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Can primary Hyperaldosteronism be Considered as a Specific Form of Diabetes Mellitus?

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Summary

Aldosterone-producing adenoma (aldosteronoma) – the most frequent form of primary hyperaldosteronism (PH) – is considered a specific form of diabetes mellitus (DM). In a previous study we demonstrated insulin resistance in patients with PH. We have therefore undertaken a study to evaluate the incidence of abnormalities of glucose metabolism in patients with PH (36 subjects) compared to control subjects with essential hypertension (EH) (21 patients). The following parameters were measured in all studied subjects: office blood pressure (by mercury sphygmomanometer in the sitting position), body mass index (BMI), plasma potassium, plasma glucose and insulin levels during oral glucose tolerance test (OGTT) (0, 60, 120 min), plasma renin activity and plasma aldosterone. Although patients with PH tended to have higher stimulated plasma glucose levels after 60 and 120 min compared to EH, these differences did not attain statistical significance. Patients with EH tended to have higher insulin levels at each measured interval, but due to a high variability these differences were again not significant. There were no significant differences between PH and EH in the proportion of diabetics (20 % vs. 14 %) or patients with impaired glucose tolerance (18 % vs. 10 %). In conclusion, we have found the absence of significant differences in the frequency of diabetes mellitus, impaired glucose tolerance and insulin resistance in patients with EH and PH. Our data thus do not support the idea of primary hyperaldosteronism as a specific type of diabetes mellitus. Furthermore, our results indicate that glucose metabolic characteristics in essential hypertension and primary hyperaldosteronism tend to be similar. The definitive conclusion with respect to the possible causal relationship between DM and PH, however, can be obtained only on larger groups of subjects, in particular after the evaluation of the effect of surgical/pharmacological treatment of primary hyperaldosteronism.

Key words

Primary hyperaldosteronism • Specific type • Diabetes mellitus • Insulin

Introduction

The most frequent form of primary hyperaldosteronism (PH), namely aldosterone-producing adenoma – aldosteronoma, is considered as a specific form of diabetes mellitus (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2000).

A possible link between these two pathological states may be explained as a deteriorating tissue response to insulin due to prolonged hypokalemia. However, there

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are no data available concerning the real frequency of diabetes mellitus in patients with primary hyperaldosteronism. Furthermore, hypokalemia is present in only 50 % of all patients, usually in the most severe forms (Gordon *et al.* 1994).

We have previously reported impaired insulin action in patients with primary hyperaldosteronism. (Widimský *et al.* 2000). Impaired insulin action was significantly improved after operation of an aldosterone-producing adenoma and spironolactone treatment, but this did not significantly influence insulin action (Šindelka *et al.* 2000).

The present study was undertaken to evaluate the frequency of abnormalities of glucose metabolism (diabetes mellitus and impaired glucose tolerance) in a larger group of patients with primary hyperaldosteronism compared to the age-, BMI- and blood pressure-matched subjects with essential hypertension. In addition, the indirect markers of insulin-resistance were used to assess the prevalence of insulin-resistance in the groups of patients with mineralocorticoid-dependent hypertension and essential hypertension.

Subjects and Methods

Two groups of subjects were studied during hospitalization: patients with primary hyperaldosteronism and those with essential hypertension who served as controls.

We have included 36 patients with primary hyperaldosteronism of the following types: 14 patients with aldosterone-producing adenoma (APA), 21 patients with idiopathic hyperaldosteronism (IHA) due to bilateral hyperplasia and one patient with unilateral hyperplasia. The diagnosis of primary hyperaldosteronism and classification into subtypes was made on the basis of laboratory measurements (decreased plasma renin activity, an increased aldosterone levels, increased aldosterone/renin ratio, postural, NaCl and dexamethasone tests and genetic screening for the exclusion of dexamethasone suppresible hyperaldosteronism (DSH)) as well as morphological methods (adrenal CT scan, adrenal venous sampling). Antihypertensive therapy was withdrawn one week before the study. In order to prevent hypokalemia, all patients were regularly treated with potassium supplements. Subjects with APA and one patient with unilateral adrenal hypertrophy (later confirmed by histology as hyperplasia) underwent unilateral adrenalectomy and the remaining patients with idiopathic hyperaldosteronism were treated by daily doses of 50-75 mg of spironolactone (Verospiron Gedeon Richter, Hungary).

The control group consisted of 21 essential hypertensive patients of corresponding age and body mass index. Antihypertensive therapy was again withdrawn one week before the study. The diagnosis was made by ruling out secondary causes of hypertension.

The following parameters were measured in all studied subjects: office blood pressure (with a mercury sphygmomanometer in the sitting position), BMI, plasma potassium, plasma glucose and insulin levels during an oral glucose tolerance test (OGTT) (0, 60 and 120 min), plasma renin activity and plasma aldosterone values. Plasma aldosterone/renin ratio was calculated as aldosterone (ng/100 ml/) to renin (ng/ml/h). The OGTT was evaluated according to the diagnostic criteria for diabetes mellitus (based on the report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2000) as follows: 2-h postload glucose (2-h PG) under 7.8 mmol/l = normal, 2-h PG between 7.8 and 11.1 mmol/l = impaired glucose tolerance, 2-h PG above 11.1 mmol/l = diabetes mellitus.

Assays

Plasma glucose concentrations were determined by the glucose oxidase method. Plasma insulin, aldosterone and renin concentrations were measured by radioimmunoassay kits (Immunotech, Czech Republic). Serum potassium concentration was determined in our Central Laboratory by usual techniques.

Statistical analysis

Statistical differences between the two groups studied were evaluated using the Mann-Whitney test and Fisher´s two-tailed test.

Results

The characteristics of patients with primary hyperaldosteronism (PH) and essential hypertension (EH) are summarized in Table 1. The results clearly confirm the diagnosis of primary hyperaldosteronism. There were not significant differences in age, BMI and blood pressure between the PH and EH groups.

No significant correlation was found between aldosterone and the studied parameters (not shown), whether calculated for both groups together or separately for PH or EH. The comparison between glucose levels during OGTT in both groups is shown in Figure 1. Although patients with PH tended to have higher stimulated plasma glucose levels after 60 and 120 min compared to EH, these differences did not reach

statistical significance. Plasma insulin levels during OGTT are depicted in Fig. 2. Patients with EH tended to have higher insulin levels at each measured interval, but again, due to the high variability these differences were not significant.

There were no significant differences between PH and EH in the proportion of diabetics (20 % vs.14 %) or patients with impaired glucose tolerance (18 % vs. 10 %).

Table 1. Characteristics of studied subjects with primary hyperaldosteronism (PH) or essential hypertension (EH).

	PH	**EH**
Age (years)	52±10	53±8
BMI (kg/m^{-2})	27.7±4.6	28.8±3.7
Casual blood pressure		
SBP (mm Hg)	163±17	163±18
DBP (mm Hg)	104±11	100±13
Plasma potassium (mmol/l)		
(normal values 3.8-5.2)	3.54±0.47	4.12±0.34
Recumbent plasma renin activity (PRA) (ng/ml/h)		
(normal values 0.7-2.6)	0.25±0.27	1.18±2.17
Recumbent plasma aldosterone (PA) (pg/ml)		
(normal values 30-150)	357±361	68±48
Plasma aldosterone (ng/100ml)/renin (g/ml/h) ratio		
(normal values < 30)	386±705	21.3±24.2

Values are means ± S.D.

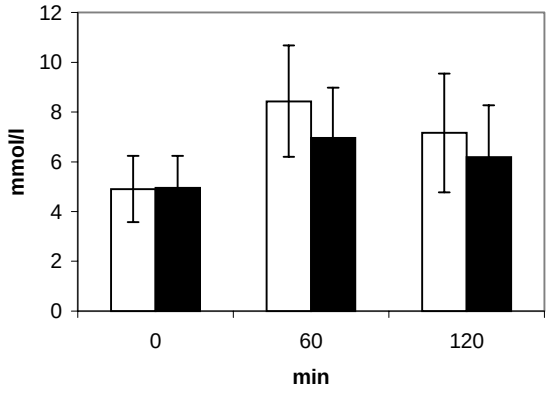

Fig. 1. *Mean plasma glucose levels during OGTT in patients with primary hyperaldosteronism (open columns) and essential hypertension (full columns).*

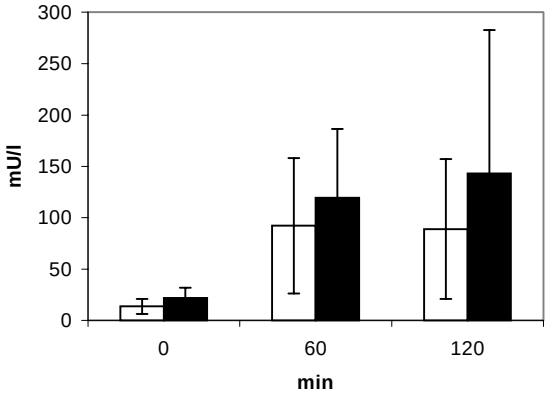

Fig. 2. *Mean plasma insulin levels during OGTT in primary hyperaldosteronism (open columns) and essential hypertension (full columns).*

Discussion

We have demonstrated that the incidence of diabetes mellitus among patients with primary hyperaldosteronism and essential hypertension is relatively high and comparable. The absence of differences between these two forms of hypertension may be explained by the high occurrence (51-93 %, depending on the degree of albuminuria) of the diabetes mellitus type II among patients with essential hypertension (Tarnow *et al.* 1994). We did not want to preselect patients with essential hypertension and

exclude those with diabetes mellitus. We have considered essential hypertensive subjects as controls due to their comparable blood pressure, age and BMI.

Although the data on the frequency of diabetes mellitus in PH and EH seem to be high, they corresponded to the estimated prevalence (14.3 %) of diabetes mellitus in individuals 40-74 years old (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2000). This fact may further question the significance of described frequency of DM in subjects with PH. We have noted not only a similar incidence of diabetes mellitus in both studied groups, but also a similar occurrence of impaired glucose tolerance and insulin resistance. These data may thus indicate similar characteristics of glucose metabolism in essential hypertension and primary hyperaldosteronism. This observation would argue against any causal relationship between diabetes mellitus and PH. Patients with PH, however, tended to a non-significantly higher prevalence of diabetes mellitus and impaired glucose tolerance. Certainly, these results might potentially become significant on a larger group of subjects.

It has been suggested that hypokalemia could be a causative factor in the development of impaired insulin action with resulting diabetes mellitus (Schatz 1988). It is therefore feasible that if we had more patients with more severe hyperaldosteronism and more prolonged duration of hypokalemia, we could reveal greater differences. This possibility is, however, unlikely since no correlation was found between aldosterone and plasma glucose and/or insulin during OGTT.

According to *in vitro* studies, a stimulating effect of insulin on aldosterone secretion may also be involved (Petrasek *et al.* 1992). However, our study failed to confirm a relationship between aldosterone and insulin levels. Similar results were obtained in a recent study on hyperinsulinemia and aldosterone secretion in essential hypertension (Haenni *et al.* 2001).

The occurrence of diabetes mellitus was in fact more frequent in patients with a milder form of hyperaldosteronism (idiopathic hyperaldosteronism). Our data are thus in agreement with previous observation (Rowe *et al.* 1980) which indicated that insulin had no biological effects in subjects with potassium deficiency. Our data thus indicate that significant differences in glucose metabolism characteristics between EH and PH are lacking. A definitive conclusion with respect to the possible causal relationship between diabetes mellitus and primary hyperaldosteronism could, however, be obtained only after a study on a larger group of subjects, in particular after evaluation of the effect of surgical/pharmacological treatment of primary hyperaldosteronism. Such a study is now being carried out in our department.

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