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Surgical outcomes and predictors of glucose metabolism alterations for growth hormone-secreting pituitary adenomas: a hospital-based study of 151 cases

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Abstract

Purpose The surgical outcome on glucose metabolism in acromegaly patients is not fully understood. We aimed to investigate the impact of surgery on glucose metabolism and identify key factors that influence alterations of glucose metabolic status in acromegaly patients.

Methods Oral glucose tolerance test was performed in 151 newly diagnosed acromegaly patients before and 3–12 months after surgery. Insulin resistance and insulin secretion was assessed. Patients were grouped as cured, discordant, and having active disease according to postoperative growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels. Receiver-operating characteristic curves were generated to determine the optimal cut-off points to predict the impact of surgery on glucose metabolism.

Results At baseline, 32.5%, 41.7%, and 25.8% patients were categorized as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes mellitus (DM), respectively. After surgery, improved glucose tolerance was observed in 87.3% patients with IGT and 66.7% patients with DM. Deterioration was observed in 14.3% patients with NGT. Glucose tolerance improved in patients with lower preoperative FBG, 2 h-BG, and HbA1c and higher HOMA-β and IGI/IR. The proportion of NGT was significantly increased in surgically cured patients (28.3% vs. 79.2%, $P < 0.001$) and those with normal GH but elevated IGF-1 levels (25.6% vs. 79.5%, $P < 0.001$), but not in patients with active disease (42.9% vs. 57.1%, $P = 0.131$). Baseline FBG < 6.35 mmol/l predicted improved glucose metabolism after surgery.

Conclusions Glucose metabolic status improved in patients with preserved β-cell function. Preoperative FBG was an independent predictor for improved glucose tolerance status after surgery.

Keywords Acromegaly · Surgery · Insulin resistance · Glucose metabolism disorders · Glucose homeostasis

Introduction

Acromegaly is an insidious disease characterized by increased circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels. Acromegaly patients are

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prone to metabolic disorders, in which carbohydrate disturbance is the major type [1]. By the time the condition is diagnosed, the prevalence of impaired glucose tolerance (IGT) or diabetes mellitus (DM) ranges from 16 to 46% and from 19 to 56%, respectively, according to different reports [2]. Insulin resistance caused by GH excess is a major contributor to glucose intolerance [3].

Trans-sphenoid surgery is recommended as the primary therapy for acromegaly [4]. Biochemical cure of the disease is defined as nadir GH after oral glucose tolerance test (OGTT) < 0.4 μg/L with age-sex normalized IGF-1 levels (IGF-1 index [IGF-1/upper limit of normal range] ≤ 1) according to the latest consensus guidelines [4, 5]. Discordance of GH and IGF-1 levels, which means normalized GH with elevated IGF-1 levels or vice versa, has been reported after treatment of acromegaly. This phenomenon makes the interpretation of surgical outcomes difficult and interferes with decision making of adjuvant therapy after surgery. Glucose intolerance is reported to improve after surgery in the vast majority of cases [6–8], but it is so far not clear what factors determine and predict the change in glucose metabolism after surgery, especially for those patients with discordant GH and IGF-1 levels.

In this study, we explored the clinical outcomes of glucose metabolism, as well as identified the key parameters that influence and predict change in glucose metabolic status in acromegaly patients after trans-sphenoid surgery.

Materials and methods

Patients

We retrospectively collected data from patients who were diagnosed with acromegaly and hospitalized in Huashan hospital, the largest tertiary referral center in East China, between November 2011 and April 2016. We used the following inclusion criteria: (1) confirmed diagnosis of acromegaly (clinical features of acromegaly, failure of GH suppression to below 1 μg/L during OGTT, plasma IGF-1 levels above the sex- and age-appropriate reference range, and radiological evidence of a pituitary tumor); (2) newly diagnosed without previous surgery or radiotherapy; (3) those who underwent trans-sphenoid surgery; (4) those who had available follow-up data at 3–12 months after surgery; and (5) those who did not undergo any adjuvant therapy before revaluation.

A total of 151 patients (69 male and 82 female, mean age: 41.7 ± 12.1 years, median follow-up period: 12 [3–12] months) constituted the cohort. Of these, 26 patients were diagnosed with DM and were treated with oral hypoglycemic drugs at the time of inclusion in the study. According to postoperative GH and IGF-1 levels at the last follow-up, patients were divided into four groups: group I (GH nadir < 0.4 μg/L and IGF-1 index ≤ 1), group II (GH nadir < 0.4 μg/L and IGF-1 index > 1), group III (GH nadir ≥ 0.4 μg/L and IGF-1 index > 1), and group IV (GH nadir ≥ 0.4 μg/L and IGF-1 index ≤ 1).

Informed consent was obtained from each patient. This study was approved by the ethics committee at our hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study protocol

At baseline and end point evaluation, after overnight fasting, patients underwent screening for GH, IGF-1, fasting blood glucose (FBG), and glycated hemoglobin (HbA_{1c}) levels. OGTT with concomitant GH was performed at every visit. Briefly, after overnight fasting, blood samples were drawn for baseline BG, insulin, c-peptide, and GH. Then, 75 g glucose was orally administered. Sampling for BG, insulin, c-peptide, and GH was carried out after 30, 60, 120, and 180 min.

Normal glucose tolerance (NGT) was defined as FBG < 5.6 mmol/L and 2 h-plasma glucose (2 h-BG) < 7.8 mmol/L. IGT was defined as FBG between 5.6 mmol/L and 6.9 mmol/L or 2 h-BG between 7.8 mmol/L and 11.0 mmol/L. DM was diagnosed when FBG > 7.0 mmol/L or 2 h-BG ≥11.1 mmol/L [9]. Insulin resistance (IR) was evaluated by HOMA-IR (homeostatic model assessment). Pancreatic β-cell function was estimated by HOMA-β (%), insulinogenic index (IGI), and insulin disposition index (IGI/IR). HOMA-IR, HOMA-β (%), and IGI, were calculated as follows: fasting insulin (mU/L) − FBG (mmol/L)/22.5; 20 × fasting insulin (mU/L)/FBG (mmol/L) − 3.5 × 100%; and insulin at 30 min (mU/L) − fasting insulin (mU/L)/glucose at 30 min (mmol/L) − FBG (mmol/L).

Assays

GH was measured by a two-site chemiluminescent immunometric assay (AutoDELFIA® hGH, PerkinElmer Life and Analytical Sciences, Wallac Oy), and the intra-assay coefficient of variation (CV) was 5.3–6.5%, inter-assay CV was 5.7–6.2%, and sensitivity was up to 0.01 μg/L (0.026 mU/L). IGF-1 was measured with the Immulite 2000 solid-phase, enzyme-labeled chemiluminescent immunometric assay (Siemens Healthcare Diagnostic Products Limited, UK). The intra-assay CV was 2.3–3.5%; inter-assay CV, 7.0–7.1%; and sensitivity, 20 μg/L. Glucose was measured by hexokinase method. Glycated hemoglobin (HbA_{1c}) was detected with high performance liquid chromatography (Tosoh HLC-723 G8 HPLC Analyzer, Japan). Insulin and c-peptide were measured by chemiluminescence immunoassay (ADVIA Centaur XP, Siemens, USA).

Statistical analysis

Data were presented as mean ± SD (or median with interquartile range) for continuous variables with normal (or non-normal) distribution, and as frequency for categorical variables. Data analysis was performed with SPSS 20.0 program (IBM Corporation, Armonk, NY, USA). Pearson's or Spearman's correlation coefficients were calculated to measure the relationships between parameters with normal or non-normal distribution. Differences among independent groups were analyzed using one-way ANOVA test followed by multiple-comparisons post-hoc Bonferroni test for data with normal distribution, or Kruskal–Wallis test for data with non-normal distribution. Paired *t*-test or Wilcoxon signed rank test was used to compare the differences between pre- and post-operation parameters with normal or non-normal distribution. Pearson's χ^2 test was used to compare the differences for categorical variables. Logistic regression analysis was used to assess the potential candidates in predicting the outcomes of glucose metabolism after surgery, and receiver-operating characteristic (ROC) curve was generated to determine the optimal cut-off points.

Results

Baseline characteristics

At diagnosis, patients were categorized into three groups: NGT group (49 Patients, 32.5%), IGT group (63 patients, 41.7%), and DM group (39 patients, 25.8%). The baseline characteristics of the three groups are shown in Table 1. Patients with DM were older; had higher FBG, 2 h-BG, HbA_{1c}, and HOMA-IR; and lower HOMA-β, IGI, and IGI/IR than those with NGT (all $P < 0.05$). There were no significant differences in BMI, disease duration, random GH, GH nadir, and IGF-1 index among the three groups (all $P > 0.05$). The baseline random GH and IGF-1 index were neither correlated with HOMA-IR nor with HOMA-β, IGI, and IGI/IR in the NGT, IGT, and DM groups (all $P > 0.05$).

Surgical outcomes of glucose tolerance

At the 3–12 months postoperative follow-up, 70.2%, 21.2%, and 8.6% of the patients, respectively, were categorized as NGT, IGT, and DM. After surgery, in the NGT group, 85.7% maintained status quo, while 14.3% developed IGT. In the IGT group, 87.3% of the patients became NGT, 12.7% remained unchanged, and no patient progressed to diabetes. In the DM group, 33.3% continued to have diabetes mellitus, 43.6% improved to IGT, while 23.1% improved to NGT (Fig. 1a).

We then focused on patients with preoperative impaired glucose metabolism (IGT and DM). Subjects were classified into 2 groups according to the change of glucose tolerance status: the improved group ($n = 81$; from IGT to NGT, DM to NGT, or DM to IGT), and the persistent or deteriorated group ($n = 21$; from IGT to IGT, IGT to DM, or DM to DM). The improved group presented with higher baseline HOMA-β and IGI/IR, and lower FBG, 2 h-BG, and HbA_{1c}

Table 1 Baseline characteristics at diagnosis

	All	NGT	IGT	DM	*P* value
Patients (*n*/%)	151	49 (32.5%)	63 (41.7%)	39 (25.8%)	
Age (years)	41.76 ± 12.33	38.39 ± 11.58	41.49 ± 12.57	46.44 ± 11.67[a]	0.009
BMI (kg/m^2)	25.6 ± 3.2	25.38 ± 2.76	25.96 ± 3.55	25.32 ± 3.13	0.576
Disease duration (years)	5.3 ± 4.33	6.36 ± 5.35	4.54 ± 3.05	5.25 ± 4.62	0.105
Random GH (μg/L)	18.73 (8.42–41.93)	12.35 (7.88–38.46)	20.06 (7.73–45.38)	19 (10.73–45.38)	0.453
GH nadir (μg/L)	11.46 (4.71–25.92)	7.64 (3.7–20.76)	14.81 (3.91–26.63)	14.33 (8.6–28.86)	0.144
IGF-1 index	2.68 ± 0.86	2.56 ± 0.74	2.7 ± 0.95	2.81 ± 0.88	0.428
FBG (mmol/L)	5.89 ± 1.63	5.03 ± 0.35	5.48 ± 0.57	7.64 ± 2.34[a,b]	0
2 h-BG (mmol/L)	9.62 ± 4.21	6.15 ± 1.14	8.65 ± 1.42	15.69 ± 3.42[a,b]	0
HbA_{1c} (%)	6.34 ± 1.94	5.57 ± 0.26	5.7 ± 0.53	8.43 ± 2.98[a,b]	0
HOMA-IR	3.6 (2.33–6.21)	2.79 (2.17–4.07)	4.07 (2.71–6.7)[a]	4.13 (2.26–6.76)[a]	0.015
HOMA-β (%)	167.89 (86.86–252.14)	178.84 (127.55–249.21)	202.08 (140.75–262.74)	63.1 (30.47–116.86)[a,b]	0
IGI/IR	5.11 (1.53–9.76)	9.59 (5.19–14.94)	5.52 (3.1–9.11)	0.96 (0.4–1.85)[a,b]	0
IGI	18.38 (5.21–43.32)	32.59 (15.38–54.93)	30.47 (9.06–46.72)	2.24 (1.23–7.55)[a,b]	0

BMI body mass index, *GH* growth hormone, *GH nadir* nadir GH during OGTT, *IGF-1* insulin-like growth factor-1, *IGF-1 index* IGF-1/upper limit of normal range for age and sex matched IGF-1 level, *FBG* fasting blood glucose, *2 h-BG* 2 h-blood glucose during OGTT

[a]$P < 0.05$ vs. NGT

[b]$P < 0.05$ vs. IGT

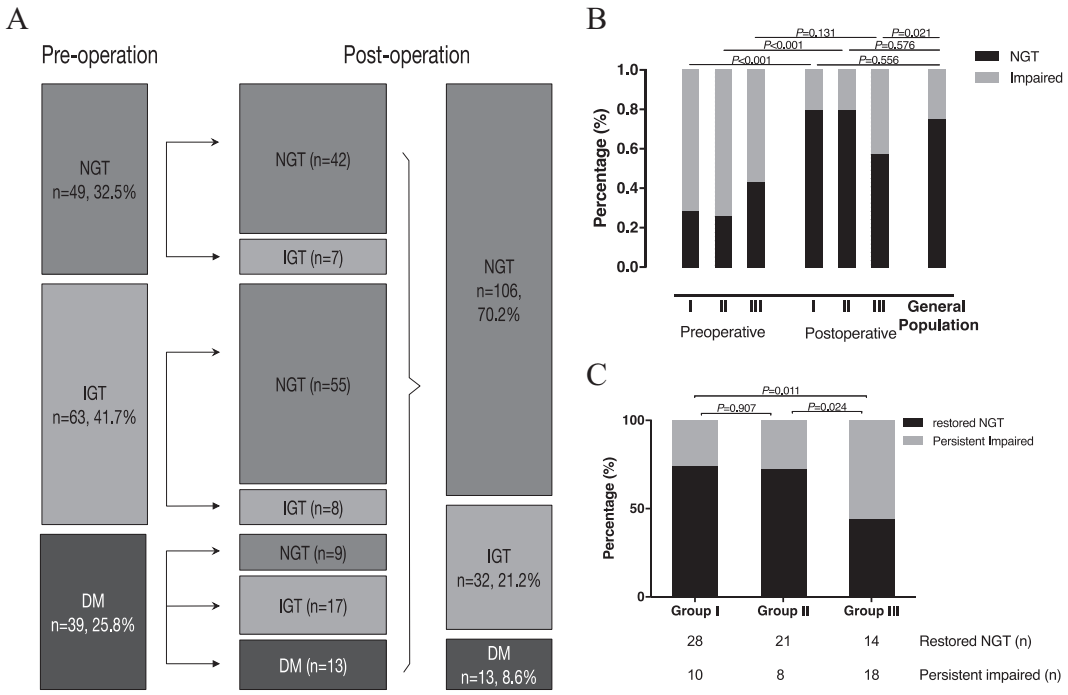

Fig. 1 Effects of surgery on glucose metabolism in patients with acromegaly. **a** shows the flowchart of the prevalence of patients' glucose tolerance status before and after surgery. **b** shows the significant improvement in glucose tolerance status in groups I and II after surgery (both $P < 0.001$), which were similar to the Chinese general population ($P = 0.556$, and 0.576), while significant improvement in glucose metabolic status did not occur after surgery in group III ($P = 0.131$). **c** highlights patients with preoperative abnormal glucose tolerance: the percentage of restored NGT patients was similar in groups I and group II ($P = 0.907$) and was significantly higher than in group III ($P = 0.011$ and $P = 0.024$)

than the persistent or deteriorated group (all $P < 0.05$). However, there were no differences with respect to age, BMI, disease duration, GH, IGF-1 index, HOMA-IR, and IGI between the 2 groups (all $P > 0.05$).

In the entire cohort, the change of random GH from baseline to post-surgery did not correlate with the reduction of HOMA-IR, HOMA-β, IGI, or IGI/IR ($P = 0.39$, 0.517, 0.699, and 0.404, respectively). While the change of IGF-1 index positively correlated with the change of HOMA-IR and negatively correlated with the change of IGI/IR ($r = 0.22$, $P = 0.008$, and $r = -0.205$, $P = 0.015$, respectively).

Changes of glucose metabolism-related parameters among cured/discordant/active disease groups after surgery

At the last visit, according to GH nadir and IGF-1 levels, 53 patients were surgically cured (group I), while 56 patients had active disease (group III). Discordances were seen in 42 patients, of whom, 39 were in group II, and 3 patients were stratified to group IV. Owing to the small size of group IV, it was not included for further analysis.

Pre- and post-operative parameters in groups I, II, and III are shown in Table 2. Pre-operative FBG, 2 h-BG, HbA_{1c}, HOMA-IR, HOMA-β, IGI, and IGI/IR were similar among the 3 groups ($P = 0.365$, 0.255, 0.608, 0.774, 0.831, 0.994, and 0.605). After surgery, random GH, GH nadir, IGF-1 index, FBG, 2 h-BG, HbA_{1c}, and HOMA-IR declined significantly in these three groups. HOMA-β decreased in group I and remained unchanged in groups II and III. IGI/IR both significantly increased in groups I and II ($P < 0.001$) and remained unchanged in group III. The change of IGI was not significant in these 3 groups (all $P > 0.05$).

Changes of glucose tolerance status among cured/discordant/active disease groups after surgery

At study entry, each group had a similar percentage of NGT (28.3% in group I, 25.6% in group II, and 42.9% in group III), IGT (50.9% in group I, 46.2% in group II, and 28.6% in group III), and DM patients (20.8% in group I, 28.2% in group II, and 28.6% in group III) ($P = 0.129$).

After surgery, most patients showed improvement in glucose metabolic status in groups I and II, which resulted in the increased proportion of NGT patients (from 28.3% to 79.2% in group I [$P < 0.001$], and from 25.6% to 79.5% in group II [$P < 0.001$]). In group III, however, the percentage of NGT was not significantly increased after surgery (NGT from 42.9% to 57.1%, $P = 0.131$) (Fig. 1b).

Table 2 Pre- and post-operative changes of the cohort

	Group I ($n = 53$)			Group II ($n = 39$)			Group III ($n = 56$)		
	GH nadir < 0.4 μg/L and IGF-1 index ≤ 1			GH nadir < 0.4 μg/L and IGF-1 index > 1			GH nadir ≥ 0.4 μg/L and IGF-1 index > 1		
	Preoperatively	Postoperatively	*P*	Preoperatively	Postoperatively	*P*	Preoperatively	Postoperatively	*P*
Random GH (μg/L)	11.97 (6.48–34.98)	0.23 (0.08–0.44)	0	16.87 (8.67–30.97)	0.31 (0.12–0.54)	0	25.27 (9.64–59.14)	2.18 (1.37–4.01)	**0**
GH nadir (μg/L)	6.65 (3.68–24)	0.12 (0.04–0.21)	0	11.31 (4.5–19.04)	0.15 (0.04–0.27)	0	16.08 (5.9–42.5)	1.25 (0.78–2.46)	**0**
IGF-1index	2.55 ± 0.78	0.69 ± 0.17	0	3.01 ± 0.85	1.41 ± 0.31	0	2.64 ± 0.9	1.96 ± 0.67	**0**
FBG (mmol/L)	5.83 ± 1.42	4.99 ± 1.05	0	6.19 ± 2.29	4.88 ± 0.53	0	5.71 ± 1.27	5.08 ± 0.61	**0**
2 h-BG (mmol/L)	9.49 ± 4.05	7.18 ± 3.27	0	10.51 ± 5.01	6.45 ± 2.42	0	9.05 ± 3.7	6.94 ± 2.63	**0**
HbA_{1c} (%)	6.56 ± 2.38	5.61 ± 0.83	0.002	6.33 ± 1.46	5.53 ± 0.44	0.001	6.16 ± 1.8	5.64 ± 0.53	**0.015**
HOMA-IR	4.04 (2.4–6.37)	1.36 (0.83–1.99)	0	3.45 (2.18–6.8)	1.49 (1.12–2.25)	0	3.35 (2.4–5.52)	1.75 (1.1–3.21)	**0**
HOMA-β (%)	180.7 (79.5253.8)	113.8 (68.1–142.3)	0	164.7 (91.9–260)	111.5 (74.3–158.1)	0.103	152.9 (86.4–235.6)	111.3 (70-203.8)	0.223
IGI/IR	5.02 (1.4–8.07)	10.16 (3.37–18.81)	0	5.38 (1.56–9.2)	7.7 (3.62–12.09)	0.013	5.17 (1.74–14.55)	6.63 (3.76–14.18)	0.495
IGI	22.56 (4.96–42.39)	13.21 (6.16–25.5)	0.054	19.7 (9.58–38.04)	11.28 (8.09–21.32)	0.339	16.59(5.15–55.66)	12.46 (4.76–24.29)	0.06

GH growth hormone, *GH nadir* nadir GH during OGTT, *IGF-1* insulin-like growth factor-1, *IGF-1 index* IGF-1/upper limit of normal range for age and sex matched IGF-1 level, *FBG* fasting blood glucose, *2 h-BG* 2 h-blood glucose during OGTT

At the end point, the composition of the glucose metabolic status was similar in groups I and II (NGT 79.2% vs. 79.5%, IGT 9.4% vs. 12.8%, and DM 11.3% vs. 7.7%, $P = 0.764$). The percentage of NGT was lower in group III than that in group I (57.1% vs. 79.2%, $P = 0.014$] and II (57.1% vs. 79.5%, $P = 0.023$), while the percentage of abnormal glucose tolerance is higher in group III (Fig. 1b).

Normal glucose tolerance was restored in some patients with preoperative impaired glucose metabolism (IGT group & DM group) after surgery. We further compared the rate of restored NGT in each group (Fig. 1c). In group I, 38 patients had abnormal glucose tolerance at study entry and 73.7% (28/38) of these patients achieved NGT after surgery. The percentage of restored NGT patients was similar in groups I and II (73.7% vs. 72.4%, $P = 0.907$), while the percentage of restored NGT patients in group III was significantly lower than that in groups I and II (43.8% vs. 73.7%, $P = 0.011$ and 43.8% vs. 72.4%, $P = 0.024$).

Predictors for surgical benefits in glucose metabolism

We analyzed the parameters which may predict the surgical outcome of glucose metabolism in patients with preoperative abnormal glucose status. According to predictors associated with improved glucose metabolism as listed in Table 3, preoperative parameters including FBG, 2 h-BG, HbA_{1c}, HOMA-β, and IGI/IR had a value of $P < 0.15$ and were included in the multivariate logistic regression analysis. FBG was identified (OR = 0.592, 95%CI: 0.393–0.891, $P = 0.012$) as an independent predictor for improved glucose metabolism. ROC curve analysis was performed to further estimate the predictive value of FBG on the change of glucose tolerance status. The cut-off value of FBG was 6.35 mmol/L, which showed the best power in predicting the surgical benefit (improvement) in glucose metabolism, with a PPV of 90.3% and an NPV of 53.3% (sensitivity: 82.3%, specificity: 69.6%, AUC: 0.78, 95% CI: 0.67–0.89, $P < 0.001$) (Fig. 2).

Discussion

In the present study of 151 newly diagnosed acromegaly patients, we showed that 32.5%, 41.7%, and 25.8% patients had NGT, IGT, and DM. After trans-sphenoidal surgery, 79.4% (81/102) patients showed improvement in glucose tolerance test, resulted in an increased proportion of NGT (70.2%) and decreased proportion of IGT (21.2%) and DM (8.6%). Improvement occurred in patients with lower preoperative FBG, 2 h-BG, HbA_{1c}, and higher HOMA-β and IGI/IR. There was a similar improvement of glucose tolerance status between patients who were cured by surgery and

Table 3 Comparison of baseline characteristics of patients with abnormal glucose tolerance status in the improved and persistent/deteriorated groups

	Change in glucose tolerance status		*P* value
	Improved ($n = 81$)	Persistent or deteriorated ($n = 21$)	
Age (years)	42.37 ± 12.19	47.29 ± 12.79	0.106
BMI (kg/m^2)	25.43 ± 3.27	26.6 ± 3.66	0.171
Disease duration (years)	4.81 ± 3.63	4.78 ± 4.03	0.97
Random GH (μg/L)	20.06 (8.31–39.04)	19.69 (12.69–53.46)	0.327
GH nadir (μg/L)	14.85 (4.5–25.24)	14 (8.88–47.69)	0.27
IGF-1 index	2.7 ± 0.87	2.88 ± 1.09	0.446
FBG (mmol/L)	6 ± 1.66	7.49 ± 2.03	0.001
2 h-BG (mmol/L)	10.63 ± 3.56	13.89 ± 5.4	0.002
HbA_{1c} (%)	6.39 ± 2.07	7.9 ± 2.6	0.01
HOMA-IR	3.87 (2.42–6.63)	4.53 (3.03–6.95)	0.358
HOMA-β (%)	171.32 (77.85–254.66)	86.54 (36.49–188.65)	0.038
IGI/IR	3.59 (1.1–7.51)	1.2 (0.35–4.51)	0.014
IGI	16.63 (4.37–34.47)	5.29 (1.65–32)	0.174

BMI body mass index, *GH* growth hormone, *GH nadir* nadir GH during OGTT, *IGF-1* insulin-like growth factor-1, *IGF-1 index* IGF-1/upper limit of normal range for age and sex matched IGF-1 level, *FBG* fasting blood glucose, *2 h-BG* 2 h-blood glucose during OGTT

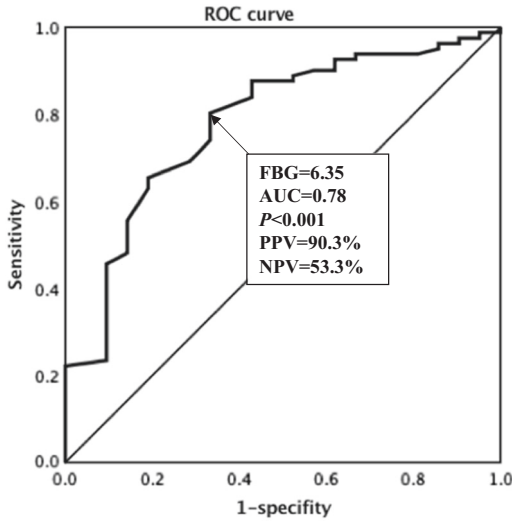

Fig. 2 ROC curve analysis of baseline predictors for surgical impact on glucose tolerance status. Preoperative FBG < 6.35 mmol/L best predicted the improvement of glucose tolerance after surgery, with a PPV of 90.3% and an NPV of 53.3% (sensitivity: 82.3%, specificity: 69.6%, AUC: 0.78, 95% CI: 0.67–0.89, $P < 0.001$)

those with normal GH but elevated IGF-1 levels. However, no significant improvement in glucose metabolic status was seen in patients with active disease (group III). Baseline FBG < 6.35 mmol/L predicted the improvement of glucose metabolism after surgery.

Impaired glucose tolerance or overt DM are well-recognized comorbidities in acromegaly patients and found in up to 50% of individuals at diagnosis [2]. In the present study, prevalence of glucose disorders was similar to the ones reported by Deval et al. [10] (3.5-fold increased risk) and Dal et al. [11] (4-fold increased risk) with a 2.7-fold increased risk compared with the Chinese population (67.5% vs. 25.2%) [12]. GH-mediated insulin resistance is a major cause of altered glucose metabolism in active acromegaly, and most patients have some degrees of hepatic and peripheral insulin resistance, even those with NGT. Literature reports showed conflicting results in the characteristics of DM patients. In a study of 148 patients, Alexopoulou et al. [13] reported that NGT patients were 10 years younger than patients with abnormal glucose metabolism, and DM patients had a higher BMI. HOMA-S was similar, but HOMA-β was reduced in the abnormal glucose metabolism group than in the NGT group. IGF-1 was higher in the abnormal glucose metabolism patients than in NGT patients, but fasting and post-OGTT GH levels were not different between groups. However, Fieffe et al. [14] reported that neither GH nor IGF-1 appeared as predictive factors for the presence of DM, while, age, BMI, and hypertension did. Kasayama et al. [15] reported that there were no significant differences of insulin resistance between IGT/DM patients and NGT patients, while HOMA-β was significantly lower in IGT/DM patients than in NGT patients. Helseth et al. [16] reported that both baseline GH and IGF-1 correlated with insulin resistance. However, Kinoshita et al. [7] reported that neither baseline GH nor IGF-1 correlated with HOMA-IR. Alexopoulou et al. [13]. too did not find any relationship between GH/IGF-1 and β cell function. In our study, patients with DM were older, had higher HOMA-IR, lower HOMA-β, IGI, and IGI/IR than those with NGT. There were no significant differences in BMI, disease duration, random GH, GH nadir, and IGF-1

index among patients with NGT, IGT, and DM. The baseline GH and IGF-1 were neither correlated with insulin resistance nor with β-cell function. The inconsistency of our results with existing literature may likely be due to differences in study populations, such as age or ethnicity, and also to a variability in the criteria applied for the diagnosis of DM and other glucose abnormalities.

We next investigated the effects of trans-sphenoidal surgery on glucose metabolism in acromegaly patients. Specific attention was given to patients with discordant GH and IGF-1 levels after surgery, owing to the unascertained management strategy of these patients. We found that FBG, 2 h-BG, and HbA_{1c} all significantly decreased in the entire cohort, regardless of surgical cure. This is probably because of the resolution of GH and IGF-1 after adenoma debulking [17]. Our results were in concordance with Helseth et al. [16], who reported that surgical treatment of acromegaly improved glucose metabolism in both cured and uncured patients. However, the results of Colao et al. [18] showed that FBG was increased by 4.3% at the 60-month follow-up after surgery, and deterioration of glucose tolerance was correlated with increased BMI, not with control of GH and IGF-1 or the lack thereof. The reason for such discrepancy is probably attributed to the different follow-up periods, which was 3 months, 3–12 months, and 60 months, in these three studies. The longer follow-up duration gives a chance for more confounding factors to occur; for example, some factors such as, age, BMI, and hypertension may be more robustly related with DM than acromegaly [14].

Decrease in insulin resistance after surgery regardless of patient cure has been widely acknowledged and accepted [7, 8, 19, 20]. However, the change of β-cell function-related parameters varied between studies. Kinoshita et al. [7] reported that HOMA-β decreased in patients who had NGT before or after surgery, but did not change in patients who still had abnormal glucose tolerance after successful surgery. IGI declined in patients who had restored NGT after surgery, but remained unaltered in other patients. However, Ronchi et al. [19] reported that the change of both HOMA-β and IGI was not significant after surgical cure. Tzanela et al. [8] reported that HOMA-β, first-phase, and second-phase insulin release all remained unaltered after trans-sphenoidal surgery. Mori et al. [21] reported that IGI showed no significant postoperative change. The reason for such discrepancy is probably owing to the different surgical outcomes among the abovementioned studies. To investigate the change of glucose metabolism-related parameters in patients with different treatment outcomes, we divided them into cured (group I), discordant (group II), and active disease groups (group III). We showed HOMA-IR significantly declined in all these groups, HOMA-β decreased in cured group and remained unchanged in discordant and active disease group, and IGI/IR both significantly increased in cured and discordant groups but remained unchanged in active group. The change of IGI was not significant in these 3 groups. After surgery, the prevalence of glucose disorders, as compared with the Chinese population, dropped from 2.8-fold increased risk to 0.9-fold increased risk in group I ($P < 0.001$), from 3.0-fold to 0.8-fold in group II ($P < 0.001$), and from 2.3-fold to 1.7-fold in group III ($P = 0.33$). Thus, there was a similar improvement of glucose tolerance status between Groups I and II. The proportion of abnormal glucose status after surgery in these two groups was very close to the general population. However, less patients achieved restored NGT after surgery in group III. In particular, HOMA-β reproduces insulin secretion under fasting conditions, whereas IGI and IGI/IR reflect insulin secretion after oral glucose load administration. Although IGI did not change after surgery, which was consistent with Kinoshita et al., IGI/IR, another β-cell function-related parameter with less interference of insulin resistance [22], was improved in cured and discordant group, but not in active group. Based on this result, we assumed that similar improvement of glucose metabolism status in cured and discordant patients was predominantly associated with the similar improvement of postprandial insulin secretion, in addition to the improvement of insulin resistance, while the improvement of postprandial insulin secretion was not detected in active disease patients, which was not reported previously.

Some researchers believe that GH correlated with insulin resistance, while others insisted that IGF-1 was a better predictor of glucose tolerance [13, 23, 24]. In our cohort, the change of insulin resistance and β-cell function was correlated with the change of IGF-1, not GH. Thus, we confirm that IGF-I concentration, which reflects integrated 24 h GH secretion is correlated with glucose metabolism better than a fasting or glucose-suppressed GH level. This is probably because of the greater stability of IGF-I than GH.

Lastly, for patients with abnormal glucose tolerance status, we tried to identify possible parameters that could predict surgical benefit after treatment. The dichotomy analysis showed that improvement of glucose tolerance status occurred in patients with higher HOMA-β and IGI/IR, indicating the patient's β-cell function was preserved to some extent. In this study, FBG was an independent predictor for improved glucose metabolism. Previous studies have attempted to screen for possible risk factors, but no consensus was reached. A study based on 92 Japanese patients who achieved remission after surgery, showed that IGI of 0.5 before surgery was the best cut-off value for restoration to normal from IGT or DM [7]. Jonas et al. evaluated the evolution of glucose tolerance in 57 patients and found that glucose tolerance status at diagnosis and SSAs treatment independently predicted impaired glucose tolerance [25]. A recently published, much larger study by

Gonzalez et al., evaluating 522 Mexican patients showed that age, female gender and the presence of a macroadenoma as well as GH > 10 μg/L and IGF-1 > 2 × ULN at diagnosis were all significantly associated with the probability of being diabetic upon last visit [26]. Comparison between studies was difficult, because different objects, remission criteria and follow-up period were used in different studies. The remission criteria of Kinoshita et al. were the 2000 Cortina consensus statement, but ours were the 2010 consensus criteria. While the IGF-1 remission criterion of Gonzalez et al. was set at 1.2 × ULN, which was different from Kinoshita's and ours, and might cause a bias during subsequent analysis. The study population of Kinoshita et al. was surgically cured patients, while ours included cured and uncured patients. Furthermore, the follow-up period of within a month in Kinoshita's study was relatively shorter than ours. On the contrary, the follow-up period of Gonzalez's study was 7.4 years, much longer than Kinoshita's and ours, which might enable more robust confounding factors to occur [14]. Jonas et al. included medical therapy and radiotherapy, which might interfere with the impact of surgery on glucose metabolism. Our results could be applied to predict the improvement of glucose tolerance status after surgery, regardless of a surgical cure. However, it should be noted that, due to the relatively low specificity (69%) of the predictive efficiency of FBG, the negative predictive value (NPV) of this parameter should be applied with caution. More rigorous studies with larger samples might be needed to assess the real value of FBG in predicting surgical benefits in glucose metabolism.

The main limitation of the current study is that this study is not blinded from the patient's point of view, and patients who are diagnosed with abnormal glucose status at baseline assessment may have lifestyle/dietary/medication modification, which may have had an impact on the glucose metabolism results in the follow-up assessment. Additionally, only 3 patients had normal IGF-1 with elevated GH after surgery, so the change of glucose metabolism in this group of discordant patients cannot be clarified by the present study.

In conclusion, improvement of glucose metabolic status occurred in patients with preserved β-cell function. There are no differences in glucose metabolic outcomes between patients who were surgically cured and with discordance of GH and IGF-1 levels. Baseline FBG < 6.35 mmol/L predicted improved glucose metabolism after surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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