SHORT COMMUNICATION

Does the Treatment of Primary Hyperaldosteronism Influence Glucose Tolerance?

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Summary

Primary hyperaldosteronism (PH) is frequently considered to be a secondary form of diabetes mellitus (DM). In our previous study we attempted to evaluate the prevalence of DM among patients with PH compared to control subjects with essential hypertension (EH). We have noted a relatively high prevalence of DM and impaired glucose tolerance in PH, but the differences between the PH and EH groups did not reach statistical significance. We performed this study to assess whether the effective treatment of PH (surgical and conservative) would improve the glucose tolerance. We have studied 24 patients with PH of the following two subtypes: aldosterone-producing adenoma (APA) treated with adrenalectomy and idiopathic hyperaldosteronism (IHA) treated with spironolactone. No significant changes of glucose levels were found in the 60th and 120th min of the oral glucose tolerance test (OGTT) in the APA group. On the other hand, fasting glucose levels were decreased significantly after adrenalectomy. Plasma glucose levels were significantly increased in the 60th min, but no differences were found in fasting values and in the 120th min in the IHA group. There was a significantly higher incidence of impaired glucose tolerance (36 % before, 45 % after treatment) and DM (9 %, 18 %) in the IHA group compared to the APA group (8 %, 32 %; DM 0 %, 0 %). In conclusion, the treatment of PH does not improve glucose tolerance. Mild worsening of glucose tolerance after treatment could be explained by an increase of the body mass index. These data, in accordance with our previous study, do not support the idea that PH is a secondary form of diabetes mellitus.

Primary hyperaldosteronism is considered to be a secondary form of diabetes mellitus (Report of the Expert Committee 2000). The possible link between these two pathological states may be explained by a deterioration of the tissue response to insulin due to prolonged hypokalemia (Schatz 1988). However, there are no data concerning the real prevalence of diabetes mellitus in patients with PH. Furthermore, hypokalemia is present in only 50 % of all patients, mostly in the most severe forms (Schatz 1988, Gordon *et al.* 1994).

In a previous pilot study, we attempted to evaluate the prevalence of DM among patients with PH compared to control subjects with essential hypertension (EH). We have noted not only a similar frequency of

diabetes mellitus in both studied groups, but also a similar occurrence of impaired glucose tolerance and insulin resistance (Widimský Jr. *et al.* 2001).

The absence of differences in impaired glucose tolerance between essential hypertension and PH may be explained by the high occurrence of Type 2 diabetes mellitus among patients with essential hypertension (Tarnow *et al.* 1994). In order to evaluate any potential relationship between PH and glucose tolerance, it would be of interest to assess the effect of treatment on glucose metabolism parameters. Therefore, the present study was undertaken to reveal if the cure of PH after adrenalectomy in aldosterone-producing adenoma (APA) patients would also lead to any potential benefit with respect to glucose levels. In addition, the effect of conservative therapy by means of spironolactone was also investigated.

Twenty-four patients with PH were studied at the time of the diagnosis and subsequently after adrenalectomy or continuous treatment with spironolactone.

The diagnosis and classification of PH into the subtypes were made on the basis of laboratory (increased aldosterone levels, decreased plasma renin activity, increased aldosterone/renin ratio, postural, NaCl infusion tests and genetic screening for the exclusion of dexamethasone-suppressible hyperaldosteronism) as well as morphological methods (adrenal CT scan, adrenal venous sampling). Antihypertensive therapy before the specific treatment of PH was withdrawn at least one week before the study. In order to prevent hypokalemia, all patients were regularly treated with potassium supplements.

Table 1. Characteristics of patients with APA and IHA. PRA and aldosterone levels in patients with IHA were influenced by diuretic therapy (spironolactone + hydrochlorothiazide).

|	Patients with APA			Patients with IHA		
	Before treatment	**After treatment (adrenalectomy)**	**Wilcoxon p-level**	**Before treatment**	**After treatment (spironolactone)**	**Wilcoxon p-level**
Age (years)	43.7±9.6	examined after 3.4 years on the average	-	53.3±7.6	examined after 3.6 years on the average	- -
BMI	25.7±4.5	26.6±4.6	0.05	30.5±3.7	33.7±3.5	0.01
Office SBP/DBP (mm Hg)	162±12/103±10	134±15/88±12	0.001/0.004	165±21/101±14	153±31/95±13	0.29/0.34
ABPM SBP/DBP (mm Hg)	151±13/97±8	118±14/80±11	0.002/0.002	162±15/100±6	136±14/85±10	0.01/0.01
Plasma potassium levels (mmol/l)	3.50±0.48	4.36±0.24	0.003	3.49±0.56	3.95±0.64	0.09
Plasma aldosterone levels (pg/ml)	344±224	113±159	0.03	191±91	549.8±502	0.001
PRA (ng/ml/h)	0.13±0.13	1.57±1.02	0.002	0.27±0.24	2.29±4.68	0.08
Aldosterone/renin ratio	532±534	7.0±5.7	0.001	304±669	330±534	NS

Values are means ± SD.

Subjects were divided into two groups which were investigated separately. The first group consisted of

13 subjects with aldosterone-producing adenomas (APA) who underwent unilateral adrenalectomy (6 men and 7

women, average age 43.8±9.6 years, mean follow-up interval 3.4 years). The second group consisted of 11 subjects with idiopathic hyperaldosteronism (IHA) who were treated by daily doses of 50-75 mg of spironolactone (8 men and 3 women, average age 53.3±3.7 years, mean follow-up interval 3.6 years). Three subjects of the IHA group were also treated with low doses of hydrochlorothiazide (12.5 mg daily).

The following parameters were measured in all the studied subjects: office BP (by mercury sphygmomanometer in the sitting position according ISH recommendations), mean BP values during 24 h ABPM (Spacelabs 90207, Redmont, California, USA), BMI, plasma potassium, plasma glucose levels during the oral glucose tolerance test (OGTT) (0, 60, 120 min), plasma renin activity, plasma aldosterone and aldosterone/renin ratio (ARR). The OGTT was evaluated according to diagnostic criteria for diabetes mellitus as follows: 2-h postload glucose (2-h PG) below 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 (Report of the Expert Committee 2000).
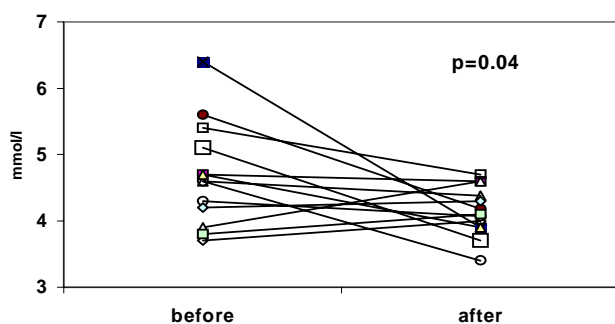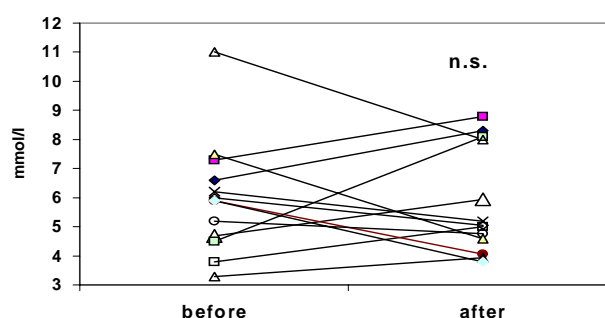

Fig. 1. *Comparison of fasting plasma glucose levels during OGTT in 13 subjects of the APA group before and after the treatment (mean values: before 4.69±0.78, after 4.15±0.39 mmol/l).*

Plasma glucose concentrations were determined by the glucose oxidase method. Plasma aldosterone and renin concentrations were measured by radio-immunoassay kits (Immunotech).

The statistical difference between paired measurements performed in each subject before and after treatment was evaluated using the Wilcoxon matched-pairs signed-ranks test. Correlations between the studied parameters were calculated by Spearman rank order test.

The characteristics of patients with APA and IHA, examined before and after treatment, are shown in Table 1. The results clearly confirm the diagnosis of PH and the efficacy of treatment. As expected, the surgical treatment of PH caused a significant fall in the office blood pressure, mean BP during ABPM, aldosterone levels and aldosterone/renin ratio, together with a significant increase in serum potassium levels. Patients with IHA however, exhibited less profound blood pressure changes after spironolactone treatment. A significant increase of BMI was noted after treatment in both groups.

Fig. 2. *Comparison of plasma glucose levels in the 120th min during OGTT in 13 subjects of the APA group before and after the treatment (mean values: before 5.90±1.96, after 5.81±1.84 mmol/l).*

Fasting and 120 min plasma glucose levels during OGTT before and after treatment in the individual patients with APA are shown in Figures 1 and 2. No significant changes were noted in glucose levels in the 60th and 120th min of OGTT. On the other hand, fasting glucose levels decreased significantly after adrenalectomy. A significant increase of plasma glucose levels was found only in the 60th min in the IHA group (p=0.05) where no significant changes were found at zero time and in the 120th min.

We have noted a significantly higher incidence of impaired glucose tolerance (36 % before, 45 % after treatment) and DM (9 %, 18%) in the IHA group, than in the APA group (8 %, 32 %), DM (0 %, 0 %). No correlation was found between plasma aldosterone or PRA and glucose levels.

The main finding of our study is the absence of improvement in plasma glucose metabolism despite the therapy in APA patients, although we observed a normalization of plasma potassium levels. It thus appears

that prolonged hypokalemia in PH does not lead to substantial changes of glucose metabolism as previously reported (Schatz 1988).

We observed only a significant fall in fasting glucose levels (at zero time in OGTT) in the APA group after the treatment, but plasma glucose levels in the 60th and 120th min argue against the improvement of glucose tolerance. These findings are in accordance with our previous pilot study (Widimský Jr. *et al.* 2001) and thus speak against the traditional view of PH being the secondary form of diabetes mellitus (Report of the Expert Committee 2002).

Similarly, all parameters in the IHA group clearly show that the aldosterone receptor blockade with spironolactone has no significant effect on glucose tolerance. In IHA patients, plasma glucose levels even increased after pharmacological therapy at each studied OGTT interval (significantly in the 60th min). This surprising finding in IHA patients could be explained by the marked BMI increase in the time period after the initiation of the treatment (3.6 years on the average). The negative influence of hydrochlorothiazide on glucose tolerance is well known, but the relatively low proportion of patients who were treated with a combination of spironolactone and low doses of hydrochlorothiazide should not interfere with our results. BMI increase in APA patients after surgery was also noted, but this increase was less prominent. It is thus difficult to imagine that this mild BMI increase would explain the absence of

changes in plasma glucose levels after the treatment in OGTT (observed in the 60th and 120th min of OGTT). The relatively higher levels of plasma aldosterone after the pharmacological treatment could be caused by combination therapy with two diuretics (spironolactone and hydrochlorothiazide) in some patients.

A significantly higher proportion of patients with impaired glucose tolerance and DM was found in the IHA group than in the APA group. This may be explained by higher BMI levels in IHA subjects. It thus seems that some metabolic characteristics in IHA may resemble to some extent those observed in essentially hypertensive patients with the Reaven syndrome (Lim *et al.* 2002). The increased incidence of impaired glucose tolerance in the APA group after adrenalectomy could be explained not only by a mild increase in BMI but might also be due to 3.4 years follow-up interval causing the age-related deterioration of glucose tolerance.

In conclusion, our study indicates the lack of causal relationship between primary hyperaldosteronism and impaired glucose tolerance, and thus does not confirm the traditional classification of primary hyperaldosteronism as a secondary form of diabetes mellitus.

Acknowledgements

References

GORDON RD, STOWASSER M, TUNNY TJ: Primary aldosteronism and other forms of mineralocorticoid hypertension. In: *Textbook of Hypertension*. JD SWALES (ed), Blackwell, Oxford, 1994, pp 865-892.

LIM PO, STRUTHERS AD, MACDONALD TM: The neurohormonal natural history of essential hypertension: towards primary or tertiary aldosteronism? *J Hypertens* **20**:11-15, 2002.

REPORT OF THE EXPERT COMMITTEE on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **23** (Suppl 1): S4-S19, 2000.

SCHATZ H: Low insulin response and hypokaliemia. *Dtsch Med Wochenschr* **113**: 1939, 1988.

TARNOW L, ROSSING P, GALL MA, NIELSEN FS, PARVING HH: Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. *Diabetes Care* **17**: 1247-1251, 1994.

WIDIMSKÝ J Jr, ŠTRAUCH B, ŠINDELKA G, ŠKRHA J: Can primary hyperaldosteronism be considered as a specific form of diabetes mellitus? *Physiol Res* **50**: 603-607, 2001.

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