Insulin Sensitivity and Pancreatic β-cell Function in Patients with Primary Hyperaldosteronism

Liam Chalk*, Arjun Deven*, Shivraj Grewal, Andin Fosam, Andrew Demidowich*, Jenny Blau, Ricardo Correa*, Constantine Stratakis*, and Ranganath Muniyappa

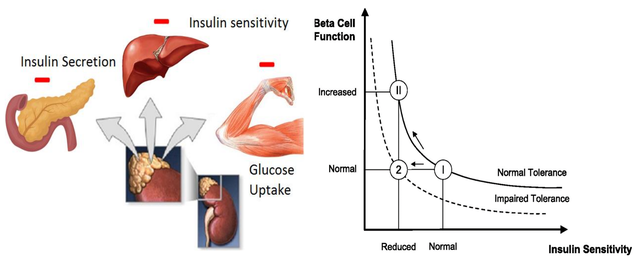
National Institute of Diabetes and Digestive and Kidney Diseases and Eunice Kennedy Shriver National Institute of Child Health and Human Development*, NIH, Bethesda, MD

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Background

- Primary hyperaldosteronism (PA) is characterized by autonomous, excessive aldosterone production causing sodium retention, increased potassium excretion, plasma renin suppression, and hypertension. Aldosterone-producing adenomas (APAs) account for around 40% and idiopathic hyperaldosteronism (IPA) for around 60% of PA cases.
- PA is associated with cardiovascular morbidity, and has been linked to the onset of metabolic syndrome and impaired glucose tolerance.
- Insulin sensitivity and β-cell function are primary determinants of glucose tolerance.
- PA has previously been correlated with impaired glucose tolerance. However, its effects on insulin sensitivity and β-cell function have shown mixed results.
- In this study, we compared indices of insulin sensitivity and pancreatic β-cell function derived from an oral glucose tolerance test in patients from two cohorts: (1) subjects with PA and (2) essential hypertension control (EHC) subjects.



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Claudio Cobelli et al. Am J Physiol Endocrinol Metab 2007; 292: E1-E15

Objective

To examine insulin sensitivity and pancreatic β-cell function in patients with primary aldosteronism

Methods

- The cohort of PA patients (n=25) with both unilateral and bilateral disease and with available OGTT data were from protocol: 00-CH-0160 (NICHD) and the EHCs were from 07-DK-0077 (NIDDK). The EHC controls (n=25) were within the age and BMI range and similar in gender composition (female, n=14) and number of subjects with type 2 diabetes (n=3).
- Each of the PA patients and EHCs were given a 75 gram oral glucose tolerance test (OGTT). Blood samples for the measurement of glucose and insulin were obtained at baseline and after ingestion of oral glucose load.
  - PA time point samples: 0, 30, 60, 90, 120, and 180 minutes.
  - EHC time point samples: -10, 0, 15, 30, 45, 60, 75, 90, 120, 150, and 180 minutes.
  - Plasma glucose and serum insulin concentrations were measured for each timepoint.
- Calculation of insulin sensitivity and β-cell function indices:
  - The oral glucose minimal model, Hepatic Insulin Resistance Index (HIRI), QUICKI, and Matsuda indices were used to estimate insulin sensitivity.
  - The insulinogenic index was used to estimate early β-cell function.
  - The disposition Index, an integrated measure of β-cell compensation, was calculated as the product of the insulinogenic index and the Matsuda index.
- Statistical analyses: Frequency distributions of all outcome variables were analyzed and log-transformed where appropriate. Data are expressed as mean (95% confidence intervals, CI) or means ± SEM. Means and 95% CIs were calculated from the log-transformed data, as appropriate, and were subsequently back transformed (by taking the antilog of the values), resulting in geometric means and corresponding 95% CIs. Differences between groups were assessed by ANOVA performed using the General Linear Models (GLM) Procedure. Independent variables included the subject's age, gender, BMI, and group (PA and EHC). A p-value of <0.05 (two-tailed) was considered significant.

Results

Clinical and Biochemical Characteristics of Patients with Primary Aldosteronism and Essential Hypertension

	Primary Aldosteronism	Essential Hypertensive Controls	p-value
Age, years	53 ± 2	53 ± 2	0.82
Systolic blood pressure, mmHg	137 ± 3	135 ± 4	0.65
Diastolic blood pressure, mmHg	83 ± 3	78 ± 3	0.22
BMI, kg/m²	30.1 ± 1.2	33.0 ± 1.7	0.15
Total cholesterol, mg/dL	160 ± 6	181 ± 10	0.09
HDL cholesterol, mg/dL	49 ± 4	54 ± 3	0.29
LDL cholesterol, mg/dL	93 ± 6	106 ± 7	0.18
Triglycerides, mg/dL	92 ± 7	110 ± 17	0.33
BUN, mg/dL	15 ± 0.9	15 ± 1.0	0.62
Fasting plasma glucose, mg/dL	89 ± 2	98 ± 5	0.08
Fasting insulin, µU/mL	16.8 ± 4.5	9.5 ± 1.4	0.14
Hemoglobin A1C, %	5.49 ± 0.09	5.75 ± 0.11	0.08
Creatinine, mg/dL	0.82 ± 0.04	0.83 ± 0.04	0.84
Potassium, mmol/L	3.68 ± 0.10	4.08 ± 0.07	0.003
Sodium, mmol/L	136.8 ± 5.1	138.8 ± 0.3	0.692
Aldosterone, ng/dL	24 ± 4		
Renin, (ng/dL)/hour	8.3 ± 7.5		

Data represented as mean ± standard error of the mean.

Figure 1. Insulin sensitivity and β-cell function in patients with primary aldosteronism and essential hypertension

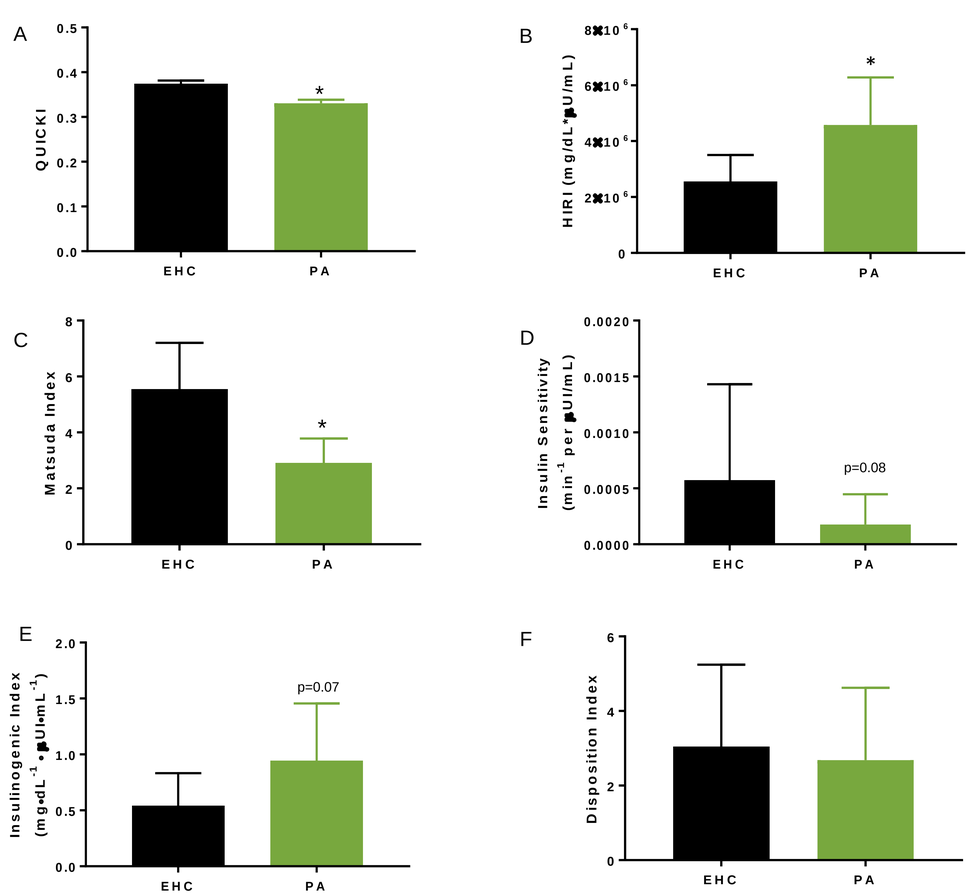

Figure 1: QUICKI (A), Hepatic Insulin Resistance Index (HIRI) (B), Matsuda Index (C), Insulin Sensitivity by Oral Minimal Model (D), Insulinogenic Index (E), and Disposition Index (F). Data is presented as adjusted means (95% CI). * indicates statistical significance (p<0.05).

Figure 2. Plasma Glucose and Insulin Concentrations during an OGTT in Patients with Primary Aldosteronism and Essential Hypertension.

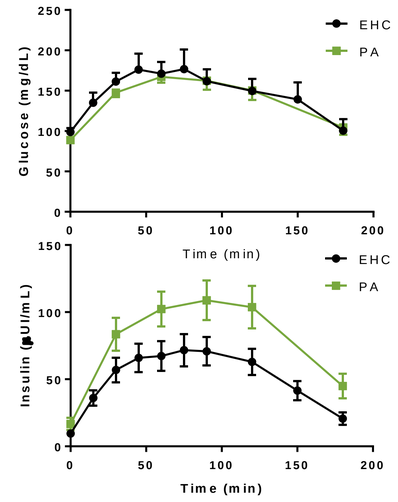

Figure 2: Time course of plasma glucose (A), and serum insulin (B) over the course of the 3-hour OGTT. Data for each time point displayed as mean ± SEM. The time course of insulin concentrations between the groups were analyzed by two-way ANOVA. * signifies P<0.05.

Summary

- There were no significant differences in age, blood pressure, or BMI, indicating proper matching of groups.
- As expected, the PA group displayed lower potassium levels compared to the controls. Though data was not collected for controls, the previously diagnosed PA patients showed high aldosterone levels, along with low renin levels.
- HIRI, an index reflecting hepatic insulin resistance, was significantly higher in PA when compared with EHC.
- Matsuda index, a measure reflecting whole-body insulin sensitivity was significantly lower in PA. Consistent with this finding, insulin sensitivity index derived from an oral minimal model tended to be lower (p<0.08).
- The insulinogenic index a measure of β-cell function was significantly higher in PA patients when compared with EHC. This suggest an appropriate compensatory increase in β-cell function in response to the lower insulin sensitivity in this cohort.
- The disposition index, an integrated measure of β-cell compensation, was similar between the two cohorts. This accounts for the similar glucose tolerance between PA and EHC groups.
- **Insulin sensitivity is significantly lower in PA and is accompanied by a compensatory increase in beta-cell function. These results suggest that excess aldosterone negatively affects insulin action without adversely impacting beta-cell function.**
- Limitations: a) Aldosterone and renin levels were not measured in control group to rule out possibility of hyperaldosteronism, b) c-peptide data was not available for both groups, c) surrogate measures of insulin sensitivity/β-cell function.
- Future Directions: a) Modeling of c-peptide data for robust measurement of β-cell function in hyperaldosteronism, b) use of hyperglycemic clamps/IVGTT studies.

References

1. Watanabe, D., Yatabe, M., & Ichihara, A. (2016). Evaluation of insulin sensitivity and secretion in primary aldosteronism. *Clinical and Experimental Hypertension, 38*(7), 613-617.
2. Fischer, E., Adolf, C., Pallauf, A., Then, C., Bidlingmaier, M., Beuschlein, F., . . . Reincke, M. (2013). Aldosterone Excess Impairs First Phase Insulin Secretion in Primary Aldosteronism. *The Journal of Clinical Endocrinology & Metabolism, 98*(6), 2513-2520.
3. Catena, C., Lapenna, R., Baroselli, S., Nadalini, E., Colussi, G., Novello, M., . . . Sechi, L. A. (2006). Insulin Sensitivity in Patients with Primary Aldosteronism: A Follow-Up Study. *The Journal of Clinical Endocrinology & Metabolism, 91*(9), 3457-3463.