Endocrine (2021) 72:96–103
https://doi.org/10.1007/s12020-020-02576-y

ORIGINAL ARTICLE

Insulin sensitivity and pancreatic β-cell function in patients with primary aldosteronism

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Received: 18 October 2020 / Accepted: 26 November 2020 / Published online: 18 January 2021

Abstract

Background Primary aldosteronism (PA) is associated with an increased risk for dysglycemia. However, the effects of hyperaldosteronism on insulin sensitivity and β-cell function are unclear.

Methods Using a cross-sectional study design, we assessed insulin sensitivity and pancreatic β-cell function from an oral glucose tolerance test (OGTT) in patients from two cohorts: subjects with PA ($n = 21$) and essential hypertension control (EHC) subjects ($n = 22$). Age, sex, BMI, and mean arterial pressure adjusted measures of insulin sensitivity and β-cell function were compared between the groups.

Results PA individuals were less insulin sensitive compared to EHC subjects (Quantitative insulin sensitivity check index [QUICKI]: 0.340 ± 0.006 vs. 0.374 ± 0.013, $p < 0.001$; Matsuda index: 4.14 ± 0.49 vs. 7.87 ± 1.42, $p < 0.001$; S_I: 11.45 ± 4.85 vs. 21.23 ± 6.11 dL/kg/min per μU/mL, $p = 0.02$). The hepatic insulin resistance index (HIRI) was higher in PA subjects (PA: 5.61 ± 1.01 vs. EHC: 4.13 ± 0.61, $p = 0.002$). The insulinogenic index (IGI), an index of β-cell function was higher in the PA cohort (PA: 1.49 ± 0.27 vs. 1.11 ± 0.21 μU/mL/mg/dL, $p = 0.03$). However, the oral disposition index (DI) was similar between the groups (PA: 4.77 ± 0.73 vs. EHC: 5.46 ± 0.85, $p = 0.42$), which likely accounts for the similar glucose tolerance between the two cohorts, despite lower sensitivity.

Conclusions In summary, insulin sensitivity is significantly lower in PA with an appropriately compensated β-cell function. These results suggest that excess aldosterone and/or other steroids in the context of PA may negatively affect insulin action without adversely impacting β-cell function.

Keywords Primary aldosteronism · Insulin sensitivity · β-cell function · Essential hypertension

Introduction

Primary aldosteronism (PA) is characterized as an autonomous production of excess aldosterone [1–3]. PA patients frequently experience hypernatremia, hypokalemia, and secondary hypertension [1, 4]. The most common etiologies of excess aldosterone secretion are idiopathic hyperplasia or adenomas [3, 4].

Patients with PA are at a higher risk of impaired glucose tolerance, metabolic syndrome, and cardiovascular disease [2, 5–13]. Studies in vitro and in rodent models suggest detrimental effects of excess aldosterone on tissue-specific metabolic processes including glycogen synthesis in skeletal muscle, increased hepatic glucose production in the liver, and impaired glucose uptake in adipose tissue [14–18]. Some studies demonstrate reduced insulin sensitivity and/or secretion in PA patients [8, 9, 13, 19–22], while other studies suggest increased or unchanged insulin sensitivity [4, 23, 24]. Thus, the causal role of insulin action and secretion in glucose intolerance associated with PA remains unresolved.

Previous studies have provided important insights into the impact of PA on glucose homeostasis, but several factors hinder consensus among the available data. First, hypertension is an insulin-resistant state, and PA is frequently associated with hypertension [25, 26]. Multiple

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studies examining insulin sensitivity in PA subjects used normotensive individuals as controls, rendering hypertension a confounding variable [19, 24]. Second, to assess insulin resistance in PA, studies utilized simple, but surrogate fasting-based indices of insulin sensitivity/secretion like the homeostatic model assessment of insulin resistance (HOMA-IR), HOMA β-cell, and the quantitative insulin sensitivity check index (QUICKI) as a primary measure [5, 10, 13, 22]. These assessments do not provide a robust estimation of insulin sensitivity when used alone. Lastly, many of these studies were conducted in Europe or Japan [4, 5, 19, 23, 24] and thus not easily generalized to a more diverse and heterogeneous US population.

In this study, we evaluated the impact of excess aldosterone on insulin sensitivity and β-cell function using an OGTT and minimal-model analysis. We hypothesized that patients with PA would exhibit reduced insulin sensitivity compared to essential hypertension controls (EHC). This study was intended to further contribute to our understanding of PA pathophysiology and its impact on metabolic function.

Methods

Study methods and subjects

A convenience sample of 43 adult subjects was accrued from participants in two natural history studies performed at the NIH Clinical Center in Bethesda, Maryland, USA. Both studies were approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (ClinicalTrials.gov Identifier: NCT00005927 and NCT00428987). All study participants provided written informed consent for the study procedures prior to participation in the two protocols.

Twenty-one patients with PA were obtained from a natural history study of adrenal gland tumors (NCT00005927). Patients met inclusion criteria by a prior diagnosis of primary aldosteronism, with confirmatory testing by intravenous saline suppression test with 4-h aldosterone cutoff of 6.8 ng/dL. PA workup was performed in accordance with guidelines [27], which included measurement of plasma aldosterone and renin, a saline suppression test, adrenal venous sampling, and computerized tomography (CT) imaging. Treatment with eplerenone ($n = 6$) or spironolactone ($n = 4$) was stopped at least 4–6 weeks before OGTT testing. Patients treated with adrenalectomy ($n = 10$) had OGTTs performed prior to the procedure. EHC ($n = 22$) were recruited from a natural history study of obesity (NCT00428987). The exclusion criteria for both cohorts included age <18 y, T2DM, pregnancy, significant liver disease, renal insufficiency, or other significant comorbidities.

Study procedures

Assessment of body composition

Bodyweight was measured using a digital balance scale (Scale-Tronix 5702, Scale-Tronix, Carol Stream, IL). Body composition was measured by dual-energy X-ray absorptiometry with a Lunar iDXA scanner (GE Healthcare, Madison, WI).

Oral glucose tolerance test

Following a 12-h inpatient overnight fast, each participant consumed a 75 g glucose solution (Fisherbrand, UN-DEX; Fisher Diagnostics, Middletown, VA) over a 2-min interval. Blood samples were collected to measure glucose and insulin concentrations at the following time points after glucose ingestion: −10, 0, 30, 60, 90, 120, and 180 min.

Measurement of insulin sensitivity using the oral glucose minimal-model analysis

Developed by Cobelli et al., the oral glucose minimal model provides a measure of insulin sensitivity during an OGTT. This model is derived from an assumption of physiologic glucose kinetics throughout an OGTT. Detailed descriptions of model parameters and formulas have been previously published [28, 29].

Assessment of glucose tolerance using surrogate indices of insulin sensitivity/resistance

QUICKI is a fasting-based surrogate measure of insulin sensitivity, calculated from fasting blood glucose and plasma insulin concentrations: $\mathrm{QUICKI} = 1/((\log(\mathrm{Insulin}_{\mathrm{fasting}}) + \log(\mathrm{Glucose}_{\mathrm{fasting}})))$ [30]. As described previously, the Matsuda index is an OGTT-derived composite estimate of whole-body insulin sensitivity [31]. The hepatic insulin resistance index (HIRI) was developed as a surrogate marker to assess the ability of insulin to suppress hepatic glucose production. In healthy states, plasma insulin suppresses hepatic glucose production (HGP) within the first 30 min of a glucose load. The inability of insulin to suppress HGP is described as hepatic insulin resistance [32]. As an insulin resistance marker, increased HIRI indicates reduced sensitivity of the liver. When derived from an OGTT, HIRI is calculated as $\mathrm{HIRI} = \mathrm{AUC}_{\mathrm{Glucose(0–30\,min)}} \times \mathrm{AUC}_{\mathrm{Insulin(0–30\,min)}}$ [33].

Measurement of β-cell function during an oral glucose tolerance test

The insulinogenic index (IGI) estimates first-phase insulin secretion and is calculated as the ratio of change in plasma

insulin concentrations to a corresponding change in plasma glucose concentrations during the first 30 min of an OGTT, $IGI = \Delta Insulin_{(0–30\,min)}/\Delta Glucose_{(0–30\,min)}$ [34]. Additionally, the oral disposition index (DI) was used as a marker of integrated islet β-cell function that accounts for insulin sensitivity. DI is calculated as the product of insulin secretion and insulin sensitivity derived from an OGTT: $DI_{oral} = AUC_{Insulin}/AUC_{Glucose} \times S_I$ [35].

Statistical analysis

Frequency distributions of all outcome variables were analyzed and log-transformed, where appropriate. Variables are presented as mean ± SEM. Comparisons between groups were assessed by independent unpaired *t*-test or The Wilcoxon–Mann–Whitney test. Group differences in indices of insulin sensitivity and β-cell function were examined using ANCOVA, with the groups (PA vs. EHC) as a fixed factor, and relevant covariates including age, sex, BMI, and mean arterial pressure (MAP). $p < 0.05$ was considered to represent statistical significance. Data were analyzed using GraphPad Prism, Version 8.4.0 (GraphPad Software Inc., San Diego, CA), and JMP Version 13.0 (SAS Institute, Cary, NC).

Results

Table 1 details the clinical characteristics of the PA ($n = 21$) and EHC ($n = 22$) cohorts. PA and EHC were similar in age, sex, BMI, and systolic and diastolic blood pressure. PA and EHC had comparable metabolic profiles, with no significant differences in fasting glucose or insulin concentrations. Unilateral aldosterone-producing adenoma (APA, $n = 16$) and bilateral idiopathic adrenal hyperplasia ($n = 5$), accounted for PA. Hemoglobin A1c was lower in the PA group (5.4 ± 0.07% vs. 5.6 ± 0.07%, $p = 0.04$). Two-hour plasma glucose concentrations during an OGTT were comparable between the groups (PA: 133.7 ± 8.6 vs. EHC: 126.1 ± 8.1 mg/dL, $p = 0.52$). Seven PA subjects had impaired glucose tolerance (IGT). There were five cases of IGT in the EHC cohort. PA participants tended to show lower potassium levels (3.7 ± 0.1 vs. 4.0 ± 0.05 mmol/L, $p = 0.06$), which is expected due to increased potassium excretion in primary hyperaldosteronism.

Time courses of plasma glucose and insulin concentrations following a 75 g OGTT are shown in Fig. 1A. Fasting plasma glucose concentrations, as well as post-OGTT glucose concentrations over time, were not significantly different between the groups. However, $AUC_{glucose}$ during an OGTT was higher in PA (23,575 ± 1059 vs. 20,513 ± 1099 mg/dL × min, $p = 0.05$) (Fig. 1B). Insulin concentrations throughout the OGTT were not significantly different between the groups (Fig. 1C). $AUC_{insulin}$ was significantly higher in PA (14,748 ± 2190 vs. 8900 ± 1087 μU/mL × min, $p = 0.02$) (Fig. 1D). Surrogate measures of insulin sensitivity were used to compare whole-body and tissue-specific insulin sensitivity. Age, sex, BMI, and MAP adjusted QUICKI (0.340 ± 0.006 vs. 0.374 ± 0.013, $p < 0.001$), Matsuda index (4.14 ± 0.49 vs. 7.87 ± 1.42, $p < 0.001$), and S_I (11.45 ± 4.85 vs. 21.23 ± 6.11 10^{-4} dL/kg/min per μU/mL, $p = 0.02$) were lower in PA subjects (Fig. 2). HIRI, an estimate of hepatic insulin resistance, was higher in PA subjects (PA: 5.61 ± 1.01 vs. EHC: 4.13 ± 0.61, $p = 0.002$), suggesting lower liver insulin sensitivity in PA (Fig. 2D). Next, we sought to determine whether β-cell dysfunction was also present in the PA cohort. The IGI, an index of β-cell function was higher in the PA cohort (PA: 1.49 ± 0.27 vs. 1.11 ± 0.21 μU/mL/mg/dL, $p = 0.03$) (Fig. 3A). Oral disposition index (DI) was similar between the groups (PA: 4.77 ± 0.73 vs. EHC: 5.46 ± 0.85, $p = 0.42$) (Fig. 3B). Within the PA cohort, QUICKI, Matsuda index, S_I, HIRI, IGI, and DI were not significantly different between patients with bilateral adrenal hyperplasia and APA patients (data not shown).

Table 1 Clinical and metabolic characteristics among PA and EHC subjects

	PA ($n = 21$)	EHC ($n = 22$)	*p*-value
Age (yr)	53.9 ± 2.6	51.8 ± 2.6	0.58
Sex (female, *n*)	12	13	
Body mass index (kg/m^2)	29.9 ± 1.3	32.5 ± 1.7	0.24
Systolic blood pressure (mmHg)	137.0 ± 2.7	135.7 ± 4.0	0.81
Diastolic blood pressure (mmHg)	82.0 ± 2.7	79.1 ± 3.0	0.52
Mean arterial pressure (mmHg)	100.2 ± 2.6	97.8 ± 3.4	0.59
Total cholesterol (mg/dL)	160.7 ± 6.2	183.2 ± 10.5	0.09
LDL cholesterol (mg/dL)	92.4 ± 6.5	106 ± 8.0	0.20
HDL cholesterol (mg/dL)	50.0 ± 4.7	55.7 ± 3.7	0.34
Triglycerides (mg/dL)	90.6 ± 7.1	108.0 ± 19.0	0.41
Fasting plasma glucose (mg/dL)	89.7 ± 1.9	91.1 ± 1.7	0.59
Fasting plasma insulin (mU/L)	12.8 ± 2.1	9.0 ± 1.5	0.18
Hemoglobin A1C (%)	5.4 ± 0.07	5.6 ± 0.07	0.04
BUN (mg/dL)	14.7 ± 1.0	15.4 ± 0.9	0.64
Creatinine (mg/dL)	0.9 ± 0.04	0.8 ± 0.04	0.62
Sodium (mEqmol/L)	135.7 ± 6.1	138.9 ± 0.4	0.61
Potassium (mEqmol/L)	3.7 ± 0.1	4.0 ± 0.05	0.06

Data are presented as an arithmetic mean ± SEM. *p*-values indicate statistical significance for comparisons between groups

n no. of subjects, *EHC* essential hypertensive controls, *PA* primary aldosteronism, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *BUN* blood urea nitrogen

Discussion

In the present study, we demonstrate that PA patients had reduced whole-body and hepatic insulin sensitivity as

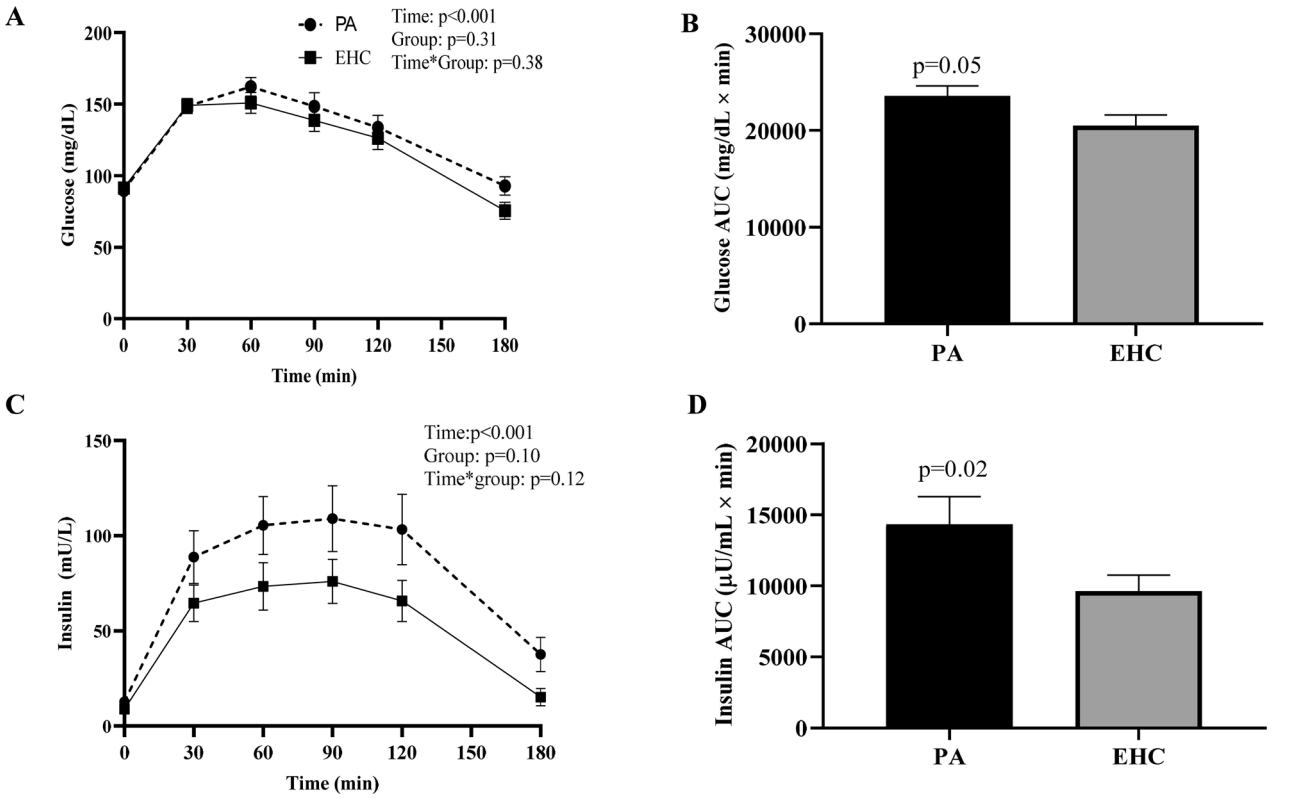

Fig. 1 Glucose and insulin responses in primary aldosteronism during OGTT. Time courses and area under the curves over 180 min are shown for plasma glucose (**A**, **B**) and insulin (**C**, **D**) during a 75 g oral glucose tolerance test. Data are shown as mean ± SEM. $p < 0.05$ indicates the significance between groups

compared to EHC. Further, PA subjects were able to mount a compensatory insulin response, resulting in comparable DI with EHC. Our results suggest that PA patients have reduced insulin sensitivity with preserved β-cell function in order to maintain glucose tolerance.

Aldosterone reduces insulin secretion by direct effects on the β-cell [36–38]. The negative effects of aldosterone on the β-cell appear to be independent of the mineralocorticoid receptors (MRs) [39]. Studies performed in murine islets suggest that aldosterone inhibits insulin secretion via increased reactive oxygen species [39]. In addition to actions on the β-cell, aldosterone may have direct effects on insulin signaling [15]. In vitro and rodent studies show that aldosterone-induced mineralocorticoid activation impairs insulin sensitivity in adipocytes and skeletal muscle [40, 41]. Reductions in insulin-mediated glucose uptake may occur via impairments in the generation of phosphatidylinositol (3,4,5)-triphosphate (PIP_3), AKT activation, and GLUT4 translocation, or indirectly through circulating factors, such as inflammatory cytokines/adipokines [9, 18]. Increased osteopontin and resistin levels and lower adiponectin concentrations have been observed in PA and may contribute to impaired insulin action [42–44]. Indeed, aldosterone is proposed to be the mediator of the cardiometabolic syndrome [45]. Oxidative stress is known to impair insulin metabolic signaling [9]. NADPH oxidase, an important enzyme in the generation of reactive oxygen species and oxidative stress is elevated in PA [46]. Aldosterone stimulates hepatic glucose production by increased gluconeogenesis [47, 48]. Lastly, aldosterone-induced hypokalemia was originally proposed to affect insulin sensitivity, but normalization of potassium levels or potassium depletion did not significantly modulate tissue insulin sensitivity [3, 49]. Thus, findings from in vivo studies in rodents and in vitro studies in β-cells, skeletal muscle, adipocytes, and hepatocytes in culture provide a mechanistic basis for impaired insulin action and β-cell function in PA.

Chen et al. [20] conducted a meta-analysis and systematic review and found that PA patients are at an increased risk for impaired glucose homeostasis (e.g., IFG, IGT, T2D) as compared to essential hypertensives. Few studies examining the abnormalities in insulin resistance and β-cell function in PA subjects have accounted for a major confounder, the presence of hypertension. Catena et al. compared insulin sensitivity using surrogate indices (HOMA-IR and QUICKI) in a cohort of 47 patients with tumoral or idiopathic aldosteronism and two control cohorts of 247 hypertensives and 102 normotensive subjects. They demonstrated that while PA

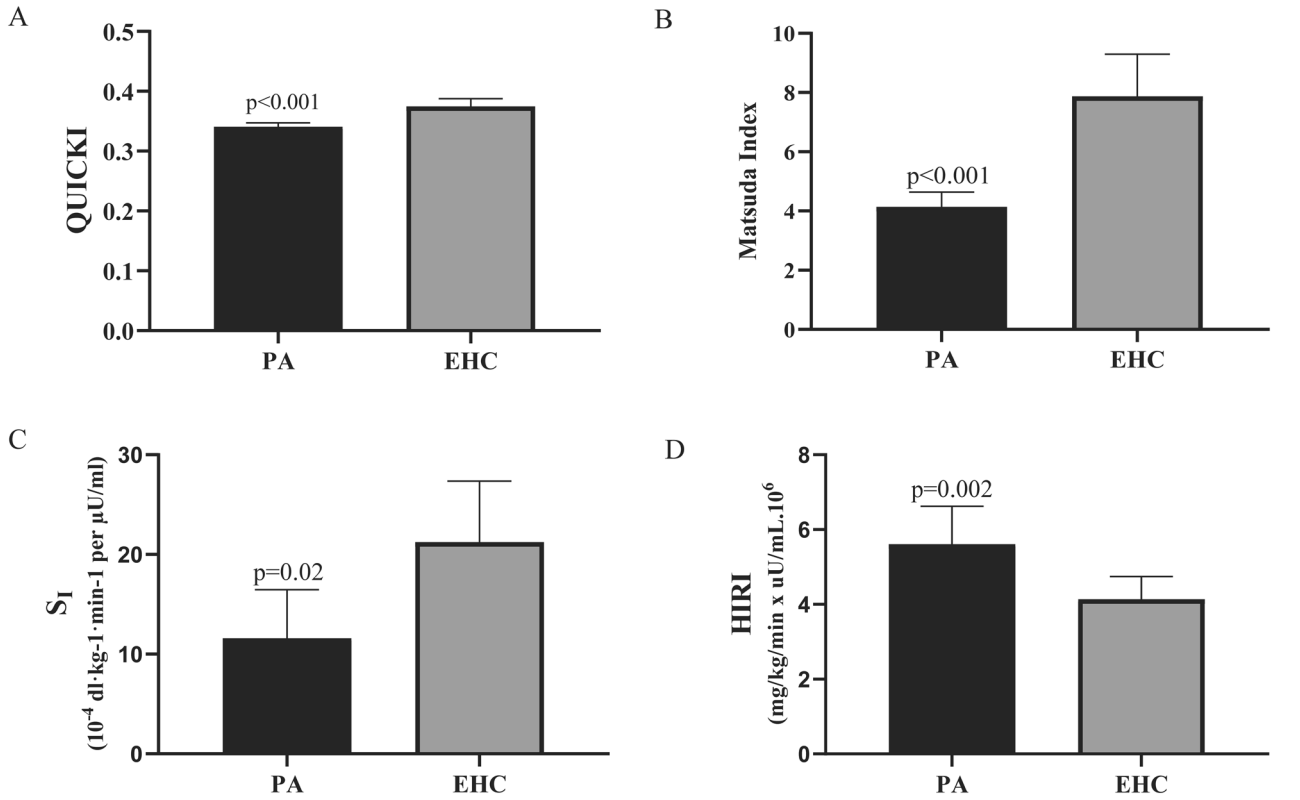

Fig. 2 Surrogate markers of insulin sensitivity in primary aldosteronism. Comparison of **A** QUICKI, **B** Matsuda, **C** S_I, and **D** HIRI between primary aldosteronism (PA) and essential hypertensive controls (EHC). S_I was derived from oral glucose minimal-model analysis. QUICKI quantitative insulin sensitivity check index, HIRI hepatic insulin resistance index. $p < 0.05$ indicates the significance between groups

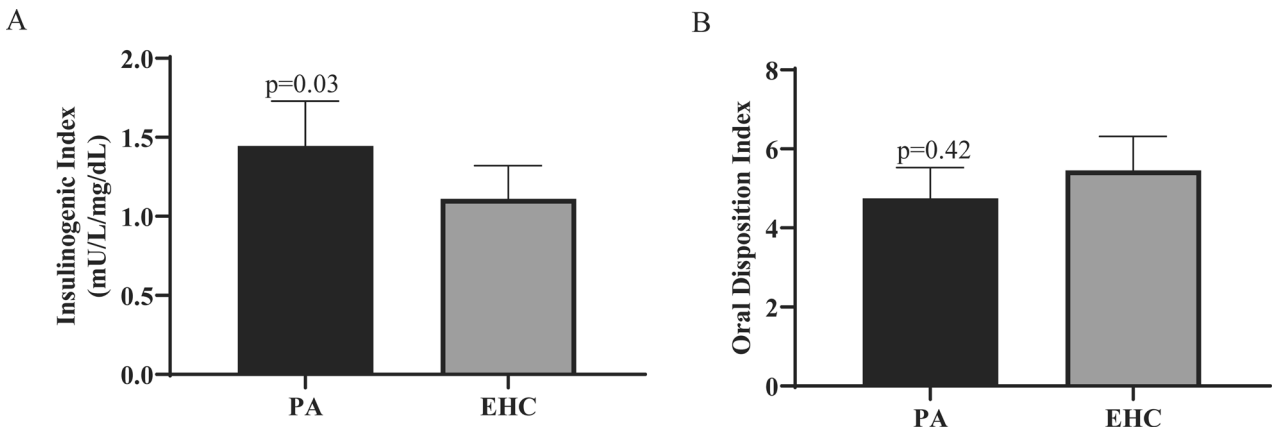

Fig. 3 β-cell function in primary aldosteronism. Group comparisons of **A** insulinogenic index and **B** oral disposition index. $p < 0.05$ indicates the significance between groups

patients were insulin-resistant when compared with normotensive controls, hypertensive patients were more insulin-resistant than PA subjects [5]. Insulin sensitivity as assessed by the euglycemic–hyperinsulinemic clamp technique in a subset of these patients was comparable between PA and EHC [5]. Similarly, there was no difference in HOMA-IR between PA subjects and EHs [22, 50]. However, when compared with normotensive cohorts, reduced insulin sensitivity has been reported in PA patients [8, 9, 13, 19–22]. Based on these studies, it is unclear whether the hypertensive state and/or the elevated aldosterone levels play a role in the reduced insulin sensitivity in PA.

In contrast to prior studies, our findings in this report suggest that the reduced whole-body and hepatic insulin

sensitivity is independent of hypertension in PA subjects. We used insulin sensitivity indices derived from both fasting insulin and glucose (HOMA-IR and QUICKI) and OGTT, a dynamic test (Matsuda index). Furthermore, we used the well-validated minimal-model analysis to derive insulin sensitivity (S_I) from insulin and glucose concentrations following an OGTT [28, 29]. Indeed, S_I measured during an OGTT is highly correlated with glucose disposal measured during the euglycemic–hyperinsulinemic clamp technique ($r = 0.70$) [51]. S_I here represents insulin action on peripheral glucose disposal and inhibition of hepatic glucose production. Moreover, we also estimated hepatic insulin resistance using HIRI. We and others have previously shown that HIRI predicts and correlates well with hepatic insulin resistance as measured with the reference glucose clamp technique ($r = 0.49$) [32]. Thus, in contrast to other studies [5, 22, 50], we used well-validated methods that demonstrated a significant reduction in insulin sensitivity in PA subjects when compared with hypertensive controls.

Our data suggest that PA does not impair β-cell function, which is contrary to several other studies. Mosso et al. demonstrated reduced insulin secretion, as assessed by HOMA-β, in PA compared to EHC [22]. Another study demonstrated an increased first-phase insulin response following unilateral adrenalectomy in nine PA patients, suggesting a direct negative effect of aldosterone on β-cell function [4]. Additionally, Watanabe et al. suggest a hypokalemia-independent impairment of early-phase insulin response to glucose in PA. While HOMA-β between their PA and EHC cohorts were comparable, IGI was significantly reduced in PA [21]. In a recently published study, patients with PA had reduced insulin secretion, increased insulin clearance and insulin sensitivity, and unchanged DI using hyperglycemic and euglycemic–hyperinsulinemic clamps [52]. Our results of an increased $AUC_{Insulin}$ and IGI suggests that β-cells in PA can adequately compensate with increased insulin production in response to reduced insulin sensitivity. The DI is not different between PA and EHC, partly explaining the similar glucose tolerance between the groups. PA patients had lower A1C compared with EHC (Table 1). Indeed, higher post-prandial but normal nocturnal and fasting blood glucose levels contribute to the high degree of intra-day glycemic variability in PA subjects compared with healthy controls [53]. We did not assess 24-h plasma glucose levels in our patients and thus cannot explain the slightly but significantly lower levels of A1C in PA subjects. Nevertheless, significant post-prandial hyperinsulinemia (Fig. 1) and higher fasting insulin levels, albeit statistically non-significant (Table 1) may contribute to glycemic variability and thus lower nadir glucose levels in PA subjects. Differences in non-insulin-mediated glucose disposal may also contribute to this finding. The discordance in the findings among these studies is partly due to different methods of assessing β-cell function and heterogeneous patient populations and control groups. Further investigation of the impact of excess aldosterone on β-cell function using larger sample sizes and state-of-the-art techniques is warranted.

Our study has some strengths and weaknesses. Notable strength in this study was its assessment of patients with PA against essential hypertensive, rather than normotensive controls. Although the cohorts were not matched, assessments were performed in similarly healthy PA and control subjects. This study was thorough in its assessment of insulin sensitivity via both surrogate indices of insulin sensitivity and an oral glucose minimal-model analysis. A limitation of this study is that plasma aldosterone and renin were not collected in the essential hypertension control group. Further, there were no follow-up metabolic assessments following treatment in the PA group. While the oral glucose minimal model is a robust estimation of insulin sensitivity, the gold standard hyperinsulinemic-euglycemic clamp would have further provided measurements of glucose disposal and hepatic glucose production. Lastly, the cross-sectional study design was limited by its observational nature and small sample size.

In conclusion, patients with primary aldosteronism had significantly reduced insulin sensitivity and elevated β-cell function compared to EHC. We propose that PA and/or other steroids in that context disrupts normal glucose homeostasis independent of hypertension. These data offer insights into the negative impact of excess aldosterone on insulin action. Further studies are warranted to explore the pathophysiological mechanisms driving glucose intolerance and β-cell dysfunction in patients with primary aldosteronism.

Funding This work was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland.

Compliance with ethical standards

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

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