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(Citation)
Diabetes & Metabolism,46(3):236-242

(Issue Date)
2020-06

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90007317

Original Article

Insulin Secretion and Sensitivity Before and After Surgical Treatment for Aldosterone-Producing Adenoma

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Abstract

Aim: Primary aldosteronism, which is usually caused by an aldosterone-producing tumor, affects glucose metabolism. The effects of this condition on insulin secretion and insulin sensitivity have remained unclear, however. To gain insight into the influence of primary aldosteronism on glucose tolerance, we comprehensively analyzed various parameters related to insulin secretion or insulin sensitivity in patients with an aldosterone-producing tumor.

Methods: Fourteen patients with an aldosterone-producing tumor were examined. Hyperglycemic and hyperinsulinemic-euglycemic clamps as well as an oral glucose tolerance test (OGTT) were performed in subjects before and after tumor excision. The time between the presurgical analysis and surgery was 27 to 559 days (194 ± 132 days), and that between surgery and postsurgical analysis was 14 to 142 days (51 ± 38 days). We evaluated various parameters related to insulin secretion or insulin sensitivity as determined by an OGTT as well as hyperglycemic and hyperinsulinemic-euglycemic clamp analyses.

Results: Surgical treatment of the tumor ameliorated hypokalemia and reduced the plasma aldosterone level. The first and second phases of insulin secretion during the hyperglycemic clamp, as well as the insulinogenic index and total insulin secretion measured during the OGTT, were improved after surgery. The insulin sensitivity index determined during the hyperinsulinemic-euglycemic clamp was reduced after surgery.

Conclusions: Primary aldosteronism impairs insulin secretion.

Keywords: primary aldosteronism, insulin secretion, insulin sensitivity, glucose tolerance

Abbreviations

OGTT, oral glucose tolerance test; PA, primary aldosteronism; IGT, impaired glucose tolerance; DM, diabetes mellitus; APA, aldosterone-producing adenoma; NGT, normal glucose tolerance; IVGTT, intravenous glucose tolerance test; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; DI, disposition index.

Introduction

Primary aldosteronism (PA) is an endocrine disorder that affects glucose metabolism [1–3]. Although cross-sectional studies have shown that PA is often associated with impaired glucose tolerance (IGT) or diabetes mellitus (DM) [3, 4], the effects of this condition on glucose tolerance remain unclear. Whereas analysis of subjects with PA before and after surgical treatment can potentially yield insight into the direct influences of the disease, information on glucose tolerance provided by such analysis is limited [5, 6]. One study found that, among 25 subjects with an aldosterone-producing adenoma (APA), a major cause of PA, 3, 9, and 13 individuals were categorized as having DM, IGT, or normal glucose tolerance (NGT), respectively, before surgical treatment and 15 and 10 individuals as having IGT or NGT, respectively, after the treatment [5]. Another study found that the number of subjects with IGT was increased after surgical treatment for APA [6]. Definitive evidence that PA impairs glucose tolerance has thus not been available to date.

On the other hand, several studies have shown that insulin secretion is impaired in individuals with PA, with indices of insulin secretion including the insulinogenic index, the area under the curve for the serum insulin concentration determined with an oral glucose tolerance test (OGTT), and the first phase of insulin secretion during an intravenous glucose tolerance test (IVGTT) having being found to be improved after the surgical treatment of PA [7–9]. Moreover, insulin sensitivity has also been shown to be improved after treatment of PA [10, 11]. These observations collectively suggest that, whereas PA influences insulin secretion and insulin sensitivity,

the effects are often not large enough to lead to a deterioration in glucose tolerance.

PA is often accompanied by hypokalemia. Given that blockade of the efflux of potassium is a key step in the stimulation of insulin secretion from pancreatic β-cells, impaired insulin secretion in individuals with PA has been attributed to hypokalemia [3]. Alternatively, a direct cellular action of aldosterone has been implicated in the impairment of β-cell function as well as in that of insulin sensitivity [12, 13]. The mechanisms underlying the impairment of insulin secretion and insulin sensitivity in individuals with PA are thus not fully understood.

To provide further insight into the influence of PA on glucose tolerance, we have now performed a comprehensive analysis of insulin secretion and insulin sensitivity in 14 patients with APA both before and after surgical treatment. We thus measured various parameters during hyperglycemic and hyperinsulinemic-euglycemic clamps as well as during an OGTT. Moreover, to clarify the mechanisms responsible for the effects of PA on insulin secretion and sensitivity, we analyzed the relation of changes in the blood levels of potassium and aldosterone to those in metabolic parameters determined by the physiological examinations.

Methods

Patients

The study conformed to the provisions of the Declaration of Helsinki of 1995 and was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 180154). All subjects provided written informed consent to the performance of clamp analyses and to publication of their data for scientific purposes. Subjects were recruited at the Division of Diabetes and Endocrinology of Kobe University Hospital from August 2009 to February 2013. Fourteen Japanese individuals (five men, nine women) were diagnosed with PA due to APA, underwent successful surgical treatment for the tumor, and were subjected to glucose clamp analyses as well as a 75-g OGTT both before and after surgery during this period. Individuals with DM underwent the glucose

clamp analyses and OGTT after they had achieved a target control level for fasting plasma glucose of <130 mg/dL in response to treatment with oral hypoglycemic agents. None of the subjects was treated with insulin, dipeptidyl peptidase–4 inhibitors, or glucagon-like peptide–1 receptor agonists.

Glucose clamp analyses and 75-g OGTT

A 75-g OGTT and consecutive hyperglycemic and hyperinsulinemic-euglycemic clamp analyses were performed during hospitalization. For the OGTT, blood samples were collected before as well as 30, 60, 90, and 120 min after glucose ingestion for the measurement of plasma glucose and serum insulin concentrations. Consecutive hyperglycemic and hyperinsulinemic-euglycemic clamp analyses were performed with the use of an artificial endocrine pancreas (STG-55; Nikkiso, Shizuoka, Japan) as previously described [14]. In brief, we first performed a hyperglycemic clamp by intravenously infusing a bolus of glucose (9622 mg/m^2) followed by a variable amount of glucose to maintain the plasma glucose level at 200 mg/dL for 90 min. Blood samples were collected before as well as 5, 10, 15, 60, 75, and 90 min after the onset of glucose infusion for measurement of plasma glucose and serum insulin levels. After the hyperglycemic clamp, a 120-min hyperinsulinemic-euglycemic clamp was performed. First- and second-phase insulin secretion during the hyperglycemic clamp were defined as the incremental area under the insulin concentration curve (μU mL^{-1} min) from 0 to 10 min (AUC_{ins10}) and from 10 to 90 min ($AUC_{ins10–90}$), respectively. An index of insulin sensitivity derived from the hyperinsulinemic-euglycemic clamp [insulin sensitivity index (ISI)] was calculated by dividing the mean glucose infusion rate during the final 30 min of the clamp (mg kg^{-1} min^{-1}) by both the plasma glucose (mg/dL) and serum insulin (μU/mL) levels at the end of the clamp and then multiplying the resulting value by 100.

For the assessment of insulin secretion, we calculated the insulinogenic index, homeostasis model assessment of β-cell function (HOMA-β) [15], the area under the curve for serum insulin concentration (AUC_{ins120}), and the ratio of the area under the curve for serum insulin concentration to

that for plasma glucose concentration ($AUC_{ins/glu120}$) from the results of the OGTT. The insulinogenic index was calculated as the change in serum insulin concentration divided by that in plasma glucose concentration from 0 to 30 min during the OGTT. For the assessment of insulin sensitivity-resistance, we calculated the composite index [16] and homeostasis model assessment of insulin resistance (HOMA-IR) [15]. A clamp-based analog of the disposition index (DI), termed the clamp DI, was calculated as the product of first-phase insulin secretion and ISI, as described previously [17]. An OGTT-based analog of DI, which we termed the oral DI, was calculated as the product of the composite index and $AUC_{ins/glu120}$, as described previously [18].

Statistical analysis

Data are presented as means ± SD. Normally distributed and non–normally distributed data were analyzed with the paired Student's *t* test and the Wilcoxon signed-rank test, respectively, with the use of SPSS version 11.0 for Windows (IBM, Armonk, NY). The correlation between changes in circulating potassium or aldosterone concentrations and those in metabolic parameters was assessed with Pearson's correlation or Spearman's correlation analysis. A P value <0.05 was considered statistically significant.

Results

Clinical and laboratory parameters for the 14 study participants (5 men and 9 women) before and after surgical treatment are shown in Table 1. The time between the presurgical metabolic analyses and surgery ranged from 27 to 559 days (194 ± 132 days), and that between surgery and the postsurgical analyses ranged from 14 to 142 days (51 ± 38 days). Whereas the number of subjects receiving potassium supplementation decreased [from 10 (71.4%) to 0], serum potassium levels were greater after surgery (Table 1). Plasma aldosterone and plasma renin activity levels were decreased and increased, respectively, and the aldosterone to active renin ratio was decreased after surgery

(Table 1). **Serum levels of ACTH and cortisol were unaltered after surgery (Table 1).** Systolic and diastolic blood pressure as well as the estimated glomerular filtration rate were decreased after surgery (Table 1). Fourteen and nine subjects received antihypertensive drugs before and after surgery, respectively. Twelve, one, four, five, and one subjects took a calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, α blocker, or β blocker, respectively, before surgery, with these numbers falling to seven, zero, two, one, and **one**, respectively, after surgery. **Serum levels of HDL cholesterol were decreased after surgery (Table 1). Five subjects administered statins both before and after surgery without changes in their dose. Two subjects who had not administered statins before surgery started to administer the drug after surgery, however. No other lipid lowering drugs were administered in the study subjects both before and after surgery.**

Plasma glucose concentrations during the OGTT did not differ between before and after surgery (Fig. 1A), whereas serum insulin concentrations at 30 and 60 min after the initiation of the test were greater after surgery than before (Fig. 1B). Before surgery, seven, four, and three subjects were categorized as having NGT, IGT, or DM, respectively, with the corresponding numbers being six, seven, and one after surgery. The glucose tolerance category remained unaltered in seven individuals after surgery (four with NGT, two with IGT, and one with DM), whereas that of four individuals improved (from IGT to NGT in two, and from DM to IGT in two) and that of three deteriorated (from NGT to IGT). Whereas AUC_{glu120} was unaltered after surgery, HOMA-β and $AUC_{ins/glu120}$, both of which reflect the capacity for insulin secretion, as well as the insulinogenic index, a measure of early-phase insulin-secretory capacity, were increased (Table 2). HOMA-IR (P = 0.106) and the composite index (P = 0.064), both of which are measures of insulin sensitivity, remained unaltered after surgery.

The serum insulin concentration at all time points during the hyperglycemic clamp was increased after surgery (Fig. 1C). Both first-phase (AUC_{ins10}) and second-phase ($AUC_{ins10–90}$) insulin

secretion during the clamp were also increased after surgery (Table 2). The hyperinsulinemic-euglycemic clamp, a gold standard for the evaluation of insulin sensitivity, revealed that ISI was decreased after surgery (Table 2). The oral DI ($P = 0.331$) and clamp DI ($P = 0.276$), both of which are products of measures of insulin secretion and insulin sensitivity, were not altered after surgery (Table 2).**Indexes for insulin secretion and insulin sensitivity determined with OGTT and clamp analysis before and after surgery in each individual were shown in Fig. 2.**

To clarify factors responsible for the surgery-associated changes in insulin secretion, we examined the relation between the changes in parameters of insulin secretion and those in the circulating levels of potassium or aldosterone. The changes in HOMA-β, the insulinogenic index, $AUC_{ins/glu120}$, and first-phase insulin secretion showed no significant correlation with the changes in the levels of serum potassium (**Fig. 3A–E**) or plasma aldosterone (**Fig. 3G–K**), whereas the change in second-phase insulin secretion showed a negative correlation with that in aldosterone level (**Fig. 2L**) but was not correlated with that in the potassium level (**Fig. 3F**). The changes in the circulating levels of potassium ($r = –0.138$, $P = 0.637$), aldosterone ($r = 0.420$, $P = 0.135$), or renin activity ($r = –0.137$, $P = 0.640$) were not correlated with that in the ISI.

Discussion

As far as we are aware, our study is the first in which insulin secretion and insulin sensitivity have been comprehensively analyzed with hyperglycemic and hyperinsulinemic-euglycemic clamps as well as with an OGTT in patients with PA both before and after surgical treatment. We found that parameters of insulin secretion including first- and second-phase secretion during the hyperglycemic clamp as well as HOMA-β, the insulinogenic index, and $AUC_{ins/glu120}$ determined with the OGTT were improved after surgery in our study subjects. First-phase insulin secretion during an IVGTT and the insulinogenic index during an OGTT were previously shown to be improved after surgery in

patients with APA [7, 8]. Our results obtained with hyperglycemic clamp analysis as well as an OGTT thus support the notion that insulin secretion is impaired by PA.

Catena *et al*. [10] found that HOMA-IR of individuals with PA was greater than that of normotensive control subjects, and this parameter of insulin sensitivity was normalized within 6 months after surgery or the initiation of pharmacological treatment. Moreover, a meta-analysis performed by Chen *et al*. [4] revealed that HOMA-IR was elevated in individuals with PA. In the present study, HOMA-IR and the composite index were unaltered and the ISI determined by clamp analysis worsened after the surgical treatment of PA. Tsurutani *et al.* [7] showed that HOMA-IR was significantly increased and the composite index significantly decreased after the surgical treatment of Japanese subjects with PA. The reason for the apparent discrepancy among the results of these various studies is unclear. Our study subjects were nonobese Japanese individuals with a body mass index of 23.5 ± 3.0 kg/m^2, similar to those of the study by Tsurutani *et al*. (21.4 to 26.8 kg/m^2, with a median of 23.1 kg/m^2) [7], whereas the body mass index of the subjects analyzed by Catena *et al.* was 28.7 ± 3.8 kg/m^2 [10]. Differences in ethnicity or body composition might thus contribute to differences in the effect of PA on insulin sensitivity.

The impairment of insulin secretion in a single patient with PA was reported to be ameliorated by potassium supplementation, suggesting that hypokalemia might be a cause of such impaired insulin secretion [3]. Serum potassium levels were also found to be correlated with the AUC for serum insulin concentration determined by an OGTT in five patients with PA [9], whereas Tsurutani *et al.* [7] found that the change in potassium level between before and after surgical treatment was not correlated with that in the insulinogenic index or in AUC_{ins} in 59 subjects with PA. In our study, the change in the level of serum potassium between before and after surgery was not correlated with any of the parameters of insulin secretion measured, consistent with the results of Tsurutani *et al.* [7] The change in plasma aldosterone concentration was negatively correlated with that in second-phase insulin secretion and tended to be negatively correlated with that in first-phase

insulin secretion in our study. In this regard, aldosterone has been shown to inhibit glucose-stimulated insulin secretion in mice [19].

We found that the level of hemoglobin A_{1c}, AUC_{glu120}, and plasma glucose concentrations during the OGTT remained unchanged after surgery, as did the oral DI and clamp DI, which reflect the capacity for whole-body glucose disposal [20–22]. In addition, the category of glucose tolerance determined by the OGTT was not consistently improved after surgery. These results collectively suggest that the effects of PA on insulin secretion and insulin sensitivity are not sufficient to cause a deterioration in glucose tolerance. These findings contrast with those obtained for pheochromocytoma, another tumor of adrenal origin that affects glucose metabolism and blood pressure, in which case both insulin secretion and glucose tolerance are improved by removal of the tumor [14, 23].

A comprehensive approach based on both clamp analyses and an OGTT is a strength of our study. Clamp analyses thus allow the assessment of insulin sensitivity and insulin secretion without the influence of the negative feedback loop between circulating glucose and insulin levels. Limitations of our study include the relatively small number of study subjects and a relatively long duration between the metabolic analyses and surgery in some individuals. We thus cannot completely exclude the possibility that factors other than tumor removal affected insulin sensitivity and insulin secretion during the study period in such patients. **Furthermore, some hypertensive drugs including angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, α blocker and β blocker, are capable to affect insulin sensitivity or insulin secretion as well as plasma aldosterone levels. It is thus also possible that the changes in those drugs might have influenced the results.**

In summary, our data indicate that PA impairs insulin secretion but has a minimal effect on glucose tolerance. A prospective study with a larger number of subjects is warranted to confirm the present results.

Acknowledgments

We thank Yoshifumi Inoue, Naoko Hashimoto, Tomokazu Matsuda, Tomoko Nishiumi, Michinori Takabe, Shinsuke Nakajima, Yuki Nishimoto, and Sachi Nishida for assistance with data collection.

Conflict of interest

The authors do not have any conflict of interest to disclose.

Funding

This work was supported by a Grant-in-Aid for Young Scientists (B) to Y.H. from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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Figure 1. Plasma glucose (A) and serum insulin (B) concentrations during an OGTT as well as serum insulin concentration (C) during a hyperglycemic clamp performed for the study subjects before (open squares) or after (closed squares) surgical treatment. Data are means ± SD. *$P < 0.05$ versus the corresponding value for before surgery.

Figure 2. Change in parameters related to insulin secretion or insulin sensitivity before and after surgical treatment in each individual. Closed triangles represent the mean values.

Figure 3. Correlation between changes in serum potassium (A–E) or plasma aldosterone (F–J) concentrations and those in HOMA-β (A, F), the insulinogenic index (B, G), $AUC_{ins/glu120}$ (C, H), AUC_{ins10} (D, I), or $AUC_{ins10–90}$ (E, J) for the study patients between before and after surgery.

Table 1. Clinical and Biochemical Parameters for the 14 Study Patients (5 Men, 9 Women) Before and After Surgical Treatment

Parameter	Before Surgery	After Surgery
Age (years)	56.1 ± 10.7	56.5 ± 11.1*
Body mass index (kg/m^2)	23.5 ± 3.0	23.3 ± 3.2
Fasting plasma glucose (mg/dL)	90.1 ± 11.7	88.2 ± 29.2
Fasting serum insulin (μU/mL)	4.5 ± 1.3	5.6 ± 2.3
Hemoglobin A_{1c} (%)	5.6 ± 0.7	5.6 ± 0.5
Total-C (mg/dL)	**186.4 ± 32.7**	**180.2 ± 37.6**
LDL-C (mg/dL)	**112.6 ± 29.4**	**116.1 ± 33.9**
HDL-C (mg/dL)	**50.0 ± 12.8**	**43.5 ± 8.1***
Triglyceride (mg/dL)	**114.2 ± 50.8**	**136.1 ± 54.9**
Systolic blood pressure (mmHg)	139.7 ± 21.2	128.5 ± 13.7**
Diastolic blood pressure (mmHg)	76.1 ± 11.6	74.6 ± 10.8**
eGFR (mL min^{-1} 1.73 m^{-2})	75.1 ± 18.9	63.3 ± 18.6*
Serum potassium (mEq/L)	3.16 ± 0.60	4.33 ± 0.39**
Plasma aldosterone (pg/mL)	535.8 ± 455.0	86.0 ± 60.2*
Plasma active renin (ng mL^{-1} h^{-1})	0.29 ± 0.17	0.80 ± 0.75*
Aldosterone to active renin ratio	2502.4 ± 2346.7	230.6 ± 216.7*
ACTH (pg/mL) (n=11)	**34.7 ± 28.5**	**47.1 ± 22.8**
Cortisol (μg/dL) (n=13)	**15.3 ± 5.3**	**16.5 ± 11.2**

Data are means ± SD. **Total-C, Total cholesterol, HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol,** eGFR, estimated glomerular filtration rate. *$P < 0.05$, **$P < 0.001$ versus the value for before surgery.

Table 2. Parameters Related to Insulin Secretion or Insulin Sensitivity Determined by OGTT and Clamp Analyses for Study Patients Before and After Surgical Treatment

Parameter	Before Surgery	After Surgery
OGTT		
HOMA-IR	1.01 ± 0.36	1.25 ± 0.57
HOMA-β	65.3 ± 23.4	85.0 ± 39.5*
Composite index	8.56 ± 6.13	6.33 ±. 2.71
Insulinogenic index	0.50 ± 0.42	0.73 ± 0.43*
AUC_{glu120} (mg dL^{-1} min)	18,060 ± 4632	17,061 ± 4244
AUC_{ins120} (μU mL^{-1} min)	4514 ± 2206	5610 ± 2501
$AUC_{ins/glu120}$	0.25 ± 0.12	0.34 ± 0.15*
Oral DI	2.10 ± 1.75	1.91 ± 0.79
Clamp analyses		
AUC_{ins10} (μU mL^{-1} min)	210.7 ± 150.0	285.0 ± 202.0*
$AUC_{ins10–90}$ (μU mL^{-1} min)	1988.6 ± 1114.2	2466.9 ± 1668.4*
Glucose infusion rate (mg kg^{-1} min^{-1})	10.22 ± 2.76	9.65 ± 2.64
ISI ($\times 10^{-2}$)	0.12 ± 0.07	0.10 ± 0.06*
Clamp DI	27.1 ± 22.2	30.0 ± 25.4

Data are means ± SD. *$P < 0.05$ versus the value for before surgery.

HOMA-β: homeostatic model assessment of β-cell function; HOMA-IR: homeostatic model assessment of insulin resistance; Oral DI: oral disposition index; GIR: glucose infusion rate; ISI: insulin sensitivity index; Clamp DI: clamp disposition index. * $P < 0.05$ vs the corresponding value for before surgery.

Figure1
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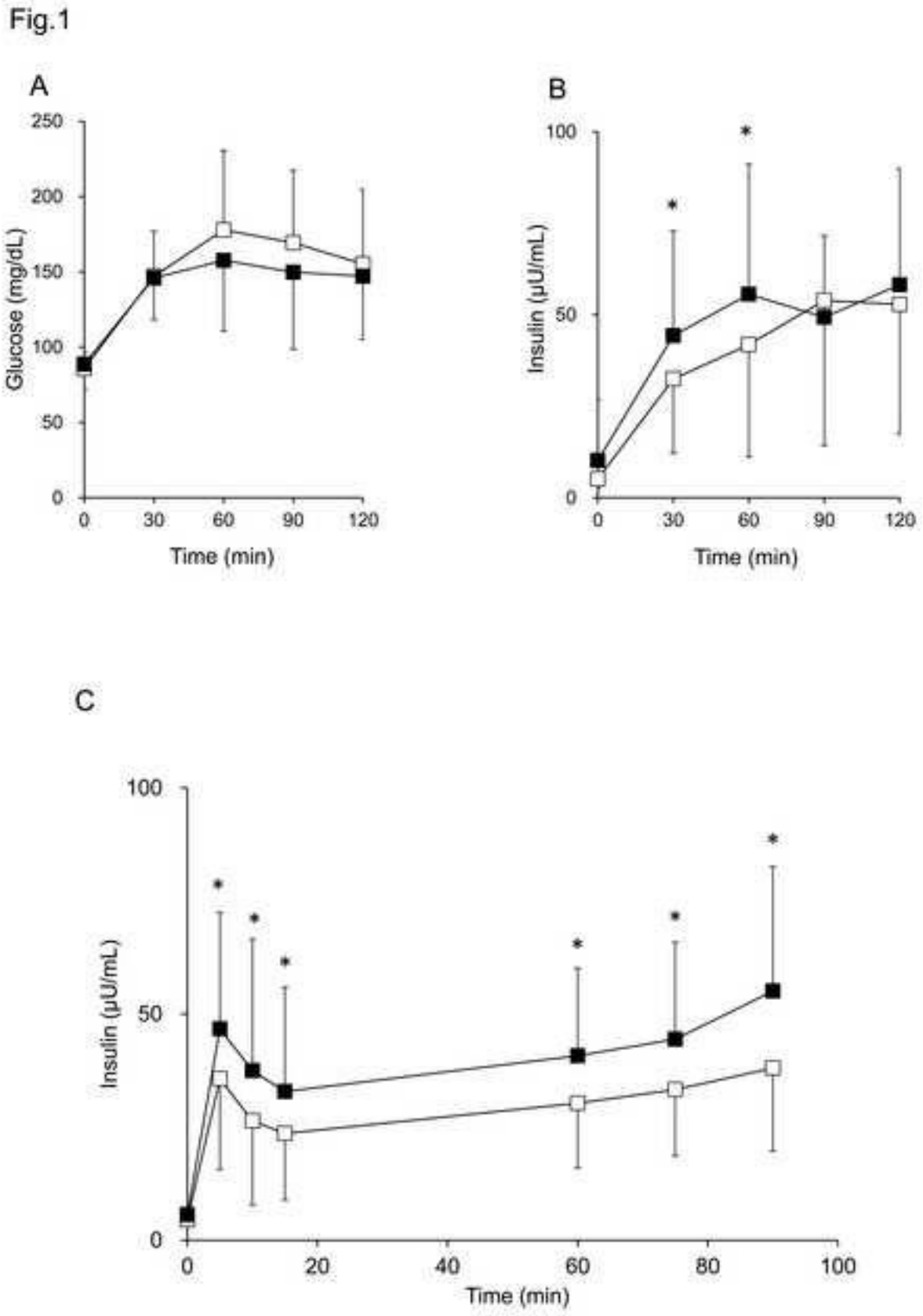

Figure2
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Fig. 2

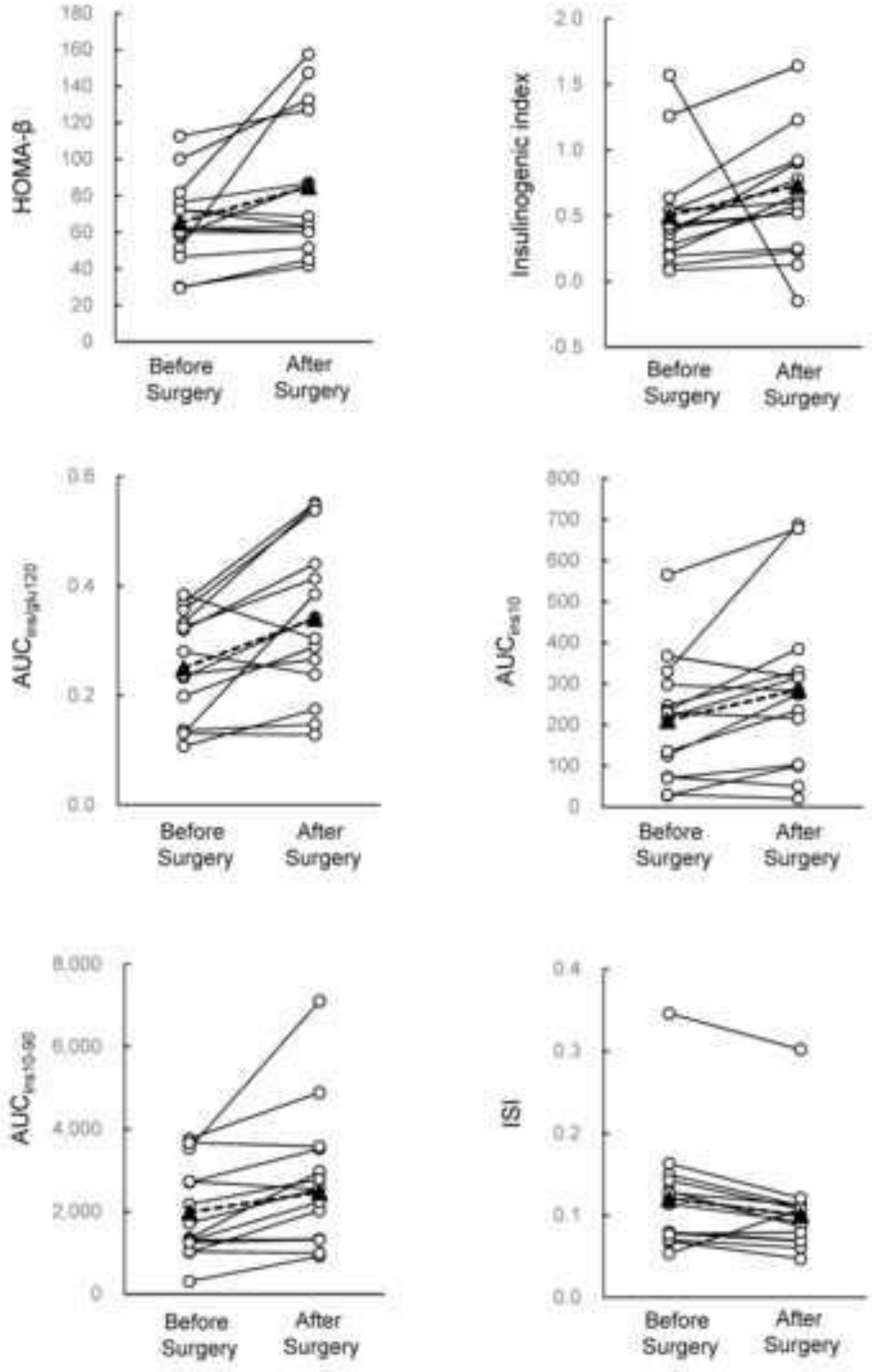

Figure3

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