Adrenal Adenoma Removal Improves Glucose Control in A Diabetic Patient with Primary Aldosteronism: A Case Report and Literature Review

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Abstract

Primary aldosteronism (PA) is a common etiology of secondary hypertension but its association with impaired glucose homeostasis is often overlooked. In this article, we report on the case of a diabetic patient with refractory hypertension, who was later diagnosed with an aldosterone-producing adenoma (APA). Surgical resection of the APA rectified his hypertension and hypokalemia and restored his blood sugar level to near normal range. Since surgery, he has not been administered any oral hypoglycemic agents but has still remained free from diabetes. Better blood sugar control following APA resection in this unique group of diabetic patients is of clinical importance since early diagnosis and surgical treatment can prevent the unnecessary life-long administration of medication and the occurrence of diabetes-associated complications. (J Intern Med Taiwan 2012; 23: 296-302)

Key Words: Adrenocortical adenoma, Diabetes mellitus, Hyperaldosteronism

Introduction

Primary aldosteronism (PA) is a disorder of aldosterone overproduction and is usually caused by an aldosterone-producing adenoma (APA) or by idiopathic hyperaldosteronism (IHA)[1]. It cannot be suppressed by sodium-loading and is not related to the renin–angiotensin axis[1]. Although PA is often characterized by refractory hypertension and hypokalemia, numerous epidemiologic studies have also reported on its association with abnormal glucose homeostasis[2,3,4,5]. The available data estimate that the prevalence of impaired glucose metabolism in PA is approximately 15–20%, which resulted in the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (DM)

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to include PA as a specific form of Type 2 DM[6]. Nearly a third of PA cases are caused by an APA and require surgical removal, which can subsequently correct the abnormal metabolism of glucose[7,8]. In this report, we present a PA patient in whom DM regressed after an APA resection and also review the literature that is associated with this finding.

Case Report

A 49-year-old male veteran visited our emergency department on 22nd August 2008 after experiencing a sudden onset of general weakness and bilateral hand numbness; he had not experienced any similar symptoms previously. He was alert on initial presentation, and physical and neurological examinations provided normal results, although decreased muscle power in both upper limbs was noted. His electrocardiogram and blood chemistry examination results showed that all data were within the normal limits, except for marked hypokalemia (K: 2.3 mEq/L; range: 3.5-5.5 mEq/L). The medical history of the patient was reviewed and revealed that he had been diagnosed with hypertension for 10 years, and was subsequently receiving metoprolol 25 mg, amlodipine 5 mg, and trichlormethiazide 1 mg once daily. In addition, he had been diagnosed with DM 5 years preceding his visit, and treatment with metformin 500 mg twice daily had been initiated 2 months prior to his presentation. The level of glycated hemoglobin (HbA1c) on 5th May 2008 was 8.7%. His mother had been diagnosed with DM and hypertension, although no other familial systemic illnesses were reported. Following potassium supplementation, the patient's symptoms alleviated.

Despite oral potassium chloride supplementation at 24 mEq per day, the nephrology clinic still detected hypokalemia (K: 2.7 mEq/L) and the manifestation of Conn's syndrome was suspected. Further diagnostics were performed after all anti-hypertensive drugs had been withdrawn for 2 weeks. The diagnostics data revealed that the concentrations of serum creatinine and potassium were 1.0 mg/dL and 2.6 mEq/L, respectively, the transtubular potassium gradient was 9, and the arterial blood had a pH of 7.451. Plasma aldosterone concentration (PAC) at 08:00 am was 47.13 ng/dL (range: 5–30 ng/dL) and plasma renin activity (PRA) was 0.72 ng/mL/h (range: 1–4 ng/mL/h). The PAC:PRA ratio was 65, which was compatible with the figure that is associated with PA. Saline infusion test with 2-Liter intravenous infusion of normal saline during a 4-hour time period demonstrated that PAC was not suppressed (29.5 ng/dL). Abdominal computed tomography with contrast medium revealed that a 1.5×1.3×1.6 cm well-defined hypodense nodular lesion was present on top of the left adrenal gland, which was tentatively considered to be a lipid-rich aldosteronoma. (Fig. 1) Laparoscopic adrenalectomy was performed, and

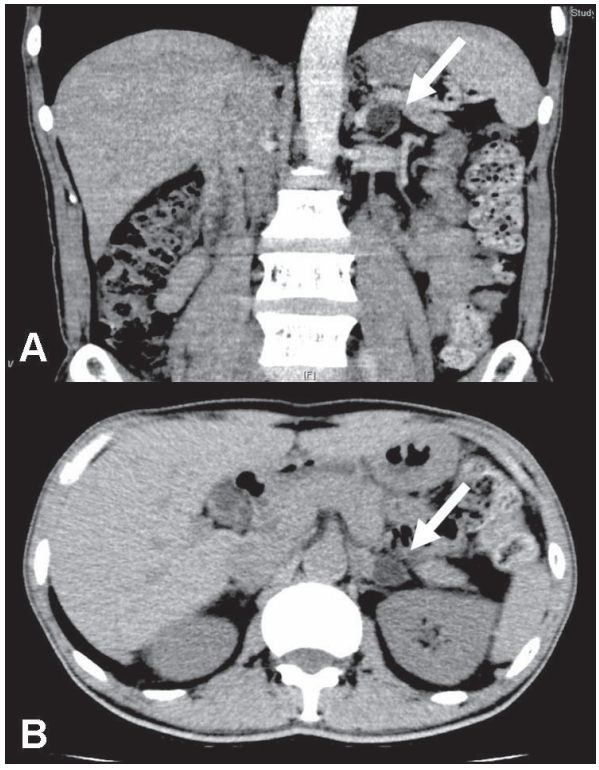

Fig. 1. (A)Coronal view and (B)axial view of contrast-enhanced abdominal computed tomography revealed a 1.5×1.3×1.6-cm well-circumscribed hypodense mass (white arrow) on top of the left adrenal gland.

histopathological examination confirmed that the lesion was an adrenocortical adenoma. Thereafter, the blood pressure and potassium level of the patient returned to within the normal ranges during a 3-year follow-up period. In addition, and rather unexpectedly, his blood glucose level also returned to the diabetic-free range, even though no oral hypoglycemic agents or lifestyle interventions were continued. (Table 1 and Fig. 2)

Discussion

In this article, we reported on a PA patient whose diabetic status was alleviated after surgical resection of an adrenocortical adenoma. PA is a common etiology of secondary hypertension; however, its association with DM is mentioned less frequently and is often overlooked. Following Conn's report describing a high prevalence of

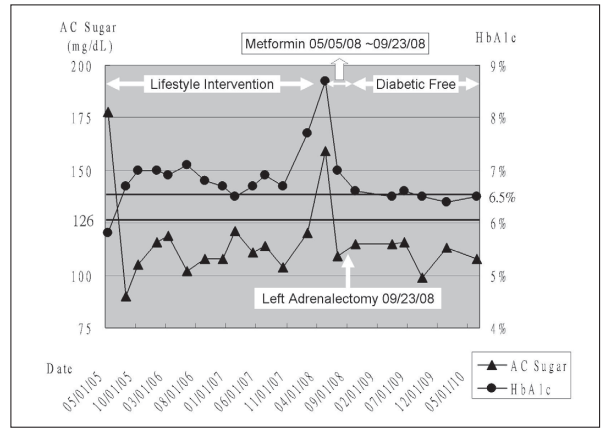

Fig. 2. Serum glucose and glycated hemoglobin data before and after surgery.

Table 1. Comparison of body mass index, blood pressure, laboratory investigations, and medications before and after surgery. QOD: once every other day; QD: once daily; BID: twice daily

	Data Prior to Surgery[%]	3 Years After Surgery[*]
Body Height (cm)	168	168
Body Weight (kg)	53	57
Body Mass Index (kg/m^2)	18.77	20.19
Systolic Blood Pressure (mmHg)	140	119
Diastolic Blood Pressure (mmHg)	100	83
Serum Potassium (mEq/L)	2.9	4.1[$]
Total Cholesterol (mg/dL)	187[$]	212
Triglyceride (mg/dL)	47[$]	50
Low-Density Lipoprotein (mg/dL)	106[$]	114
High-Density Lipoprotein (mg/dL)	72[$]	69
Aspartate Aminotransferase (U/L)	20	40
Alanine Aminotransferase (U/L)	19	34
Abdominal Computed Tomography	No fatty liver[$]	Not performed
Abdominal Sonography	Not performed	No fatty liver
Medication	Atorvastatin 20 mg QOD Metoprolol 2.5 mg QD Amlodipine 5 mg QD Trichlormethiazide 1 mg QD Metformin 500 mg BID	Atorvastatin 20 mg QOD
Diet Control	Yes	No

% Performed 1 day prior to surgery.

* Data from an annual health examination.

$ Performed on a different date.

impaired glucose metabolism in PA patients in 1965[9], many studies have conducted research to explain this finding. To date, several possible pathogeneses have been proposed, including hypokalemia-related insulin hyposecretion and aldosterone-induced insulin resistance.

Depolarization of pancreatic β-cells (through the closure of K-ATP channels) is required for the secretion of insulin[10]. Potassium is essential in maintaining resting membrane potential, and hence, β-cell depolarization susceptibility may vary in different serum potassium concentrations. In a study by Henquin et al., supra-physiologic potassium levels augmented insulin secretion in isolated perfused rodent pancreases, probably by shifting the resting membrane potential to a less negative value[11]. Conversely, Mondon et al. reported impaired insulin secretion in a potassium-deficient rat following intravenous glucose infusion[12]. Previously, it was thought that potassium depletion in PA could impair insulin secretion by modulating its receptor function, and although previous human studies have supported this theory[13], the presence of normokalemic hyperaldosteronism has generated uncertainty toward the hypothesis. Other factors must contribute to impaired glucose metabolism, since it does not occur only in the hypokalemia population, which consist of no more than a third of the PA population[14].

Insulin resistance contributes to the pathogenesis of DM, and its association with PA has been described in previous reports. Sindelka et al. demonstrated that 9 PA patients were insulin resistant by using a hyperinsulinemic euglycemic

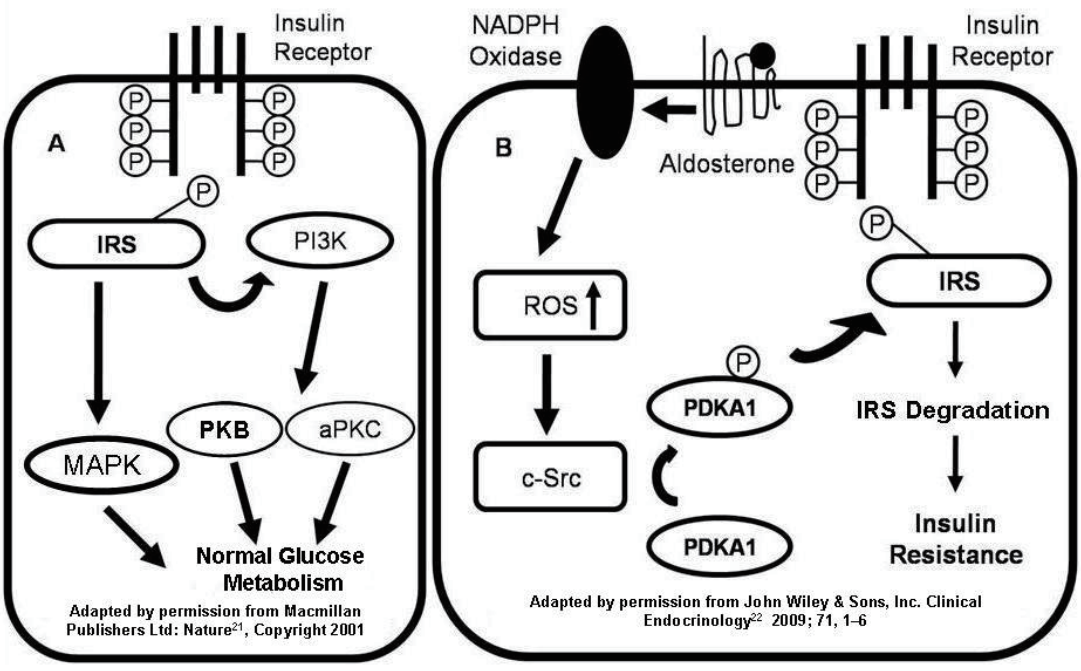

Fig. 3. (A) Simplified signal pathway for the normal metabolism of glucose.
(B) Proposed molecular mechanism of aldosterone-induced insulin resistance. Aldosterone increased NADPH oxidase activation and subsequent ROS production through the mineralocorticoid receptor. Activation of tyrosine kinase, c-Src, and PDKA1 by ROS leads to IRS phosphorylation and degradation. Aldosterone induces insulin resistance by decreasing the expression of IRS and its downstream product. IRS-1: insulin receptor substrate 1; MAPK: mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase; PKB: protein kinase B; PKC: protein kinase C; NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase; ROS: reactive oxygen species; c-Src: tyrosine kinase; PDKA-1: phosphoinositide-dependent kinase A-1.

Table 2. Literature reporting glucose metabolism improvement following surgical resection of an aldosteronoma

Literature	Number of Cases Studied	Parameters Measured	Result
Shimamoto et al[7]	7	Euglycaemic hyperinsulinaemic glucose clamp 75 g Oral glucose tolerance test (OGTT)	Improved insulin sensitivity Lower plasma glucose level after OGTT
Sindelka et al[8]	5	Euglycaemic hyperinsulinaemic glucose clamp	Improved Insulin sensitivity
Conn et al[9]	12	Plasma insulin and glucose level 100 g OGTT	Normalization of insulin secretion curve Normalization of glucose metabolism
Catena et al[15]	20	Euglycaemic hyperinsulinaemic glucose clamp Homeostasis model assessment (HOMA) index Quantitative insulin sensitivity check (QUICK) index Plasma insulin and glucose level	Normalization of insulin action Restoration of normal HOMA index Restoration of normal QUICK index Normalization of glucose/insulin ratio
Giacchetti et al[18]	25	HOMA index QUICK index 75 g OGTT Plasma insulin and glucose level	Lower plasma glucose after OGTT No change in HOMA and QUICK index No change in fasting plasma glucose

clamp[8]. Furthermore, a larger prospective study compared the homeostasis model assessment index in 47 PA patients with their normotensive-matched controls, and discovered that the former group was significantly resistant to insulin[15]. In addition to PA, the detrimental effect of aldosterone excess on insulin sensitivity has also been addressed in both essential hypertension[16] and general population[17]. Current researches are focusing on the negative effect of aldosterone on insulin signaling. Several studies have reported that aldosterone may induce insulin resistance through several cellular pathways. Kraus et al. reported that the major insulin signaling elements (protein kinase B and mitogen-activated protein kinase) had diminished activation in cultured adipocytes that were pre-treated with aldosterone[18]. Furthermore, Hitomi et al. suggested that aldosterone may impair insulin signaling by downregulating insulin receptor substrate-1 in vascular smooth muscle cells[19]. (Fig. 3) These findings have provided comprehensive information on the development of abnormal glucose metabolism in PA patients. Although the presence of DM in our patient could be considered to be co-incidental, the regression from overt diabetes to impaired glucose tolerance after adrenalectomy, as reported in the literature[7,9,15], confirms the deleterious effect of aldosterone on glucose metabolism.

The 2 most common subtypes of PA are APA and IHA, both of which are associated with impaired glucose homeostasis. Surgical resection is the standard treatment for APA, while the administration of a mineralocorticoid antagonist is the standard treatment for IHA[1]. Improved insulin sensitivity after adrenalectomy has been documented in several reports[7,8,9,15,20]. (Table 2) However, although spironolactone (a mineralocorticoid antagonist) is effective as an anti-hypertensive agent it cannot restore hyperglycemia in patients with IHA[8]. This frustrating outcome may arise from the failure to re-establish a normal aldosterone concentration compared with surgery. Recently, Catena et al. found that impaired insulin sensitivity in patients with PA is rapidly and persistently reversed following either an adrenalectomy or the administration of spironolactone after a follow-up of approximately 5.7 years[15]. Further investigations enrolling a larger number of patients are required to validate the aforementioned findings.

Conclusion

Impaired glucose tolerance is common in patients with PA. Multifactorial mechanisms are likely to cause this intolerance, although aldosterone-induced insulin resistance is considered to have a critical role. Our case study demonstrated that abnormal glucose metabolism is reversible after APA resection, which is compatible with results reported in previous studies. Timely diagnosis and surgery are important to prevent the unnecessary life-long administration of medication and the occurrence of diabetes-associated complications. Data regarding the medical treatment of hyperglycemia in IHA patients are limited; therefore, further investigations are required to discover the best treatment regimen.

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原發性高醛固酮症的糖尿病患者在接受手術移除腎上腺皮質腺瘤後血糖控制的改善 -病例報告及文獻回顧

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摘 要

原發性高醛固酮症是造成次發性高血壓的常見原因，但此疾病與葡萄糖代謝異常的相關聯性卻很常被忽略。我們報告一位患有醛固酮分泌腺瘤併頑固性高血壓及低血鉀的糖尿病患者，在接受腫瘤切除手術之後，除了血壓與血鉀恢復正常之外，血糖亦趨近於正常，且後續追蹤時再也無須接受藥物治療。手術切除醛固酮分泌腺瘤對於改善此種獨特糖尿病亞型的血糖控制有其重要臨床意義，及時的診斷與治療將使病人免於不必要的終身藥物治療及糖尿病的相關併發症。