DIABETES MELLITUS IN PRIMARY ALDOSTERONISM

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DIABETES MELLITUS PRI PRIMÁRNOM ALDOSTERONIZME

Abstract

**Kreze Sen. A, Kreze-Spirova E, Mikulecky M:
Diabetes mellitus in primary aldosteronism
Bratisl Lek Listy 2000, 101 (4): 187–190**

Background: **Information concerning diabetes mellitus associated with primary aldosteronism is scarce.**
Objectives: **To determine the prevalence of diabetes mellitus in its two main pathogenetic forms of primary aldosteronism and to evaluate its association with several clinical variables.**
Patients: **Fifty in-patients (31 female and 19 male, aged 16—66), diagnosed during the years 1980—1998 as aldosterone producing adenoma (n=26) or as idiopathic hyperaldosteronism (n=24).**
Methods: **Morning fasting plasma glucose was measured by glucoso oxidase method in all patients. In the presence of higher values, confirmatory measurements were performed on the next day. The results were evaluated retrospectively by the diagnostic criteria of American Diabetes Association, 1997. Statistical significance of the association between diabetes mellitus and clinical variables was evaluated by chi-square test.**
Results: **Diabetes mellitus was ascertained in 6 patients out of 50 (12 %; interval of 95 % confidence 5—24 %). Diabetes was accompanied significantly more often with idiopathic hyperaldosteronism (10—47 %) than with aldosterone producing adenoma (0—13 %). Patients with the family history of diabetes suffered more often (9—76 %) from this disease than those without the history (1—19 %). Obesity, longer (>5 years) duration of hypertension and hypokalaemia did not affect the occurrence of diabetes.**
Conclusions: **The occurence of diabetes in primary aldosteronism was connected significantly with its idiopathic subtype and positive family history of diabetes.** ***(Tab. 2, Ref. 11.)***
Key words: diabetes mellitus, primary aldosteronism, subtypes of primary aldosteronism.

Abstrakt

Kreze Sen. A., Kreze-Spirová E., Mikulecký M.:
Diabetes mellitus pri primárnom aldosteronizme
Bratisl. lek. Listy, 101, 2000, č. 4, s. 187–190

Pozadie problému: O diabete vyskytujúcom sa pri primárnom aldosteronizme je málo informácií.
Cieľ: Zistiť prevalenciu diabetes mellitus pri dvoch hlavných patogenetických formách primárneho aldosteronizmu a posúdiť jeho súvislosť s viacerými klinickými faktormi.
Pacienti: 50 hospitalizovaných pacientov (31 žien a 19 mužov vo veku 16—66 rokov), z nich u 26 išlo o aldosterón-produkujúci adenóm, u 24 o idiopatický hyperaldosteronizmus.
Metódy: U všetkých pacientov sa stanovila glykémia ráno nalačno glukózo-oxidázovou metódou. Pri vyššej hodnote sa robilo overujúce vyšetrenie ďalší deň. Výsledky sa vyhodnotili retrospektívne kritériami Americkej diabetickej asociácie z roku 1997. Štatistická významnosť väzby diabetu na klinické faktory sa hodnotila chí-kvadrátovým testom.
Výsledky: Diabetes mellitus sa zistil u 6 pacientov (12 %; interval 95 % spoľahlivosti 5—24 %). Diabetes sa významne častejšie spájal s idiopatickým hyperaldosteronizmom (10—47 %) ako s aldosterón-produkujúcim adenómom (0—13 %). Pacienti s diabetickou rodinnou záťažou boli postihnutí diabetom častejšie (9—76 %) ako podskupina s negatívnou rodinnou anamnézou (1—19 %). Obezita, dlhšie trvanie (>5 rokov) hypertenzie a hypokáliémia nemali vplyv na výskyt diabetu.
Závery: Výskyt diabetu pri primárnom aldosteronizme sa signifikantne spájal s jeho idiopatickou formou a s pozitívnou diabetickou rodinnou anamnézou. *(Tab. 2, lit. 11.)*
Kľúčové slová: diabetes mellitus, primárny aldosteronizmus, subtypy primárneho aldosteronizmu.

Information concerning diabetes mellitus associated with primary aldosteronism is scarce. There exists, to the best of our knowledge, only one study (Conn, 1965) analysing the frequency of glucose intolerance in primary aldosteronism. Recent overviews (Genuth, 1990; Gross, 1995; Lofler and Blanc, 1995) and textbooks (Ganda, 1994; Schlaghecke, 1995; Watkins et al., 1996; Mac-

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Tab. 1. Occurrence of diabetes mellitus in corresponding subgroups of primary aldosteronism.

Criterion	Subgroup	N	N_d	L	M	U	chi-square
Pathogenetic	idiopathic	24	6	10%	25%	47%	
form	adenoma	26	0	0%	0%	13%	7.396**
Diabetes in	not present	42	3	1%	7%	19%	
family history	present	8	3	9%	38%	78%	4.057*
Duration of	≤5 years	22	2	1%	9%	29%	
hypertension	>5 years	27	4	4%	15%	34%	0.383
Body mass	normal	31	2	1%	6%	21%	
index	obesity	19	4	6%	21%	46%	2.278
Serum	normal	31	4	4%	13%	30%	
potassium	low	19	2	1%	11%	33%	0.065

N = sample size, N_d = number of cases with diabetes, L (M, U) = lower 95 % confidence interval (mean, upper 95 % confidence limit), significance of the difference between two corresponding subgroups is shown by chi-square value (at 1 degree of freedom). * $p<0.05$, ** $p<0.01$

Tab. 1. Výskyt diabetes mellitus v porovnávaných podskupinách primárneho aldosteronizmu.

Kritérium	Podskupina	N	N_d	D	P	H	chí-kvadrát
Patogenetická	idiopatická	24	6	10%	25%	47%	
forma	adenóm	26	0	0%	0%	13%	7,396**
Diabetes	neprítomný	42	3	1%	7%	19%	
v rodine	prítomný	8	3	9%	38%	78%	4,057*
Trvanie	≤5 rokov	22	2	1%	9%	29%	
hypertenzie	>5 rokov	27	4	4%	15%	34%	0,383
Body mass	normálny	31	2	1%	6%	21%	
index	obezita	19	4	6%	21%	46%	2,278
Káliémia	normálna	31	4	4%	13%	30%	
	znížená	19	2	1%	11%	33%	0,065

N = počet pacientov v podskupine, N_d = počet pacientov s diabetom, D, P, H = dolná, priemer, horná medza 95 % intervalu spoľahlivosti, významnosť rozdielu medzi dvomi porovnávanými podskupinami uvádza hodnota chí-kvadrátu (pri jednom stupni voľnosti). * $p<0,05$, ** $p<0,01$

Farlane, 1997) are quoting in unison this sole source, repeating Conn's (1965) notion that primary aldosteronism is accompanied in about half of cases by abnormal glucose tolerance. Some of these authors add that the real prevalence is probably lower (Ganda, 1994; Watkins et al., 1996). They, however, do not corroborate this statement by any quantitative reasoning. Moreover, no attempt has been made so far to define simple clinical variables which could exert influence on development of diabetes in primary aldosteronism.

The present study was conducted in order to extend the data concerned with prevalence of diabetes in primary aldosteronism and to analyse possible connections of this secondary diabetes with pathogenetical form of primary aldosteronism, family history of diabetes, body mass index, hypokalaemia and duration of arterial hypertension.

Patients and methods

The diagnosis of aldosterone producing adenoma (9 males, aged 26—62 years; 17 females, aged 28—66 years) and that of idiopathic hyperaldosteronism (11 males, aged 36—65 years; 13 females, aged 16—59 years) was established during 1990—1998 at the Institute of Endocrinology. Primary aldosteronism was diagnosed on the basis of elevated urinary aldosterone and supressed plasma renin activity. Investigations used to differentiate aldosterone producing adenoma from idiopathic hyperaldosteronism included computerized abdominal tomography, adrenal vein catheterization and examination of surgically removed adrenals. In patients with a history of diagnosed diabetes mellitus, the glycated haemoglobin was determined and the daily glucose measurements (morning fasting plasma glucose plus 3 to 7 additional glycaemia readings) were estimated for several times during they stay at the Institute of Endocrinology. In all other patients the morning fasting plasma glucose, or the morning fasting plasma glucose plus glycaemia 2 hours after the breakfast were routinely estimated. In the presence of higher values, the confirmatory measurements were performed on a different day: the morning fasting plasma glucose or the oral glucose tolerance test. Plasma glucose concentrations were determined by glucose oxidase method (Glucoanalyser Beckman). Results were retrospectively reviewed by diagnostic criteria of American Diabetes Association, 1997.

The investigated clinical variables were as follows: pathogenetic subtypes of primary aldosteronism (idiopathic hyperaldosteronism versus aldosterone producing adrenal adenoma), family history of diabetes (negative versus positive), duration of arterial

Tab. 2. Analogy of Table 1 for impaired fasting glycaemia.

Criterion	Subgroup	N	N_d	L	M	U	chi-square
Pathogenetic	idiopathic	24	1	0%	4%	21%	
form	adenoma	26	1	0%	4%	20%	0.003
Diabetes in	not present	42	2	1%	5%	16%	
family history	present	8	0	0%	0%	37%	2.421
Duration of	≤5 years	22	0	0%	0%	15%	
hypertension	>5 years	27	2	1%	7%	24%	0.756
Body mass	normal	31	0	0%	0%	11%	
index	obesity	19	2	1%	11%	33%	1.950
Serum	normal	31	0	0%	0%	11%	
potassium	low	19	2	1%	11%	33%	1.950

Tab. 2. Analógia s tabuľkou 1 pre hraničnú glykémiu nalačno.

Kritérium	Podskupina	N	N_d	D	P	H	chí-kvadrát
Patogenetická	idiopatická	24	1	0%	4%	21%	
forma	adenóm	26	1	0%	4%	20%	0,003
Diabetes	neprítomný	42	2	1%	5%	16%	
v rodine	prítomný	8	0	0%	0%	37%	2,421
Trvanie	≤5 rokov	22	0	0%	0%	15%	
hypertenzie	>5 rokov	27	2	1%	7%	24%	0,756
Body mass	normálny	31	0	0%	0%	11%	
index	obezita	19	2	1%	11%	33%	1,950
Káliémia	normálna	31	0	0%	0%	11%	
	znížená	19	2	1%	11%	33%	1,950

hypertension (≤5 years versus >5 years), obesity (absent versus body mass index >30) and hypokalaemia (absent versus serum potassium ≤3.5 mmol/l).

Statistical significance of association between diabetes mellitus and the investigated clinical variables was evaluated by calculating the 95% confidence intervals (CI) for percentages of diabetes occurrence and by chi-square test at the level alpha=0.05.

Results

Diabetes mellitus was present in 6 out of 50 patients (12 %; 95 % CI 5—24 %) and was confirmed by our glycaemia measurements; in other words, no new cases of diabetes were found. Of these 6 diabetics, one was treated with insulin, three were on oral hypoglycaemic agents and two on diet alone. *De novo* was diagnosed impaired fasting glycaemia in 2 patients (4 %; 95 % CI 0—14 %). The impaired glucose tolerance was ascertained in 2 out of 3 patients in whom the oral glucose tolerance test was performed.

Idiopathic hyperaldosteronism was accompanied by diabetes mellitus significantly more often ($p<0.01$) than aldosterone producing adenoma (Tab. 1). In fact, there was no patient with diabetes in aldosterone producing adenoma group. Patients with family history of diabetes suffered more often from this disease ($p<0.05$) than those without positive family history of diabetes. Other variables — obesity, longer (>5 years) duration of arterial hypertension and hypokalaemia — did not affect the occurrence of diabetes.

No significant association of studied clinical variables with 2 cases of impaired fasting glycaemia was found (Tab. 2).

Discussion

All proportions in the present paper were evaluated not only as the point estimates (e.g. 0 % of diabetes in aldosterone producing adenoma group) but also as interval estimates (e.g. 95 % CI for this point estimate was 0—13 %), taking into account also the corresponding sample sizes. Thus, for example, the absence of diabetes in our 26 cases of aldosterone producing adenoma does not preclude the presence of diabetes in other samples from the same population: according to the prediction, it would vary between 0 % and 13 %.

The aldosterone producing adenoma was diagnosed in 26 out of our 50 patients (52 %; 95 % CI 37—66 %), while the idiopathic hyperaldosteronism in 24 out of 50 patients (48 %; 95 % CI 34—63 %). These proportions do not differ substantially from the recently reported frequencies (65 % and 30—40 %) of these two main pathogenetic subtypes of primary aldosteronism (Litchfield and Dluhy, 1995).

Results obtained by the present study indicate that diabetes mellitus may be more frequently associated with idiopathic hyperaldosteronism than with aldosterone producing adrenal adenoma. The estimated prevalence of diabetes in idiopathic hyperaldosteronism (10—47 %) is significantly higher than the prevalence of 4 % of diabetes mellitus in general Slovak population (Health Statistics Yearbook of the Slovak Republic 1999). In contrast, the prevalence of diabetes in aldosterone producing adenoma (0—13 %) is comparable with the prevalence of diabetes in general population of Slovakia.

Conn (1965) described glucose intolerance in 14 out of his 27 patients (52 %; 95 % CI 32—71 %) with aldosterone producing

adenoma and reported them in detail. Reevaluation of these data by diagnostic criteria of American Diabetes Association (1997) confirms 3 cases of diabetes (11 %; 95 % CI 2—29 %) and 9 cases (33 %; 95 % CI 17—54 %) of impaired glucose tolerance. The estimated prevalence of diabetes in our patients with aldosterone producing adenoma (0—13 %) is not at variance with mentioned results obtained from Conn's data. The prevalence of impaired glucose tolerance can not be compared because with our patients the oral glucose tolerance test was performed only in 3 subjects out of 50. As it was a retrospective study, the use of oral glucose tolerance test reflects our normal clinical practice.

Depletion of potassium was thought to be a promoting cause of glucose intolerance in primary aldosteronism (Conn, 1965; Genuth, 1990). Irrelevance of hypokalaemia in this respect with our cases can be explained by the fact that circulating levels of potassium do not necessarily reflect its intracellular pool. Moreover, the role of hypokalaemia in this respect appears to be questionable (Watkins et al., 1996).

In conclusion, the occurrence of diabetes in our 50 patients with primary aldosteronism was limited to its idiopathic subtype and exhibited a connection with positive family history of diabetes. Continuing studies of extended data are desirable.

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Received January 24, 2000.
Accepted March 10, 2000.