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**IGF-I/IGFBP- 3 Ratio:
a Mechanistic Insight into the Metabolic Syndrome**

Short Running Title

Sierra-Johnson/ IGF-I/IGFBP-3 Ratio and Cardiometabolic Disease

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Abstract

Recent reports suggest that insulin-like growth factor 1 (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP-3) have independent and opposing mechanistic effects on insulin. Our aim was to assess the relationship between the IGF-I/IGFBP-3 ratio and the metabolic syndrome. We examined 3,281 subjects (1,463 men; 1,818 women aged 20 to 49 years), otherwise healthy adults, who participated in the Third National Health and Nutrition Examination Survey (NHANES III) and had the recently released measurements of IGF-I and IGFBP-3. Insulin resistance was estimated using the computer homeostatic model assessment (HOMA-2). The updated ATP-III definition of the metabolic syndrome was used. We applied adjusted logistic and linear regression models. After adjusting for age and race, men and women in the lowest quartile of the IGF-I/IGFBP-3 ratio were 3 times more likely to meet the ATP-III definition of the metabolic syndrome and twice as likely to be insulin resistant. Mean values of the IGF-I/IGFBP-3 ratio decreased significantly as the number of metabolic syndrome components increased (ANOVA $p < 0.0001$). Area under **the receiver operating characteristics** curve for detecting insulin resistance using the IGF-I/IGFBP-3 ratio was 0.760, significantly improving upon either protein alone ($p = 0.01$). In conclusion, the IGF-I/IGFBP-3 ratio is significantly associated with the metabolic syndrome. Calculating the ratio of these two proteins may provide insight into the metabolic syndrome clustering phenomenon.

Keywords: IGF-I/IGFBP-3 ratio, IGF-I, IGFBP-3, metabolic syndrome, insulin resistance, NHANES

Epidemiological studies have suggested that higher insulin-like growth factor-1 (IGF-I) concentrations are independently associated with a reduced risk of cardiovascular disease.¹⁻³ Low IGF-I concentrations have been reported to contribute to processes leading to plaque weakening, plaque rupture, and acute coronary events.⁴⁻⁵ Furthermore, recent evidence suggests that low levels of IGF-I are related to the development of type 2 diabetes.^{6,7} IGF-I may play an important role in glucose homeostasis by enhancing glucose uptake and improving insulin sensitivity.

The biological effects of IGF-I are modulated by IGF-binding proteins such as insulin-like growth factor binding protein 3 (IGFBP-3), which is the major binding protein (>80%) for IGF-I and circulates throughout the body controlling the access of IGF-I to cell surface receptors, thus **potentially** playing an important role in glucose metabolism.⁸⁻¹⁶ Furthermore, a recent animal study showed that IGF-I and IGFBP-3 have marked, opposing and independent physiological effects on peripheral insulin action via central mechanisms, demonstrating the first acute in-vivo effect of IGFBP-3 on insulin.¹⁷ Measurement of IGFBP-3 could be used as a surrogate for free IGF-I.^{3,16}

While low IGF-I serum levels detect subjects at increased cardiovascular risk, high IGFBP-3 levels detect subjects that are prone to be insulin resistant.^{12,15,16} Therefore the IGF-I/IGFBP-3 ratio may represent a balance between cardiac and metabolic risk, raising the possibility of identifying subjects at particular high cardiometabolic risk that could shed some insight into the risk factor clustering pathophysiology.

Given the recently released data from the Third National Health and Nutrition Examination Survey (NHANES III) of IGF-I and IGFBP-3, we identify a unique opportunity to study the relationship of the IGF-I/IGFBP-3 ratio to increased cardiometabolic risk. The aim of the present study was to assess whether the IGF-I/IGFBP-3 ratio was related to the metabolic syndrome. In particular we posed the question of whether the IGF-I/IGFBP-3 ratio would improve upon the ability to predict high cardiometabolic risk than with either IGF-I or IGFBP-3 considered alone. To accomplish these aims we used an otherwise healthy representative sample of the US population aged 20-49 years old.

Research Design and Methods

Study Sample

NHANES III is a representative sample of the US non-institutionalized civilian population. It consists of a periodic survey conducted by the United States National Center for Health Statistics designed to provide an estimate of the health of the nation. NHANES III covers the years 1988 to 1994. Detailed methods used in NHANES III are available for public access on the internet and have been published elsewhere.^{18,19}

We limited the present analysis to recently released data (October 2006) from NHANES on subjects who had serum measurements of both IGF-I and IGFBP-3 (n=6061) and to non-pregnant women aged ≥ 20 years and < 50 years (to avoid hormonal differences due to menopause), who attended a morning medical examination and who had fasted ≥ 8 hours. We excluded data for those judged by their interviewer to have provided unreliable

data, those with missing data for the metabolic syndrome components and subjects who had self reported diabetes, myocardial infarction and/or stroke (to study an otherwise representative healthy population). This resulted in a final analytic sample of 3,281 subjects (1,463 men; 1,818 women). We determined the insulin sensitivity index by using the updated computer model of the homeostatic model assessment 2 (HOMA-2) index.²⁰ Insulin resistance was defined as the upper quartile of HOMA-2 index distribution.

Measurement of IGF-I and IGFBP-3

IGF-I and IGFBP-3 were measured using standard laboratory protocols by Diagnostic Systems Laboratories Inc (DSL, Webster TX). Details of quality control measures are described elsewhere.²¹

Metabolic Syndrome Definition

We used the updated Adult Treatment Panel III (ATP-III) definition of the metabolic syndrome.²² This was met when 3 or more of the following criteria were present: waist circumference ≥ 102 cm (40 in) in men and ≥ 88 cm (35 in) in women; HDL < 1.03 mmol/L (40 mg/dl) in men and < 1.30 mmol/L (50 mg/dl) in women or specific treatment for this lipid abnormality; triglycerides ≥ 1.7 mmol/L (150 mg/dl) in men and women or specific treatment for this lipid abnormality; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg in men and women or treatment of previously diagnosed hypertension; and fasting glucose ≥ 5.6 mmol/L (100 mg/dl) in men and women.

Statistical Analysis

The analysis of the NHANES III data was conducted following the guidelines in ‘Analytic and Reporting Guidelines: The Third National Health and Nutrition Examination Survey, NHANES III (1988 to 1994)’. We defined “low IGF-I/IGFBP-3 ratio” as the lowest sex-specific quartile of the IGF-I/IGFBP-3 ratio (≤ 0.06 in men; ≤ 0.05 in women) and we then compared with the upper three quartiles and we defined the “normal IGF-I/IGFBP-3 ratio”

We applied logistic and multiple linear regression models adjusted for age and sex to determine the association between IGF-I/IGFBP-3 ratio and metabolic syndrome. Age, race and sex were always included as covariates. The predictive value of each component was assessed by comparing R^2 values of the models obtained from each group.

Incremental additive value was judged by the increase in R^2 obtained when IGF-I, IGBP-3 and IGF-I/IGFBP-3 ratio were added to the metabolic syndrome components.

To analyze the additional contribution of IGF-I, IGBP-3 and IGF-I/IGFBP-3 ratio to detect insulin resistance, we constructed receiver operating characteristics (ROC) curves, and to assess if the areas under the **receiver operating characteristics** curve (AUC) obtained using different predictors were significantly different, we used the method of Delong.²³ All analyses were performed using the SAS windows version and SUDAAN

9.0.3

Results

Descriptive Characteristics

Overall, subjects with low IGF-I/IGFBP-3 ratio were older and had on average higher mean values for BMI, waist circumference, triglycerides, fasting glucose, blood pressure levels, and HOMA2 index than subjects with a normal IGF-I/IGFBP-3 ratio. Also, the percentage of subjects who met the criteria for insulin resistance and the ATP-III metabolic syndrome were significantly higher in subjects with low IGF-I/IGFBP-3 ratio. In contrast, subjects with low IGF-I/IGFBP-3 ratio had significantly lower HDL-cholesterol than with normal IGF-I/IGFBP-3 ratio (Table 1).

Relationships of IGF-I, IGFBP-3 and IGF-I/IGFBP-3 ratio to the Metabolic Syndrome

Mean values of the IGF-I/IGFBP-3 ratio decreased significantly as the number of metabolic syndrome components increased (ANOVA $p < 0.0001$, panel A, Figure 1).

Despite the high correlation between IGF-I and IGFBP-3, there were significant differences in their respective correlations with the metabolic syndrome components. We found significant correlations between IGF-I/IGFBP-3 ratio and all metabolic syndrome components including HOMA-2 after adjusting for age, sex and race.

After adjusting for age and race, men in the lowest quartile of the IGF-I/IGFBP-3 ratio were 3.1 times more likely to meet the ATP-III definition of the metabolic syndrome and twice as likely to be insulin resistant. Women in the lowest quartile of the IGF-I/IGFBP-3 ratio were 3.6 times more likely to meet the ATP-III definition of the metabolic syndrome and twice as likely to be insulin resistant. In both sexes, the lowest quartile of the IGF-I/IGFBP-3 ratio provided significant odds ratios for the components of the metabolic syndrome (Table 2). To further evaluate the quantitative levels of the

component measures of the metabolic syndrome, we conducted multiple regression analyses in which the independent variable was the quantitative level of the IGF-I/IGFBP-3 ratio. After controlling for age, sex, race and HOMA-2, the IGF-I/IGFBP-3 ratio was still an independent predictor of all the metabolic syndrome components except for diastolic blood pressure (Table 3).

Diagnostic Accuracy to detect Cardiometabolic Risk

To evaluate the diagnostic accuracy of IGF-I, IGFBP-3 and IGF-I/IGFBP-3 ratio to detect subjects that were insulin resistant, we constructed ROC curves (Figure 2) Overall, the diagnostic accuracy when adding the IGF-I/IGFBP-3 ratio, as judged by the AUC, was improved to 0.760, compared to 0.661 for IGF-I and 0.688 for IGFBP-3 alone, $p=0.01$.

Discussion

The novel findings of this cross-sectional analysis of a representative multi-ethnic sample of the US civilian general population are that a low IGF-I/IGFBP-3 ratio was significantly associated with high cardiometabolic risk, specifically metabolic syndrome and/or insulin resistance. Also, that the IGF-I/IGFBP-3 ratio had a stronger association with all metabolic syndrome components than either IGF-I or IGFBP-3 alone. A low IGF-I/IGFBP-3 ratio was associated with an approximate threefold increased likelihood of having the metabolic syndrome in both men and women. Given the different and opposing mechanistic effects of IGF-I and IGFBP-3, these findings suggest for the first

time that the IGF-I/IGFBP-3 ratio may provide a potential pathway to that leads to the development of the risk factor clustering phenomenon. This pathway merits further exploration.

Mechanistic Considerations

IGFBP-3 binds to IGF-I in plasma, prolonging the half-life in the circulation and blocking its interactions with the IGF-I receptor.²⁴ At the tissue level, the affinity of IGFBP-3 for IGF-1 reduces the binding of cells to IGFBP-3, hence permitting free binding between IGF-I and its receptors.^{11,13} IGF-I homeostasis is complicated and the binding proteins form complexes with IGF-I to modulate its actions. IGFBP-3, which is regulated by GH and IGF-I, serves as the main reservoir for plasma IGF-I. Conversely, IGFBP-1 is mainly regulated by insulin and is thought to be an acute regulator of IGF-I. Depending on the metabolic condition, IGFB's either inhibits or potentiates IGF-I actions. IGFBP-1 is a dynamic regulator of free IGF-I, especially coming from the liver and has diurnal variation; conversely, IGFBP-3 is a slower, more stable regulator of free systemic IGF-I that does not show diurnal variation.¹⁶

Experimental infarction models suggest that IGF-I may promote survival of myocytes exposed to ischemic injury in part by enhancing glucose uptake.²⁵⁻²⁶ Also, TNF- α reduces IGF-I and increases IGFBP-3 in vascular smooth muscle cells, which may in turn decrease cell survival in atherosclerotic plaques, promoting plaque rupture leading to the development of the atherosclerotic process.²⁷

Regarding IGFBP-3 and its role in the pathogenesis of cardiometabolic disease, previous studies have shown divergent results. Both high and low serum IGFBP-3 concentrations have been related to cardiovascular disease.^{16,28-29} In our study, high serum IGFBP-3 concentrations were associated with the metabolic syndrome and insulin resistance; however, this issue remains controversial; as there are factors known to affect IGFBP-3 concentrations such as age, cardiometabolic status, time the blood sample is taken and/or dietary factors.³⁰ Future studies should aim at standardizing measuring conditions to have valid comparisons between different studies.

Strengths and Limitations

An important limitation of our study is the cross-sectional design that does not allow us to determine causality. Another important limitation is that we did not analyze IGFBP-1 because it was not available from NHANES III. A strength of our study is the use of a US national representative sample with a large sample size. NHANES was designed with the aim that the results of this analysis are generalizable to all persons in the US. NHANES uses a stratified multistage probability sampling design to produce estimates generalizable to the US population.

Practical Implications

This study adds to a growing body of evidence linking the IGF system to cardiovascular risk in both men and women.³¹ Understanding the complex pathways that lead to the metabolic cluster-phenomenon and cardiovascular disease is paramount. A low IGF-I/IGFBP-3 ratio suggests that increased IGFBP-3 reduces the availability of IGF-I; thus, detecting subjects at a particular high cardiometabolic risk that would otherwise be missed. The ability of a low IGF-I/IGFBP-3 ratio to detect subjects at high cardiovascular risk demands prospective investigation. Its use should be evaluated to determine intervention effects or disease progression in clinical studies. Clinical utility would have to await confirmation in longitudinal studies of cardiovascular disease endpoints and wide availability of inexpensive, well standardized assays. Also, there might be some future therapeutical implications due to the recent introduction of a new complex in which IGF-I is bound to IGFBP-3, and has been found to be safe and efficacious in humans and it is being developed as part of new diabetic therapeutics.^{8,32}

Conclusions

In conclusion, we have found that the IGF-I/IGFBP-3 ratio is significantly associated with the metabolic syndrome. A low IGF-I/IGFBP-3 ratio may provide a mechanistic insight into the metabolic pathways among the different cardiometabolic entities.

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Table 1. Descriptive characteristics

Variables	Normal IGF-I/IGFBP-3 ratio M± SD (n=2,462)			Low IGF-I/IGFBP-3 ratio M± SD (n=819)		
	Pooled	Men	Women	Pooled	Men	Women
Age (yrs)	32 ±8	32 ±8	32 ±8	36 ±8*	36 ±8	36 ±8
BMI (kg/m ²)	26.2 ±5	26.1 ±4	26.4 ±6†	28.7 ±6*	27.9 ±5	29.4 ±7†
Females n(%)	1364(55)	-	-	454 (55)	-	-
Race-Ethnicity n(%)						
Non-Hispanic white	787 (75)	355 (77)	432 (72)	264 (75)	110 (74)	154 (76)
Non-Hispanic black	829 (12)	334 (10)	495 (14)	198 (10)	91 (11)	107 (10)
Mexican-American	749 (6)	365 (6)	384 (6)	325 (8)	150 (9)	175 (7)
Other	97 (7)	44 (7)	53 (8)	32 (7)	14 (6)	18 (7)
<i>Metabolic syndrome components</i>						
Waist circumference (cm)	88 ±14	91 ±12	86 ±14†	95 ±14*	96 ±13	94 ±15†
Triglycerides (mmol/L)	1.21 ±0.7	1.36 ±0.9	1.09 ±0.6†	1.65 ±1.2*	1.80 ±1.4	1.52 ±1.1†
HDL-cholesterol (mmol/L)	1.30 ±0.3	1.21 ±0.3	1.38 ±0.3†	1.26 ±0.3*	1.18 ±0.3	1.32 ±0.4†
Fasting glucose (mmol/L)	5.15 ±0.4	5.31 ±0.4	5.02 ±0.5†	5.29 ±0.5*	5.41 ±0.4	5.20 ±0.5†
Systolic blood pressure (mmHg)	116 ±13	121 ±12	113 ±13†	120 ±15*	123 ±13	118 ±15†
Diastolic blood pressure (mmHg)	73 ±11	76 ±11	72 ±10†	76 ±12*	79 ±12	74 ±12†

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HOMA/2	1.16 ±0.6	1.14 ±0.6	1.17 ±0.6†	1.38 ±0.10*	1.31 ±0.8	1.44 ±0.8†
Insulin resistance, n(%)	424 (17)	167 (15)	257 (18)†	232 (28)*	89 (24)	143 (31)†

* p<.01 for normal vs. low IGF-I/IGFBP-3 ratio, † p< .05 for differences between sexes within each group. IGF-I/IGFBP-3 was divided in sex-specific groups with normal and with low values (≤0.06 in men; ≤0.05 in women).

Abbreviations: Insulin-like growth factor 1, IGF-I; Insulin-like growth factor binding protein 3, IGFBP-3; High density lipoprotein, HDL-cholesterol; Homeostasis model assessment, HOMA-2.

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Table 2. Age and race adjusted logistic regression showing the association between low IGF-1/ IGFBP-3 ratio and individual components of the metabolic syndrome, metabolic syndrome as a definition and insulin resistance.

Parameter	Men N=1,463		Women N=1,818	
	$\beta \pm SE$	OR (95%CI)	$\beta \pm SE$	OR (95%CI)
<i>ATP-III Metabolic Syndrome Components</i>				
High Waist circumference	0.354 \pm 0.10	2.03 (1.3-3.1)†	0.570 \pm 0.07	3.13 (2.3-4.2)*
High Triglycerides	0.477 \pm 0.09	2.59 (1.8-3.8)*	0.610 \pm 0.10	3.39 (2.2-5.2)*
Low HDL-Cholesterol	0.252 \pm 0.09	1.65 (1.2-2.4) †	0.192 \pm 0.07	1.47 (1.1-2.0)†
High Fasting Glucose	0.221 \pm 0.09	1.56 (1.1-2.2) †	0.320 \pm 0.11	1.89 (1.2-2.9)†
High Blood Pressure	0.216 \pm 0.08	1.54 (1.1-2.2)†	0.145 \pm 0.10	1.33 (0.9-2.1)
<i>Definitions</i>				
ATP-III Metabolic syndrome	0.572 \pm 0.11	3.14 (2.0-5.1)*	0.640 \pm 0.10	3.60 (2.4-5.5)*
Insulin Resistance	0.366 \pm 0.11	2.08 (1.3-3.3)*	0.379 \pm 0.09	2.14 (1.5-3.0)*

* P<0.001, †P<0.05

Abbreviations: Insulin-like growth factor 1, IGF-I; Insulin-like growth factor binding protein 3, IGFBP-3; High density lipoprotein, HDL-cholesterol; Homeostasis model assessment, HOMA-2.

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Table 3. Adjusted* multiple linear regression models for IGF-I/ IGFBP-3 ratio and the metabolic syndrome components

Parameter	$\beta \pm SE$	t Ratio	P	Additional R ²
<i>Metabolic Syndrome Components</i>				
Waist circumference	-104.76 \pm 9.69	-10.81	<0.0001	0.03
Triglycerides	-8.083 \pm 0.79	-10.20	<0.0001	0.03
Systolic blood pressure	-26.271 \pm 11.84	-2.22	0.026	0.01
Diastolic blood pressure	-10.054 \pm 9.56	-1.05	0.293	NS
HDL-Cholesterol	0.781 \pm 0.30	2.54	0.011	0.01
Fasting glucose †	-1.195 \pm 0.39	-3.04	0.002	0.02

*Adjusted for age, sex, race and HOMA2 † Adjusted for age, sex, race and fasting insulin

Abbreviations: Insulin-like growth factor 1, IGF-I; Insulin-like growth factor binding protein 3, IGFBP-3; High density lipoprotein, HDL-cholesterol; Homeostasis model assessment, HOMA-2.

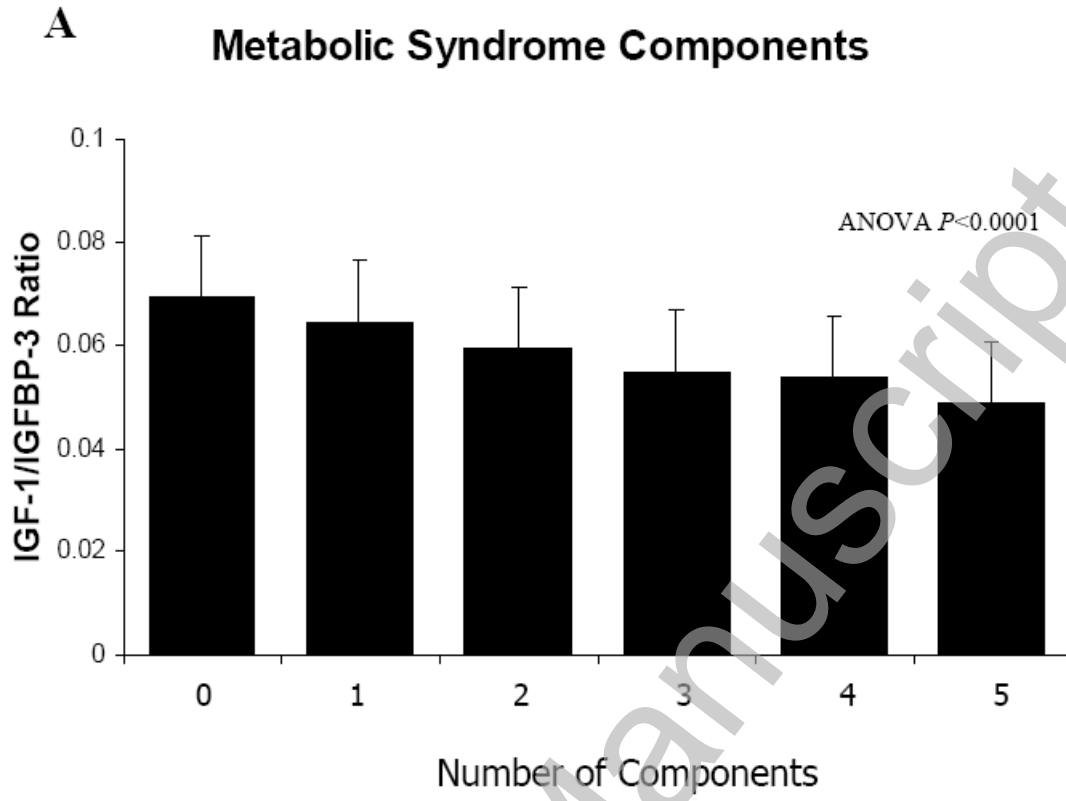
Legend to Figures

Figure 1. IGF-I/IGFBP3 ratio distribution according to the number of metabolic syndrome components.

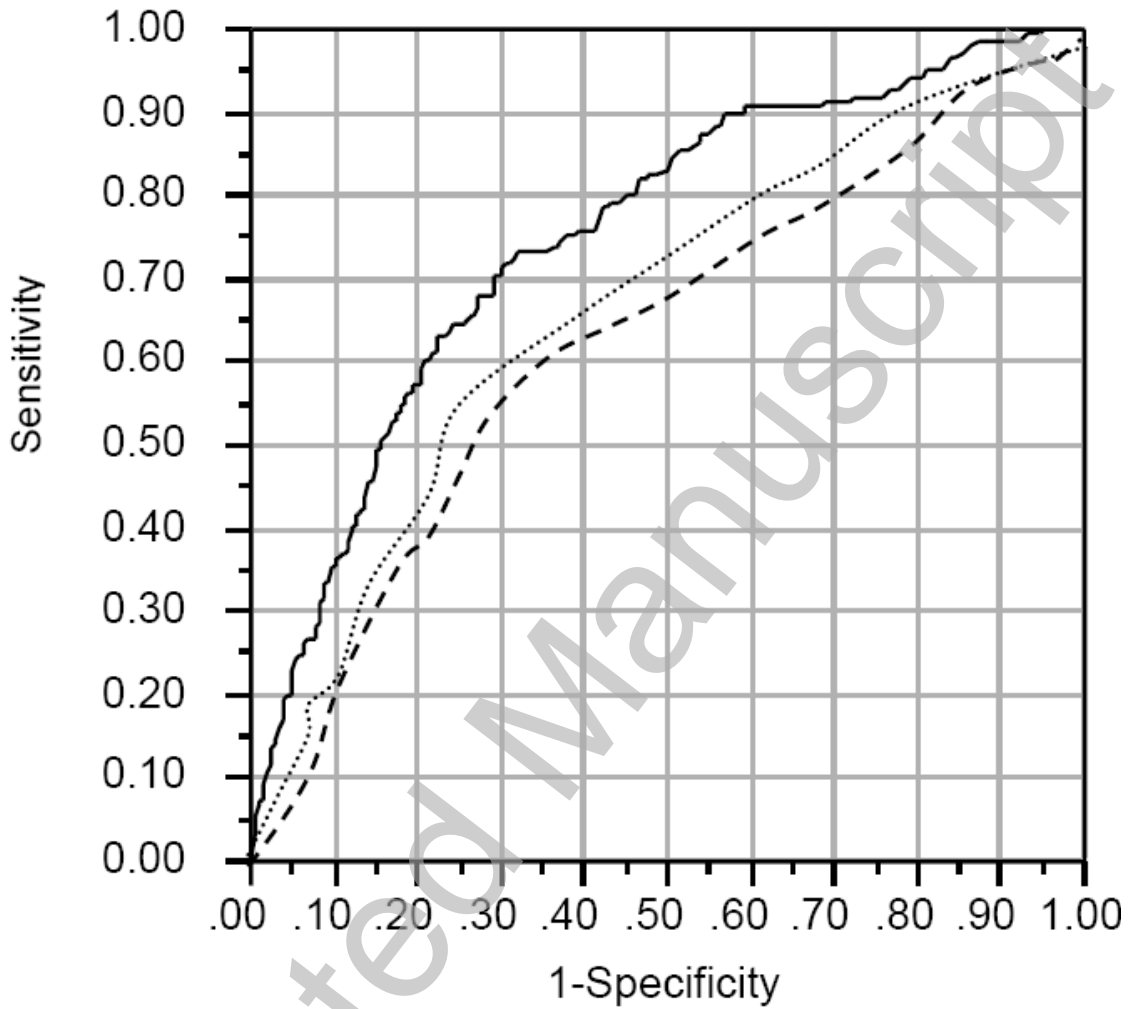
Figure 2. Receiver operating characteristics curves between IGF-I, IGFBP3, and IGF-I/IGFBP3 ratio to detect subjects that were insulin resistant.

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Insulin Resistance



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