional HOMA-IR. We also found significant associations with WC, WHR, SBP, DBP in control subjects. BMI and DBP had been found to be significant in previous study\textsuperscript{28,40}. These associations have been modified potential confounders such as age, gender or additional HOMA-IR. Although the mechanisms of these associations remain uncover, these findings indicate IGFBP7 might associated the multiple biological effects and it may be an interventional target for multiple metabolic alterations. Based our previous studies, we have found several small molecular disruptors could reduce the capability of combination of IGFBP7 with insulin and then lessen IR status (unpublished data). These findings might provide a new strategy for blocking the progression of Mets and diabetes and improving metabolic condition.

After adjustment of age, sex and HOMA-IR, IGFBP7 also associated with MetS. This result indicated that IGFBP7 might be an independent predictor for MS. Together with the evidences with the associations of IGFBP7 with metabolic components, These findings indicated that IGFBP7 independently associated with MetS and its biological effects might be mediated by obesity, LDL and HDL etc.

In summary, we found that serum IGFBP7 levels are associated with IR and MetS and indicated that increased serum IGFBP7 might be one of circulating mechanism of MetS. IGFBP7 might be a new interventional target for IR and Mets.

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Author Contributions

M.L. and Y.Z. conceived and designed the project. M.W. and Y.L. performed laboratorial determination. J.L., H.W., L.C. and D.Z. participated in the epidemiological investigation. Y.L. and J.L. carried out data analysis and Y.Z., Y.L. drafted the manuscript. H.G. and M.L. discussed and refined the manuscript. All authors approved the final version of the paper for submission.

Additional Information

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