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CLINICAL STUDY

Opposite associations of age-dependent insulin-like growth factor-I standard deviation scores with nutritional state in normal weight and obese subjects

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Abstract

Objective: Insulin-like growth factor-I (IGF-I) has been suggested to be a prognostic marker for the development of cancer and, more recently, cardiovascular disease. These diseases are closely linked to obesity, but reports of the association of IGF-I with measures of obesity are divergent. In this study, we assessed the association of age-dependent IGF-I standard deviation scores with body mass index (BMI) and intra-abdominal fat accumulation in a large population.
Design: A cross-sectional, epidemiological study.
Methods: IGF-I levels were measured with an automated chemiluminescence assay system in 6282 patients from the DETECT study. Weight, height, and waist and hip circumference were measured according to the written instructions. Standard deviation scores (SDS), correcting IGF-I levels for age, were calculated and were used for further analyses.
Results: An inverse U-shaped association of IGF-I SDS with BMI, waist circumference, and the ratio of waist circumference to height was found. BMI was positively associated with IGF-I SDS in normal weight subjects, and negatively associated in obese subjects. The highest mean IGF-I SDS were seen at a BMI of 22.5–25 kg/m^2 in men (+0.08), and at a BMI of 27.5–30 kg/m^2 in women (+0.21). Multiple linear regression models, controlling for different diseases, medications and risk conditions, revealed a significant negative association of BMI with IGF-I SDS. BMI contributed most to the additional explained variance to the other health conditions.
Conclusions: IGF-I standard deviation scores are decreased in obesity and underweight subjects. These interactions should be taken into account when analyzing the association of IGF-I with diseases and risk conditions.

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Introduction

Insulin-like growth factor-I (IGF-I) plays a major role in regulating cell growth and differentiation and is a major mediator of the various effects of growth hormone (GH). In consequence, serum levels of IGF-I are often used to assess the status of the GH axis (1–4) and, in consequence, IGF-I has been established as a useful marker for monitoring GH substitution in GH-deficient states (5) and for monitoring treatment effects in acromegaly (4).

In addition to these well established applications, several recent studies have provided evidence that IGF-I levels are positively associated with the risk for certain malignancies (6, 7) and negatively associated with cardiovascular risk factors and diseases (8–11). Although the relationship between IGF-I and cardiovascular disease remains inconclusive, with other studies showing detrimental effects of IGF-I on cardiovascular risk (12–14), these data clearly demonstrate that IGF-I is no longer a marker exclusively used for the diagnosis and follow-up of patients with disorders of GH secretion, but is of interest in many other diseases such as malignancies and cardiovascular disorders.

Since obesity is often causally involved in the pathogenesis of these diseases, it is crucial to characterize precisely a possible association of IGF-I levels with nutritional status before discussing a causal link

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between IGF-I and various disease states. In conditions of underweight such as anorexia nervosa or cachexia, decreased IGF-I and increased GH levels due to GH insensitivity are found (15–18). Obesity is characterized by blunted GH secretion (16, 19) but reports of IGF-I levels in obese subjects are divergent. Some authors have reported decreased levels of IGF-I (20–22), while others have found normal levels (23–25), which could be due to an increased GH sensitivity in obese subjects (25). Negative correlations of IGF-I levels to visceral fat areas, assessed by computed tomography scan (23, 26, 27) have been reported even in the absence of significant correlations between body mass index (BMI) and IGF-I (23), suggesting that the amount of visceral fat is an important determinant of IGF-I levels.

Since all available studies about the association between obesity and IGF-I levels have been conducted in small populations, the present study aimed to assess this question in a population of more than 6000 subjects participating in the DETECT study, a large multistage cross-sectional study in Germany. To minimize the influence of age, IGF-I levels were measured with an automated immunoassay system, for which recent age-dependent reference values in a large cohort of normal-weight healthy subjects have been published (29), and were expressed as standard deviation scores (SDS).

Subjects and methods

Subjects

The study was approved by the local ethics committee and all patients gave written informed consent. IGF-I was measured in 3723 women and 2559 men, a random sample from the DETECT study, representative of the total DETECT population.

DETECT is a large multistage cross-sectional study of 55 518 unselected consecutive patients (59% women and 41% men; over 17 years of age) in 3188 primary care offices in Germany, with a prospective 12-month component in a random subset of 7519 patients, characterized additionally by an extensive standardized laboratory program with focus on cardiovascular (CV) risk assessment. Patients' self-assessments and physicians' assessments of each patient were obtained. Table 1 summarizes the patients' characteristics in detail. Further details are available at http://www.detect-studie.de. The design, methods and baseline characteristics of DETECT, and first prevalence data have been published by Wittchen *et al.* (30).

Instruments and measurements

Physicians' diagnoses were classified as definite, possible or not present, and current medication was recorded. In the case of diabetes, type 1 or type 2 was indicated. Laboratory values, obtained in the central laboratory in Graz, were additionally used for the diagnosis of dyslipidemia. Doctors were advised to measure weight, height, blood pressure, and waist and hip circumference according to the manual instructions. Systolic and diastolic blood pressures were measured by indirect cuff sphygmomanometry after several minutes of rest in the sitting position. Waist circumference (WC) was measured with a tape measure midway between the lowest rib and the pelvis; hip circumference (HC) was measured at the widest circumference of the hip. The following anthropometric parameters were calculated: BMI, WC (in cm), HC (in cm), waist-to-hip ratio (WHR) (WC divided by the HC), waist-to-tallness-ratio (WTR) (WC divided by measured height in cm).

Table 1 Patients characteristics.

	Female ($n = 4438$) %	**Male** ($n = 3081$) %
Sex	59.0	41.0
Age (mean/S.D.)	57.0/14.9	58.7/13.5
BMI (mean/S.D.)	26.7/5.3	27.7/4.2
Diabetes type 2[a]	17.3	27.4
Kidney diseases	2.9	5.9
Liver diseases	5.7	6.7
Cancer	3.2	3.6
CHD[b]	9.7	20.6
Hypertension[c]	55.9	67.0
Dyslipidemia[d]	57.8	71.9
Fibrate intake	1.1	2.7
HRT[e]	12.8	—

[a]Clinical diagnosis of type 2 diabetes; [b]clinical diagnosis of CHD, coronary heart disease; [c]systolic blood pressure (SBP) $> = 140$ mmHg or diastolic blood pressure (DBP) $> = 90$ mmHg or intake of antihypertensive medication (NHANES criteria); [d]levels above total cholesterol >240 mg/dl, LDL-cholesterol >160 mg/dl or HDL cholesterol <40 mg/dl; [e]hormone replacement therapy for women.

For the assessment of confounding conditions, physicians' diagnoses were used except for the following: dyslipidemia (levels of total cholesterol >6.2 mmol/l (240 mg/dl), low density lipoprotein-cholesterol >4.1 mmol/l (160 mg/dl) or high density lipoprotein-cholesterol <1.0 mmol/l (40 mg/dl)) and hypertension (systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) $> = 90$ mmHg or intake of antihypertensive medication (NHANES criteria)).

IGF-I measurements

Blood samples were collected and shipped by courier within 24 h to the central laboratory at the Medical University of Graz (Austria). IGF-I was measured with an automated chemiluminescence system (Nichols Advantage, Bad Vilbel, Germany). The maximal intra- and interassay coefficients of variation were 5% and 7% respectively. Reagents and secondary standards were used as recommended by the manufacturer. IGF-I levels were transformed to age-dependent IGF-I SDS according to Brabant *et al.* (29).

Statistical analyses

BMI dependent IGF-I SDS means and standard deviations were illustrated with fractional polynomial fit after smoothing the means and standard deviations in each BMI class using the smoothing window BMI − 1 to BMI + 1. Multiple linear regression models were used to assess the influence of different nutritional parameters on IGF-I SDS, controlling for different diseases and risk conditions. Model fits were tested using the Pregibon link test. To account for the stratified sampling design, we calculated confidence intervals with the Huber-White sandwich method. The difference between the model proposed by Brabant *et al.* (29) and the model estimated in our sample was tested with a *t*-test, using the normality of regression coefficients. We also used a *t*-test for comparison of the IGF-I SDS levels in different age groups. All statistical analyses were conducted with the software package STATA 8 (Stata Statistical Software: Release 9.0. College Station, TX: Stata Corporation, 2005).

Results

There were no differences in IGF-I, BMI, or age among those who were fasted and the non-fasted subjects. We estimated the linear regression model used for calculation of the IGF-I SDS proposed by Brabant *et al.* (29) in our sample. Our model differed significantly ($P < 0.001$) from that of Brabant *et al.* The IGF-I SDS mean in our sample was 0.08 ($P < 0.001$) and 0.08 ($P < 0.001$) after exclusion of subjects with a BMI > 30 and < 18. Lower IGF-I SDS values ($P < 0.001$) were found in younger (mean = −0.15, 18–44 years) age groups and higher values ($P < 0.001$) in older age groups (mean = 0.34, 66 + years). The means of patients aged 45–65 years were not different to zero. Therefore, we additionally adjusted for age in our regression analysis. IGF-I SDS were calculated in different BMI groups with a width of 2.5 starting from $\leq 17.5\,kg/m^2$ as shown in Table 2. In the total sample, IGF-I SDS increased with increasing BMI groups up to a BMI of $27.5–30\,kg/m^2$ in women and

Table 2 IGF-I SDS in BMI, WTR, and WC groups.

	Total group[a]						**Subjects with diabetes, cancer, kidney, liver diseases or HRT excluded**					
	Female ($n = 3723$)			Male ($n = 2559$)			Female ($n = 2377$)			Male ($n = 1606$)		
	n	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.
BMI < = 17.5	17	−0.33*	0.49	3	−0.18	0.65	16	−0.36*	0.5	2	−0.43	0.69
17.5 < BMI < = 20	195	−0.07*	0.86	15	−0.67*	0.76	162	−0.09*	0.82	13	−0.70*	0.82
20 < BMI < = 22.5	593	0.06*	0.82	136	−0.14*	0.88	458	0.04*	0.82	104	−0.13	0.89
22.5 < BMI < = 25	780	0.15	0.84	**531**	**0.08**	**0.93**	536	0.09	0.8	**382**	**0.05**	**0.85**
25 < BMI < = 27.5	707	0.18	0.91	719	−0.01	0.89	438	0.14	0.87	488	0.02	0.87
27.5 < BMI < = 30	**551**	**0.21**	**0.92**	539	−0.07*	0.89	**321**	**0.19**	**0.79**	316	−0.07	0.86
30 < BMI < = 32.5	390	0.13	0.86	317	−0.13*	0.88	189	0.11	0.82	170	−0.08	0.83
32.5 < BMI < = 35	234	0.02*	0.81	164	−0.2*	0.99	124	−0.04*	0.82	72	−0.18	1.07
35 < BMI < = 37.5	125	−0.06*	0.90	69	−0.34*	1.05	71	−0.16*	0.69	29	0.08	1.07
37.5 < BMI < = 40	59	−0.24*	0.81	30	−0.05	0.89	27	−0.17*	0.73	15	0.07	0.66
BMI > 40	72	−0.5*	0.77	36	−0.53*	1.17	35	−0.41*	0.69	15	−0.76*	0.84
WTR < = 0.25	1	1.88	—	—	—	—	—	—	—	—	—	—
0.25 < WTR < = 0.35	3	0.37	0.22	1	−0.74	—	3	0.37*	0.22	1	−0.74	—
0.35 < WTR < = 0.45	523	−0.13*	0.73	**82**	**0.00**	**0.76**	438	−0.13*	0.74	**69**	**0.01**	**0.78**
0.45 < WTR < = 0.55	1404	0.15	0.90	842	−0.02	0.88	961	0.10	0.84	649	−0.03	0.85
0.55 < WTR < = 0.65	**1246**	**0.18**	**0.87**	1250	−0.04	0.91	**709**	**0.15**	**0.83**	729	−0.03	0.88
0.65 < WTR < = 0.75	460	0.06*	0.89	330	−0.20	1.02	226	0.08	0.83	137	−0.07	1.00
0.75 < WTR < = 0.85	73	−0.21*	0.78	46	−0.11	1.05	34	−0.30	0.69*	19	−0.06	1.02
0.85 < WTR < = 0.95	13	−0.40*	0.69	6	−0.41*	1.57	6	−0.39	0.56*	1	−1.67	—
WTR > 0.95	—	—	—	2	−1.33	0.64	—	—	—	1	−0.88	—
WC < = 50	1	1.88	—	—	—	—	—	—	—	—	—	—
50 < WC < = 60	17	−0.04	0.65	1	−0.74	—	14	−0.04	0.71	1	−0.74	—
60 < WC < = 70	263	−0.16*	0.74	18	−0.54*	1.03	223	−0.15*	0.75	13	−0.72*	1.14
70 < WC < = 80	762	0.06*	0.82	72	0.01	0.78	560	0.01*	0.79	**61**	**0.06**	**0.8**
80 < WC < = 90	**994**	**0.19**	**0.89**	319	−0.04	0.83	**666**	**0.17**	**0.83**	252	−0.05	0.83
90 < WC < = 100	832	0.16	0.88	**890**	**0.03**	**0.92**	480	0.12	0.83	618	−0.01	0.88
100 < WC < = 110	549	0.14	0.9	719	−0.07*	0.88	280	0.08	0.86	418	−0.01	0.82
110 < WC < = 120	201	0.02*	0.88	358	−0.18*	0.97	109	0.00*	0.81	171	−0.11	1
120 < WC < = 130	76	−0.28*	0.79	125	−0.11	1.03	32	−0.22*	0.6	52	0.00	0.99
130 < WC < = 140	22	−0.38*	0.8	38	−0.41*	1.19	10	−0.33*	0.69	12	−0.24	0.79
WC > 140	6	−0.54*	0.77	19	−0.23	1.34	3	−0.96*	0.87	8	−0.22	1.29

[a] $n = 6282$ valid observations with measured IGF-I and anthropometric parameters.
* Significantly different ($P < 0.05$) from group with highest IGF-I SDS mean (reference group marked in bold), tested by multiple *t*-test.

22.5–25 kg/m^2 in men, and then decreased with further BMI increments. The maximum mean IGF-I SDS values were 0.21 and 0.08 in women and men respectively. When subjects with diabetes, cancer, renal or liver diseases or hormone replacement therapy were excluded, the results were very similar, with IGF-I SDS somewhat lower than in the total population. In this subset of 3983 subjects, peak mean IGF-I SDS values were 0.19 in women (BMI 27.5–30 kg/m^2) and 0.05 in men (22.5–25 kg/m^2). In men, high mean IGF-I scores of 0.08 and 0.07 were also found in the BMI groups of 35–37.5 kg/m^2 and 37.5–40 kg/m^2, which may be influenced by the small number of subjects included in these groups.

Figure 1 shows the blotted IGF-I SDS in the total sample and after exclusion of subjects with diabetes, cancer, and kidney or liver diseases. Mean values and 1st and 2nd SDS are shown as smoothed lines.

Table 2 also shows the means and standard deviations of IGF-I SDS among groups with different WC and WTR. Again, IGF-I SDS increased in the lower WC and WTR groups up to a maximum at a WC between 80 and 90 cm and a WTR between 0.55 and 0.65 for females and at a WC between 90 and 100 cm and a WTR between 0.35 and 0.45 for males, and then decreased with higher WC and WTR values.

To calculate which anthropometric parameter contributed most to explained variance (R^2) of IGF-I SDS, we carried out linear regression analyses with each nutritional parameter. As several conditions could possibly influence IGF-I SDS, we controlled for cancer, coronary artery disease, diabetes, hypertension, dyslipidemia, liver diseases, renal diseases, age, and intake of fibrates or sex hormone replacement therapy (HRT, in women). The results are shown in Table 3. There was a weak negative association (indicated by a negative β-S.D.; an increase of one S.D. of the nutritional parameter leads to the indicated increase change of IGF-I SDS) of IGF-I SDS with BMI and other nutritional, anthropometric parameters in both men and women. BMI contributed most to the additional explained variance in the other health conditions.

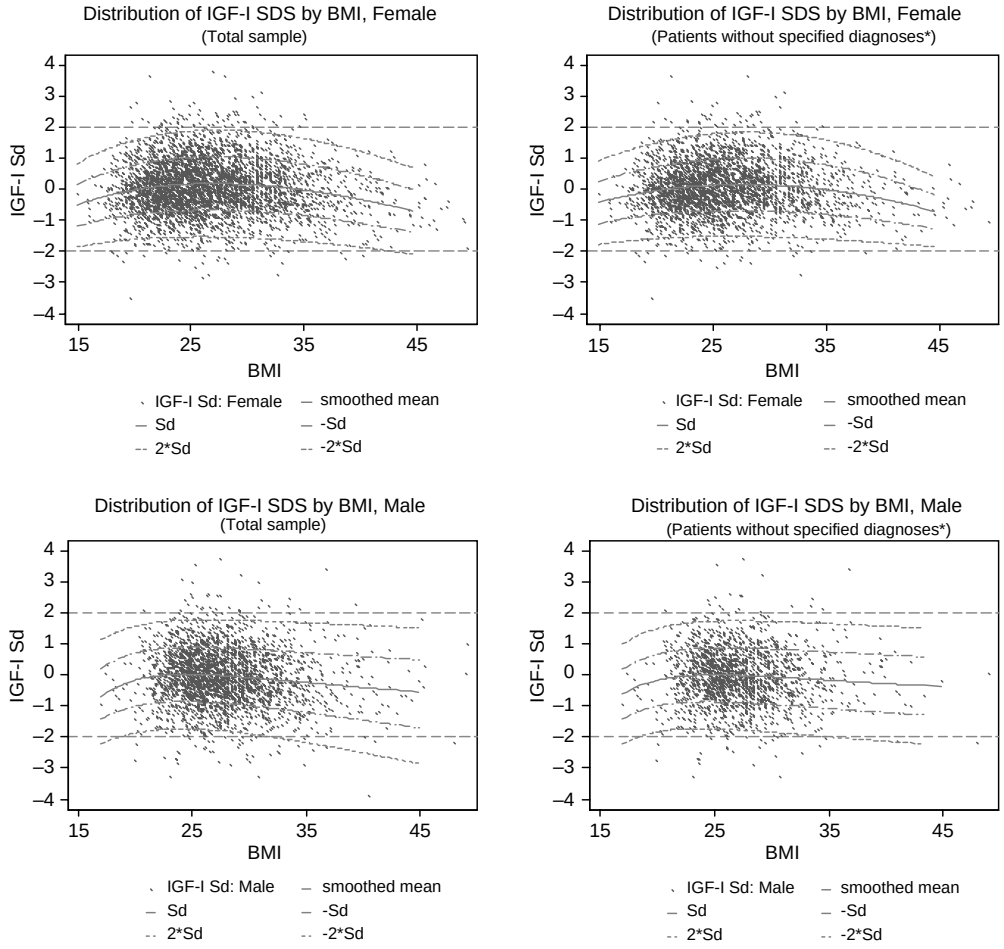

Figure 1 IGF-I SDS blotted over BMI with smoothed lines indicating mean values and 1st and 2nd S.D. (Left panels) Total sample: upper panel, women; lower panel, men. (Right panels) Subjects with diabetes, cancer, kidney or liver diseases, or hormone replacement therapy excluded: upper panel, women; lower panel, men.

Table 3 IGF-I SDS: additional explained variance of nutritional parameters (model 2) to explained variance by the following conditions: diabetes, liver diseases, kidney diseases, CAD, cancer, hypertension, dyslipidemia, fibrate intake, HRT, and age (model 1). R^2: explained variance. Beta S.D.: standardized regression coefficient. Increase of nutritional parameter for one SD leads to the indicated change of IGF-I SDS.

	Model 1[a]	Model 2[b]															
		BMI			WC			HC			WHR			WTR		
	R^2	R^2	Beta-S.D.	CI (95%)	R^2	Beta-S.D.	CI (95%)	R^2	Beta-S.D.	CI (95%)	R^2	Beta-S.D.	CI (95%)	R^2	Beta-S.D.	CI (95%)
Total																
Female	8.03	8.91	−0.07	−0.098 −0.049	8.58	−0.07	−0.093 −0.037	8.4	−0.05	−0.072 −0.023	8.05	−0.01	−0.042 −0.01	8.65	−0.07	−0.092 −0.039
Female, 18–44 years	1.32	2.01	−0.06	−0.112 −0.015	1.6	−0.05	−0.102 −0.012	1.7	−0.05	−0.093 −0.001	1.29	0.00	−0.051 −0.052	1.68	−0.05	−0.102 −0.006
Female, 45–65 years	4.63	5.2	−0.06	−0.094 −0.021	5.09	−0.06	−0.099 −0.016	4.92	−0.04	−0.076 −0.004	4.67	−0.01	−0.052 −0.023	5.19	−0.06	−0.1 −0.02
Female, 65 + years	4.25	5.33	−0.08	−0.132 −0.037	4.92	−0.07	−0.127 −0.021	4.55	−0.05	−0.094 −0.003	4.3	−0.03	−0.077 −0.022	4.99	−0.07	−0.12 −0.022
Male	3.26	3.95	−0.08	−0.122 −0.041	3.68	−0.07	−0.11 −0.022	3.41	−0.04	−0.079 −0.007	3.57	−0.06	−0.104 −0.017	3.86	−0.08	−0.124 −0.037
Male, 18–44 years	4.41	4.43	−0.01	−0.11 −0.082	5.13	−0.09	−0.178 −0.006	4.52	0.00	−0.083 −0.09	5.67	−0.09	−0.15 −0.031	4.97	−0.08	−0.175 −0.017
Male, 45–65 years	2.79	3.81	−0.10	−0.149 −0.041	3.16	−0.06	−0.123 −0.002	3.02	−0.05	−0.112 −0.017	2.97	−0.05	−0.122 −0.022	3.54	−0.09	−0.149 −0.025
Male, 65 + years	3.63	4.08	−0.07	−0.146 −0.004	3.75	−0.04	−0.118 −0.042	3.72	−0.03	−0.102 −0.043	3.66	−0.02	−0.102 −0.064	3.85	−0.05	−0.128 −0.028
BMI < = 25																
Female	9.43	9.61	0.03	−0.003 −0.066	9.48	0.02	−0.024 −0.064	9.59	0.03	−0.007 −0.067	9.45	−0.01	−0.045 −0.032	9.47	0.02	−0.026 −0.056
Female, 18–44 years	1.21	1.3	0.02	−0.037 −0.079	1.22	0.01	−0.07 −0.089	1.19	0.00	−0.064 −0.074	1.19	0.01	−0.063 −0.075	1.21	0.00	−0.074 −0.079
Female, 45–65 years	6.42	6.47	0.02	−0.039 −0.071	6.47	0.02	−0.047 −0.086	6.65	0.03	−0.018 −0.087	6.43	−0.01	−0.061 −0.046	6.43	0.01	−0.054 −0.07
Female, 65 + years	9.19	10.62	0.09	0.019 −0.169	9.2	−0.01	−0.099 −0.083	9.75	0.06	−0.02 −0.142	9.71	−0.06	−0.141 −0.028	9.2	0.01	−0.074 −0.089
Male	3.66	4.54	0.10	0.024 −0.181	3.7	−0.02	−0.102 −0.064	4	0.04	−0.018 −0.107	4.17	−0.07	−0.151 −0.005	3.9	−0.05	−0.133 −0.031
Male,18–44 years	6.57	10.01	0.21	0.048 −0.375	6.87	−0.06	−0.211 −0.091	7.69	0.08	−0.04 −0.195	8.37	−0.11	−0.215 −0.002	7.44	−0.11	−0.271 −0.057
Male, 45–65 years	4.22	4.38	0.04	−0.072 −0.158	4.24	0.02	−0.13 −0.165	4.41	0.04	−0.084 −0.171	4.27	−0.03	−0.185 −0.128	4.35	−0.04	−0.177 −0.097
Male, 65 + years	10.31	11.16	0.10	−0.041 −0.255	10.31	0.00	−0.132 −0.141	10.55	0.04	−0.05 −0.126	10.49	−0.05	−0.182 −0.085	10.31	0.00	−0.133 −0.132
25 < BMI < = 30																
Female	9.16	9.16	−0.01	−0.049 −0.038	9.17	−0.01	−0.061 −0.041	9.08	0.00	−0.043 −0.047	9.08	−0.01	−0.052 −0.04	9.24	−0.02	−0.069 −0.025
Female, 18–44 years	10.3	11.54	0.01	−0.021 −0.214	11.55	0.11	−0.035 −0.247	12.76	0.14	0.02 −0.251	10.36	−0.02	−0.136 −0.098	11.23	0.083	−0.044 −0.21
Female, 45–65 years	4.87	5.01	−0.02	−0.094 −0.036	5.12	−0.04	−0.125 −0.037	4.87	−0.00	−0.063 −0.062	4.97	−0.02	−0.089 −0.042	5.31	−0.05	−0.127 −0.023
Female, 65 + years	5.58	5.58	−0.00	−0.069 −0.063	5.58	0.00	−0.068 −0.068	5.66	−0.02	−0.098 −0.048	5.66	0.03	−0.045 −0.103	5.65	−0.02	−0.08 −0.045
Male	3.7	3.71	0.01	−0.038 −0.055	3.72	0.01	−0.043 −0.071	3.7	0.02	−0.037 −0.069	3.67	−0.01	−0.072 −0.053	3.7	−0.00	−0.06 −0.057
Male, 18–44 years	3.09	3.34	0.04	−0.064 −0.136	3.16	−0.02	−0.122 −0.082	3.43	−0.04	−0.139 −0.068	3.26	0.02	−0.12 −0.152	3.21	−0.03	−0.14 −0.087
Male, 45–65 years	1.06	1.07	−0.01	−0.076 −0.061	1.12	0.02	−0.066 −0.109	1.15	0.03	−0.058 −0.11	1.08	−0.01	−0.114 −0.087	1.07	0.00	−0.088 −0.096
Male, 65 + years	5.74	5.74	0.01	−0.077 −0.087	5.8	0.03	−0.08 −0.133	5.83	0.03	−0.061 −0.115	5.76	−0.02	−0.118 −0.087	5.74	0.00	−0.1 −0.102
BMI > 30																
Female	7.21	9.71	−0.13	−0.179 −0.073	8.79	−0.11	−0.159 −0.053	8.37	−0.08	−0.131 −0.029	7.29	−0.02	−0.072 −0.028	8.63	−0.09	−0.14 −0.043
Female, 18–44 years	7.5	14.77	−0.18	−0.284 −0.08	10.2	−0.12	−0.247 −0.001	12.86	−0.14	−0.236 −0.046	7.88	0.04	−0.076 −0.152	9.7	−0.10	−0.224 −0.02
Female, 45–65 years	5.47	7.16	−0.10	−0.174 −0.02	6.84	−0.10	−0.183 −0.018	7.12	−0.10	−0.175 −0.023	5.47	0.00	−0.079 −0.082	6.78	−0.09	−0.165 −0.015
Female, 65 + years	6.8	8.67	−0.14	−0.236 −0.034	7.55	−0.08	−0.165 −0.011	6.81	0.01	−0.074 −0.088	7.8	−0.09	−0.164 −0.006	7.5	−0.07	−0.147 −0.014
Male	6.75	7.19	−0.06	−0.127 −0.016	6.82	−0.02	−0.105 −0.056	6.77	−0.01	−0.096 −0.076	6.9	−0.04	−0.125 −0.045	6.85	−0.03	−0.102 −0.046
Male, 18–44 years	19.83	19.86	0.02	−0.174 −0.209	21.07	−0.11	−0.315 −0.088	21.63	0.11	−0.075 −0.29	26.02	−0.17	−0.277 −0.065	19.83	−0.00	−0.208 −0.204
Male, 45–65 years	8.99	9.29	−0.04	−0.126 −0.044	8.99	0.00	−0.096 −0.106	9.32	−0.01	−0.13 −0.113	9.33	0.02	−0.11 −0.14	9.09	−0.03	−0.118 −0.067
Male, 65 + years	4.99	6.09	−0.11	−0.266 −0.054	5.08	−0.03	−0.203 −0.145	5.97	−0.01	−0.261 −0.074	5.58	0.10	−0.17 −0.364	5.05	−0.02	−0.171 −0.128

[a]Estimated association of IGF-I SDS and diabetes, liver diseases, kidney diseases, CAD, cancer, hypertension, dyslipidemia, fibrate intake, HRT, and age; [b]estimated association of IGF-I SDS and nutritional parameters, diabetes, liver diseases, kidney diseases, CAD, cancer, hypertension, dyslipidemia, fibrate intake, HRT, and age.
CI, confidence intervals; CAD, coronary artery disease; HRT, hormone replacement therapy.

When analyzing subgroups with normal and underweight (BMI $\leq 25\,kg/m^2$), overweight (BMI $25-30\,kg/m^2$), and obese subjects (BMI $> 30\,kg/m^2$), we found diverging results. In normal and underweight subjects we found a positive association between IGF-I SDS and BMI in men, but not in women. Subgroup analysis revealed that this effect was most pronounced in men aged 18–44 years, but it was not significant in men of other age groups, whereas a significant positive association was found in women aged 65 years or older, but not in women of other age groups. There were no significant associations between IGF-I and BMI in overweight individuals. Obese women showed a marked negative correlation that was most pronounced in women aged 18–44 years. In obese men, BMI was not significantly associated with IGF-I SDS but in the young age group, WHR was significantly negatively associated with IGF-I SDS. In most age subgroups, BMI added most to the explained variance compared with other anthropometric parameters. Only in men aged 18–44 years did the WHR prove to have the strongest association with IGF-I SDS.

Discussion

To our knowledge, this is the largest study to date assessing the association of IGF-I with nutritional status. In addition, age-dependent IGF-I SDS calculated from the largest published reference sample for IGF-I measurement (29) were used instead of IGF-I levels to analyze associations between IGF-I and various nutritional parameters. By this approach, the confounding effects of the age-dependent decline in IGF-I levels could be excluded. The IGF-I SDS mean in our sample was slightly higher than zero and there was a less steep age-related decline than in Brabant *et al.* (29). The reason for these differences is unclear. Possibly, differences in morbidities might have played a role. Due to this difference, we additionally adjusted for age in our regression analyses.

Our study clearly established opposite associations of nutritional parameters with IGF-I SDS in normal weight and obese subjects.

It is known that IGF-I levels are decreased in underweight individuals (15–18) and this has been attributed to GH resistance. The present data extend this observation by showing a continuous increase in IGF-I SDS throughout the normal weight range in both sexes and even further in women. In men with a BMI $\leq 25\,kg/m^2$, we also found a positive correlation after controlling for possibly confounding health conditions and medications. This observation might indicate that GH sensitivity is not only reduced in severe underweight states, but also may steadily increase within the normal BMI range.

In obese subjects, on the other hand, mean IGF-I SDS decreased with BMI. This confirms the results of some (20–22) but not all (23–25) previous studies. In our subgroup of obese subjects, an increase of one S.D. of BMI led to a mean decrease of 0.13 and 0.06 IGF-I SDS in women and men respectively. In the literature, a more pronounced impairment of GH secretion in obesity is described, with a reduction of GH production to a quarter of that in normal weight subjects (30). Based on these results on GH secretion in obesity, our results suggest that the reduction in GH secretion is only partially translated into reduced IGF-I secretion. The reason for this is unclear, but again, an increase in GH sensitivity has been discussed (25). In a population-based study with 400 subjects, a negative correlation of IGF-I with BMI was found that disappeared after adjustment for age (26). We found significant effects of BMI, even after adjustment for age and other health conditions. Possibly, the larger sample number of our study has revealed these associations.

BMI adds about 1% to the explained variance of IGF-I SDS in the total population and up to 7% in obese subgroups. Overall, different health conditions only render about 3–8% of explained variance in the total group and up to 20% in obese subgroups. These results show that a major part of IGF-I SDS variance still needs to be explained by other factors not assessed in this study, such as genetics or others.

In some studies, a strong negative correlation of visceral fat mass with IGF-I has been found indicating that visceral fat rather than overall body mass determines IGF-I levels (27, 28). We have studied several anthropometric indicators of visceral fat accumulation including the WC and the WTR, which have been shown to correlate with intra-abdominal fat (32). Surprisingly, it was the BMI rather than these parameters that added most to explained variance of IGF-I SDS in our total population. However, in the subgroup of young men, the WHR had a better association with IGF-I than with BMI. Since in the study of Kunitomi *et al.* (28), younger and middle-aged obese men were also investigated, differences between patient populations might be one important explanation for the differences between earlier reports and our study. Moreover, an age-dependent decline in IGF-I, excluded by our approach to the analysis of IGF-I SDS, might have further confounded the findings of previous studies.

The influence of BMI on IGF-I levels is of considerable relevance for studies investigating the association between IGF-I and various disease states. So far, only a few of these studies have adjusted their IGF-I values to BMI. Laughlin *et al.* (11) have, in a prospective study, investigated the association between IGF-I and cardiovascular risk in a large cohort of older adults from the Rancho Bernardo Study. They found a significant increase in both cardiovascular and all-cause mortality for every unadjusted IGF-I decrease of 40 μg/l (1 SD), which was still significant after adjusting for age. However, when adjusted for age, sex, BMI and prevalent disease, the difference was no longer significant.

In conclusion, our results indicate that BMI is a slightly better predictor of IGF-I than other anthropometric indicators of nutritional state, and they provide data on the magnitude of this influence in relation to age, BMI and sex. There are opposite associations of BMI to IGF-I SDS in normal weight and in obese individuals. The associations are particularly strong in obese subjects and, in addition, there are sex differences in some subgroups. The data stress the importance of clearly defining subject populations when analyzing the associations of hormonal parameters with nutrition and body composition. These interactions must be taken into account when studying the associations of IGF-I and health conditions that are related to obesity, such as cardiovascular diseases or cancer. Moreover, IGF-I is used to monitor therapy in acromegaly (4) and GH deficiency (1, 3, 33). The association of BMI with IGF-I should be taken into account when titrating therapy in these patients and, possibly, age- and BMI-dependent reference values should be considered in the future.

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