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Serum Insulin-Like Growth Factor I (IGF-I), IGF-Binding Proteins 2 and 3, and the Risk for Development of Malignancies in Adults with Growth Hormone (GH) Deficiency Treated with GH: Data from KIMS (Pfizer International Metabolic Database)

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Context: The association between IGFs and cancer in adults with GH deficiency (GHD) receiving GH replacement requires investigation.

Objective: The objective was to examine the association between IGF-I, IGF-binding protein 2 (IGFBP-2), and IGFBP-3 SD scores (SDSs) in GH-deficient adults receiving GH therapy and the occurrence of *de novo* malignancies.

Design: Serum IGF-I, IGFBP-2, and IGFBP-3 levels in GH-deficient patients who developed a malignancy since receiving GH were compared with patients with idiopathic GHD but without malignancy. Measurements were related to age-, sex-, and body mass index-specific SDS reference regions.

Setting: The setting included the KIMS (the Pfizer International Metabolic Database).

Patients: One hundred patients with *de novo* malignancy during GH therapy were compared with 325 patients with idiopathic GHD without malignancy.

Intervention(s): Serum samples were obtained as close as possible to the diagnosis of malignancy, or after approximately 2 yr of GH replacement in KIMS.

Main Outcome Measures: Associations between relative risk (RR) of malignancy and IGF-I, IGFBP-2, and IGFBP-3 SDSs were assessed in multiple log-linear Poisson working regression models, controlling for age, sex, onset of GHD, and GH naivety at KIMS entry.

Results: No association between IGF-I SDSs and RR was observed ($P = 0.48$). Increasing IGFBP-2 and IGFBP-3 SDSs were associated with increasing RRs [18% per unit IGFBP-2 SDSs (95% confidence interval, 7–30%; $P = 0.0006$), 13% per unit IGFBP-3 SDS (2–26%; $P = 0.01$)].

Conclusions: IGF-I levels targeted to within normal age-related reference ranges during GH replacement were not associated with the occurrence of malignancies. Higher IGFBP-2 and/or IGFBP-3 SDSs may be associated with increased cancer risk. **(*J Clin Endocrinol Metab* 95: 0000–0000, 2010)**

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Abbreviations: CI, Confidence interval; GHD, GH deficiency; IGFBP, IGF-binding protein; RR, relative risk; SDS, SD score.

The IGFs are well known as key regulators of energy metabolism and growth of both normal and malignant cells (1, 2). The IGFs comprise a complex system with two growth factors (IGF-I and IGF-II), cell-surface receptors, six specific high-affinity IGF-binding proteins (IGFBP-1 to IGFBP-6), and IGFBP proteases, as well as an acid-labile subunit. Regulation of IGF-I secretion in adults is complex and is not solely dependent on GH status but also on factors such as age, sex, and hormonal and nutritional status. Experimental data suggest that some IGFs play a role in the development and progression of cancer (3) and that signal transduction networks rather than individual genes govern the course of tumorigenesis (4). In line with this, considerable epidemiological data have highlighted a possible link between circulating GH and/or IGF-I levels and cancer development in humans (5–7). Studies within a normal population suggest that high-normal serum IGF-I levels may be associated with an increased risk of malignancies (5, 6). As GH therapy increases IGF-I levels, it is important to consider the role of the IGF hormone axis in the development of cancer in adults with GH deficiency (GHD) receiving GH replacement.

Several studies have reported increased cancer risk in patients with untreated GHD (8–10). Among patients receiving GH therapy, results have been more variable (10–13). Some studies reported an increased incidence of malignancy in hypopituitary patients receiving GH therapy relative to the general population (11), whereas others showed no increased risk (10). This study examined the association between circulating levels of IGF-I, IGFBP-2, and IGFBP-3 during GH replacement therapy and the relative risk (RR) of cancer in patients with GHD.

Patients and Methods

Patient groups

This study used data from KIMS (Pfizer International Metabolic Database), a pharmacoepidemiological survey of adults with GHD. The survey is performed in accordance with The Declaration of Helsinki (14). Central IGF-I measurement (but not IGFBP-2 or IGFBP-3 measurement) is routinely offered for patients in KIMS (15).

The association between *de novo* malignancy (excluding nonmelanoma skin cancers) and IGF-I SD score (SDS), IGFBP-2 SDS, and IGFBP-3 SDS during GH replacement in patients enrolled in KIMS was assessed. Serum samples during GH replacement were available from 100 (mean ± SD age, 60.2 ± 12.0 yr at cancer diagnosis; 41% females; etiology of GHD, 76 cases were pituitary adenoma) of the 180 patients with a *de novo* malignancy in KIMS (database frozen in June 2006). Serum samples were retrieved as close as possible before malignancy was diagnosed [on average, 7.7 months before diagnosis and 3.6 yr after KIMS entry (Table 1)]. The most common malignancies were prostate cancers (n = 20), lung cancers (n = 14), breast cancers (n = 11), malignant melanoma (n = 8), and brain tumors (n = 6). The distributions of the etiologies of GHD and the types of cancer diagnoses in the patients with malignancy who were included and excluded in the study were similar ($P > 0.40$).

To illustrate the general distribution of IGF-I and IGFPBs during well-established treatment in patients in KIMS, serum samples from during the maintenance phase of GH replacement [defined as 19–30 months after KIMS entry (on average, 2.1 yr)] were retrieved and analyzed for 325 patients with idiopathic GHD without a tumor diagnosis (mean ± SD age, 38.0 ± 14.0 yr at serum sample date; 39% females). To assess whether IGFs in this group were representative of those of patients without malignancies in KIMS, data on IGF-I levels from all KIMS patients for whom there was a routine central measurement during maintenance GH replacement recorded in the database were analyzed ("IGF-I-only reference"; n = 4239; mean ± SD age, 47.0 ± 15.0 yr at reported IGF-I sample date; 49% females].

The three groups differed in several ways, including in terms of sex, age, onset of GHD, and GH-treatment naivety at KIMS entry (Table 1). The prescribed GH dose closest to the blood sample date was similar between groups.

At KIMS entry, patients diagnosed with a malignancy and patients in the idiopathic GHD group had on average 2.7 and 1.8 pituitary hormone deficits in addition to GHD, respectively ($P < 0.0001$); the IGF-I-only reference group had 2.43. Percentages with isolated GHD were 7, 24, and 10%, respectively. All other hormone deficiencies were replaced before GH replacement was started. GH reserve was most commonly assessed by insulin tolerance test (~65%), followed by arginine (~15%); percentages were similar between the study groups.

IGF measurement

Serum IGF-I, IGFBP-2, and IGFBP-3 concentrations were measured using a specific in-house RIA (1). For the IGF-I-only reference group, IGF-I levels were measured at a central facility by RIA after acid/ethanol precipitation of IGFBPs (Nichols Institute Diagnostics, San Juan Capistrano, CA) or by a chemiluminescent immunoassay [Nichols Advantage System (Nichols Institute Diagnostics), followed by Immulite 2500 (DPC Siemens, Munich, Germany)]. For each assay, age- and sex-specific reference ranges were used to determine IGF-I SDS (15, 16).

Statistical methods

Serum IGF-I, IGFBP-2, and IGFBP-3 were related to recently published age-, sex-, and body mass index-specific univariate or multivariate 95% reference regions in terms of SDSs (17). Analyses assessing associations between cancers and IGF SDS were conducted using multiple log-linear Poisson working regression models with model-robust SE estimates (18). RR estimates were adjusted for age at blood sample date, sex, onset of GHD, and GH naivety at KIMS entry. IGF-I SDS was kept in the final multiple SDS model, even if it was not statistically significant, because of its importance in the titration of GH dose and safety evaluations in GH-deficient patients.

Univariate SDS variables were classified as in Table 2. Numerical SDS variables consisted of individual values. Age was actual age at blood sample. Treatment naivety and onset of GHD were dichotomized as in Table 1. The explanatory value of each variable was evaluated using likelihood-ratio tests. The 95% confidence intervals (CIs) were Wald based. $P < 0.05$ was con-

TABLE 1. Background statistics for the three patient groups studied according to age at the time when the blood sample (or IGF sample date for patients in the IGF-I-only reference group) was taken

	Age at blood sample date											
	<40 yr			40–59 yr			≥60 yr			All ages		
Variable, mean (SD)	Malignancy	Idiopathic GHD[a]	IGF-I-only reference group[a]	Malignancy	Idiopathic GHD[a]	IGF-I-only reference group[a]	Malignancy	Idiopathic GHD[a]	IGF-I-only reference group[a]	Malignancy	Idiopathic GHD[a]	IGF-I-only reference group[a]
Number of subjects	10	200	1394	34	98	1978	56	27	867	100	325	4239
Females (%)	60	39	52	59	36	50	27	44	43	41	39	49
Semi or true GH-naive patients (%)[b]	60	73	70	65	57	69	66	96	72	65	70	69
Adult-onset GHD (%)	60	14	43	100	58	92	100	93	100	96	34	77
Age at KIMS baseline (yr)	31 (7)	26 (6)	27.7 (6)	51 (5)	47 (6)	48 (6)	64 (6)	66 (5)	65 (5)	56 (12)	36 (14)	45 (15)
Age at blood sample date (yr)	33.6 (6)	28 (6)	30 (6)	53.9 (5)	49 (6)	50 (6)	67.7 (5)	68 (5)	67 (5)	59.6 (12)	38 (14)	47 (15)
Age at cancer diagnosis (yr)	34.2 (7)	N/A	N/A	54.7 (5)	N/A	N/A	68.2 (5)	N/A	N/A	60.2 (12)	N/A	N/A
GH dose at KIMS baseline (mg/d)	0.34 (0.28)	0.33 (0.27)	0.37 (0.30)	0.37 (0.31)	0.38 (0.28)	0.33 (0.26)	0.28 (0.25)	0.19 (0.13)	0.26 (0.20)	0.32 (0.28)	0.34 (0.27)	0.33 (0.26)
GH dose closest to blood sample date (mg/d)	0.41 (0.23)	0.54 (0.34)	0.54 (0.34)	0.45 (0.26)	0.44 (0.23)	0.42 (0.25)	0.34 (0.19)	0.30 (0.12)	0.33 (0.20)	0.38 (0.22)	0.49 (0.30)	0.44 (0.28)
Time between closest GH dose and blood sample (months)[a]	2.4 (4.1)	1.6 (4)	2.4 (5.0)	1.9 (4.2)	1.4 (3.2)	2.4 (5.0)	2.3 (4.8)	2.2 (4.5)	2.7 (5.5)	2.2 (4.5)	1.6 (3.8)	2.4 (5.1)
Time between blood sample and diagnosis of malignancy (months)	6.9 (4.6)	N/A	N/A	9.8 (12.9)	N/A	N/A	6.5 (8.5)	N/A	N/A	7.7 (10.0)	N/A	N/A
IGF-I (μg/ml)[c]	249 (147)	160 (88)		150 (62)	161 (72)		135 (50)	141 (64)		151 (76)	158 (82)	
IGFBP-2 (μg/ml)	165 (103)	223 (186)		291 (153)	210 (137)		375 (275)	240 (142)		325 (235)	221 (169)	
IGFBP-3 (μg/ml)	4268 (1421)	3353 (1265)		3967 (1171)	3312 (1107)		3383 (1153)	3200 (825)		3670 (1221)	3328 (1186)	
Univariate IGF-I SDS	1.1 (2.5)	−1.1 (2.8)	−0.5 (1.9)	0.7 (1.8)	0.5 (2.5)	0.7 (1.5)	0.8 (1.7)	0.9 (1.8)	0.8 (1.4)	0.79 (1.8)	−0.45 (2.8)	0.31 (1.7)
Univariate IGFBP-2 SDS	−0.7 (0.9)	−1.0 (1.4)		−0.4 (1.1)	−1.1 (1.3)		−0.5 (1.3)	−1.0 (1.1)		−0.50 (1.2)	−1.05 (1.3)	
Univariate IGFBP-3 SDS	0.5 (1.6)	−0.7 (2.1)		0.7 (1.6)	−0.3 (2.1)		0.4 (1.8)	0.2 (1.3)		0.51 (1.7)	−0.5 (2.1)	
Bivariate IGF-I × IGFBP-3 SDS	2.4 (0.9)	2.2 (1.6)		2.0 (0.8)	2.1 (1.4)		1.9 (1.0)	1.8 (0.9)		1.99 (1.0)	2.15 (1.5)	
Bivariate IGF-I × IGFBP-2 SDS	2.2 (0.9)	2.4 (1.6)		1.7 (0.8)	2.1 (1.4)		1.6 (0.9)	1.8 (0.9)		1.69 (0.9)	2.23 (1.5)	
Bivariate IGFBP-2 × IGFBP-3 SDS	1.4 (0.8)	2.0 (1.2)		1.6 (0.6)	1.9 (1.1)		1.6 (1.0)	1.5 (0.7)		1.58 (0.9)	1.94 (1.2)	
Trivariate IGF-I × IGFBP-2 × IGFBP-3 SDS	2.2 (0.8)	2.4 (1.4)		1.9 (0.7)	2.2 (1.2)		1.9 (0.9)	1.9 (0.7)		1.96 (0.9)	2.30 (1.3)	

Values shown are mean (SD).

a The date at which the blood sample was taken for the idiopathic and IGF-I-only reference groups (all available KIMS patients without a malignancy) was the last sample date available in the period 19–30 months after KIMS start.

b Semi or true GH-naive patients were patients with no previous experience of GH treatment or a halt in treatment for at least 6 months before KIMS entry. Non-GH-naive patients have been treated continuously with GH.

c In the IGF-I-only reference group, routine IGF-I measurements recorded in KIMS were made using one of three different methods (RIA, Advantage, and Immulite). Therefore, no mean and SD values are given for IGF-I (μg/ml).

TABLE 2. RR estimates from final multiple log-linear regression models

	% of patients with a malignancy (no. of malignancies)/ (no. of malignancies + idiopathic GHD)	Crude unadjusted univariate SDS assessment RR	Adjusted single univariate SDS assessment[a] RR	Adjusted triple univariate SDS assessment[b] RR	95% CI[c]
Categorical models[a]					
IGF-I SDS			Model 1A	Model 4A	
Less than −2	10 (8/78)	0.38	1.04	1.51	0.71–3.19
−2 to 0	20 (18/90)	0.75	1.05	1.00	0.68–1.46
0–1	27 (27/101)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
1–2	22 (18/81)	0.83	0.98	0.87	0.59–1.28
>2	39 (29/75)	1.45	1.09	0.94	0.65–1.34
IGFBP-2 SDS			Model 2A		
Less than −2	10 (9/92)	0.38	0.57	0.55	0.31–0.95
−2 to −1.5	22 (13/60)	0.84	0.83	0.86	0.57–1.29
−1.5 to −0.5	26 (31/120)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
−0.5 to 0	25 (15/60)	0.97	1.27	1.37	0.94–2.00
More than 0	34 (32/93)	1.33	1.27	1.39	0.98–1.98
IGFBP-3 SDS			Model 3A		
Less than −2	10 (7/70)	0.45	0.92	0.61	0.27–1.36
−2 to 0	19 (25/130)	0.87	1.06	1.03	0.69–1.54
0–1	22 (23/104)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
1–2	31 (27/87)	1.40	1.25	1.29	0.89–1.88
More than 2	53 (18/34)	2.39	1.65	1.92	1.23–2.97

	RR/unit increase SDS (*P* value)	RR/unit increase SDS (95% CI)	RR/unit increase SDS	95% CI
Numerical models[a]		Model 1B	Model 4B	
IGF-I SDS	1.20 (<0.0001)	1.02 (0.95–1.10)	0.96	0.87–1.07
		Model 2B		
IGFBP-2 SDS	1.24 (<0.0001)	1.16 (1.06–1.26)	1.18	1.07–1.30
		Model 3B		
IGFBP-3 SDS	1.27 (<0.0001)	1.08 (1.00–1.18)	1.13	1.02–1.26

For the categorical models, the central category (ref.) was used as the reference in the RR calculation.

[a] Controlling for age at time of blood sample, sex, onset of GHD, and naivety to GH treatment at KIMS start. Each IGF SDS was evaluated separately (unconditionally) in a multiple regression model.

[b] Controlling for age at time of blood sample, sex, onset of GHD, and naivety to GH treatment at KIMS start. SDS for each hormone/protein was evaluated simultaneously (conditionally) in a log-linear multiple Poisson working regression model. Model 4A (categorical) and 4B (numerical).

sidered statistically significant. Models labeled "A" and "B" correspond to the categorical and numerical versions, respectively. Analyses were performed with SAS PROC GENMOD (1999–2001; SAS (r) Proprietary Software Release 8.2; SAS Institute, Cary, NC).

Results

IGF-I SDS was relatively similar between the three patient groups except in those under 40 yr of age ($P = 0.01$) (Table 1). IGFBP-2 and IGFBP-3 SDS values were higher in the malignancy group than the idiopathic GHD group in all three age categories ($P \leq 0.0001$) (Table 1). Bivariate and trivariate SDSs were similar between groups (all $P > 0.12$).

After adjustment for age, sex, onset of GHD, and naivety to GH treatment at KIMS entry, RR per unit IGF-I SDS decreased from 1.20 to 1.02 (Table 2, Crude model and Model 1B, respectively). For IGFBP-2 and IGFBP-3, associations with RR remained significant after adjustment (Table 2: IGFBP-2 in Model 2B, RR of 1.16, 95% CI of 1.06–1.26; IGFBP-3 in Model 3B, RR of 1.08, 95% CI of 1.00–1.18). The final triple SDS regression models (Table 2, Models 4A and 4B) estimated the effects of any single univariate SDS variable with control over the other two univariate SDS variables and also over age, sex, onset of GHD, and GH-naivety. The estimated RR for malignancy after this control was 0.96 (95% CI, 0.87–1.07; $P = 0.48$) per unit IGF-I SDS, 1.18 (95% CI, 1.07–1.30; $P = 0.0006$) per unit IGFBP-2 SDS, and 1.13 (95% CI, 1.02–1.26; $P = 0.01$) per unit IGFBP-3 SDS (Table 2, Model 4B).

Assessments of bivariate and trivariate SDSs did not produce any significant or consistent results compared with the triple univariate SDS models (data not shown).

For the IGF-I-only reference group, the estimated RR per unit IGF-I SDS was 1.18 when unadjusted and 1.02 when adjusted for age-, sex-, onset of GHD, and GH naivety (95% CI, 0.87–1.20).

Discussion

This investigation of the association between IGFs and malignancies is the first to compare measurements during GH therapy of IGF-I, IGFBP-2, and IGFBP-3 in GH-deficient patients. IGF-I levels were targeted to within the normal age-related reference range during treatment. It had been speculated previously that perturbation of IGF-I levels, even within the normal range, may alter the risk of cancer (7). However, results show that there was no association between IGF-I levels during the maintenance phase of GH therapy and the occurrence of cancer. In contrast, elevations in IGFBP-2 and/or IGFBP-3 levels were associated with an increased cancer risk.

IGFBP-2 is the second most abundant circulating IGFBP. IGFBP-2 levels show little diurnal variation and are not influenced by meals or glucose infusion. We found no change in IGFBP-2 levels during GH treatment (data not shown), which is consistent with previous studies on short- and long-term exposure to exogenous GH in healthy adults (19, 20). However, there was an increased RR for *de novo* malignancies with increasing IGFBP-2 SDS. This finding could indicate that IGFBP-2 is produced by tumors or that IGFBP-2 has a role in promoting malignancies. Recent studies provide evidence of a role for IGFBP-2 in cancer growth and also show normalization of IGFBP-2 after successful cancer therapy (21, 22).

IGFBP-3 is the most ubiquitous of the IGFBPs. The relationship between elevated IGFBP-3 levels and an increased risk of malignancies in the present study is intriguing. A systematic review and meta-regression analysis has shown previously that high IGFBP-3 levels were associated with increased risk of premenopausal breast cancer in the general population (6). However, unraveling the role of IGFBP-3 in cancer is complicated, and recent studies on IGFBP-3 polymorphisms and cancer risk have had contradictory outcomes in diverse populations and in multiple types of cancer (23, 24). Thus, the association between IGFBP-3 levels and the risk of cancer needs additional investigation.

The selection of reference subjects is of critical importance. Ideally, if all data are not available, data from a random sample of patients should serve as a reference. This approach was not possible because of the limited availability of serum samples. However, the observation of the same RR of 1.02 per unit IGF-I SDS for the idiopathic GHD group and the IGF-I-only reference group confirms that IGF-I SDS data from the former group were representative of the total population of KIMS patients in estimation of RR.

In addition to certain confounding factors for which it was impossible to control (*e.g.* nutrition and other hormone replacement therapies), the timing of samples may not have been optimal. For instance, it was not possible to check the robustness of the assumptions about maintenance dosing in a controlled manner. The present findings should therefore be confirmed in longitudinal cohort-based studies in which IGF measurements are collected over an extended time period.

In conclusion, it is reassuring that there was no association between IGF-I levels and cancer occurrence in adults with GHD treated with GH. However, it remains prudent to measure IGF-I levels regularly as part of ongoing safety surveillance during GH therapy. Although the findings regarding IGFBP-2 and IGFBP-3 levels require additional confirmation, it is important that clinicians treating patients with GH are aware that any changes in the IGF system may reflect altered cancer risk.

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