

Postoperative Changes in Metabolic Parameters of Patients with Surgically Controlled Acromegaly: Assessment of New Stringent Cure Criteria

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Abstract

The criteria for surgical cure of acromegaly have become more stringent during the past decades and a change from Cortina to new consensus criteria has recently been proposed. However, the superiority of the new consensus over Cortina criteria with respect to postoperative metabolic parameters remains to be ascertained. We retrospectively assessed metabolic parameters, the body habitus, and other health-related parameters of 48 patients with surgically controlled acromegaly who met the Cortina criteria [normalized insulin-like growth factor-1 (IGF-1) level and nadir growth hormone (GH) level <1.0 ng/ml during postoperative oral glucose tolerance test]. The 48 patients were divided into two groups. Group A ($n = 33$) met the new consensus criteria (normalized IGF-1 and nadir GH level <0.4 ng/ml). Group B ($n = 15$) met Cortina criteria, but their nadir GH ranged from 0.4 to 1.0 ng/ml. In both groups, the level of triglyceride and homeostasis model assessment-insulin resistance (HOMA-IR) was significantly decreased 1 year after the operation ($P < 0.05$). High-density lipoprotein cholesterol showed a significant increase only in group B ($P = 0.02$). However, the two groups did not differ with respect to the postoperative improvement rate of these parameters and the other health-related parameters including body mass index, blood pressure, anterior pituitary function, and self-estimated quality of life scale. In conclusion, our findings show that with respect to changes in metabolic parameters and the body habitus assessed 1 year after surgery, the stricter consensus criteria seemed not to be superior to Cortina criteria.

Key words: acromegaly, surgical cure, Cortina criteria, new consensus criteria, metabolic parameters

Introduction

As growth hormone (GH) and insulin-like growth factor-1 (IGF-1) play important roles in regulating the body metabolism, acromegaly presents with a wide variety of visceral and external symptoms and multiple metabolic abnormalities. Dyslipidemia, abnormal glucose tolerance, and cardiovascular events in patients with active acromegaly lead to premature mortality. While the standardized mortality rate

of patients with uncontrolled acromegaly reaches 1.2–1.5,¹⁾ good control of acromegaly by medication and/or surgery improves these metabolic parameters and results in a nearly normal mortality rate.^{2,3)}

The criteria for the surgical cure have become more stringent. In the 1970s and 1980s, the cut-off for the randomly measured GH level indicative of postsurgical cure was tentatively set at 5.0–2.5 ng/ml.^{4,5)} In the year 2000, an international committee proposed criteria comprised of a postoperatively normalized IGF-1 and nadir GH level during the 75-g oral glucose tolerance test (OGTt) of under 1.0 ng/ml (Cortina criteria).⁶⁾ New stricter consensus criteria promulgated in 2010 were based on the GH secretory dynamics in a normal population, i.e., a normalized IGF-1 and nadir GH level below 0.4 ng/ml.⁷⁾

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While recent studies showed significant improvement in the metabolic parameters in both patient groups judged to be cured by the Cortina criteria and new consensus criteria,^{8,9)} the superiority of the new criteria in terms of metabolic parameters, as well as the health status and mortality rate of operated acromegalics, have not been established.

To assess the validity of the new criteria, we compared the metabolic parameters, body habitus, blood pressure, anterior pituitary function, and quality of life of operated patients who met the new consensus criteria and patients who met Cortina criteria, but whose nadir GH level ranged from 0.4 to 1.0 ng/ml.

Subjects and Methods

Patients

The study subjects were 48 patients (16 men, 32 women) whose initial treatment was endoscopic transsphenoidal surgery. Three months after surgery all were judged to be in postsurgical control defined as fulfillment of the Cortina criteria (normalized IGF-1 and nadir GH levels during postoperative OGTt < 1.0 ng/ml. Complete pre- and postoperative data sets of their metabolic parameters, including serum triglyceride (TG), total cholesterol (T-chol), low- and high-density lipoprotein (LDL, HDL), homeostasis model assessment-insulin resistance (HOMA-IR), and body mass index (BMI) were available. Patients who had undergone preoperative medical and/or radiation treatment were excluded from our study.

Of the 48 patients, 33 met both Cortina and the new consensus criteria 3 months after surgery. They were assigned to group A. The other 15 patients met Cortina criteria; however, their nadir GH level ranged from 0.4 to 1.0 ng/ml and they were assigned to group B.

Among these 48 patients, postoperative GH of the first 12 patients was measured by chemiluminescent enzyme immunoassay (CLEIA) using CLEIA Immulyze GH kit (Mitsubishi Chemical and Yatron, Tokyo, Japan) during 2006 to February 2010. Since March 2010, the postoperative GH was measured by CLEIA using Siemens Immulyze GH II kit (Siemens Healthcare Diagnostics, NY) in which standardized recombinant GH has been employed for calibration. The GH values (X) measured using the former kit were converted into standardized GH values (Y) according to the formula provided by the supplier of the kit; $Y = 0.7332 \times X + 0.1054$.

Metabolic parameters

Serum TG, T-chol, LDL, and HDL were measured 1 month before and 1 year after the operation. To

calculate pre- and postoperative HOMA-IR we used the following formula:

$$\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mg/dl}) / 405.$$

The HDL improvement ratio was calculated with the formula

$$(\text{postoperative value} - \text{preoperative value}) / \text{preoperative value}.$$

To assess the improvement ratio of other parameters we used the formula

$$(\text{preoperative value} - \text{postoperative value}) / \text{preoperative value}.$$

The BMI was recorded before and 1 year after surgery.

Blood pressure

The blood pressure is the averaged morning blood pressure recorded during in-hospital comprehensive pre- and postoperative acromegaly assessments usually performed 1 month before and 3 months after the surgery. When pre- or postoperative in-hospital assessment was unavailable, the recorded blood pressure was the average of the in-home morning blood pressure obtained for several days prior to the outpatient clinic visits.

Impaired glucose metabolism

In the 14 patients diagnosed preoperatively with diabetes mellitus (DM), who had HbA1c (NGSP) of 6.5% or greater, we evaluated changes in their treatment including insulin and/or oral hypoglycemic agents.

Anterior pituitary function

Anterior pituitary hormonal function was assessed in 44 patients before and 6–12 months after surgery; 39 patients underwent the triple bolus injection test (TBit) [insulin 0.12 U/kg, luteinizing hormone-releasing hormone (LH-RH) 100 µg, and thyrotropin-releasing hormone (TRH) 500 µg].

Patients with cardiac disease, serious diabetes, or epilepsy that rendered insulin hypoglycemic stress testing counter-indicated underwent the quadruple test with 100 µg LH-RH, 500 µg TRH, 100 µg corticotropin-releasing hormone (CRH), and 100 µg growth hormone-releasing hormone (GRH). Their GH reserve was assayed with the growth hormone-releasing peptide-2 (GHRP2) test ($n = 5$).

Melmed and Kleinberg criteria¹⁰⁾ were used to determine intact pituitary hormone secretion. The peak GH level was set at > 3 ng/ml, for adrenocorticotropin (ACTH)-cortisol, the peak cortisol level was > 18 µg/dl or an increase of 7 µg/dl above the basal level. For thyroid-stimulating hormone (TSH), the peak value

was > 2.5-fold the basal level or > 6 mU/l. The peak prolactin value was set at greater than twice the basal level. Patients with adenoma immunohistochemically positive for prolactin were excluded from patients assessed for prolactin deficiency. For LH, the peak value was > 3-fold the basal level or a 10 IU/l increase from the basal level. For follicle stimulating hormone (FSH), the peak value was > 2-fold the basal level or a 2 IU/l increase from the basal level.

In patients who underwent the GHRP-2 test, GH secretory function was judged normal when the peak GH level exceeded 9 ng/ml.¹¹ Except for IGF-1, blood hormones were measured with the electrochemiluminescence immunoassay; for IGF-1 we used the immunoradiometric assay.

Quality of life

The physical and mental health status of 29 of the 48 patients was assessed with the 36-item Short Form Health Survey (SF-36) 1 year after surgery (group A, $n = 21$; group B, $n = 8$).

Statistical analyses

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan); it features a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Depending on the data set characteristics, the data were analyzed with the Fisher exact test, the Student *t*-test, the paired *t*-test, the Wilcoxon test, and the Mann–Whitney test. Differences of $P < 0.05$ were considered statistically significant.

Ethical considerations

This retrospective study was approved by the Ethics Committee of Kagoshima University Hospital (reference No. 29-18, URL: <http://com4.kufm.kagoshima-u.ac.jp/information/department/015/015-02.html>, <http://www.kufm.kagoshima-u.ac.jp/~ns/pdf/research-list20170906.pdf>). All authors certify that this study was conducted in accordance with the Helsinki declaration (revised in 2000) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (effective February 9, 2015) as ordered by the Ministry of Health, Labor and Welfare, Japan. Informed consent for the treatment and for the use of their data in general research on hypothalamo-pituitary disease was obtained from all patients. Study-specific informed consent was waived due to the retrospective and noninvasive nature of our study. An opt-out approach was offered to all patients. To protect patient privacy, all data were collected and analyzed under anonymization in an unlinkable fashion.

Results

Baseline characteristics (Table 1)

The patient age ranged from 26 to 72 years (median 57 years). There was no statistical difference in the age, gender, tumor size, Knosp grade, preoperative GH level, and preoperative IGF-1 level between the two groups. The preoperative BMI was 24.3 (median, range 20.6–31.0) in group A and 21.9 (median, range 18.2–29.7) in group B; the difference was statistically significant ($P = 0.04$).

Table 1 Baseline characteristics of the 48 acromegalics

	Total	Group A	Group B	<i>P</i> value
Age (years): median (range)	57 (26–72)	56 (26–72)	60 (31–72)	0.14 ^b
Gender (men /women)	16/32	13/20	3/12	0.32 ^a
Maximum tumor diameter: median (range)	15 (3–36)	15 (5–35)	15 (3–36)	0.38 ^b
Preoperative body mass index: median (range)	23.9 (18.2–31)	24.3 (20.6–31)	21.9 (18.2–29.7)	0.04 ^b
Knosp grade (III, IV/0–II)	3/45	2/31	1/14	>0.99 ^a
Preoperative GH (ng/ml): median (range)	9.8 (1.0–85)	9.6 (1.0–85)	10.4 (4.0–28.6)	0.77 ^b
Preoperative IGF-1 (ng/ml): median (range)	554 (253–992)	570 (253–992)	484 (268–795)	0.12 ^b
Preoperative IGF-1 SD score: median (range)	6.33 (2.7–11.7)	6.42 (2.7–11.7)	5.99 (3.1–8.5)	0.18 ^b
Postoperative GH (ng/ml): median (range)	1.2 (0.1–5)	0.8 (0.1–3.9)	1.4 (0.5–5)	0.08 ^b
Postoperative nadir GH (ng/ml) during OGTT: median (range)	0.23 (0.10–0.90)	0.18 (0.10–0.33)	0.60 (0.40–0.90)	<0.01 ^b
Postoperative IGF-1 (ng/ml): median (range)	149 (57–265)	144 (57–265)	156 (69–205)	0.82 ^b
Postoperative IGF-1 SD score: median (range)	0.3 (–2.8–2.6)	0.1 (–2.8–2.6)	0.3 (–2.1–1.6)	0.34 ^b

^aFisher's exact test, ^bStudent *t*-test. GH: growth hormone, IGF-1: insulin-like growth factor-1, OGTT: oral glucose tolerance test.

Due to the classification of the 48 patients into groups based on postoperative nadir GH levels, it is not surprising that the random postoperative GH and nadir GH level was lower in group A than group B ($P = 0.08$ and $P < 0.01$, respectively). On the other hand, unexpectedly, the postoperative IGF-1 level and its standard deviation (SD) were not different between the two groups ($P = 0.82$ and $P = 0.34$, respectively).

Postoperative changes in metabolic parameters (Table 2)

One year after surgery, and in the total of 48 patients, TG and HOMA-IR were significantly lower than the preoperative values ($P < 0.01$, in both) and the HDL level was significantly higher than the preoperative one ($P < 0.01$). There was no significant pre- and postoperative change in T-chol, LDL, and the BMI ($P = 0.53$, $P = 0.85$, and $P = 0.34$, respectively).

Group A manifested significant improvements in TG and HOMA-IR (both $P < 0.01$), as did group B (TG, $P = 0.02$, HOMA-IR, $P < 0.01$). In group B, the HDL level was also significantly improved ($P = 0.02$).

There was no significant difference between the groups with respect to the improvement ratio of T-chol, HDL, TG, HOMA-IR, and the BMI (Fig. 1). The improvement ratio of LDL tended to be better in group B than group A ($P = 0.08$) (Fig. 1).

Blood pressure

The blood pressure levels shown in Fig. 2 are the averaged morning blood pressure recorded during in-hospital comprehensive pre- and postoperative acromegaly assessments usually performed 1 month before and the 3 months after surgery. When pre- or postoperative in-hospital assessment was unavailable, the recorded blood pressure was the average of the in-home morning blood pressure obtained for several days prior to the outpatient clinic visits.

Postoperatively, the systolic and diastolic blood pressure was significantly reduced in both groups ($P < 0.03$) (Fig. 2). There was no difference in the blood pressure improvement rate [(preoperative–postoperative value)/preoperative value] between groups A and B (systolic, $P = 0.41$ and diastolic, $P = 0.54$, respectively).

Impaired glucose metabolism

DM was preoperatively diagnosed in 14 patients (29.2%); eight had been medically treated (insulin, $n = 7$; oral antidiabetics, $n = 1$). Postoperatively, six continued medical treatment (reduced insulin doses, $n = 3$; oral antidiabetics, $n = 3$). In both groups A and B patients the insulin dose could be reduced.

Table 2 Changes in metabolic parameters of 48 operated acromegalics

	T-chol (mg/dl) Mean \pm SD, median	HDL (mg/dl) Mean \pm SD, median	TG (mg/dl) Mean \pm SD, median	LDL (mg/dl) Mean \pm SD, median	HOMA-IR Mean \pm SD, median	BMI Mean \pm SD, median
Total	187.6 \pm 33.2, 188.5	57 \pm 15.8, 57.5	112.8 \pm 54.7, 104.5	111.2 \pm 28.3, 113.4	2.88 \pm 2.21, 2.35	24 \pm 2.79, 23.9
Preoperative						
Group A	181.7 \pm 30.7, 182	54.9 \pm 15.1, 54	117.8 \pm 55, 117	105.1 \pm 25.9, 107	3.43 \pm 2.42, 2.87	24.6 \pm 2.39, 24.3
Group B	200.7 \pm 35.9, 199	61.6 \pm 16.9, 60	101.7 \pm 54.2, 80	124.8 \pm 29.3, 124.4	1.62 \pm 0.72, 1.62	22.7 \pm 3.32, 21.9
Total	189.9 \pm 36.8, 185.5	63.9 \pm 19.8, 63*	84.2 \pm 45.6, 78*	111.9 \pm 28.9, 108.5	1.17 \pm 0.88, 0.98*	24.3 \pm 3.52, 23.9
Postoperative						
Group A	184.4 \pm 29, 182	59.6 \pm 13.6, 56	91 \pm 48.5, 82*	109.4 \pm 27.3, 106.4	1.29 \pm 0.97, 1.08*	25 \pm 3.37, 24.8
Group B	202.2 \pm 48.8, 200	73.4 \pm 27.4, 70*	69.2 \pm 35.6, 56*	117.5 \pm 32.3, 115	0.88 \pm 0.52, 0.79*	22.6 \pm 3.38, 21.7

* $P < 0.05$, paired *t*-test. BMI: body mass index, HDL: high density lipoprotein, HOMA-IR: homeostasis model assessment-insulin resistance, LDL: low density lipoprotein, TG: triglyceride, T-chol: total cholesterol.

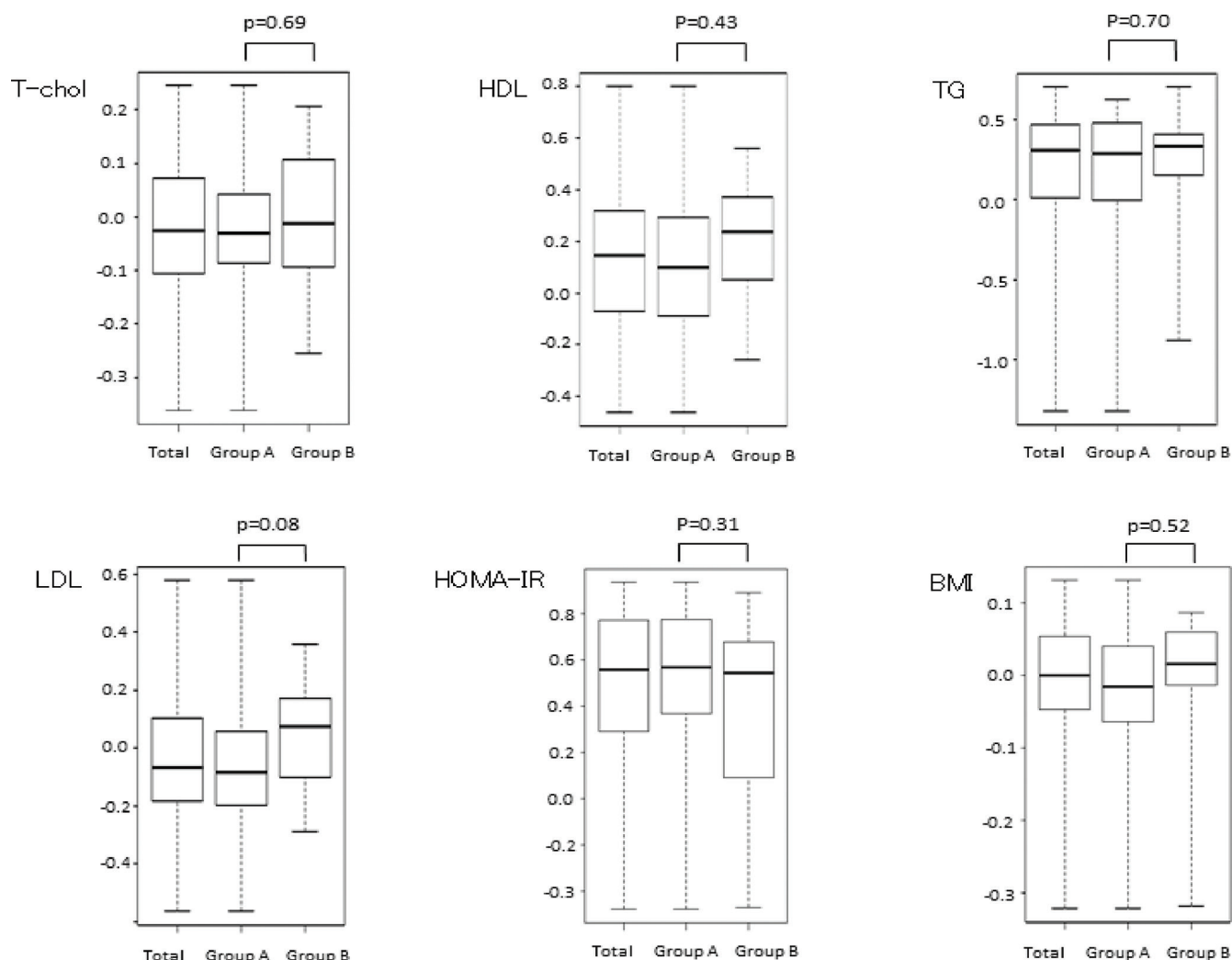


Fig. 1 Rate of improvement in metabolic parameters in all ($n = 48$), group A ($n = 33$), and group B patients ($n = 15$). There was no significant difference between groups A and B. The LDL improvement rate tended to be higher in group B than group A ($P = 0.08$, Student *t*-test). BMI: body mass index, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment-insulin resistance, LDL: low-density lipoprotein, T-chol: total cholesterol, TG: triglyceride.

Table 3 Changes in the secretory function of anterior pituitary hormone assessed with the provocation test

		Total	Group A	Group B	
Five axes other than GH	Preoperative	7/44 (15.9%)	5/32 (15.6%)	2/12 (16.6%)	$P > 0.99^a$
	Postoperative	3/44 (6.8%)	3/32 (9.3%)	0/12 (0%)	$P = 0.55^a$
	Rate of improvement	4/7 (57.1%)	2/5 (40%)	2/2 (100%)	$P = 0.42^a$
GH	Postoperative	3/35 (8.6%)	3/26 (11.5%)	0/9 (0%)	$P = 0.55^a$

^aFisher's exact test, GH: growth hormone.

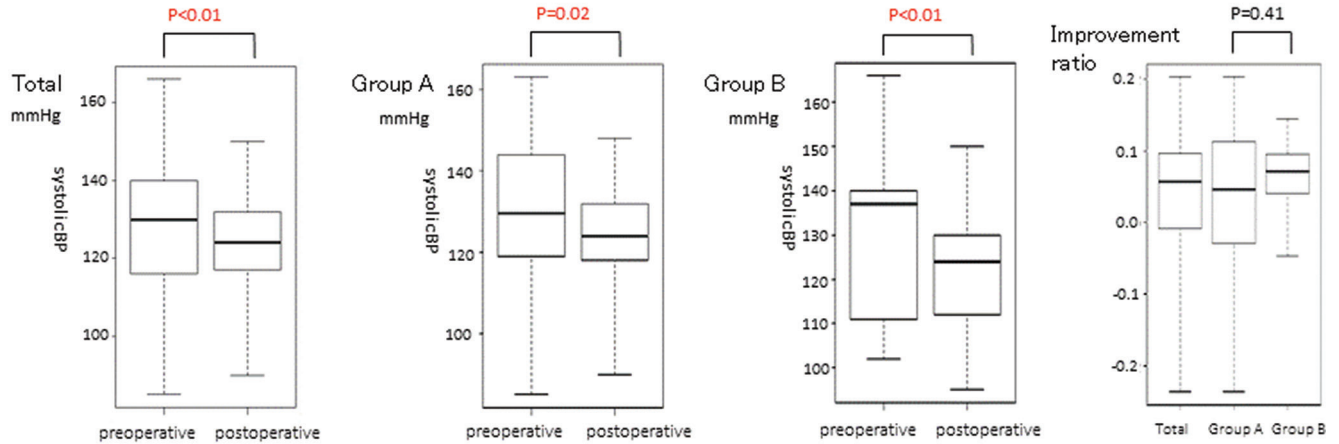
Anterior pituitary function

Before the surgery, at least one among five anterior pituitary hormone functions (other than GH) was judged to be impaired in seven of 44 patients (15.9%) (Table 3). Of these, five were in group A and the other two were in group B. The impaired

hormone was PRL in three, the ACTH-cortisol axis in three and TSH in one patient.

Among the seven patients with preoperatively impaired anterior pituitary hormone functions (group A, $n = 5$; group B, $n = 2$), four experienced postoperative alleviation (group A, $n = 2$; group B, $n = 2$).

a. systolic pressure



b. diastolic pressure

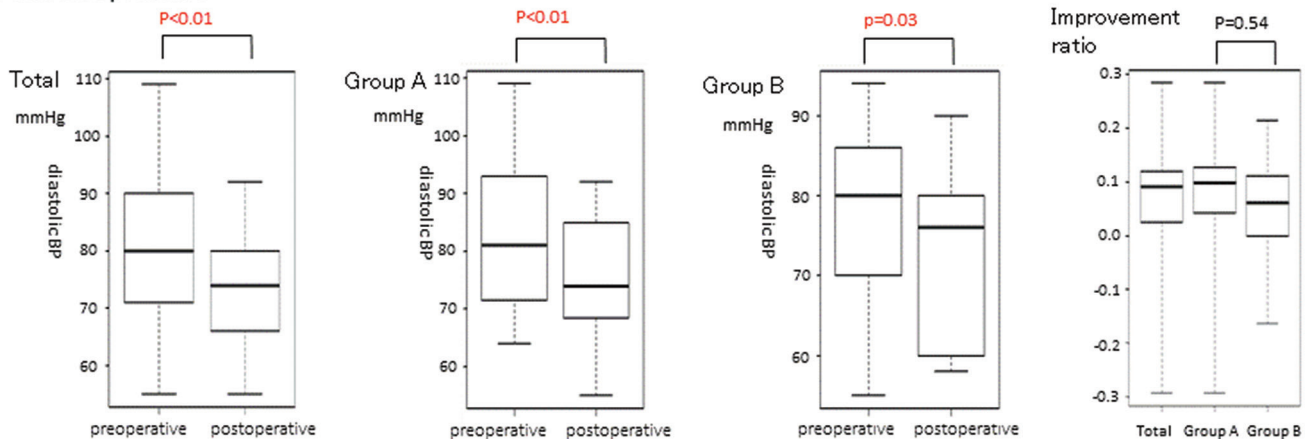


Fig. 2 Postoperative changes in the blood pressure of all ($n = 48$), group A ($n = 33$), and group B patients ($n = 15$). The systolic and diastolic pressure was reduced significantly in both groups ($P < 0.03$, paired t -test). There was no difference in the improvement rate of the two groups.

Postoperatively, impaired GH secretion was observed in three of 35 patients (8.6%) who underwent GH provocation tests; all three were in group A.

SF-36 scores

The postoperative SF-36 scores for the three components (physical, mental, and social component) were not different between the two groups (physical, $P = 0.98$; mental, $P = 0.37$; social, $P = 0.79$, Mann–Whitney test). Postoperative median and interquartile range (25–75th percentile) for these three components was 48.7 (43.5–57.5), 50.5 (45.7–55.3), and 47.0 (39.6–56.5) in group A. It was 53.0 (37.6.5–56.9), 54.6 (48.5–59.4), and 48.3 (40.7–52.0) in group B.

Discussion

We assessed the superiority of the new stricter consensus over the traditional Cortina criteria for

cure of acromegaly by surgery. To this end, we compared several metabolic parameters and other health-related parameters between our two patient groups; group A who met the new consensus criteria for the surgical cure and group B who met the Cortina criteria, but whose nadir GH ranged from 0.4 to 1.0 ng/ml.

Our findings demonstrate that several parameters were significantly improved in patients whose acromegaly was controlled by surgery, but they deny the superiority of the new consensus criteria at least in terms of the parameters we assessed.

Glucose metabolism

Excess GH in acromegalics results in hyperinsulinemia, impaired glucose tolerance (IGT), and the later manifestation of overt DM.^{12,13} The reported incidence of IGT and DM in acromegalics is 16–46% and 19–56%, respectively.^{14,15} We and others^{16,17} found that in patients with surgically controlled

acromegaly the rate of IGT and DM was significantly decreased. In the presence of active acromegaly, HOMA-IR, an indicator of insulin resistance, was increased; it was also reduced by surgical control.¹⁶⁾ In our patients, surgery significantly decreased HOMA-IR; however, the rate of improvement was not different in the two groups.

According to Niculescu et al.¹⁸⁾ in acromegalics, HOMA-IR is more strongly affected by the IGF-1 than the GH level. In our patients, postoperative HOMA-IR was moderately correlated with the IGF-1 but not the GH level ($r = 0.372$, $P = 0.01$ vs. $r = -0.20$, $P = 0.18$). The postoperative similarity in the HOMA-IR improvement ratio ($P = 0.31$) in our series may reflect the similarity in the postoperative IGF-1 level ($P = 0.82$) of both groups.

Lipid metabolism

Patients with active acromegaly were shown to have elevated TG, LDL, free fatty acid (FFA), and lipoprotein(a), and lower HDL levels.^{19,20)}

While these lipid metabolic changes are thought to contribute to early atherosclerosis and cardiovascular disease, successful surgical or medical control improves the altered lipid profiles.^{2,21)}

In our 48 operated patients, the TG level was significantly decreased; HDL was significantly increased in group B. The rate of improvement in the lipid profiles was not different in our two groups. According to Ku et al.,⁸⁾ there was no difference in the FFA concentration in their two groups neither (R1 and R2 compatible with group A and group B in our study).

BMI

As the GH and the IGF-1 levels have a key role in the body habitus, patients with active acromegaly manifest elevated anthropometric indicators, such as their body weight, BMI, and their waist and hip circumference.^{22,23)} There is no consensus on the effect of acromegaly control on the body habitus.^{8,24)} Our patients experienced no significant postoperative changes in the BMI. The lack of marked elevation of BMI in Asian acromegalics might contribute to the absence of the postoperative change.^{8,25)} Their normal to slightly higher BMI may be attributable to their lifestyle, diet, or genomic background (like GH receptor exon).²⁶⁾

Anterior pituitary function

In both groups impaired anterior pituitary function was markedly improved by surgery; there was no inter-group difference in the improvement rate. Although there was no statistical significance, only group A patients manifested postoperative impairment of anterior pituitary hormones.

We²⁷⁾ and others^{28,29)} reported that approximately 10% of acromegalics presented with postoperative GH deficiency. In the current series, three of 35 (8.6%) patients who underwent postoperative GH provocation manifested GH deficiency. All of these were in group A. Because the tumor size, the degree of lateral extension, and the preoperative GH level were almost the same in the two groups, the surgical insults on the pituitary gland may have been stronger in group A.

Clinical relevance of the stricter consensus criteria

The new consensus criteria for biochemical remission (nadir GH < 0.4 ng/ml and normal IGF-1) were promulgated in 2010; they are based on the GH secretory dynamics in healthy controls determined after the highly sensitive (<0.05 µg/l) GH assay became widely available.⁷⁾

Our findings deny the superiority of the new consensus over the Cortina criteria with respect to metabolic features evaluated. Anterior pituitary hormone impairment was observed only in patients determine to be cured by the new consensus criteria (group A). Ku et al.⁸⁾ detected no difference in the metabolic outcomes between their two groups (R1 and R2 compatible with groups A and B in our study).

When we and others applied the new consensus criteria for surgical cure of acromegaly, the nadir GH level of many patients remained above the upper normal limit (0.14–0.25 ng/ml) of healthy control.^{30,31)} This suggests that the dysregulation of GH secretory dynamics, including suppression of GH secretion by hyperglycemia, can be considered to persist after successful surgery.³¹⁾

Ours is the second report to show that several metabolic parameters in operated acromegalics who met the new consensus criteria for cure were not different from patients who met Cortina criteria but not the new consensus criteria. Unlike the earlier study,⁸⁾ we included HDL, LDL, and TG, commonly used parameters for a diagnosis of metabolic syndrome.

Study limitations

Advances in atherosclerosis research identified factors including acidic LDL and adiponectin that are involved in the development or prevention of atherosclerosis.³²⁾ The risk for atherosclerosis can now be predicted by assessing arterial endothelial dysfunction with noninvasive methods such as flow-mediated dilation.³³⁾ These parameters not investigated in our study might be different in the two groups.

We did not consider the intention of medical intervention to intercurrent illnesses which may have been different in our two groups and may have

affected the parameters. Our follow-up period may have been too short and patient population may have been too small for confirming or denying the superiority of the new consensus criteria. Needless to say, the goal of the improvement of deranged metabolic parameters in acromegalics is to prevent premature death and to normalize the standardized mortality rate.

Therefore, multi-institutional prospective and longitudinal investigations on a wider range of metabolic parameters, intercurrent illness, and mortality must be performed to determine whether the new consensus are superior to Cortina criteria for the evaluation of surgical cure of acromegaly.

Until the clinical relevance of new consensus criteria is established through such prospective and longitudinal studies, we may be able to refrain from adjuvant treatments in stable patients who remain “controlled” based on the Cortina consensus criteria and with no active acromegalic symptoms, such as progression of acral overgrowth and excessive sweating.³⁴⁾

Conclusion

Our retrospective survey of changes in several metabolic parameters 1 year after surgery in Japanese acromegalics did not confirm the superiority of the new consensus criteria for surgical cure. Before accepting the new consensus criteria for surgical cure of acromegaly that demand a postoperative nadir GH level <0.4 ng/ml, assessment of the longitudinal change of more metabolic parameters, intercurrent illnesses, and the mortality rate in larger series of acromegalics should be conducted.

Conflicts of Interest Disclosure

We declare that each of us participated sufficiently in the work to take public responsibility for this paper content. Moreover, we declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper reported. All authors who are members of The Japan Neurological Society have registered online self-reported COI Disclosure Statement Forms through the JNS member website.

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