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Association between glycaemic status and the risk of acromegaly: a nationwide population-based cohort study

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ABSTRACT

Objectives Although evidence suggests that the overall prevalence of type 2 diabetes mellitus (T2DM) was already higher in the acromegaly group than in the general population several years before diagnosis, the effect of glycaemic status on the risk of developing acromegaly remains unclear.

Design Retrospective cohort study.

Setting Data were obtained from the National Health Insurance Services in Korea. Baseline glycaemic status was defined based on fasting plasma glucose levels and prescription records, and it was classified into three categories: normal fasting glucose (NFG), impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM) or five categories: NFG, IFG, new-onset T2DM, well-controlled T2DM and poorly controlled T2DM.

Participants A total of 9 707 487 adults without acromegaly participated in the national health screening programme in 2009 and were followed up until 2019.

Primary and secondary outcome measures The main outcome of interest was the diagnosis of incident acromegaly.

Results Over a median follow-up period of 9.2 years, 434 people (4.5 cases per 100 000 people) developed acromegaly at least 1 year after enrolment. Participants with IFG and T2DM exhibited an increased risk of acromegaly, with hazard ratios (HR) of 2.27 (95% CI 1.84 to 2.80) and 2.45 (95% CI 1.78 to 3.39), respectively, compared with those with NFG. When participants were categorised into five glycaemic status groups, an increased risk of acromegaly was observed in those with new-onset T2DM (HR 2.18, 95% CI 1.38 to 3.43) and well-controlled T2DM (HR 2.29, 95% CI 1.28 to 4.09), similar to individuals with IFG, with the highest risk found in individuals with poorly controlled T2DM (HR 3.07, 95% CI 1.88 to 5.01). These associations are persistent across various subgroups, regardless of age, sex, lifestyle factors and the presence of comorbidities.

Conclusions The results of this study supported that alterations in glucose metabolism, including IFG and T2DM, are associated with an increased risk of acromegaly.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study leveraged data from the National Health Insurance Service, a well-validated longitudinal national dataset.
⇒ This research employed a large sample size to explore the association between glycaemic status and acromegaly, a rare and incurable condition that poses challenges for analysis in large-scale prospective studies.
⇒ Due to the absence of biochemical data for diagnosing acromegaly, we relied on a national registry for rare, incurable diseases to define cases of acromegaly.
⇒ The generalisability of these findings may be restricted to the adult population in Korea.

INTRODUCTION

Acromegaly is a rare endocrine disease that is characterised by excess circulating levels of growth hormone (GH), usually caused by a GH-secreting pituitary adenoma.[1] Owing to its slow and insidious onset, the diagnosis of acromegaly is often delayed, leading to increased comorbidities and mortality and long-term complications.[1 2] Most patients have a high prevalence of metabolic complications including impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM) several years before diagnosis.[2 3] Since the mortality in patients with acromegaly is determined not only by disease duration but also by biochemical control and the accessibility of advanced therapies for acromegaly-related complications,[4 5] early diagnosis and treatment are critical to achieving a good prognosis and avoiding long-term comorbidities.

GH, a counter-regulatory hormone, opposes insulin's effects on glucose metabolism by inhibiting hepatic gluconeogenesis suppression[6] and increasing free fatty acid (FFA) levels through enhanced lipolysis.[7 8] This leads to glucose-fatty acid competition, reducing glucose utilisation in muscle.[9] Consequently, T2DM occurs more frequently in patients with acromegaly than in the general population,[1 2 10 11] and the prevalence of DM progressively increases with prolonged disease duration.[11] Patients with acromegaly and concomitant T2DM have

increased overall mortality and cardiovascular morbidity and mortality compared with those without T2DM.[12 13] A recent Korean study showed that patients with acromegaly had a higher prevalence of T2DM than the general population (54.5% vs 15.1%), and the overall prevalence of T2DM was already higher in the acromegaly group than in the general population (30.5% vs 8.6%), even two years before the diagnosis of acromegaly.[14]

However, large-scale population-based data on the effect of blood glucose levels before the diagnosis of acromegaly on the risk of developing acromegaly are lacking. Therefore, we investigated the association between glycaemic status and the risk of acromegaly in the general population of Korea using a large-scale population dataset from the National Health Insurance Service (NHIS).

METHODS

Data sources

This study used data from the NHIS, a public database on healthcare utilisation and health screening, which contains longitudinal data on 97% of the Korean population.[15 16] In Korea, a 'rare incurable disease' refers to diseases in which the number of patients is less than 20 000 or unknown due to difficulty in diagnosis, which is determined according to the procedures and standards prescribed by the Ordinance of the Ministry of Health and Welfare based on the 'Rare Disease Management Act'.[17] Since 2009, the government has provided financial support through the NHIS by reducing medical expenses for patients with rare incurable diseases. Both imaging (MRI or CT) compatible with acromegaly and biochemistry results (GH overproduction proven by the glucose tolerance test) are required to obtain the code for acromegaly (V112) and register in the rare incurable disease registry for financial support.[18] This study protocol was approved by the Institutional Review Board of Hallym University College of Medicine (no. 2023-01-006) and was conducted in accordance with the Declaration of Helsinki of the World Medical Association. The requirement for informed consent was waived because we used anonymous and de-identified data according to the confidential guidelines of the NHIS of Korea.

Study population

We initially included 10 628 070 participants who underwent national health examinations in 2009 (index year). Of these, participants under 20 years of age (n=41 822), those with missing data on fasting plasma glucose levels or other parameters such as body composition indices (waist circumference (WC), weight, height), lifestyle factors (income, smoking, alcohol consumption, physical activity) and additional metabolic factors (blood pressure, creatinine and total cholesterol levels) (n=683 138), those with type 1 diabetes (n=170 855) and those with pre-existing acromegaly at baseline (n=570) were excluded from the study. We also excluded 24 198 patients who died or were diagnosed with acromegaly within 1 year of the index year. In total, 9 707 487 individuals were included in the analysis (figure 1). The study population was followed up from baseline to the onset of acromegaly, date of death, or 31 December 2019, whichever came first.

Ascertainment of acromegaly

The outcome of this study was newly diagnosed acromegaly. A diagnosis of acromegaly was defined as a patient who had a history of outpatient care or hospitalisation based on both the International Classification of Diseases, 10th revision (ICD-10) code (E22.0), and the code for financial support by reducing medical expenses (V112).[12 19] Incident acromegaly was identified until 31 December 2019.

Definition of glycaemic status

T2DM was defined either by searching for ICD-10 codes E11-14 and at least one prescription of anti-diabetic medications or a fasting plasma glucose (FPG) level of ≥126 mg/dL.[20] Non-diabetic participants were further divided into two groups according to their FPG levels: normal fasting glucose (NFG, FPG<100 mg/dL) and IFG (FPG 100–125 mg/dL).[21] In addition, we classified patients with T2DM into three categories based on glycaemic recommendation by American Diabetes Association[22] and their history of prescribing anti-diabetic medications: new-onset (FPG≥126 mg/dL without prescription of anti-diabetic medications), well-controlled (FPG≤130 mg/dL with prescription of anti-diabetic medications), and poorly controlled T2DM (FPG>130 mg/dL with prescription of anti-diabetic medications). We also divided the study population into four groups according to the FPG quartiles. FPG levels by quartiles are ≤85 mg/dL for Q1, 86–92 mg/dL for Q2, 93–101 mg/dL for Q3 and ≥102 mg/dL for Q4.

Measurements of covariates

Anthropometric and laboratory measurements were performed after overnight fasting. Quality control of laboratory tests was conducted by the procedures of the Korean Association of Laboratory Quality Control.[23] Body mass index (BMI) was calculated as body weight in kilograms (kg) divided by height squared (m^2). Information on current smoking status, alcohol consumption (at least one drink per week) and regular exercise (mid-term exercise on at least 5 days or vigorous exercise on at least 3 days per week) was obtained from a questionnaire completed during the health examination. A low-income level was defined as a lower 25% of the income distribution. Obesity was defined as BMI≥25 kg/m^2.[24] Hypertension was defined as systolic blood pressure (BP)≥140 mm Hg or diastolic BP≥90 mm Hg or the presence of I10–13 and I15 with anti-hypertensive medications at the time of screening.[25] Dyslipidaemia was defined as total cholesterol ≥240 mg/dL or the presence of E78 with anti-hyperlipidemic medications.[26] Chronic kidney disease (CKD) was defined using the ICD-10 codes N18 or N19, and an estimated glomerular filtration rate (eGFR) of

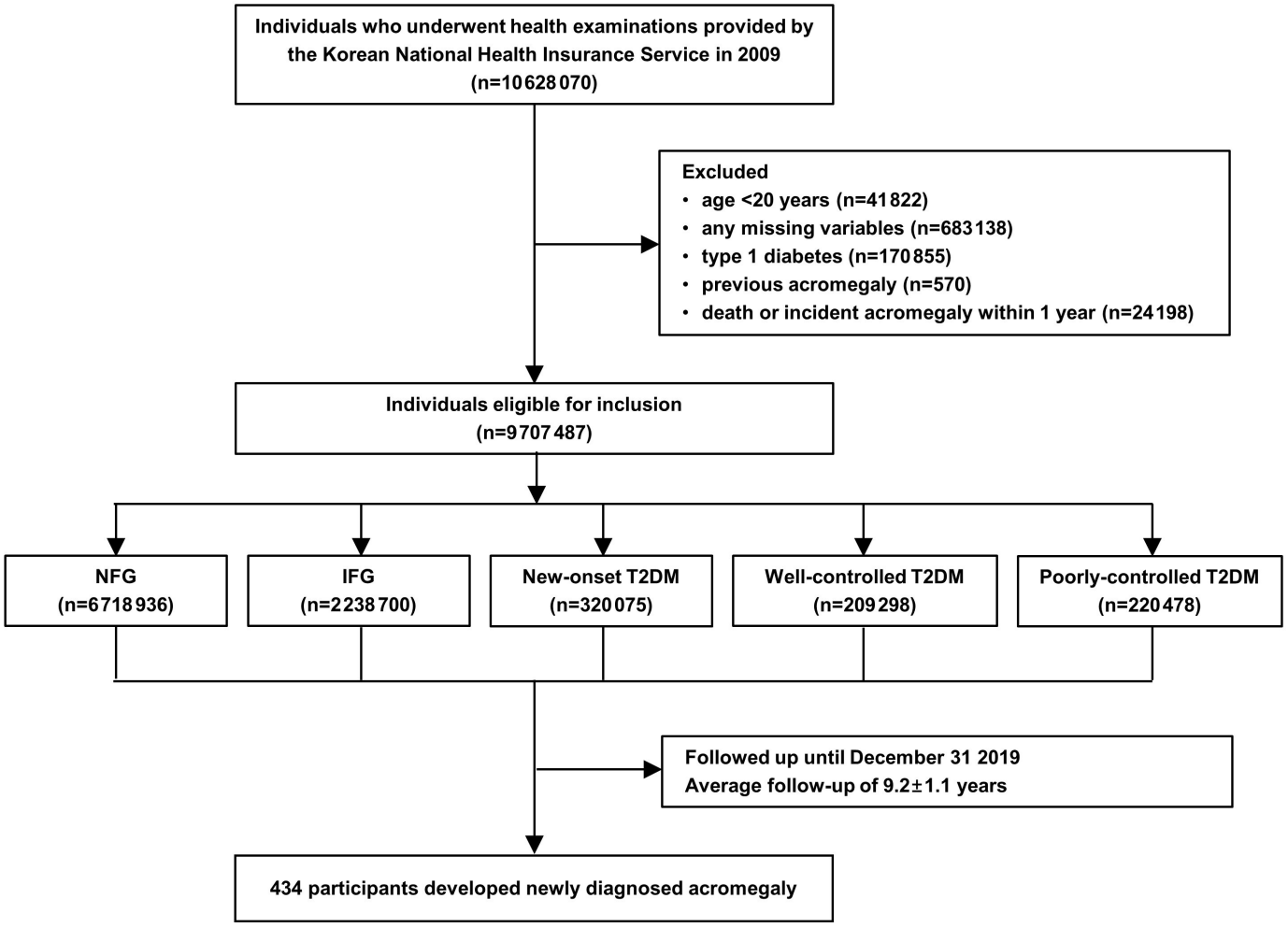

Figure 1 Flowchart of the study population. IFG, impaired fasting glucose; NFG, normal fasting glucose; T2DM, type 2 diabetes mellitus.

<60 mL/min/1.73 m^2 was assessed using the CKD Epidemiology Collaboration Equation on more than two occasions during the medical check-up.[25] The presence of cancer was defined as at least one claim under ICD-10 codes C00-C97[27] and chronic obstructive pulmonary disease (COPD) as having ICD-10 code J43–J44 (except J430) and medication use at least two times per year.[28]

Statistical analysis

Descriptive statistics were used to assess the baseline characteristics of the study population. Results were described as mean±SD for continuous variables and counts (percentage, %) for categorical variables. Continuous variables were compared using a t-test or analysis of variance, while categorical variables were compared using the χ^2 test. The incidence rate of acromegaly was calculated by dividing the number of events by the total number of person-years of follow-up and exhibited per 1000 person-years. Kaplan-Meier curves were obtained to estimate the cumulative incidence of acromegaly, and the log-rank test was used to analyse the differences between the groups. Cox proportional hazards regression analysis was performed to compare the relative risk of acromegaly between groups, with adjustments for age, sex, income, smoking status, alcohol consumption, regular exercise, obesity, hypertension, dyslipidaemia, CKD, cancer, COPD and height. Subgroup analyses were also conducted, stratified by age, sex, income, lifestyle factors (smoking, drinking and regular exercise) and the presence or absence of comorbidities (obesity, hypertension, dyslipidaemia, CKD, cancer and COPD), through stratified analysis and interaction testing using a likelihood ratio test. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a two-sided p value<0.05.

Patient and public involvement

Neither patients nor the public participated in the design, conduct, reporting or dissemination plans of this research. Involvement of patients or the public was not appropriate or feasible for this retrospective study.

RESULTS

Baseline characteristics of the study population

Among the 9 707 487 participants with complete follow-up data, 434 (4.5 cases per 100 000 people) had incident acromegaly events during the median follow-up period

Table 1 Baseline characteristics of study population according to glycaemic status

	Total	Glycaemic status			P value
		NFG	IFG	T2DM	
n	9 707 487	6 718 936	2 238 700	749 851	
Men (%)	5 299 768 (54.6)	3 439 419 (51.2)	1 386 991 (62.0)	473 358 (63.1)	<0.0001
Age (years)	47.1±14.0	45.1±13.8	49.8±13.2	56.7±12.1	<0.0001
Age group (%)					
20–39 years	3 040 839 (31.3)	2 473 845 (36.8)	505 537 (22.6)	61 457 (8.2)	
40–64 years	5 431 466 (56.0)	3 556 870 (52.9)	1 396 812 (62.4)	477 784 (63.7)	
≥65 years	1 235 182 (12.7)	688 221 (10.2)	336 351 (15.0)	210 610 (28.1)	
Height (cm)	163.9±9.2	163.9±9.2	164.3±9.2	162.8±9.2	<0.0001
Weight (kg)	63.9±11.6	62.9±11.5	66.0±11.6	66.6±11.7	<0.0001
BMI (kg/m^2)	23.7±3.2	23.3±3.2	24.4±3.2	25.1±3.3	<0.0001
WC (cm)	80.2±9.1	78.8±9.0	82.4±8.7	85.5±8.5	<0.0001
FPG (mg/dL)	96.8±22.5	87.5±7.7	107.8±6.6	146.5±48.0	<0.0001
SBP (mmHg)	122.4±15.0	120.5±14.5	125.8±15.1	129.2±15.8	<0.0001
DBP (mmHg)	76.3±10.1	75.28±9.9	78.3±10.1	79.32±10.3	<0.0001
TC (mg/dL)	195.1±36.7	192.5±35.5	201.8±37.6	197.8±41.9	<0.0001
eGFR (mL/min/1.73 m^2)	87.7±45.4	89.0±49.1	85.1±35.3	83.8±36.6	<0.0001
Low income (%)	1 890 980 (19.5)	1 315 860 (19.6)	420 311 (18.8)	154 809 (20.7)	<0.0001
Smoking (%)	2 538 675 (26.2)	1 712 441 (25.5)	623 262 (27.8)	202 972 (27.1)	<0.0001
Drinking (%)	4 712 486 (48.5)	3 199 825 (47.6)	1 175 584 (52.5)	337 077 (45.0)	<0.0001
Regular exercise (%)	1 735 929 (17.9)	1 149 301 (17.1)	423 650 (18.9)	162 978 (21.7)	<0.0001
Obesity (%)	3 151 734 (32.5)	1 886 714 (28.1)	899 583 (40.2)	365 437 (48.7)	<0.0001
Hypertension (%)	2 551 650 (26.3)	1 356 172 (20.2)	764 305 (34.1)	431 173 (57.5)	<0.0001
Dyslipidaemia (%)	1 654 944 (17.1)	894 516 (13.3)	477 365 (21.3)	283 063 (37.8)	<0.0001
CKD (%)	657 836 (6.8)	393 693 (5.9)	176 786 (7.9)	87 357 (11.7)	<0.0001
MI (%)	35 633 (0.4)	18 852 (0.3)	9253 (0.4)	7528 (1.0)	<0.0001
Stroke (%)	31 173 (0.3)	16 753 (0.3)	7881 (0.4)	6539 (0.9)	<0.0001
Cancer (%)	122 334 (1.3)	77 690 (1.2)	30 109 (1.3)	14 535 (1.9)	<0.0001
COPD (%)	518 326 (5.3)	331 197 (4.9)	126 533 (5.7)	60 596 (8.1)	<0.0001

P value derived using ANOVA and χ^2 tests. Data are expressed as mean±SD, or n (%).
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IFG, impaired fasting glucose; MI, myocardial infarction; NFG, normal fasting glucose; SBP, systolic blood pressure; TC, total cholesterol; T2DM, type 2 diabetes mellitus; WC, waist circumference.

of 9.2±1.1 years. Baseline characteristics of the study population according to the presence of acromegaly are shown in online supplemental table 1. Patients with acromegaly had higher height, weight, BMI, WC and systolic and diastolic BP compared with controls, while their total cholesterol levels were lower. In patients with acromegaly, a higher prevalence of obesity, hypertension and cancer, as well as a lower prevalence of dyslipidaemia, was found. Patients with acromegaly had significantly higher mean FPG levels (96.8±22.5 vs 103.8±25.0, p<0.001) and more prevalence of IFG (23.1% vs 37.1%) and T2DM (7.7% vs 12.2%) than patients without acromegaly at baseline (p<0.001).

The demographic and clinical characteristics of the study population according to the glycaemic status are shown in table 1. Compared with those with NFG, individuals with IFG or T2DM were more likely to be male, older, have higher weight, BMI, WC, FPG, systolic and diastolic BP, and lower GFR at baseline. The prevalence of obesity, hypertension, dyslipidaemia, CKD, MI, stroke, cancer and COPD was higher in patients with IFG and T2DM than in those without IFG or T2DM.

Cumulative incidence of acromegaly according to glycaemic status

The cumulative incidence of acromegaly according to glycaemic status was analysed (figure 2). The annual

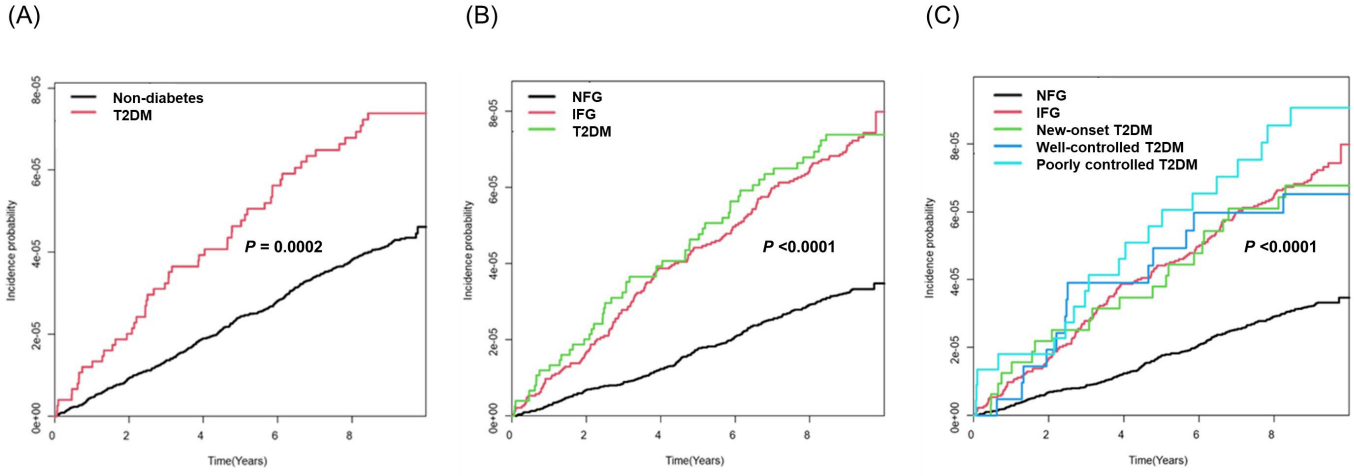

Figure 2 Kaplan-Meier curves for the cumulative incidence of acromegaly according to (A) the presence of T2DM, (B) three categories (NFG, IFG and T2DM) and (C) five categories (NFG, IFG, new-onset T2DM, well-controlled T2DM and poorly controlled T2DM) of glycaemic status. IFG, impaired fasting glucose; NFG, normal fasting glucose; T2DM, type 2 diabetes mellitus.

incidence of acromegaly was significantly higher in the T2DM group than in the non-diabetic group (0.796 vs 0.463 per 100 000 person-years; log-rank test, p=0.0002) (figure 2A). When non-diabetic patients were further divided into NFG and IFG, patients with IFG (0.787 per 100 000 person-years) had an increased risk of acromegaly compared with those with NFG (0.355 per 100 000 person-years), similar to those with T2DM (log-rank p between three categories, p<0.0001) (figure 2B). When subjects with T2DM were further categorised into new-onset, well-controlled and poorly controlled T2DM groups, the annual incidence of acromegaly was higher in new-onset and well-controlled T2DM groups (0.730 and 0.708 per 100 000 person-years, respectively), and even higher in poorly controlled T2DM group (0.976 per 100 000 person-years) (log-rank p between five categories, p<0.0001) (figure 2C).

Risk of acromegaly according to glycaemic status

The risk of acromegaly according to the degree of glycaemic control was performed by multivariate analyses (table 2). The T2DM group had a higher incidence of acromegaly compared with the non-diabetes group (unadjusted HR 1.72, 95% CI 1.29 to 2.29). The increased risk of acromegaly in the T2DM group was maintained (HR 1.72, 95% CI 1.27 to 2.33) after adjusting for age, sex, smoking, alcohol consumption, exercise, income, diabetes, hypertension, dyslipidaemia, CKD, cancer, COPD and height.

When the glycaemic status was divided into NFG, IFG and T2DM, the risk of acromegaly increased in patients in the IFG (HR 2.27, 95% CI 1.84 to 2.80) and T2DM groups (HR 2.45, 95% CI 1.78 to 3.39) compared with the NFG group after adjusting for all covariates (p for trend <0.0001). Next, we divided glycaemic status into NFG, IFG and new-onset, well-controlled and poorly controlled T2DM. The risk of acromegaly was significantly increased in patients with IFG (HR 2.27, 95% CI 1.84 to 2.80), new-onset (HR 2.18, 95% CI 1.38 to 3.43) well-controlled T2DM (HR 2.29, 95% CI 1.28 to 4.09) and even higher in poorly controlled T2DM (HR 3.07, 95% CI 1.88 to 5.01), using NFG as reference, after adjusting for all confounding variables.

Subgroup analyses

We used subgroup analysis to take into account covariates that could affect the findings on the relationship between T2DM and incident acromegaly (table 3). In all subgroups, the risk of acromegaly was higher in the IFG and T2DM groups than in the NFG group. The increased risk of acromegaly in the IFG and T2DM groups was more pronounced in patients without hypertension (p for interaction 0.0112) and dyslipidaemia (p for interaction 0.0299). No effect modification was observed according to age, sex, low income, smoking status, alcohol consumption, regular exercise and the presence of obesity, CKD, cancer and COPD. In addition, the risk of acromegaly according to five glycaemic status categories was calculated for all subgroups (online supplemental table 2). In comparison with the NFG group, the increased risk of acromegaly in IFG, new-onset, well-controlled and poorly controlled T2DM was found in all subgroups, and the increased risk of acromegaly was more pronounced in individuals without hypertension (p for interaction 0.0078) and dyslipidaemia (p for interaction 0.0433).

Risk of acromegaly according to glucose quartiles

The risk of acromegaly showed a stepwise increase according to FPG quartiles (online supplemental table 3). The HRs (95% CI) of acromegaly were 1.24 (0.89–1.74), 1.61 (1.17–2.20) and 3.20 (2.38–4.30) in the Q2, Q3 and Q4 of FPG, respectively, compared with those in the Q1 of FPG. The risk of acromegaly was significantly increased in the higher quartiles of FPG in all subgroups, regardless of age and sex. The risk of acromegaly in Q3 and Q4 of the FPG was significantly increased even among participants

Table 2 Risk for incident acromegaly by (A) the presence of T2DM, (B) three categories and (C) and five categories of glycaemic status

	Number (n)	Events (n)	Follow-up duration (PY)	Incidence rate (per 1000 PY)	HR (95% CI) Unadjusted	Adjusted
A						
Non-diabetic	8957636	381	82354240.42	0.463	1 (ref)	1 (ref)
T2DM	749851	53	6658556.12	0.796	1.72 (1.29, 2.29)	1.72 (1.27, 2.33)
P for trend					0.0002	0.0005
B						
NFG	6718936	220	61897914.92	0.355	1 (ref)	1 (ref)
IFG	2238700	161	20456325.5	0.787	2.21 (1.81, 2.71)	2.27 (1.84, 2.80)
T2DM	749851	53	6658556.12	0.796	2.24 (1.66, 3.02)	2.45 (1.78, 3.39)
P for trend					<0.0001	<0.0001
C						
NFG	6718936	220	61897914.92	0.355	1 (ref)	1 (ref)
IFG	2238700	161	20456325.5	0.787	2.21 (1.81, 2.71)	2.27 (1.84, 2.80)
New-onset T2DM	320075	21	2875834.25	0.730	2.05 (1.31, 3.21)	2.18 (1.38, 3.43)
Well-controlled T2DM	209298	13	1835752.7	0.708	1.99 (1.14, 3.48)	2.29 (1.28, 4.09)
Poorly controlled T2DM	220478	19	1946969.18	0.976	2.74 (1.72, 4.38)	3.07 (1.88, 5.01)
P for trend					<0.0001	<0.0001

Adjusted HR was determined by conducting a multivariate Cox proportional hazards regression analysis adjusting for age, sex, smoking status, alcohol consumption, regular exercise, low income, obesity, hypertension, dyslipidaemia, CKD, cancer, COPD and height.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IFG, impaired fasting glucose; NFG, normal fasting glucose; PY, person years; T2DM, type 2 diabetes mellitus.

not taking anti-diabetic medication: 1.58 (1.16–2.17) and 3.18 (2.37–4.28), respectively.

DISCUSSION

This nationwide, population-based cohort study is the first to demonstrate an association between glycaemic status and the risk of acromegaly in the general Korean population. The risk of acromegaly increased twofold in patients with IFG compared with those with NFG during 9.2 years of follow-up, similar to the increased risk in patients with T2DM. The risk of acromegaly increased in patients with poorly controlled T2DM more than in those with new-onset and well-controlled T2DM. Moreover, these associations remained consistent irrespective of age, sex, lifestyle factors and the presence of comorbidities. These results suggest that abnormal glucose metabolism may serve as a surrogate marker for identifying individuals who are at higher risk of developing acromegaly.

GH, a counter-regulatory hormone, antagonises the hepatic and peripheral effects of insulin on glucose metabolism and inhibits insulin-induced suppression of hepatic gluconeogenesis.[6] In addition, GH increases circulating levels of FFA by activating lipolysis and inhibiting the uptake of FFA into adipose tissue.[7 8] This lipolytic effect of GH results in glucose-fatty acid substrate competition and reduces glucose utilisation in the muscles.[9] Since insulin resistance is normally counterbalanced by increased insulin secretion from pancreatic β-cells in patients with acromegaly, impaired glucose tolerance occurs with reduced insulin secretion.[29] Pancreatic β-cell dysfunction and the consequent decline in insulin secretion contribute significantly to the development of T2DM in insulin-resistant patients with acromegaly.[30]

Several epidemiological studies have reported that T2DM occurs more frequently in patients with acromegaly than in the general population.[1 2 10 11] A recent Korean study found that even 2 years before the acromegaly diagnosis, the acromegaly group already had a higher prevalence of T2DM than the general population.[14] The present study is the first nationwide cohort study to examine the effect of blood glucose levels before the diagnosis of acromegaly on the risk of developing acromegaly in the general Korean population. The HR for developing acromegaly was twice as high in subjects with IFG and T2DM than in subjects with NFG. Moreover, even in people not taking anti-diabetic medications, a small increase in FPG levels above 102 mg/dL significantly increased the risk of acromegaly. Likewise, previous studies have demonstrated that about 50% of patients with acromegaly had pre-diabetes at the time of diagnosis.[3 31] The prevalence of T2DM increases progressively with disease duration.[11] Patients with biochemically uncontrolled acromegaly have a higher frequency of T2DM than their control counterparts.[32] Moreover, T2DM has been suggested as

Table 3 Risk for incident acromegaly by glycaemic status in subgroups

Subgroups		HR (95% CI)			P for interaction
		NFG	IFG	T2DM	
Sex	Male	1 (Ref.)	1.80 (1.35, 2.41)	2.09 (1.37, 3.20)	0.0518
	Female	1 (Ref.)	2.95 (2.21, 3.99)	2.98 (1.89, 4.70)	
Age	20–39	1 (Ref.)	2.35 (1.62, 3.41)	2.19 (0.89, 5.43)	0.3787
	40–64	1 (Ref.)	2.13 (1.64, 2.78)	2.72 (1.91, 3.87)	
	≥65	1 (Ref.)	3.15 (1.36, 7.27)	1.09 (0.29, 4.02)	
Low income	No	1 (Ref.)	2.54 (2.03, 3.20)	2.51 (1.76, 3.58)	0.0884
	Yes	1 (Ref.)	1.34 (0.79, 2.29)	2.35 (1.20, 4.57)	
Smoking	No	1 (Ref.)	2.56 (2.02, 3.25)	2.52 (1.74, 3.65)	0.1814
	Yes	1 (Ref.)	1.63 (1.06, 2.50)	2.37 (1.31, 4.28)	
Drinking	No	1 (Ref.)	2.63 (1.99, 3.48)	2.67 (1.77, 4.01)	0.3607
	Yes	1 (Ref.)	1.95 (1.44, 2.66)	2.25 (1.39, 3.66)	
Regular exercise	No	1 (Ref.)	2.34 (1.86, 2.95)	2.34 (1.63, 3.38)	0.6798
	Yes	1 (Ref.)	2.11 (1.30, 3.42)	2.93 (1.58, 5.45)	
Obesity	No	1 (Ref.)	2.63 (1.96, 3.52)	3.66 (2.32, 5.78)	0.0668
	Yes	1 (Ref.)	1.99 (1.49, 2.66)	1.85 (1.21, 2.82)	
Hypertension	No	1 (Ref.)	2.49 (1.93, 3.21)	3.85 (2.56, 5.79)	0.0112
	Yes	1 (Ref.)	1.86 (1.30, 2.67)	1.50 (0.93, 2.42)	
Dyslipidaemia	No	1 (Ref.)	2.52 (2.01, 3.14)	2.83 (1.99, 4.04)	0.0299
	Yes	1 (Ref.)	1.18 (0.65, 2.14)	1.34 (0.68, 2.64)	
CKD	No	1 (Ref.)	2.29 (1.85, 2.84)	2.49 (1.79, 3.46)	0.9911
	Yes	1 (Ref.)	2.35 (0.93, 5.92)	2.34 (0.72, 7.65)	
Cancer	No	1 (Ref.)	2.30 (1.86, 2.85)	2.47 (1.78, 3.43)	0.9925
	Yes	1 (Ref.)	2.14 (0.58, 7.98)	2.52 (0.49, 13.00)	
COPD	No	1 (Ref.)	2.24 (1.80, 2.77)	2.45 (1.76, 3.42)	0.5488
	Yes	1 (Ref.)	3.76 (1.51, 9.37)	3.14 (0.94, 10.47)	

The HRs were determined by conducting a multivariate Cox proportional hazards regression analysis adjusting for age, sex, smoking status, alcohol consumption, regular exercise, low income, obesity, hypertension, dyslipidaemia, CKD, cancer, COPD and height.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IFG, impaired fasting glucose; NFG, normal fasting glucose; T2DM, type 2 diabetes mellitus.

a predictor of disease activity, mortality and difficulty in disease control in patients with acromegaly.[33 34]

Women, particularly those in the premenopausal state, have a lower incidence of insulin resistance than men of a similar age.[35] In contrast, women with active untreated acromegaly showed higher insulin resistance and more frequent features of metabolic syndrome than men.[36] The present study consistently showed that there is no difference in the risk of acromegaly according to glycaemic status between the sexes. Regarding age, the association between glycaemic status and acromegaly did not demonstrate a significant difference across age groups. These results are consistent with previous studies showing that patients with acromegaly develop T2DM at a younger age than the general population.[37] The increased risk of acromegaly by IFG and T2DM status was more pronounced in subgroups without hypertension and dyslipidaemia. This association may be attenuated in the presence of risk factors for T2DM, such as hypertension and dyslipidaemia. In fact, in patients with acromegaly, hypertension was an independent risk factor for the presence of diabetes.[37 38]

This study has several strengths. This study used a large sample to examine acromegaly, a rare incurable disease that is difficult to analyse in large prospective studies. It also used a well-validated longitudinal national database and included important anthropometric and biochemical parameters. However, this study is subject to several limitations. First, patients with acromegaly were identified using claims data and not confirmed by biochemical data. Thus, the frequency of acromegaly may have been underestimated if acromegaly events had not led to claims. To improve diagnostic accuracy, acromegaly was defined using a national registry for rare incurable diseases, and this method has been validated in previous Korean studies using the NHIS cohort database.[12 14 19]

Second, defining T2DM was based on claims and health examination data. Patients with untreated diabetes may have been overlooked because clinical data such as glycated haemoglobin and diabetes duration were not included in the NHIS data. Additionally, we could not obtain comprehensive data related to T2DM, such as dietary habits, family history of diabetes and medications that may affect glucose metabolism. Therefore, despite adjusting for multiple covariates associated with T2DM, the possibility of residual or unmeasured confounding factors remains. Although we adjusted for the presence of obesity, hypertension and dyslipidaemia as covariates, we were unable to include metabolic syndrome in the adjustments due to the lack of data on triglyceride and high-density lipoprotein cholesterol levels. Sensitivity analyses using methods such as multiple imputation were also not feasible. Furthermore, we were unable to analyse temporal changes in glucose levels over the follow-up period. Third, because of its retrospective observational design, causality could not be determined. To minimise the possible effects of reverse causality, subjects with pre-existing acromegaly and acromegaly events within 1 year of the index year were excluded. However, given that diagnostic delay generally spans several years, it is possible that some participants with altered glucose metabolism may have already had undiagnosed acromegaly at baseline. Finally, the generalisation of our findings to other ethnic groups may be limited, since we used data from the NHIS check-up programme for Koreans.

Conclusion

In conclusion, the results of this nationwide population-based cohort study added to the evidence that alterations in glucose metabolism, including IFG and T2DM, are associated with an increased risk of acromegaly. We also showed that these associations persisted after adjusting for all available covariates that could affect the findings on the relationship between T2DM and incident acromegaly. Larger studies over a longer period of time are needed to determine if alterations in glucose metabolism are a surrogate marker for identifying patients at high risk of developing acromegaly and if there are ethnic differences in this association.

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