CLINICAL STUDY

Prediction of incident diabetes mellitus by baseline IGF1 levels

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Abstract

Objective: IGF1 is associated with metabolic parameters and involved in glucose metabolism. Low-IGF1 has been implicated in the etiology of glucose intolerance and subjects with pathological causes of either low- or high-IGF1 are at risk of diabetes. We hypothesized that both low- and high-IGF1 levels increase the risk of diabetes and aimed to assess the role of IGF1 in the risk of developing diabetes in a large prospective study.

Design: An analysis of two prospective cohort studies, the DETECT study and SHIP.

Methods: We measured IGF1 levels in 7777 nondiabetic subjects and assessed incident diabetes mellitus during follow-up.

Results: There were 464 cases of incident diabetes during 32 229 person-years (time of follow-up in the DETECT study and SHIP: 4.5 and 5 years respectively). There was no heterogeneity between both studies ($P > 0.4$). The hazard ratios (HRs) of incident diabetes in subjects with IGF1 levels below the 10th or above the 90th age- and sex-specific percentile, compared to subjects with intermediate IGF1 levels, were 1.44 (95% confidence interval (CI) 1.07–1.94) and 1.55 (95% CI 1.06–2.06) respectively, after multiple adjustment. After further adjustment for metabolic parameters, the HR for low-IGF1 became insignificant. Analysis of IGF1 quintiles revealed a U-shaped association of IGF1 with risk of diabetes. Results remained similar after exclusion of patients with onset of new diabetes within 1 year or with borderline glucose or HbA1c levels at baseline.

Conclusions: Subjects with low- or high-IGF1 level are at increased risk of developing diabetes.

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Introduction

Diabetes mellitus is a major cause of morbidity and death worldwide. The main causes of diabetes known today are obesity and related consequences, such as insulin resistance, hypertension, dyslipidemia, and inflammation (1–4). Experimental evidence suggests that insulin-like growth factor 1 (IGF1) counteracts these mechanisms at various levels (5, 6).

However, clinical data to support this evidence are scarce. Smaller studies suggest that low-IGF1 or a genetic polymorphism causing low-IGF1 level is associated with increased risk of glucose intolerance or diabetes (7, 8) and patients with low-IGF1 in GH deficiency have an increased prevalence of metabolic syndrome (9).

On the other hand, acromegalics with high-IGF1 due to GH excess are at high risk of diabetes (10). Correspondingly, we found increased prevalence of diabetes in subjects with both low- and high-IGF1 in a cross-sectional study (11).

Therefore, we hypothesized that subjects from the general population with either low- or high-IGF1 are at increased risk of diabetes. To test this hypothesis, we assessed the incidence of diabetes in nondiabetic subjects as a function of IGF1 in two cohorts, namely, the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study and the Study of Health in Pomerania (SHIP).

Subjects and methods

Subjects

Both studies conformed to the principles of the Declaration of Helsinki and were approved by the local ethics committees. All subjects gave written informed

consent. The SHIP only included subjects of Caucasian origin. In the DETECT study, we did not record ethnicity, but, being representative of the German population, the participants were mainly of Caucasian ethnicity.

In the DETECT study, all information was collected by the treating physicians. The baseline evaluation was performed on one of two specified half-days in September 2003 (12). All patients were invited to a follow-up visit at 1 year and at 4.5 years. Diabetes was recorded at baseline, at 1-year-follow-up visit in 2004 and at 4.5-year follow-up visit between September 2007 and February 2008.

In the SHIP, baseline data were collected from 1997 through 2001 (13). All participants were invited to a follow-up visit at 5 years. Diabetes was recorded at baseline and during the 5-year follow-up from 2003 to 2006. Figure 1 shows the flowchart of subjects included in this study. Altogether, the total study population comprised 7777 subjects.

Instruments and measures

Blood was sampled and medical information was collected as described previously (9, 14). Subjects were either fasting or non-fasting in the DETECT study and non-fasting in the SHIP.

In both the studies IGF1 was determined only at baseline with an automated chemiluminescence system (Nichols Institute Diagnostics, San Clemente, CA, USA). The maximal intra- and inter-assay coefficients of variation were 5 and 7% respectively. Glucose was

determined enzymatically (Roche Diagnostics). HbA1c was determined chromatographically (ADAMS HA 8160 analyzing system and Recipe Chemicals + Instruments GmbH in the DETECT study and SHIP respectively).

We defined diabetes mellitus both at baseline and at follow-up as self-reported history of diabetes, intake of oral antidiabetic drugs or insulin, or HbA1c levels $\geq 6.5\%$ (15). Hypertension and dyslipidemia were defined as described previously (11).

Statistical analysis

We calculated age- and sex-specific percentiles of IGF1 using 5-year strata of age. In a power calculation, assuming a 1.5-fold increased risk of incident diabetes in subjects with IGF1 levels below the 10th or above the 90th percentile, we calculated a power of 0.814, of 0.670, and 0.971 for the DETECT study, SHIP, and both studies combined.

Discrete survival time models (16) were calculated with defined survival times at 1-year and 4.5-year follow-ups in the DETECT study and 5-year follow-up in the SHIP. Complementary log–log regression models (17) were performed in the person×year data to estimate the hazard ratios (HRs) of incident diabetes as a function of baseline IGF1.

Besides crude analyses (model 1), we adjusted for the following covariates: model 2 – age, sex, and study; model 3 – model 2 + smoking status, education, family status, physical activity, and alcohol consumption; model 4 – model 3 + hypertension, glucose, dyslipidemia, and waist-to-height ratio.

For sensitivity analyses, we assessed whether the effects persisted after exclusion of the first year of follow-up or after exclusion of patients with borderline glucose (non-fasting glucose > 140 mg/dl) or HbA1c (6.0–6.5%) at baseline.

All statistical analyses were performed using STATA 10.1. A value of $P < 0.05$ was considered statistically significant. The S.E.M. and confidence intervals (CIs) of parameter estimates were calculated by the Huber–White–Sandwich (18) matrix to account for the clustered sampling design.

Results

Baseline characteristics

Table 1 displays the selected baseline demographic and clinical characteristics of the subjects included in this study. Among the classes of IGF1, there were differences in education, physical activity, alcohol consumption, hypertension, HbA1c, and measures of obesity in at least one of the two cohorts. Table 2 displays the differences between subjects lost to follow-up and the subjects included in this study.
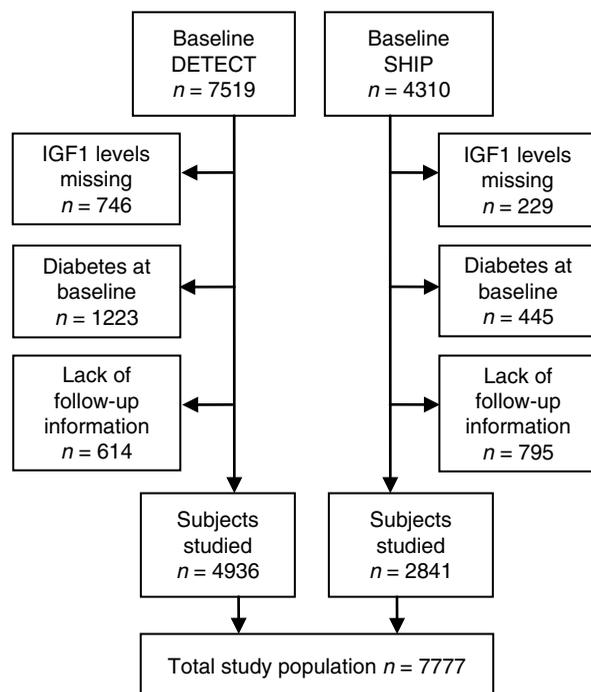
Figure 1 Flowchart of subjects included.

Table 1 Baseline characteristics stratified by study and IGF1 levels.

	DETECT					SHIP				
	Low-IGF1 (n=489)	Intermediate IGF1 (n=3958)	High-IGF1 (n=489)	P value*,†	P value*,‡	Low-IGF1 (n=278)	Intermediate IGF1 (n=2286)	High-IGF1 (n=277)	P value*,†	P value*,‡
Female gender (%)	61.8	61.5	61.8	0.897	0.897	52.5	52.7	52.7	0.962	0.990
Age (years)	56.8 (14.0)	56.2 (14.2)	56.1 (14.1)	0.404	0.796	48.9 (15.0)	47.9 (15.1)	47.6 (15.3)	0.339	0.690
Smoking (%)										
Never smoker	52.3	55.8	55.6			34.4	37.7	36.2		
Ex-smoker	21.0	23.1	23.1	0.715	0.715	31.2	34.0	33.3	0.983	0.899
Current smoker	26.7	21.1	21.2	0.715	0.715	34.4	28.3	30.4	0.065	0.482
Education (%)										
≤9 years	44.8	39.0	39.0			39.1	32.5	38.0		
10 years	26.8	27.0	26.6	0.715	0.990	46.0	48.6	46.4	0.084	0.144
≥11 years	28.5	34.0	34.4	0.005	0.984	14.9	18.9	15.6	0.028	0.069
Family status (%)										
Married	68.3	71.0	73.1			65.1	68.6	66.1		
Single	12.2	10.0	6.5	0.133	0.032	17.6	18.1	20.2	0.883	0.364
Divorced/widowed	19.6	19.0	20.4	0.586	0.493	16.9	13.2	13.4	0.088	0.799
Physical activity (%)										
<2 h/week	36.9	29.4	32.0	0.001	0.399	78.6	72.8	74.3	0.040	0.610
≥2 h/week	63.1	70.6	68.0		0.034	21.4	27.2	25.7		
Any intake of alcohol (%)	78.9	84.4	80.9	0.003	0.275	68.4	67.5	65.7	0.764	0.558
BMI (kg/m²)	27.5 (5.2)	26.5 (4.6)	26.2 (3.9)	0.000	0.000	27.7 (5.2)	26.9 (4.5)	26.9 (4.2)	0.012	0.914
WHtR	0.57 (0.09)	0.55 (0.08)	0.55 (0.08)	0.000	0.942	0.53 (0.08)	0.52 (0.08)	0.52 (0.07)	0.006	0.631
Incident diabetes mellitus (%)	7.0	4.2	7.6	0.002	0.016	6.5	5.2	6.1	0.375	0.514
HbA1c (%)	5.3 (0.4)	5.3 (0.3)	5.3 (0.4)	0.864	0.252	5.3 (0.5)	5.2 (0.5)	5.3 (0.5)	0.003	0.262
Glucose (mg/dl)	93.7 (17.2)	91.7 (15.5)	92.4 (16.1)	0.025	0.343	96.2 (15.1)	95.6 (14.3)	95.9 (13.2)	0.541	0.695
Hypertension (%)	61.2	54.1	57.1	0.002	0.182	46.9	42.1	44.8	0.123	0.392
Dyslipidemia (%)	45.6	45.8	50.1	0.763	0.090	39.1	44.5	44.9	0.092	0.885
hsCRP (mg/l)	6.1 (7.9)	4.1 (6.8)	3.5 (6.7)	0.000	0.084	7.0 (6.9)	5.4 (5.7)	5.9 (7.5)	0.010	0.585

Low: <10th percentile; intermediate: 10th–90th percentile; high >90th percentile. Missing value: smoking, n=159 (2.1%); education, n=148 (1.9%); family status, n=67 (0.9%); physical activity, n=67 (0.9%); any intake of alcohol, n=210 (2.7%); BMI, n=67 (0.9%); WHtR, n=295 (3.9%); HbA1c, n=26 (0.3%); glucose, n=47 (0.6%). *P value from logistic regression analyses for categorical data and linear regression analyses for dimensional data. †P value for test low versus intermediate IGF1 level. ‡P value for test high versus intermediate IGF1 level.

Table 2 Baseline characteristics of subjects lost to follow-up and subjects included in the study.

	Study population (n=7777)	Dropout (n=1406)	*P* value*
Female gender (%)	58.3	53.3	0.000
Age (years)	51.1 (18.1)	53.2 (15.1)	0.000
IGF1 level	138.6 (53.5)	144.7 (61.7)	0.001
Low-IGF1 (%)	10.4	9.6	0.061
Intermediate IGF1 (%)	80.1	80.8	
High-IGF1 (%)	9.5	9.6	
Smoking (%)			
Never smoker	48.6	37.9	0.016
Ex-smoker	26.9	25.3	
Current smoker	24.5	36.8	
Education (%)			
≤9 years	37.4	45.2	0.000
10 years	34.8	32.1	
≥11 years	27.8	22.8	
Family status (%)			
Married	69.9	56.2	0.000
Single	13.0	22.0	
Divorced/widowed	17.1	21.3	
Physical activity (%)			
<2 h/week	53.2	41.5	0.000
≥2 h/week	46.8	58.5	
Any intake of alcohol (%)	77.6	69.5	0.000
BMI (kg/m^2)	26.8 (4.9)	26.7 (4.6)	0.563
WHtR	0.54 (0.09)	0.54 (0.08)	0.448
HbA1c (%)	5.3 (0.5)	5.3 (0.4)	0.173
Glucose (mg/dl)	93.9 (15.2)	93.3 (15.2)	0.196
Hypertension (%)	50.6	47.3	0.041
Dyslipidemia (%)	45.4	44.3	0.375
hsCRP (mg/l)	5.6 (7.5)	4.5 (6.9)	0.028

Low: <10th percentile; intermediate: 10th–90th percentile; high >90th percentile. BMI, body mass index; WHtR, waist to height ratio. *P value from logistic regression analyses for categorical data and linear regression analyses for dimensional data.

Associations between IGF1 and incident diabetes

In the DETECT study and SHIP, 310 and 154 subjects respectively, developed diabetes during follow-up (464 pooled cases during 32 229 person-years). The incidence rate was 14.4 per 1000 person-years.

In the DETECT study, the crude HRs for incident diabetes below the 10th and above the 90th percentile of IGF1 were 1.60 (95% CI 1.16–2.20) and 1.44 (95% CI 1.03–2.01) respectively. In the SHIP, the crude HRs pointed to the same direction but were weaker and not significant (1.25 (95% CI 0.76–2.06) and 1.18 (95% CI 0.71–1.97) respectively). The χ^2 test for homogeneity (19) revealed no heterogeneity among studies ($P=0.400$ and 0.509 respectively). Since the power for the SHIP was too low and we found no heterogeneity, we decided to pool the data from both studies.

Table 3 displays the association of IGF1 with diabetes. High IGF1 was consistently associated with increased risk of diabetes after full adjustment. Low IGF1 was associated with increased risk of diabetes after adjustment for multiple covariates, but this association

became weaker and insignificant after further adjustment for hypertension, glucose, dyslipidemia, and waist-to-height ratio. Additional adjustment for C-reactive protein did not change the results (data not shown). IGF1 used as a continuous quadratic term remained a significant and independent predictor after full adjustment. The results were similar for men and women after separate analysis by sex (data not shown). Analysis of IGF1 quintiles revealed a U-shaped association with the lowest risk of future diabetes in the 3rd quintile of IGF1 (Fig. 2).

Sensitivity analyses

To address the problem of reverse causation (the possibility that precursors of diabetes influence IGF1 levels rather than IGF1 levels being causally related to the development of diabetes), we assessed whether the effects persisted after exclusion of the first year of follow-up (only in the DETECT study since 1-year follow-up was not available in the SHIP). In another analysis, we excluded patients with borderline glucose (non-fasting glucose >140 mg/dl) or HbA1c (6.0–6.5%) at baseline in the pooled studies. Even though type 1 diabetes is unlikely to occur in the adult age, we ran an additional sensitivity analysis by exclusion of subjects aged <35 years, to rule out type 1 diabetes with certainty. Table 3 displays the results. The effect estimates remained similar in the sensitivity analyses and the significances remained unchanged.

Discussion

The main finding of our study is a U-shaped association of IGF1 levels with risk of incident diabetes. This association was persistent after multiple adjustments even though the strength of the effect was weak to moderate. The association of low IGF1 with incident diabetes became weaker and insignificant after further adjustment for abdominal obesity, hypertension, glucose, and dyslipidemia.

We cannot rule out that low IGF1 levels are truly confounded by these metabolic markers, i.e. that these markers influence both IGF1 levels and diabetes risk. However, it is also possible that these markers are in the causal pathway of low IGF1 and diabetes.

Evidence suggests a reciprocal association between low IGF1 levels and metabolic syndrome. On one hand, there is evidence that IGF1 protects against production of free fatty acids, systemic inflammation, β-cell dysfunction, insulin resistance, and hypertension and, thus, low IGF1 promotes metabolic syndrome and development of diabetes (5, 6). On the other hand, the GH–IGF1 axis is blunted in obese subjects and partially restored after weight loss intervention such as bariatric surgery (20), possibly suggesting an opposite causality.

Table 3 Associations between IGF1 and incident diabetes in IGF1 percentiles and continuous IGF1.

	Low-IGF1 (n=767)				Intermediate IGF1 (n=6244) (reference)	High-IGF1 (n=766)				IGF1 continuous					
										Linear coefficient			Quadratic coefficient		
	n (%)	HR	95% CI	P value	n (%)	n (%)	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Crude															
Incident diabetes	52 (6.8)	1.48	1.10–1.99	0.009	286 (4.6)	54 (7.1)	1.52	1.14–2.03	0.005	0.76	0.66–0.88	0.000	1.02	1.01–1.04	0.000
Adjusted for age, gender, and study															
Incident diabetes	52 (6.8)	1.48	1.10–1.99	0.009	286 (4.6)	54 (7.1)	1.57	1.17–2.09	0.002	0.76	0.66–0.88	0.000	1.02	1.01–1.04	0.000
Adjusted for age, gender, smoking status, education, family status, physical activity, alcohol, and study															
Incident diabetes[a]	52 (6.8)	1.44	1.07–1.94	0.015	286 (4.6)	54 (7.1)	1.55	1.16–2.06	0.003	0.77	0.66–0.89	0.001	1.02	1.01–1.04	0.001
Incident diabetes[b]	28 (8.3)	1.54	1.03–2.31	0.037	146 (5.4)	34 (9.8)	1.89	1.30–2.75	0.001	0.71	0.58–0.88	0.001	1.03	1.01–1.05	0.001
Incident diabetes[c]	31 (4.5)	1.51	1.03–2.21	0.036	167 (2.9)	34 (4.7)	1.64	1.13–2.36	0.008	0.72	0.59–0.87	0.001	1.03	1.01–1.05	0.001
Incident diabetes	52 (7.6)	1.46	1.09–1.97	0.012	281 (5.1)	52 (7.7)	1.51	1.12–2.03	0.006	0.77	0.66–0.89	0.001	1.02	1.01–1.04	0.001
Adjusted for age, gender, smoking status, education, family status, physical activity, alcohol, hypertension, glucose, dyslipidemia, WHtR, and study															
Incident diabetes	52 (6.8)	1.25	0.92–1.69	0.159	286 (4.6)	54 (7.1)	1.58	1.18–2.12	0.002	0.82	0.71–0.96	0.011	1.02	1.01–1.03	0.007

Low: <10th percentile; intermediate: 10th–90th percentile; high >90th percentile. HR, hazard ratio from discrete survival analyses; CI, confidence interval.
[a]Analyses performed only in the DETECT study, exclusion of patients with only 1-year follow-up.
[b]Exclusion of patients with glucose >140 mg/dl or HbA1c 6.0–6.49%.
[c]Exclusion of patients aged <35 years.

IGF1 is mainly bound to IGF-binding proteins (IGFBPs-1 to -6) and other plasma proteins. IGFBPs protect IGF1 from rapid degradation and regulate its bioavailability (6). Moreover, IGFBPs are modulated by insulin. IGFBP-1 correlates positively with insulin sensitivity and high-IGFBP-2 suggests high-insulin sensitivity and might be increased by insulin (21). Thus, IGF1 levels in this study also reflect the complex interplay between insulin, glucose metabolism, and the IGF system.

There is no clear explanation for the association of high-IGF1 level with increased risk of diabetes. GH stimulates IGF1 secretion and decreases insulin sensitivity (22). In transgenic mice, overexpressing IGF1, hypoglycemia, and resistance to diabetes were found (23). However, mice overexpressing GH have high-IGF1, insulin resistance, and increased likelihood of developing diabetes (24).

Potentially, though speculative, in subjects with high-IGF1, GH secretion is increased causing insulin resistance and diabetes. In fact, we have found the prevalence of acromegaly to be higher than expected in the DETECT study (25). Yet, most subjects with abnormally high-IGF1 level did not have pathologically increased GH secretion. Therefore, if increased GH is the cause of elevated diabetes risk, the increase must be subclinical in most cases. Thus, the pathomechanisms involved in the association of IGF1 with the development of diabetes are likely to be different for low and high levels of IGF1: although a lack of protective effects against diabetes seems to play a role in low-IGF1 state, potentially increased GH secretion or other, unknown, causes might be involved in states of high-IGF1.

This study confirms and extends the findings of Sandhu *et al.* (7) and of Vaessen *et al.* (8). They have found an increased risk of glucose intolerance or diabetes in subjects with low-IGF1 level or a genetic polymorphism associated with low-IGF1 level respectively. However, unlike this study, those studies have not found a U-shaped association with increased risk of diabetes at both low- and high-IGF1 levels. Potential reasons for these differences include differences in study size or design and mere chance. Both studies were significantly smaller than our studies and had fewer events. Moreover, Vaessen *et al.* (8) used a dichotomized predictor, not allowing assessing curvilinear associations. In addition, the findings of Vaessen *et al.* (8) were not confirmed by another study (26).

This study has several strengths and limitations. A major strength is the prospective design, the size, and large number of events. This allows making assumptions on causality and detecting weak to moderate effects. Furthermore, the fact that the same method was used for IGF1 measurement and there was no heterogeneity between the studies also allowed pooling the two cohorts.

We did not measure insulin, homeostatic model assessment (HOMA) index, GH secretion, or IGFBPs. Thus, we were not able to further analyze the
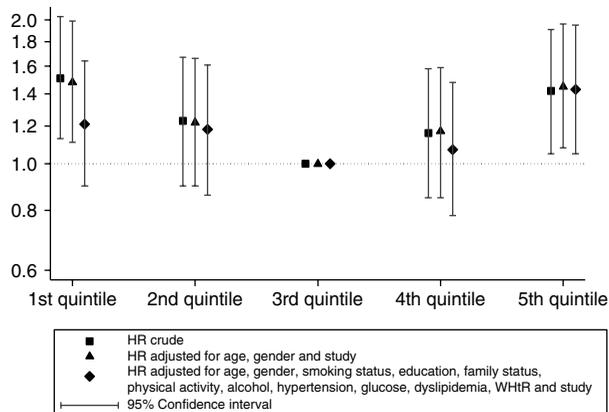
Figure 2 U-shaped association of incident diabetes mellitus and IGF1.

associations between these systems. This study was mainly designed to identify whether IGF1 levels can be used as biomarkers for diabetes risk rather than to elucidate the complex interplay of associated factors. Further studies, assessing the factors mentioned above, are needed to answer the question how these factors interact with IGF1 and diabetes.

Like in any cohort study, we cannot rule out residual confounding. Moreover, the number of events is still too limited for a detailed subgroup analysis. The follow-up time might be too short to detect late effects. In addition, we cannot exclude that the dropouts from this study were informative. To address this issue, we compared the dropouts and completers at baseline. Even though some differences were significant, these differences were generally small. Therefore, we think a potential bias due to dropout is likely to be small.

We cannot rule out reverse causation with certainty. However, to address this problem we excluded subjects with incident diabetes within 1 year or with border-line glucose or HbA1c. This did not change or even increased the effect estimates. Therefore, reverse causation appears unlikely and IGF1 seems to play a true causal role in the development of diabetes.

This study was performed in a mainly Caucasian, European population, representative of the German population. We do not know whether our findings are generalizable to other populations or ethnicities.

In summary, we have shown that subjects with low- or high-IGF1 level are at increased risk of developing diabetes. IGF1 is an independent predictor of diabetes. Therefore, IGF1 might improve risk stratification for incidence of diabetes, if our results are confirmed and validated in further studies. Though our study did not allow elucidating the underlying pathomechanisms, it seems likely that different mechanisms are involved in the associations of low- and high-IGF1 with risk of diabetes. Further studies are needed to confirm these findings, to test generalizability, and to elucidate the underlying pathomechanisms.

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