Effects of transsphenoidal adenomectomy on glucose metabolism and free fatty acid induced insulin resistance in acromegaly

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This certifies that the Master's Thesis of
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<ABSTRACT>

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Background: Acromegaly is frequently accompanied with abnormal glucose metabolism. Underlying mechanisms are unclear as are the factors that influence abnormal glucose tolerance. In addition, the effects of the transsphenoidal adenomectomy (TSA) on glucose metabolism and free fatty acid (FFA) have not been well studied. The aim of this study was to investigate the factors associated with abnormal glucose tolerance and the effects of TSA on glucose metabolism and FFA induced insulin resistance in acromegaly.

Methods; A total of 228 Patients with GH secreting pituitary adenoma were enrolled. All of them were treated with TSA, and were evaluated with 75 g oral glucose tolerance tests (75 g OGTT) at 6 month intervals for at least 1 year after TSA. Growth hormone (GH), insulin-like growth factor 1 (IGF-1), glucose and FFA were measured before and after surgery. The remission of acromegaly was considered as GH nadir < 1ng/mL by 75g OGTT. After TSA, magnetic resonance image was taken for determine the extent of tumor resection. Data, collected up to one year after surgery, were used to compare with baseline findings.

Result: The mean age at the time of surgery was 43.3 ± 0.5 years, and the male/female ratio was 0.76 (99/129). Initial GH and IGF-1 were 23.6 ± 21.8 and 702.0 ± 277.8, respectively. Remission with total resection (RT), non-remission with total resection (NRT), and non-remission with subtotal resection (NRS) were 83.7%, 7%, and 8.4% of total patients, respectively. After TSA, glucose, FFA and hemoglobin A1c (HA1c) were significantly decreased in RT (p=0.001), homeostasis model assessment of insulin resistance was significantly improved in RT and NRT groups (p=0.001), accompanied with reduction of GH. Incidence of diabetes mellitus (DM) was reduced (42.5% to 23.7%), and while normal glucose tolerance (NGT) was increased (34.4% to 64.0%), significantly in RT and NRT than NRS (p=0.001).

Conclusion: Glucose and FFA were significantly reduced, and HOMA-IR was normalized after TSA with total resection. The improvement in insulin resistance appeared to result from the reduction of GH, as measured by HOMA-IR and FFA.

Key words: Acromegaly, Insulin resistance, Glucose metabolism, Free fatty acid, Transsphenoid adenomectomy

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I. INTRODUCTION

Acromegaly is a rare endocrine disease related with the excessive production of growth hormone (GH) and is frequently accompanied with impaired glucose tolerance (IGT) and diabetes mellitus (DM)[1]. Approximately, one third of acromegaly patients have DM[2]. Glucose metabolic abnormalities in acromegaly, include hepatic and peripheral insulin resistance as well as an increased hepatic glucose production[3-5]. Insulin resistance is accompanied with obesity, DM and hypertension (HTN)[6, 7]. Also, acromegaly may contribute to increases in cardiovascular complications and mortality[5]. Approximately 60% of acromegalic patients die from cardiovascular disease[5]. Acquired GH excess is a potential precipitating factor for DM[2]. GH suppresses glucose metabolism and induces lipid oxidation, increasing the availability of free fatty acid (FFA)[3]. Thereafter, elevated serum levels of FFA induce insulin resistance. In fact, it has been suggested that overall mortality in patients with acromegaly is correlated with the degree of GH control, and if GH secretion is controlled, mortality rates become similar

to those recorded in non-acromegalic population[8]. However, the mechanism of GH induced DM is not completely understood. Also, the factors that determine abnormal glucose tolerance remain unclear[7, 9]. In addition, the effects of TSA on glucose metabolism and FFA have not been well studied. In this study, our purpose was to analyze the factors associated with abnormal glucose tolerance and the effects of TSA on glucose metabolism and FFA induced insulin resistance with acromegaly. Also, we were tried to find alternative or supplemental indicators reflective of reduction in cardiovascular risk along with GH after TSA.

II. MATERIALS AND METHODS

1. Patients

In this retrospective study of acromegaly treated with transsphenoidal adenomectomy (TSA), we analyzed patients who satisfied the following inclusion criteria: 1) received TSA at Severance Hospital Pituitary and Neurosurgery Center between January 2000 and September 2010 by a single neurosurgeon; 2) between the ages of 15 to 80; and 3) Performed 75 g oral glucose tolerance tests (75 g OGTT) before and after TSA, at least two times or more. The exclusion criteria included as follows: 1) patients who had other malignancy; 2) severe liver (Child-Pugh class C) or kidney disease (end stage renal disease; ESRD).

2. Research Design

All patients received preoperative 75 g OGTT to diagnose acromegaly. To determine the effects of surgery, OGTT was performed at 6 month intervals, for at least 1 year. Using preoperative baseline OGTT data, the subjects ultimately enrolled were classified into four metabolic groups depending on fasting serum glucose (FBG) levels and levels of 2 hours after 75 g glucose loading (P2G), according to the criteria set by the American Diabetes Association [10]. Four groups were defined as follows: normal glucose tolerance (NGT) where FBG < 100 mg/dL and P2G < 140 mg/dL; impaired fasting glucose (IFG) where 100 ≤ FBS <126 mg/dL; IGT where 140 ≤ P2G < 200 mg/dL; and DM where FBS ≥ 126 mg/dL and/or P2G ≥ 200 mg/dL. Patients previously diagnosed or suspected with DM, were classified according to the results of OGTT. As 75 g OGTT was performed after 8 hours of fasting, the results were not

affected by anti diabetic medicine. Each group was compared with baseline clinical and biochemical parameters. Surgical outcomes were defined as remission where nadir GH <1 ng/mL and non-remission where nadir GH ≥1 ng/mL using postoperative 75 g OGTT data and magnetic resonance image (MRI) finding of remnant tumor. The patients were divided into three groups defined as follows; remission with total resection (RT) where nadir GH <1 ng/mL and no remnant tumor who found in MRI; non-remission with total resection (NRT) where nadir GH ≥1ng/mL and no remnant tumor who found in MRI; and non-remission with subtotal resection (NRS) where nadir GH ≥1ng/mL and visible remnant tumor in MRI. Differences in levels of the investigated parameters recorded before and after surgery were compared.

3. Laboratory measurements

GH and serum glucose were measured at 0, 30, 60, 90 and 120 minutes, and FFA, insulin and c-peptide were measured at 0 and 120 minutes during 75g OGTT. IGF-1, hemoglobin A1c (HbA1c) and routine biochemical markers included blood urea nitrogen (BUN), creatinine (Cr), albumin, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) were also measured before surgery and 6 month intervals after the operation. Insulin resistance was estimated by homeostasis model assessment insulin resistance scores (HOMA-IR).

HOMA-IR was calculated according to the following formula:

HOMA-IR=Fasting serum insulin(μunit/mL) x Fasting plasma glucose(mmol/L)/22.5

4. Statistical analysis

All continuous variables were expressed as mean ± SD, and medians with interquartile ranges in the case of non-normal distributed variables. The Pearson's chi-square test, ANOVA, linear correlation and multiple linear regression analyses were performed to assess the association between the presence of DM and various clinical and laboratory parameters. Changes in GH, IGF-1, glucose and FFA at five days, as well as six and twelve months after surgery were compared using repeated ANOVA. The categorical data analysis for repeated measures was used to prove the difference on DM prevalence after TSA. We analyzed the data using two-sided p-values, and a p-value less than 0.05 was considered to be statistically significant. All statistical analysis was conducted using the SPSS and SAS.

III. RESULTS

A total of 260 subjects with GH secreting pituitary adenoma received TSA; however, 30 subjects were lost to follow up, 1 patient was ESRD on hemodialysis, and 1 patient had lung cancer. Ultimately, 228 patients (99 men, 129 women) were enrolled in this study.

1. Preoperative clinical and laboratory characteristics

Preoperative patients' demographic and clinical characteristics are summarized in Table 1. The mean age at the time of surgery was 43.3 ± 0.5 years. BMI was 25.1 ± 3.3 kg/m^2. The initial levels of GH, IGF-1, FBG and P2G were: 23.6 ± 21.8 ng/mL, 702.0 ± 277.8 ng/mL, 111.7 ± 35.6 mg/dl and 160.7 ± 77.5mg/dl, respectively. Fasting (0h FFA) and 2 hours after 75 g glucose loading FFA (2h FFA) were 501.8 ± 273.2 and 121.89 ± 135.4, respectively. DM and HTN were present in 42.5% and 28.9% of all subjects.

For NGT, IFG, IGT and DM, there were 76 (34.4%), 81 (35.5%), 43 (18.9%) and 94 (42.5%) patients, respectively. IFG and IGT were accompanied in 33 patients. Fifty-two subjects, who were previously diagnosed with DM, were mostly dispersed among the in IFG, IGT and DM group. Thirty-two patients used oral anti-diabetic drugs, 13 subjects received insulin and 7 patients received no medication. Subjects in the DM group were significantly older than the other groups (p=0.001). The prevalence of HTN was significantly increased in DM subjects compared to other groups (p=0.033).

2. Correlation analysis between preoperative serum GH levels and other parameters.

There were significant positive correlations between GH levels and fasting glucose (r=0.207, p=0.021), HbA1c (r=0.305, p=0.033) and LDL cholesterol (r=0.284, p=0.021) levels at baseline. Also, GH levels inversely correlated with age (r=-0.194, p=0.003) and blood urea nitrogen (BUN) (r=-.188, p=0.005). There was no significant association between serum GH levels and HOMA-IR, and FFA (Table 2). Increased in FBG was associated with a patient's age, BMI, serum GH and 2h FFA (Table 3).

3. Multivariate analysis correlated with the presence of DM and other parameters at preoperation.

Multivariate analysis revealed that the presence of DM was associated with patient age (OR 1.17, 95% CI 1.05-1.29, p=0.003) and 2 h FFA (OR 1.01, 95% CI 1.0-1.02, p=0.036).

Table 1. Preoperative characteristics of the subjects with acromegaly based on glucose metabolic status.

	All n=228	NGT n=76(34.4%)	IFG n=81(35.5%)	IGT n=43(18.9%)	DM n=94(42.5%)	*p*
Age(years)	43.3±0.5	38.6±10.4	43.6±11.2	46.3±10.7	49.7±10.9	0.001*
Sex(M;F)	99;129	39;39	40;41	14;29	15;37	0.110
BMI(kg/m^2)	25.1±3.3	25.0±3.7	25.4±3.1	25.1±2.9	24.7±2.6	0.821
DM	52(22.8%)	4(4.3%)	6(20.4%)	7(16.3%)	37(71.1%)	0.001*
OAD use	32(14.1%)	2(2.6%)	12(12.2%)	12(12.2%)	18(19.1%)	0.001*
Insulin use	13(5.7%)	0(0%)	3(3.2%)	3(3.2%)	10(10.6%)	0.001*
HTN	66(28.9%)	13(17.1 %)	13(16.0%)	18(42.9%)	20(21.3%)	0.033‡
IGF-1 (ng/mL)	702.0±278	689.6±226.3	720.9±244.7	715.5±236.1	683.1±194	0.111
GH (ng/mL)	23.6±21.8	24.0±20.4	19.5±18.7	19.3±14.3	28.5±38.9	0.162
FBG (mg/dL)	111.7±35.6	91.2±6.8	108.7±6.9	105.3±10.9	155.0±52.2	0.001*
P2G (mg/dL)	160.7±77.5	107.5±22.9	138.2±36.2	165.8±18.3	265.3±76.6	0.001*
Insulin (mIU/L)	18.1±21.8	16.9±30.9	18.4±13.3	19.9±16.4	20.1±18.9	0.979
Homa IR	5.1±5.7	3.7±5.8	4.8±3.4	5.1±3.9	6.6±7.0	0.020‡
C-peptide (ng/mL)	2.9±1.7	3.0±2.2	2.9±0.7	2.9±0.8	2.7±1.8	0.821
HbA1c (%)	7.7±2.1	5.8±2.1	6.4±0.7	6.2±0.8	8.6±2.2	0.001*
BUN (mg/dL)	10.6±4.0	11.1±3.6	11.7±4.1	11.6±3.3	12.2±4.1	0.256
Cr (mg/dL)	0.7±0.2	0.7±0.2	0.7±0.1	0.7±0.1	0.7±0.2	0.275
Albumin (mg/dL)	4.5±0.4	4.5±0.4	4.5±0.4	4.5±0.3	4.4±0.4	0.189
Cholesterol (mg/dL)	177.9±36.1	175.8±37.1	183.2±35.5	182.5±38.7	173.9±38.4	0.521
TG(mg/dL)	146.4±95.1	158.2±62.7	140.7±84.2	135.5±95.6	149.6±114	0.703
HDL-C (mg/dL)	48.9±11.4	48.2±12.7	52.4±11.6	53.0±11.3	46.7±9.2	0.334
LDL-C (mg/dL)	109.6±40.8	106.1±43.3	123.8±36.5	124.7±39.9	101.8±39.7	0.372
0h FFA (μEg/L)	501.8±273	420.0±169.6	467.2±275.5	514.1±292.3	585.4±318.7	0.226
2hFFA (μEg/L)	121.89±35	81.5±28.2	102.7±45.3	94.9±35.0	212.7±26.2	0.016*

p-value *<0.001; †<0.01;‡<0.05

Mean ±SD, median (inter quartile range), [a] chi-square test, one way analysis of variances among groups, fasting Glucose(mmol/L) x fasting Insulin(mIU/L) / 22.5, IGF-1;insulin like growth factor-1, GH; growth hormone, Homa IR; insulin resistance index,

Table 2. Pearson's correlation coefficients of preoperative GH with clinical parameters.

Variables	Correlation coefficient	*p*-value
Age (years)	-0.194	0.003*
BMI (kg/m^2)	-0.051	0.445
Initial IGF-1 (ng/mL)	0.125	0.070
Albumin (g/dL)	-0.46	0.496
Total cholesterol (mg/dL)	0.057	0.476
Triglyceride (mg/dL)	0.162	0.055
HDL-C (mg/dL)	-0.129	0.293
LDL-C (mg/dL)	0.284	0.021‡
FBG (mg/dL)	0.207	0.002*
P2G (mg/dL)	0.074	0.168
0h FFA(μEg/L)	-0.132	0.295
2h FFA (μEg/L)	-0.009	0.944
BUN (mg/dL)	-0.188	0.005†
Cr (mg/dL)	-0.118	0.080
Insulin (mIU/L)	-0.028	0.816
C-peptide (ng/mL)	0.011	0.923
HbA1c (%)	0.305	0.033‡
HOMA-IR	0.198	0.094

*<0.001; †<0.01; ‡<0.05

Table 3. Metabolic variables associated with preoperative FBG by multiple linear regression analyses.

Variables	β±SE	P-value	R^2
Age(yr)	1.086±0.304	0.001	0.582
GH(ng/mL)	0.382±0.084	0.001	
2h FFA (μEg/L)	0.134±0.024	0.001	
BMI(kg/m^2)	2.253±0.965	0.024	

GH; growth hormone, FFA; free fatty acid, BMI; body mass index, SE; standard errors

4. Surgical outcomes after TSA

Hormonal status was significantly improved after TSA. Among the enrolled patients, IGF-1 and GH were significantly decreased as 312.6 ± 148.2ng/mL (p=0.001) and 1.5 ± 2.3ng/mL (p= 0.022) after 12 months, respectively. RT, NRT, and NRS were 83.7%, 7%, and 8.4% of total patients, respectively. GH was significantly decreased in RT, NRT and NRS groups. But, in NRT and NRS, GH was not normalized by OGTT. IGF-1 was only significant reduction in RT group.

5. Postoperative glucose parameters change

According to the response of TSA and initial glucose tolerance, the changes of glucose parameters were analyzed (Table 4). Glucose parameters were improved after TSA in total subjects. FBG, P2G and HbA1c were significantly decreased in the RT group compared to the other groups (p=0.001). Especially, in DM patients, glucose reduction was apparent. The patients in NRT had significant FBG reduction, but had no difference in P2G. There were no significant changes of the glucose levels in NRS group. HOMA-IR was normalized and significantly reduced compared with baseline levels in RT and NRT groups (both, p=0.001). By corresponding changes in GH, glucose parameters were improved (Fig 1.A~D). FBG and P2G were significantly decreased in RT and NRT groups (Fig C, D). But there was no difference in NRS. Serum insulin levels were also decreased, but there were no statistical differences (Table 4). The area under the curve (AUC) of postoperative OGTT was significantly decreased compared that of baseline OGTT in RT group (Fig 2). But there was no significant difference in NRT and NRS.

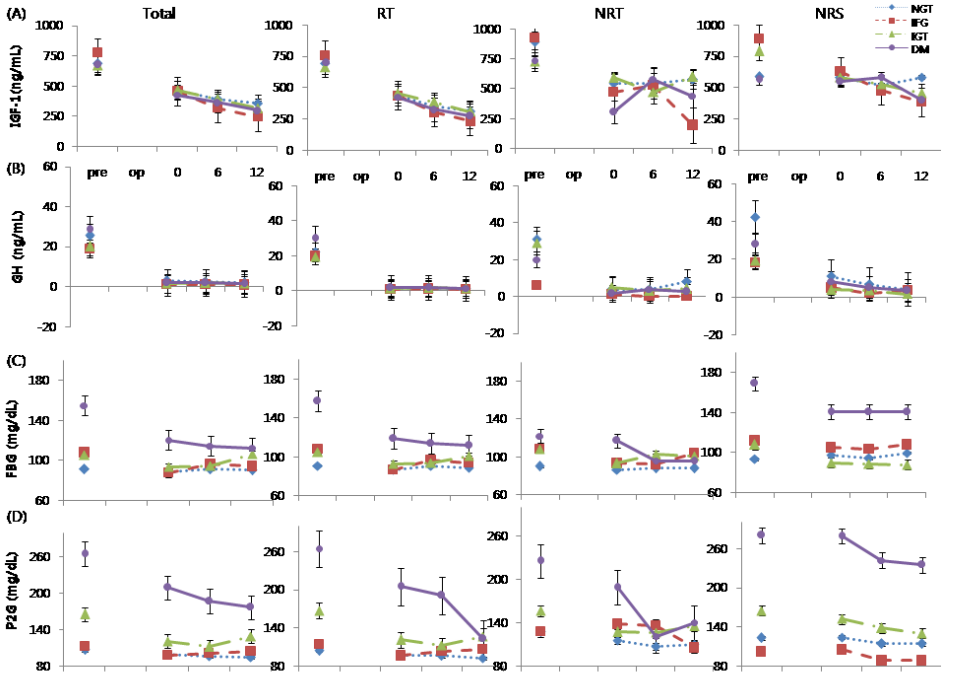
Table 4. Change of glucose parameters after TSA operation

	Group	Pre op	0m	6m	12m	*p*
IGF-1 (ng/mL)	Total (n=228)	702±278	457±147	374±165	313±148	0.001*
	RT (n=192)	702±220	440±140	345±140	287±127	0.001*
	NRT (n=16)	791±282	502±138	565±258	481±144	0.288
	NRS (n=20)	631±234	585±94	528±161	459±193	0.233
GH (ng/mL)	Total	23.6±21.8	2.0±3.7	2.0±3.5	1.5±2.3	0.022‡
	RT	22.7±26.0	1.3±1.3	0.5±0.7	0.4±0.5	0.001*
	NRT	23.2±15.1	3.0±2,4	2.3±1.9	2.2±1.5	0.048‡
	NRS	32.6±24.7	8.3±9	3.7±3.4	2.4±2.1	0.002‡
FBG (mg/dL)	Total	117±36	96±23	103±65	100±30	0.001*
	RT	113±36	95±22	98±22	98±26	0.001*
	NRT	107±18	98±14	97±9.6	96±13	0.005†
	NRS	113±45	105±34	104±42	108±39	0.395
P2G (mg/dL)	Total	161±78	129±67	123±65	124±71	0.001*
	RT	160±77	126±65	122±65	122±71	0.001*
	NRT	166±46	136±45	118±42	131±63	0.086
	NRS	165±70	152±96	130±87	138±79	0.054
Insulin(mIU/L)	Total	18.1±21.8	12.4±16.3	8.6±8.3	6.6±4.9	0.458
	RT	18.6±23.3	10.4±13.2	8.0±5.7	6.1±3.7	0.267
	NRT	3.1±1.1	2.7±2.2	1.5±0.4	1.4±0.5	0.430
	NRS	13.5±3.7	17.6±8.7	16.5±8.3	6.6±4.9	0.273
C-pep(ng/mL)	Total	2.9±1.7	1.9±1.4	2.2±3.7	2.5±4.2	0.095
	RT	2.7±1.3	2.1±1.6	2.2±1.4	2.5±4.2	0.008†
	NRT	11.3±2.1	7.5±2.1	7.3±2.3	6.2±2.5	0.051
	NRS	2.9±1.8	1.8±1.3	2.2±3.9	2.3±3.7	0.067
Homa-IR	Total	5.1±5.7	3.6±6.5	2.5±4.6	1.7±1.7	0.001*
	RT	5.2±5.7	2.7±3.7	2.1±1.8	1.5±1.2	0.001*
	NRT	4.1±2.2	4.0±4.6	1.2±0.7	1.2±0.7	0.001*
	NRS	3.6±1.5	7.6±3.9	7.4±5.3	7.4±1.7	0.126
HbA1c (%)	Total	7.7±2.1	7.2±1.7	6.9±1.9	6.3±2.3	0.702
	RT	7.6±2.1	7.1±1.7	6.9±1.9	6.1±2.4	0.030‡
	NRT	6.9±0.8	6.9±0.8	6.9±1.9	7.1±0.4	0.708
	NRS	8.3±2.1	7.5±2.1	7.3±2.3	6.2±2.5	0.070

Repeat measured ANOVA, *<0.001; †<0.01 ;‡< 0.05

IGF-1; insulin-like growth factor-1, GH; growth hormone, FBG; fasting blood glucose, C-pep; c-peptide at fasting, P2G; levels of serum glucose at 2 hours after 75g glucose loading, op; operation, m; months after operation, yr; year

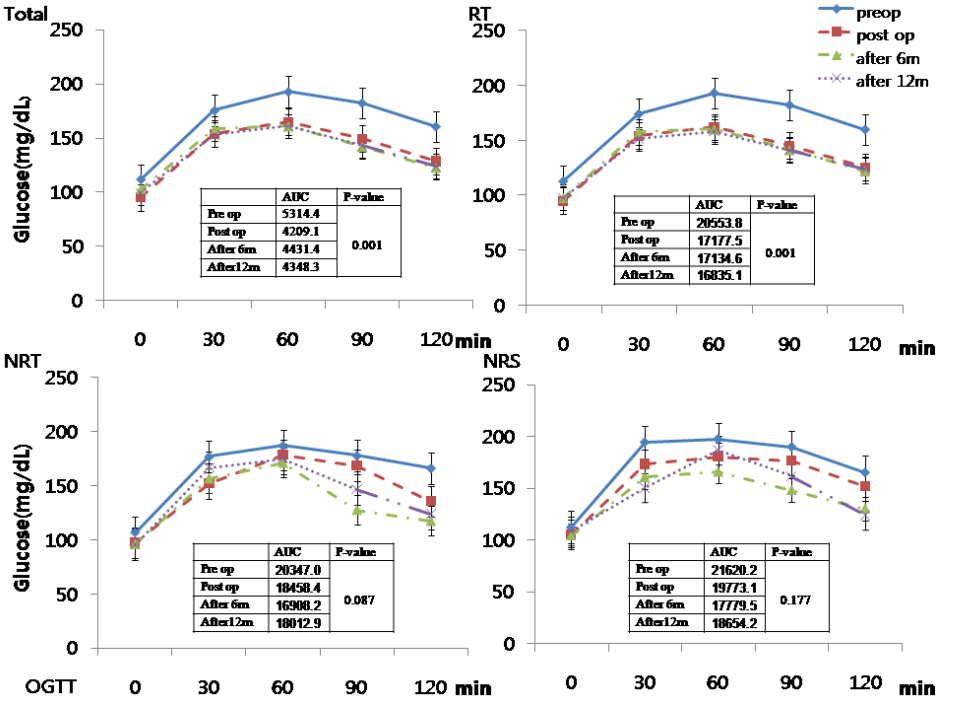
Figure1. Change of glucose parameters in metabolic subgroups after operation



(a) IGF-1 was significantly decreased after TSA in RT.
(b) GH was significantly decreased after TSA in total subject but was not normalization in NRT and NRS.
(c) Change of FBG after operation was significant in RT and NRT.
(d) P2G was significantly decreased in RT and NRT, especially in DM subgroup.

NGT; Normal glucose tolerance, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, DM; diabetes mellitus, RT; remission with total resection, NRS; non-remission with subtotal resection, NRT; non-remission with total resection, GH; growth hormone, IGF-1; insulin like growth factor-1, month; months after TSA, min; minute, op; operation.

Figure 2. The area under the curve of pre and postoperative OGTT



Area under the curve (AUS) was immediately decreased after TSA in RT. There were no significant difference in NRT and NRS.

6. Postoperative lipid parameters change

Lipid parameters are summarized in Table 5. There were no significant differences in postoperative total cholesterol, TG, HDL-C and LDL-C compared with baseline measurements. Both 0h and 2h FFA were significantly decreased after surgery (both, p=0.001) in RT group (Fig 3). But, in NRS and NRT groups, only 120m FFA was significantly reduced (p=0.001).

7. Metabolic group composition change after TSA.

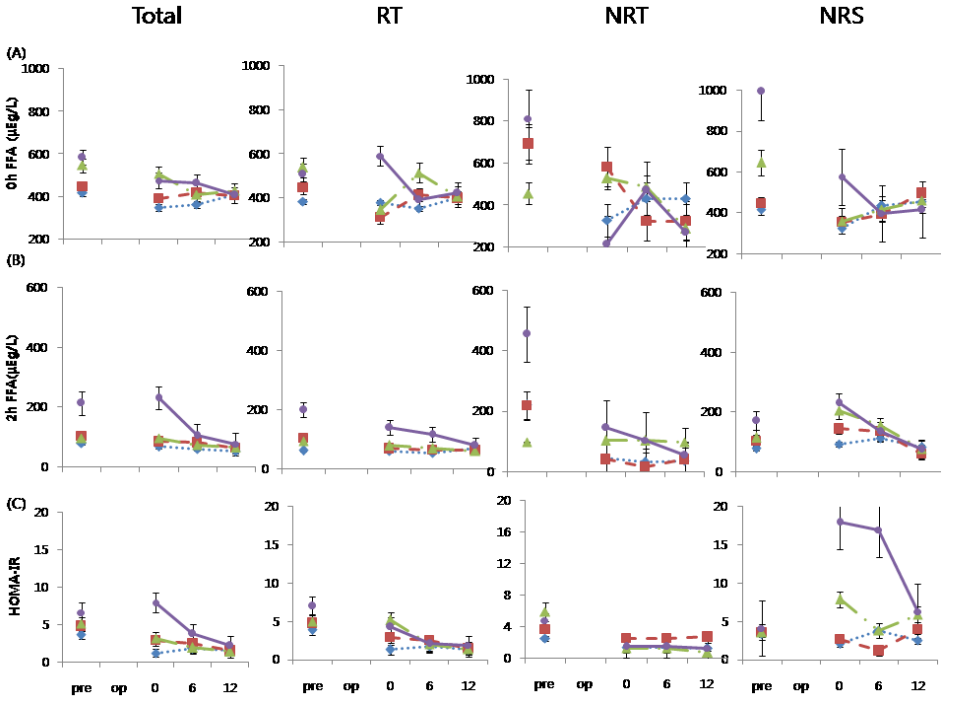
All subjects were redistributed according to postoperative OGTT results. IFG, IGT and DM groups were reduced, and while NGT was increased by 75g OGTT (p=0.001) in all of RT, NRT and NRS groups (Table 6). In RT group, DM was significantly decreased (43.1% to 14.5%), and NGT was increased (33.0% to 69.4%) immediately after TSA. Also IFG and IGT were significantly decreased. Moreover, these compositions were consisted until more than 1year. NRT also had decreased DM from 50% to 36.5%, increased NGT 25% to 43.8%. Also, after 12 month, NGT was more increased in NRT up to 60% (Fig 3). However, in NRS group, NGT was mild increased, there was no significant difference in DM subgroup.

Table 5. Change of lipid profile after operation

		Pre op	6m	12m	*p*
Total cholesterol (mg/dL)		178±36	185±43	191±47	0.184
TG (mg/dL)		146±125	119±72	104±52	0.672
HDL-C(mg/dL)		49±11	55±12	53±15	0.231
LDL-C (mg/dL)		110±41	106±27	116±33	0.305
0h FFA (μEg/L)	Total (n=228)	502±273	407±217	413±225	0.002‡
	RT (n=192)	471±260	411±216	406±229	0.001*
	NRT (n=16)	694±242	398±190	447±169	0.076
	NRS (n=20)	647±369	361±204	459±217	0.904
2h FFA (μEg/L)	Total	122±135	77±70	74±72	0.001*
	RT	113±130	80±72	72±82	0.001*
	NRT	218±194	140±130	99±55	0.001*
	NRS	114±115	143±172	57±55	0.001*

Repeat measured ANOVA, *<0.001; †<0.01 ;‡< 0.05
Op; operation, m; months after operation, 0h FFA; fasting free fatty acid, 2h FFA; levels of FFA at 2 hours after 75g glucose loading, TG; triglyceride, C; cholesterol

Figure 3. Change of lipid profile in metabolic subgroups after operation



(a) 0h FFA was decreased correlate with GH in RT, especial in DM subgroup.

(b) 2h FFA was significantly improved in DM, all subjects, after operation.

(c) HOMA IR was normalized in RT and NRT groups within 6month after TSA. But in NRS, HOMA IR was immediately elevated and subsequently decreased.

NGT; Normal glucose tolerance, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, DM; diabetes mellitus, RT; remission with total resection, NRS; non-remission with subtotal resection, NRT; non-remission with total resection, GH; growth hormone, IGF-1; insulin like growth factor-1, month; months after TSA, min; minute, op; operation.

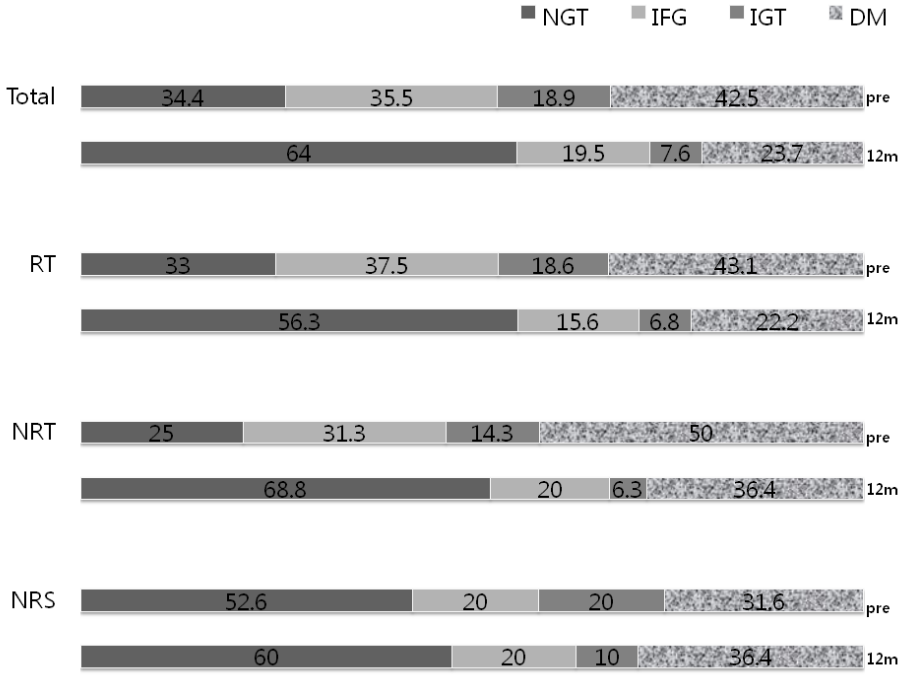
Table 6. Change of the composition among metabolic subgroups after TSA

		Pre op	0m	6m	12m	*p*
NGT	Total (n=228)	76(34.4%)	145(63.6%)	134(64.1%)	119(64.0%)	
	RT (n=192)	62(33.0%)	129(69.4%)	113(63.5%)	108(56.3%)	
	NRT (n=16)	10(52.6%)	9(45.0%)	12(60.0%)	12(60.0%)	
	NRS (n=20)	4(25.0%)	7(43.8%)	9(56.3%)	11(68.8%)	
IFG	Total	81(35.5%)	30(13.6%)	40(19.1%)	36(19.5%)	
	RT	72(37.5%)	20(10.4%)	33(17.2%)	30(15.6%)	
	NRT	4(20.0%)	3(18.8%)	2(10.0%)	4(20.0%)	
	NRS	5(31.3%)	4(25.0%)	4(25.0%)	3(20.0%)	0.001
IGT	Total	43(18.9%)	29(13.2%)	23(11.1%)	15(7.6%)	
	RT	35(18.6%)	18(9.7%)	14(7.9%)	11(6.8%)	
	NRT	4(20.0%)	3(15.8%)	1(5.0%)	2(10.0%)	
	NRS	2(14.3%)	1(6.3%)	1(6.3%)	1(6.3%)	
DM	Total	94(42.5%)	37(16.7%)	47(22.5%)	44(23.7%)	
	RT	81(43.1%)	27(14.5%)	39(21.9%)	36(22.2%)	
	NRT	6(31.6%)	6(31.6%)	3(17.7%)	2(10.0%)	
	NRS	7(50.0%)	4(25.0%)	5(35.7%)	4(36.4%)	

Categorical data analysis for repeated measures

RT; remission with total resection, NRS; non-remission with subtotal resection, NRT; non-remission with total resection, NGT; normal glucose tolerance, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, DM; diabetes mellitus.

Figure 4. Postoperative change of the metabolic subgroups composition, compared to baseline.



NGT; Normal glucose tolerance, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, DM; diabetes mellitus, RT; remission with total resection, NRT; non-remission with total resection, NRS; non-remission with subtotal resection, m; month after TSA

IFG, IGT and DM groups were reduced, and while NGT was increased at 12 month after TSA compared with preoperation.

IV. DISCUSSION

Acromegaly is frequently accompanied with glucose intolerance and diabetes mellitus. Over 50% of acromegaly patients have IGT or DM. GH excess may induce insulin resistance and abnormal glucose metabolism. Also, it may contribute to increase in cardiovascular complications and mortality.

In this study, we analyzed the effects of TSA operation on glucose metabolism in acromegaly patients. The patients were diagnosed acromegaly by 75 g OGTT, nadir GH over 1 ng/mL. All of them had pituitary adenomas, and underwent TSA operation. Follow up detail data was, subsequently, collected for at least 12 months postoperatively. A total 228 subjects were analyzed; there were 94 patients with DM. The patients in the DM group were older, and had greater elevated glucose and FFA levels than those in the other groups. Average BMI over the normal range (BMI >25kg/m^2). An increase in HTN was accompanied with DM.

Glucose and lipid parameters were improved after surgery in RT group. FBG and P2G were reduced immediately after TSA, especially the patients with DM in RT group. Calculated HOMA-IR was also significantly decreased within 6 months in RT and NRT groups. But there was no significant difference in NRS group. And 0h and 2h FFA were significantly reduced in RT subjects within 6 months. Percent of NGT was increased in all subgroups. This is considered due to the reduction of GH by TSA. It might be contributed to improve glucose metabolism. But the effect of TSA with subtotal resection was insufficient than total resection for glucose improvement. This implies

means that insulin resistance was improved rapidly after successful operation with total tumor resection.

It is well known that high plasma levels of FFA induced insulin resistance[6, 7, 9]. Insulin resistance (IR) is a state of which normal amounts of insulin are inadequate to induce normal responses from target tissues (muscle, liver and adipose tissue)[6]. IR is key to the pathology of type 2 DM. The causes of IR are genetic and may also lead to acquired factors of obesity, physical inactivity and hormonal abnormality[6]. IR in humans may be induced by increased FFA availability and accumulation of intracellular fat[11]. A previous study revealed that FFA competes with glucose for substrate oxidation in muscle tissue of the heart and diaphragm[9]. FFA inhibits glucose uptake in muscles and reduces glucose phosphorylation[7, 9]. Intracellular fat accumulation induced by FFA elevation has been shown to be refractory to the anti-lipolytic effects of insulin[7]. High plasma FFA levels reduce the sensitivity of pancreas beta cells to glucose. And it impairs insulin secretion, leading to elevation of plasma glucose produced in the liver. Additionally, it may also contribute to the development of secondary hyperinsulinemia and DM[6, 7]. Therefore, elevated serum FFA may predict insulin resistance in acromegaly patients.

GH also augments IR in the liver and peripheral tissue[3]. Because GH has anti-insulin effects, it serves as a counter-regulatory hormone[2]. GH induces increased glucose production and decreased peripheral glucose uptake[12]. The physiologic effects of GH on substrate metabolism include promoting nitrogen retention during energy surplus, and switching the source of fuel from carbohydrates and protein to lipids when food or energy are lacking[3]. GH may also allow for the saving the vital proteins

for survival. GH has acute and chronic metabolic effects. The acute effects include stimulation of lipolysis and increased FFA levels in the blood[3]. FFA elevation is the most sensitive response to GH [12]. Prolonged GH exposure in adequate nutrient supply and increased insulin induces hepatic IGF-1 production[13]. IGF-1 increases lean body mass, induces body organ growth and storage of protein. It may also contribute to increased body weight. The effects of GH on glucose metabolism may decrease sensitivity to insulin[3, 9, 12]. GH decreases glucose uptake and/or glucose oxidation by direct effect, or secondary to an increase in lipid oxidation[3, 9]. These functions of GH seem to induce glucose and lipid abnormalities in acromegaly patients.

Acromegaly patients commonly have hyperinsulinemia, impaired glucose tolerance and overt DM due to insulin resistance. Also, HTN is increased in those subjects. These abnormalities contribute to increases in cardiovascular morbidity and mortality. Although surgical and medical treatment of acromegaly may reduce these risk factors, a viable method for predicting reduction of morbidity and mortality risk is not well known. GH was classically used to predict responses to treatment and to assess cardiovascular risk reduction[14]. In previous studies, the effects of TSA on glucose metabolism were analyzed in an attempt to detect a predictor of risk in acromegalic patients. Moller et al. [15] reported that plasma insulin and glucose levels were significantly decreased after TSA surgery in 6 acromegaly patients. Puder et al.[14] suggested that a normal postoperative serum IGF-1 value was more predictive of insulin sensitivity involving 66 patients. Serri et al.[16] analyzed 53 postoperative patients, and revealed that a significantly higher prevalence of abnormal glucose tolerance was found in active disease status. However, these studies had not compared

individual changes of substrate before and after surgery. Also, only a minimal number of acromegalic patients were included in the studies (less than 50, purely treated with TSA operation). In our study, 228 patients treated with TSA surgery were analyzed. Before and after operation, detail data of clinical and biochemical markers including glucose, lipid and insulin resistance were collected. After operation, the percentages of DM and IGT, level of serum glucose, FFA and HOMA-IR were decreased, and were accompanied with GH reduction in RT. This reflects that the TSA with total resection of GH secreting tumor improves insulin resistance via the reduction of GH and FFA. This may contribute to a reduced prevalence of cardiovascular disease in treated acromegaly patients.

This is the first report to detail glucose metabolism and FFA induced insulin resistance after TSA in Korean acromegaly patients. FFA and HOMA-IR data were obtained, which represented insulin resistance in our subjects. These parameters may be useful as supplementary indices for calculating post- operative cardiovascular risk, as well as GH.

V. CONCLUSION

TSA with total resection of GH secreting pituitary tumor improved glucose metabolism and insulin resistance. Prevalence of DM, IGT and IFG were reduced after the operation. FFA and HOMA-IR might be useful for predicting a cardiovascular risk and treatment responses.

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ABSTRACT(IN KOREAN)

말단 비대증 환자에서 접형골 뇌하수체 선종 절제술이 당 대사와 유리 지방산에 의한 인슐린 저항성에 미치는 영향

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최 은 영

배경; 말단비대증은 성장 호르몬의 과다로 인한 전신증상이 나타나는 질환으로 비정상적인 포도당 대사가 자주 동반된다. 이러한 내당능 장애의 원인 기전은 아직 불분명하다. 또한 접형골 뇌하수체 선종 절제술(trans-sphenoid adenomectomy, TSA)이 혈당 및 유리 지방산의 대사에 미치는 효과는 아직 잘 모르는 상태이다. 본 연구에서는 말단비대증에서 당 대사 및 유리 지방산에 의한 인슐린 저항성에 대한 TSA의 치료 효과와 비정상적인 당 대사에 영향을 미치는 관련 인자를 조사하기로 하였다.

방법; 성장호르몬을 분비하는 뇌하수체 선종을 지닌 환자를 조사하였다. 그들 모두 TSA 수술을 받았고 수술 전후에 6개월 간격으로 최소 1년 동안 75 g 경구 당 부하 검사를 시행하였다.

성장 호르몬 (GH), 성장인자 1(IFG-1), 혈중 포도당과 유리 지방산(FFA), 인슐린 등은 수술 전과 수술 후 측정 되었다. 수술 후 완치여부는 경구 당부하 검사 후 GH 최저치가 1ng/mL 미만인 것으로 판단하였다. 자기공명 영상(MRI)을 수술 후 시행하여 남아있는 종양 여부를 확인하였다. 수술 후 1년까지 수집된 데이터를 수술 전과 비교하였다.

결과; 총 228명의 환자가 이 연구에 등록 되었다. 수술 당시 평균 연령은 43.3±0.5세 이었고, 여성/남성의 비율은 0.76 (99/129) 였다. 초기 GH과 IGF-1은 각각 23.6 ± 21.8, 702 ± 278 이었다. 종양의 완전 절제 후 완치 (RT), 불완전 절제 후 비 완치 (NRS), 완전 절제 후 비 완치 (NRT)는 각각 83.7%, 8.4%, and 7% 이었다. 성공적인 TSA후 혈당과 유리 지방산 및 인슐린 저항성 지표는 GH의 감소와 함께 모두 감소하였고 특이 RT 군에서 보다 의미 있게 감소하였다. 수술 후 내당능 장애와 당뇨 군은 의미 있게 감소하였고(42.5% to 23.7%) 정상 혈당 군은 증가하였다 (34.4% to 64.0%), 이러한 변화는 특히 RT와 NRT 군에서 두드러졌다 (p=0.001).

결론; GH 분비 뇌하수체 종양의 완전 절제 후 혈당과 유리 지방산이 크게 감소하였고 HOMA-IR은 정상화 되었다. 인슐린 저항성의 개선은 수술 후 GH 의 감소에 의한 결과이며, 이것은 HOMA-IR과 FFA로 측정 할 수 있다.

핵심되는 말: 말단 비대증, 인슐린 저항성, 내당능 장애, 유리 지방산, 접형골 뇌하수체 선종 절제술