J. Endocrinol. Invest. 35: 925-929, 2012
DOI: 10.3275/8511

# Beyond waist circumference in an adult male population of Southern Italy: Is there any role for subscapular skinfold thickness in the relationship between insulin-like growth factor-I system and metabolic parameters?

S. Savastano[1], A. Barbato[2], C. Di Somma[3], B. Guida[4], G. Pizza[1], L. Barrea[2], S. Avallone[2], M. Schiano di Cola[2], P. Strazzullo[2], and A. Colao[1]

[1]Division of Endocrinology, Department of Molecular and Clinical Endocrinology and Oncology; [2]Department of Clinical and Experimental Medicine, University Federico II of Naples; [3]IRCCS SDN Foundation; [4]Physiology Nutrition Unit, Department of Neuroscience, University Federico II of Naples, Naples, Italy

**ABSTRACT.** ***Background:*** **Apart from waist circumference, other adiposity measures, such as subscapular skin fold (SST), arouse growing interest due to their relationship to metabolic complications and cardiovascular risk. The IGF-I system is deregulated in obese subjects in proportion to their degree of visceral adiposity.** ***Aim:*** **To examine the association among IGF-I, IGF-binding protein (BP)-1 and -3 levels and different measures of adiposity in a sample of adult male population in Southern Italy.** ***Materials and methods:*** **A complete database for this analysis was available for 229 (age range 50-82 yr) participating at 2002-2004 Olivetti Heart Study follow-up.** ***Results:*** **After adjustment for age, IGF-I was inversely associated with body mass index (BMI) and waist circumference ($p<0.05$). IGFBP-1 was inversely associated with BMI, waist circumference, SST, homeostasis model assessment (HOMA) index, fat mass. HOMA index, age, and SST significantly predicted the IGFBP-1 plasma levels, with 24% of IGFBP-1 variability explained at a linear regression analysis.** ***Conclusions:*** **IGFBP-1 inversely correlated to adiposity and HOMA index. Among adiposity indexes, SST was the best predictor of IGFBP-1 levels. The evaluation of some components of the IGF system, and simple measures of body adiposity, such as SST, may represent a further tool to better evidence phenotype profiles associated to the pathogenetic mechanism of cardiovascular risk factor clustering in male adults.**

**(J. Endocrinol. Invest. 35: 925-929, 2012)**


## INTRODUCTION

Large epidemiological studies have evidenced that the subscapular skinfold thickness (SST), a simple measure of truncal subcutaneous fat, might represent a better and more direct measure of body adiposity than body mass index (BMI) (1, 2), although with a high variability depending on differences in dietary intake and physical activity (3). The influence of excess truncal subcutaneous fat on insulin sensitivity has been reported to be similar to that of waist circumference in some ethnic groups. Thus, SST was also included as a defining anthropometric parameter of the metabolic syndrome (MS) in Asian Indians, particularly in South Asians (4).

IGF-I as well as its most abundant binding proteins (BP) IGFBP-1 and IGFBP-3, the main components of the IGF-I system, are deregulated in proportion to the degree of visceral adiposity (5-8). In that, a possible pathogenetic role of IGF-I and its BP has been proposed in the past few years in aging (9), obesity (10), insulin resistance (IR) (11) and Type 2 diabetes (T2DM) (12, 13), MS (14, 15) and cardiovascular disease (CVD) (16, 17). We also previously reported that lower IGF-I levels, age-normalized, are associated with increased prevalence of severe hypertension and T2DM in a population of healthy subjects (18).

To our knowledge, there have been no attempts to evaluate the SST in an Italian population in relation to IGF system in the setting of cardiovascular risk.

We took advantage of the Olivetti Heart Study (OHS) database, an epidemiological investigation of metabolic, nutritional, and genetic precursors of CVD in an occupational-based sample of an adult male population in Southern Italy to examine the relationships among IGF-I, IGFBP-1 and -3, anthropometric and biochemical parameters of MS.

## MATERIALS AND METHODS

### *Population*

The OHS population is given by the male workforce of the Olivetti factories of Pozzuoli (Naples) and Marcianise (Caserta). The general characteristics of the study and its methodological procedures have been previously described (19, 20). The local Ethics Committee approved the study protocol, and participants provided their informed consent to participate. Among 994 subjects (age range 32-82 yr) participating at Olivetti Heart Study, examined between November 2002 and May 2004, a complete database for IGF-I, IGFBP-1, and IGFBP-3 were available in 229 subjects.

A fasting venous blood sample was obtained for determination of study biochemical variables. The blood specimens were im-

Key-words: IGF-I, IGFBP, body composition, subscapular skinfold thickness.

Correspondence: S. Savastano, MD, PhD, Department of Molecular and Clinical Endocrinology and Oncology, Division of Endocrinology, University Federico II of Naples, via S. Pansini 5, 80131 Naples, Italy.

E-mail: sisavast@unina.it

Accepted June 4, 2012.

First published online July 9, 2012.

mediately centrifuged and stored at –70 C until analyzed. Serum glucose, total, HDL-, and LDL-cholesterol, triglycerides, creatinine were measured by automated methods (Cobas-Mira, Roche, Milan, Italy). Serum insulin concentration was measured by radioimmunoassay (Insulina Lisophase, Technogenetics, Milan, Italy). Insulin sensitivity was estimated by the homeostasis model assessment (HOMA) index which is the product of fasting plasma insulin (μU/ml) and fasting plasma glucose (mmol/l)/22.5, as described by Matthews et al. (21).

Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, Texas, USA). The International Reference Preparation (IRP) used in the calibration of the IGF-I assay was WHO second 87/518. The sensitivity of the assay was 0.8 μg/l. The normal IGF-I range 41-60, and over 60-yr-old subjects was 100-300, and 78-260 μg/l, respectively. The intra-assay coefficients of variation (CV) were 3.4, 3.0, and 1.5% for low, medium, and high points on the standard curve, respectively. The interassay CV were 8.2, 1.5, and 3.7 % for low, medium, and high points on the standard curve, respectively. IGFBP-1 and IGFBP-3 levels were measured by two enzyme-linked immunosorbent assay (Diagnostic System Laboratories Inc, Webster, Texas, USA). The IGFBP-1 assay had a sensitivity of 0.04 μg/l; the intra- and interassay CV were 9.6, 9.5, and 7.3% for the low, medium, and high points of the curve, respectively; the interassay CV were 11.4, 10.4, and 8.2% for the low, medium, and high points of the curve, respectively. IGFBP-3 reference values for adult male population were 1500-4600 μg/l. The IGF-I/IGFBP-3 ratio, an approximation of the free fractions of IGF-I, was estimated in order to get a better understanding of the relative concentration changes of IGF-I and IGFBP-3 levels. The values for the molecular mass of IGF-I and IGFBP-3 used for the calculation were 7649 Da and 28 500 Da, respectively (22).

### *Anthropometric indexes*

Body weight and height were measured on a standard beam balance scale. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest centimeter. BMI was calculated as weight (kg) divided by the height square ($m^2$). Waist circumference was measured at the umbilicus level with the subject standing erect with the abdomen relaxed, arms at the sides and feet together. The measurements were performed to the nearest 0.1 cm with a flexible inextensible plastic tape. SST was measured just below the inferior angle of the scapula at 45° to the vertical using a Lange skinfold calliper (Beta Technology Inc., Santa Cruz, CA, USA).

### *Bioelectrical impedance analysis*

Body composition was determined by Bioelectrical Impedance Analysis (BIA). Resistance and reactance were measured by a single investigator with a single-frequency 50 kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Firenze, Italy) according to the standard tetrapolar technique, with the subject in supine position and the electrodes placed on the dorsal surface of the right foot and ankle, and right wrist and hand. The body composition was calculated from bioelectrical measurements and anthropometric data by applying the software provided by the manufacturer, which incorporated validated predictive equations for total body water, fat mass (FM) and free FM, and extra-cellular water, while soft tissue hydration was evaluated as impedance vectors in the Resistance-Reactance Graph by BIA Vector as previously reported (23).

Table 1 - *Characteristics of study population (no.=229*).*

| | Mean | Range |
|---|---|---|
| IGF-I (μg/l) | 155.5 | 30.0-418.8 |
| IGFBP-1 (μg/l) | 16.7 | 0.14-133.4 |
| IGFBP-3 (μg/l) | 3868.8 | 1550-4620 |
| Age[a] (yr) | 61.6 | 50.1-81.6 |
| Free fat mass % | 75.2 | 64.1-83.7 |
| Fat mass % | 24.8 | 16.4-35.9 |
| BMI (kg/m$^2$) | 27.1 | 18.8-35.7 |
| Waist circumference (cm) | 97.6 | 65.0-126.4 |
| SST (mm) | 21.7 | 7.8-43.2 |
| Systolic blood pressure (mmHg) | 138.2 | 99.0-192.0 |
| Diastolic blood pressure (mmHg) | 87.9 | 62.0-116.0 |
| Total cholesterol (nmol/l) | 57.05 | 2.69-8.13 |
| HDL-cholesterol (nmol/l) | 1.24 | 0.56-2.48 |
| Triglycerides (nmol/l) | 1.44 | 0.29-3.77 |
| Fasting glucose (nmol/l) | 5.63 | 3.66-15.65 |
| Fasting insulin[a] (mUI/ml) | 9.1 | 1.6-38.3 |
| HOMA index[a] | 1.9 | 0.89-15.5 |

The complete database among participants at Olivetti Heart Study examined between November 2002 and May 2004 (Ref. 19-20 in the text) were available in 229 subjects.*Two diabetic participants were treated with insulin. IGFBP1: IGF-binding protein-1; IGFBP3: IGF-binding protein-3; BMI: body mass index; SST: subscapular skinfold thickness; HOMA: homeostasis model assessment. [a]Log-transformed values.

### *Statistical analysis*

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS-PC version 11; SPSS Inc., Chicago, Illinois, USA). As the distributions of age, insulin, HOMA index, deviated significantly from normality, they were normalized by log transformation and log-transformed values were used in the analysis. Results were expressed as means and range or 95% confidence intervals (CI) unless otherwise indicated. Two-sided *p*-values <0.05 were considered statistically significant. Multiple linear regression analyses or analyses of covariance were used to evaluate the relationship of various determinants with IGF-I or IGFBP-1.

Linear regression analysis and analysis of covariance were used to evaluate the relationship of anthropometric and biochemical variables to IGFBP-1 levels, accounting for the effect of confounders.

## RESULTS

The main characteristics of the study population are given in Table 1. Obesity, hypertension, and T2DM were respectively present in 18.3%, 63.2%, and 14.0% of participants. There were 9.2% of subjects with T2DM on current treatment, of them two were treated with insulin. The results were not affected by exclusion of these two subjects from the analysis. There were not participants affected by severe kidney failure (glomerular filtration rate range from 30 to 115 ml/min according to Cockroft and Gault formula) or severe liver impairment. A normal hydration status was found in all the study participants according to the BIA Vector analysis.

After adjustment for age, IGF-I plasma levels were inversely associated with BMI and waist circumference ($p<0.05$) (Table 2). IGFBP-1 plasma levels were inversely

Table 2 - *Correlations between anthropometric and metabolic variables, IGF-I, IGF-binding protein (IGFBP)-1 and IGFBP-3.*

| | IGF-I | *p* | IGFBP-1 | *p* | IGFBP-3 | *p* |
|---|---|---|---|---|---|---|
| BMI (kg/m²) | –0.146 | 0.028 | –0.319 | <0.001 | 0.076 | ns |
| Waist circumference (cm) | –0.142 | 0.033 | –0.303 | <0.001 | –0.029 | ns |
| SST (cm) | –0.038 | ns | –0.310 | <0.001 | 0.040 | ns |
| Fat mass (%) | –0.125 | ns | –0.171 | 0.010 | –0.051 | ns |
| HOMA index[a] | –0.102 | ns | –0.406 | <0.001[b] | –0.087 | ns |
| Fasting insulin[a] (mUI/ml) | –0.087 | ns | –0.365 | <0.001[b] | –0.077 | ns |

[a]log-transformed values; [b]expressed as Spearman rho coefficient. Correlations between IGF-I system, anthropometric and metabolic measurements in study population (no.=229). Bivariate correlations between variables accounting for age were examined using Pearson's correlation coefficient and their values are singularly evidenced. BMI: body mass index; SST: subscapular skinfold thickness; HOMA: homeostasis model assessment.

associated with BMI, waist, SST circumference, FM, HOMA index, insulin ($p<0.05$). No significant associations were observed with IGFBP-3 or with IGF-I/IGFBP-3 and the study variables.

To evaluate the relative influence of adiposity's measures on IGFBP-1 plasma level accounting for potential confounders, each anthropometric factor was alternatively introduced in a multiple linear regression equation with age and HOMA index as covariates.

To allow a comparative evaluation of the effects of these different factors on IGFBP-1, z-scores were calculated for each factor and used for the analysis. The results of these analyses are showed in Figure 1, which provides the changes in IGFBP-1 plasma levels for 1-SD change in the specified factors. Among the different measures of adiposity, after adjustment for potential confounders, SST ($p=0.001$), BMI ($p=0.006$), and waist circumference ($p=0.033$) were inversely and statistically associated to IGFBP-1 levels.

To compare the relative predictive power of anthropometric and metabolic factors associated with IGFBP-1, we performed a stepwise multiple linear regression analysis using models that included as measures of adiposity SST (the best measure of adiposity associated with IGFBP-1), along with all other variables found to be significantly associated with plasma IGFBP-1. Using these models, HOMA index entered at the first step and appeared to be the factor exerting the most powerful influence on IGFBP-1, explaining 16% of IGFBP-1 variability. Age entered at the second step, followed by SST. The total proportion of IGFBP-1 variability explained by these models was 24% (Table 3). The multiple linear regression analysis was also performed according to the BMI tertiles (Table 4). Probably due the small sample size for each tertile of BMI, we are unable to find the relation between SST and IGFBP-1 as reported in the whole population and also the relations with age and HOMA are weaker than in the analysis using the whole study population.

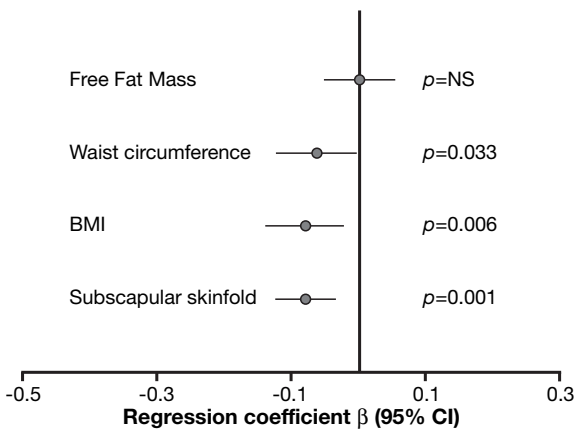


Fig. 1 - *Changes in IGF-binding protein (IGFBP)-1 plasma levels for 1-SD change in the specified factors. Linear regression analysis comparing different anthropometric measurements as predictor of IGFBP-1 in study population. BMI: body mass index. IGFBP-1 values have been log transformed.*

Table 3 - *Stepwise multiple linear regression analysis.*

| Step | Variable inserted | *p* | $R^2$ |
|---|---|---|---|
| 1 | HOMA index | <0.001 | 0.16 |
| 2 | HOMA index | <0.001 | 0.21 |
| | Age | <0.001 | |
| 3 | HOMA index | <0.001 | |
| | Age | 0.001 | 0.24 |
| | SST | 0.003 | |

Independent variables: homeostasis model assessment (HOMA) index (Log-transformed values), age, and subscapular skinfold thickness (SST). Stepwise forward linear regression analysis: variation in plasma IGF-binding protein-1 (IGFBP-1) levels explained by model with selected variables (no.=229).

Table 4 - *Stepwise multiple linear regression analysis according to body mass index (BMI) tertiles. First tertile of BMI (no.=82).*

| Step | Variable inserted | *p* | $R^2$ |
|---|---|---|---|
| | First tertile of BMI (no.=82) [Variables excluded: STT and age] | | |
| 1 | HOMA index[a] | <0.001 | 0.12 |
| | Second tertile of BMI (no.=75) [Variable excluded: STT] | | |
| 1 | HOMA index[a] | 0.002 | 0.11 |
| 2 | HOMA index[a] | 0.001 | 0.20 |
| | Age | 0.002 | |
| | Third tertile of BMI (no.=72) [Variables excluded: HOMA index[a] and STT] | | |
| 1 | Age | 0.014 | 0.071 |

Stepwise forward linear regression analysis: variation in plasma IGF-binding protein-1 (IGFBP-1) levels explained by model with selected variables according to BMI tertiles (no.=229). HOMA: homeostasis model assessment; SST: subscapular skinfold thickness. [a]Log-transformed values.

## DISCUSSION

The complex regulation of the main components of the IGF-I system is under the integrated control of GH, nutritional factors, and glucose metabolism (12, 24). In particular, IGF-I and IGFBP-3, are part of the GH/IGF-I axis, while IGF-I and IGFBP-1 are considered also components of the obesity-IR axis, and are inversely associated with insulin, BMI, and MS (5, 6, 8, 12).

Our data confirmed the inverse association between IGFBP-1 and IR in this unselected sample of adult male par-

ticipants in the OHS, and evidenced that SST was the best measure of adiposity associated with IGFBP-1. As expected, waist circumference, BMI and FM exerted a similar inverse effect on IGF-I levels, also after adjustment for age. No significant associations were observed with IGFBP-3 or with IGF-I/IGFBP-3 and the study variables. To the best of our knowledge, the inverse correlation between IGFBP-1 and SST has not been reported before in the setting of cardiovascular risk estimate in a Italian adult male population.

A strong body of evidence shows that IGFBP-1 might be considered a reliable laboratory biomarker of cardiovascular risk (15, 16, 25) and insulin sensitivity, both in the absence (26) and presence of T2DM (27). However, a high variability in serum IGFBP-1 levels has been reported among healthy individuals, with insulin as the primary determinant of IGFBP-1 expression both *in vitro* and *in vivo* (28). In particular, insulin and IGF-I are considered non-genetic factors responsible for 28% and 8% of the variation in IGFBP-1 levels, respectively. In this context, other variables such as diet and lifestyle habits and, perhaps, body composition might be additional unexplained factors accounting for the remaining variability in serum IGFBP-1 levels. Large epidemiological studies in healthy population have evidenced the inverse correlation IGFBP-1 and visceral adiposity (29). However, no epidemiological study has considered IGFBP-1 in relation to different adipose tissue depots. Indeed, in addition to waist circumference (30), several investigators have emphasized the importance of subcutaneous adipose tissue accumulation, especially in the truncal and central regions, as a contributory factor linked to the development of IR (31-33). SST is a measure of truncal subcutaneous fat that has been proposed as a better predictor of IR in subjects from both Asian Indian (1) and Northern European population (2) than intra-abdominal adipose tissue. In our study, beyond BMI and waist circumference, SST was the best measure of adiposity associated with IGFBP-1. Although at the stepwise multiple regression analysis HOMA index was the best predictor of IGFBP-1 variability, confirming the previous reported data, age and SST entered at the second and third step, respectively, as adjunctive variables accounting for IGFBP-1 variability in our series.

The relationship between IGF-I plasma concentrations and body weight is non-linear, with positive association in lean subjects, but an inverse relationship at higher BMI levels (34). Obesity, and abdominal obesity in particular, is associated with secondary depression of the GH-IGF-I axis (7, 10). We previously reported that the prevalence of IGF-I deficiency/insufficiency was up to 31% in a population of severely obese patients submitted to bariatric surgery (35), being waist circumference and FM the major determinants of IGF-I (23). Moreover, low IGF-I has been associated with higher prevalence of cardiovascular disease and mortality (18), whereas high IGF-1 levels tend to be associated with an increased risk for CV mortality in an elderly population (36). The results of this study provide further evidence that in adult males there is inverse association of IGF-I with waist circumference, BMI, and FM. However, although a strong association has been reported between IGF-I/IGFBP-3 ratio and MS (37) and anthropometric measures (5), we were not able to find any association between body composition and IGF-I/IGFBP-3 ratio. This finding was, however in keeping with previous observations that IGF-I/IGFBP-3 ratio may vary among populations (5, 38) and might have a scarce usefulness in the assessment of MS in a population of older men (15).

The main limitations of our study are the cross-sectional nature of the data and of the study population, made only by male subjects, restraining our results to a similar white male adult population. In addition, as the prevalence of T2DM and hypertension was different from that of a healthy population, the data obtained in this study should be interpreted with marked caution. Furthermore, in obese patients, subtle variations of the hydration of soft tissues can affect the accuracy of BIA in estimating body composition. Nevertheless, as a normal hydration was evidenced in all study participants, this eventuality or the subsequent possible bias on the results of this study could be minimized (39). Finally, taking into account the complex and integrated control of GH, nutritional factors and glucose metabolism (25), the inclusion of patients with T2DM, although <15%, could have influenced IGF-I axis status.

In conclusion, albeit not proving causal association, our findings complemented previously published observations on the relationship between IGF system and IR and, in addition, provided a link between the main components of the IGF system and different measures of adiposity. Translating our results in clinical practice, these data suggested that, adding to classical CVD risk factors the evaluation of some components of the IGF system, such as IGF-I and IGFBP-1, and simple measures of body adiposity, such as SST, may represent a further tool to better evidence phenotype profiles associated to the pathogenetic mechanism of cardiovascular risk factor clustering in male adults.

## ACKNOWLEDGMENTS

This study has been in part by the Ministry of University Research of Italy, PRIN, with the number 2008/LFK7J5_001 and by Ricerca finalizzata - art.12 bis Decreto Legislativo 229/99.

### *Competing interests*

The authors declare that they have no competing interests.

### *Authors' contributions*

SS conceived the study, analyzed statistical data, and wrote the manuscript. BA contributed to the study design, to performing statistics, and drafting manuscript. DSC, GB, and PG performed the clinical investigation. BL, AS, and SCM gathered the data. SP and CA critically revised the manuscript. All Authors read and approved the final manuscript.

## REFERENCES

1. Vikram NK, Pandey RM, Misra A, Goel K, Gupta N. Factor analysis of the metabolic syndrome components in urban Asian Indian adolescents. Asia Pac J Clin Nutr 2009, 18: 293-300.
2. Mensink M, Feskens EJ, Kruijshoop M, de Bruin TW, Saris WH, Blaak EE. Subscapular skinfold thickness distinguishes between transient and persistent impaired glucose tolerance: Study on Lifestyle-Intervention and Impaired Glucose Tolerance Maastricht (SLIM). Diabetic Med 2003, 20: 552-7.
3. Kromhout D, Bloemberg B, Seidell JC, Nissinen A, Menotti A. Physical activity and dietary fiber determine population body fat

levels: the Seven Countries Study. Int J Obes Relat Metab Disord 2001, 25: 301-6.
4. Misra A, Wasir JS, Pandey RM. An evaluation of candidate definitions of the metabolic syndrome in adult Asian Indians. Diabetes Care 2005, 28: 398-403.
5. Faupel-Badger JM, Berrigan D, Ballard-Barbash R, Potischman N. Anthropometric correlates of insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFBP3) levels by race/ethnicity and gender. Ann Epidemiol 2009, 19: 841-9.
6. Parekh N, Roberts CB, Vadiveloo M, Puvananayagam T, Albu JB, Lu-Yao GL. Lifestyle, anthropometric, and obesity-related physiologic determinants of insulin-like growth factor-1 in the Third National Health and Nutrition Examination Survey (1988-1994). Ann Epidemiol 2010, 20: 182-93.
7. Rasmussen MH. Obesity, growth hormone and weight loss. Mol Cell Endocrinol 2010, 316: 147-53.
8. Lewitt MS, Hilding A, Brismar K, Efendic S, Ostenson CG, Hall K. IGF-binding protein 1 and abdominal obesity in the development of type 2 diabetes in women. Eur J Endocrinol 2010, 163: 233-42.
9. Lombardi G, Di Somma C, Rota F, Colao A. Associated hormonal decline in aging: is there a role for GH therapy in aging men? J Endocrinol Invest 2005, 28 (3 Suppl): 99-108.
10. Franco C, Bengtsson BA, Johannsson G. The GH/IGF-1 Axis in Obesity: Physiological and Pathological Aspects. Metab Syndr Relat Disord 2006, 4: 51-6.
11. Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB, Wareham NJ. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. Lancet 2002, 359: 1740-5.
12. Frystyk J. Free insulin-like growth factors -- measurements and relationships to growth hormone secretion and glucose homeostasis. Growth Horm IGF Res 2004, 14: 337-75.
13. Rajpathak SN, Gunter MJ, Wylie-Rosett J, et al. The role of insulin-like growth factor-I and its binding proteins in glucose homeostasis and type 2 diabetes. Diabetes Metab Res Rev 2009, 25: 3-12.
14. Ruan W, Lai M. Insulin-like growth factor binding protein: a possible marker for the metabolic syndrome? Acta Diabetol 2010, 47: 5-14.
15. Yeap BB, Chubb SA, Ho KK, et al. IGF1 and its binding proteins 3 and 1 are differentially associated with metabolic syndrome in older men. Eur J Endocrinol 2010, 162: 249-57.
16. Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. J Clin Endocrinol Metab 2004, 89: 114-20.
17. Yeap BB, Chubb SA, McCaul KA, et al. Associations of IGF1 and IGFBPs 1 and 3 with all-cause and cardiovascular mortality in older men: the Health In Men Study. Eur J Endocrinol 2011, 164: 715-23.
18. Colao A, Di Somma C, Cascella T, et al. Relationships between serum IGF1 levels, blood pressure, and glucose tolerance: an observational, exploratory study in 404 subjects. Eur J Endocrinol 2008, 159: 389-97.
19. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M. Uric acid metabolism and tubular sodium handling: results from a population based study. JAMA 1993, 270: 354-9.
20. Galletti F, Barbato A, Versiero M, et al. Circulating leptin levels predict the development of metabolic syndrome in middle-aged men: an 8-year follow-up study. J Hypertens 2007, 25: 1671-7.
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985, 28: 412-9.
22. Oscarsson J, Johannsson G, Johansson JO, Lundberg PA, Lindstedt G, Bengtsson BA. Diurnal variation in serum insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations during daily subcutaneous injections of recombinant human growth hormone in GH-deficient adults. J Clin Endocrinol Metab 1997, 46: 63-8.
23. Savastano S, Di Somma C, Belfiore A, et al. Growth hormone status in morbidly obese subjects and correlation with body composition. J Endocrinol Invest 2006, 29: 536-43.
24. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res 2003, 13 : 113-70.
25. Petersson U, Ostgren CJ, Brudin L, Brismar K, Nilsson PM. Low levels of insulin-like growth-factor-binding protein-1 (IGFBP1) are prospectively associated with the incidence of type 2 diabetes and impaired glucose tolerance (IGT): the Söderåkra Cardiovascular Risk Factor Study. Diabetes Metab 2009, 35: 198-205.
26. Mogul HR, Marshall M, Frey M et al. Insulin-like growth factor-binding protein-1 as a marker for hyperinsulinemia in obese menopausal women. J Clin Endocrinol Metab 1996, 81: 4492-5.
27. Gibson JM, Westwood M, Young RJ, White A. Reduced insulin-like growth factor binding protein-1 (IGFBP-1) levels correlate with increased cardiovascular risk in non-insulin dependent diabetes mellitus (NIDDM). J Clin Endocrinol Metab 1996, 81: 860-3.
28. Wolk K, Larsson SC, Vessby B, Wolk A, Brismar K. Metabolic, anthropometric, and nutritional factors as predictors of circulating insulin-like growth factor binding protein-1 levels in middle-aged and elderly men. J Clin Endocrinol Metab 2004, 89: 1879-84.
29. Hu D, Pawlikowska L, Kanaya A, et al; Health, Aging, and Body Composition Study. Serum insulin-like growth factor-1 binding proteins 1 and 2 and mortality in older adults: the Health, Aging, and Body Composition Study. J Am Geriatr Soc 2009, 57: 1213-8.
30. Pouliot MC, Després JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994, 73: 460-8.
31. Haffner SM, Stern MP, Hazuda HP, Pugh J, Patterson JK. Do upper-body and centralized adiposity measure different aspects of regional body-fat distribution? Relationship to non-insulin-dependent diabetes mellitus, lipids, and lipoproteins. Diabetes 1987, 36: 43-51.
32. Jensen MD. Is visceral fat involved in the pathogenesis of the metabolic syndrome? Human model. Obesity (Silver Spring) 2006, 14 (Suppl 1): 20S-4S.
33. Bays HE. Adiposopathy is "sick fat" a cardiovascular disease? J Am Coll Cardiol 2011, 57: 2461-73.
34. Lukanova A, Söderberg S, Stattin P, et al. Nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations (Sweden). Cancer Causes Control 2002, 13: 509-16.
35. Savastano S, Angrisani L, Di Somma C, et al. Relationship between growth hormone/insulin-like growth factor-1 axis integrity and voluntary weight loss after gastric banding surgery for severe obesity. Obes Surg 2010, 20: 211-20.
36. Chisalita SI, Dahlström U, Arnqvist HJ, Alehagen U. Increased IGF1 levels in relation to heart failure and cardiovascular mortality in an elderly population: impact of ACE inhibitors. Eur J Endocrinol 2011, 165: 891-8.
37. Sierra-Johnson J, Romero-Corral A, Somers VK, et al. IGF-I/IGFBP3 ratio: a mechanistic insight into the metabolic syndrome. Clin Sci (Lond) 2009, 116: 507-12.
38. Teramukai S, Rohan T, Eguchi H, Oda T, Shinchi K, Kono S. Anthropometric and behavioral correlates of insulin-like growth factor I and insulin-like growth factor binding protein 3 in middle-aged Japanese men. Am J Epidemiol 2002, 156: 344-8.
39. Savastano S, Belfiore A, Di Somma C, et al. Validity of bioelectrical impedance analysis to estimate body composition changes after bariatric surgery in premenopausal morbidly women. Obes Surg 2010, 20: 332-9.