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A 10-YEARS LONGITUDINAL STUDY OF ADOLESCENT DIABETICS WITH INITIAL NEPHROPATHY

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ABSTRACT

The data from a 10-years prospective study among 85 boys and 64 girls, mean age 14,1 ±3,8 years with mean diabetes duration 8,45 ±3,7 years are analyzed. Using a complex prospective screening we found the frequency of microalbuminuria (MAU) and estimated some parameters of progression of the renal damage. The patients were divided into 3 groups: no MAU, with MAU and with clinical signs of nephropathy. We traced the dynamics of glomerular filtration, albumin excretion and arterial pressure. The effect of ACEIs was according to the level of proteinuria. In diabetics with macroalbuminuria a short-lasting effect run out to the end of the 2-nd year. In MAU-positive ptients ACEIs led to delay of nephropathy for 10-years in 86,48%, progression in 8,1% and regression to normoalbuminuria in 5,4%. In 15% of all the diabetics we found a significant raise of proteinuria. In 21,73% of patients with "borderline" albuminuria there was a progression after the 5-th year with a cumulative index 4,58% or 0,91%.

Key words: diabetes mellitus, diabetic nephropathy, microalbuminuria, glomerular filtration rate, adolescence

INTRODUCTION

Diabetes mellitus (DM) as a group of metabolic diseases, characterizing with hyperglycemia is a result of offence in insulin secretion, insulin action or (and) both (9,10) and damages all organs and systems in the organism, but concerns most of all the blood vessels (1). Nowadays a 1/2 000 healthy Bulgarian child is diabetic and the annual incidence rate of disease is 7-10/100 000 children (4). The renal involvement in DM is the second very important complication and its clinical appearance is 5.45% (6).

MATERIAL AND METHODS

Using a complex prospective screening to establish the frequency of microalbuminuria (MAU) as a marker of an initial diabetic nephropathy (DNP) in children and adolescents, to trace its evolution, by assessing the indexes of progression: MAU, blood pressure (BP) and glomerular filtration rate (GFR) for a 10-year period.

We studied 149 patients with DM type-1, 85 boys and 64 girls, mean age 14.1 ±3.8 years and DM duration 8.45 ±3.7 years for a 10-years period. In 89 patients (59.73%) the treatment was conventional insulin regimen and in 60 patients (40.27%) - intensified insulin regimen with human insulin (HM). The patients formed 2 groups, according to the albumin excretion (AE): diabetics without MAU (109), diabetics with MAU (37) and 3 patients withdrew the study, because of their macroalbuminuric excretion.

1. MAU:
   1) semi-quantitative methods: a 24h urine sample with immunochemical tests: a) Micral (Boehringer – Mannheim); b) Microbumintest (Miles Inc., USA)
   2) a quantitative method: immunoturbidometry with analyzer Cobas mira plus (Hoffman-La Roche) with Randox test, using original program: Randox urinary albumin control-low and elevated; sensitivity limits: 9.7-206.2 mg/l albumin in urine.
2. GFR: a) standard 4h - creatinine clearance - normal values: 60-100ml/min/1.73mI; b) Tc-99m DTPA clearance – normal values 180-236ml/min/1.73ml, "Diacam", Siemens
3. Metabolic control: IMX-Abbot, USA by MEIA method; referent values of HbA1c-4.4-6.4%.
4. Test for provoking MAU by graded exercise – using veloergometry type KE 22 Medicor, Budapest on 75W and 100W by original method for children and adolescents.
5. Sphygmomanometry: with aneroid sphygmomanometer, using Korotkoff method (Vth phase): in rest and at graded exercise
6. Dynamic renal scintigraphy with Tc-99m DTPA using "Diacam" (Siemens) for the first time in Bulgaria (Varna) for studying an initial DNP.
7. Indexes for progression: a) AE:

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1) raising of AE versus the initial values per year (ug/min/year or mg/l/year);
2) % of its raising versus the initial per year (Δ%/year):

b) GFR: 1/ rate of reduction of GFR (ml/min/month or ml/min/year); 2/% of its reduction versus the initial (supra-normal) per year (Δ%/year)

3) BP:
1) raising of BP versus the initial per year (mm Hg/year);
2) % of raising BP versus the initial per year – (Δ%/year).

We used the following statistic methods: graphic analysis, alternative analysis, statistic assessment, variation analysis – statistic significant is the value under 5% ($p < 0.05$) and Microsoft Excel – Windows' 98 for data processing.

RESULTS AND DISCUSSION

In our study for a 10-years period 5 of normoalbuminuric patients progressed to MAU after the 5-th year and all were in the beginning with borderline albuminuria. This showed a cumulative risk of 4.58% (5/109 patients).

In the MAU-group, treated with angiotensin-converting enzyme inhibitors (ACEI), 3 patients developed macroalbuminuria or the progression in MAU-diabetics was 8.10% for the treated patients . In the normoalbuinuric patients there were 23 with borderline values: 7.2-20ug/min. After the 5-th year 5 of them progressed to microalbuminuria, so 8 diabetics fell in the group of progressors. Their share was 5.48% of all examined cases.

In the MAU-diabetics, 2 patients regressed to normal albumin excretion, using Enalapril (Renitec). The values of their MAU were not so high - between 50-70mg/ml or the share of diabetics "regressors" was 5.40% among the MAU-group.

If we show the data for the evolution of proteinuria, BP and GFR for the 10 years in the different groups of patients according to AE, GFR and BP, we will receive the following results: (Tables 1, 2 and 3; Figures 1, 2, 3 and 4).

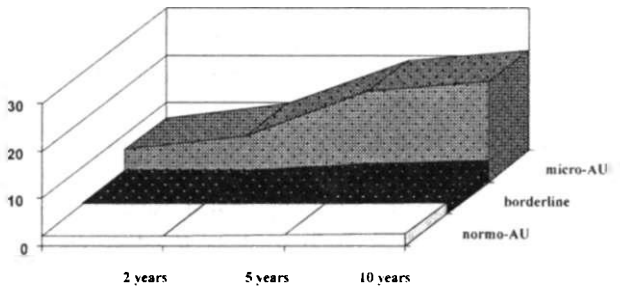

Fig.1. Dynamics of proteinuria for 10 years

Our results about the dynamics of proteinuria in children and adolescent diabetics correlate with these reported by other authors. According to the data of patients in the Microalbuminuria Captopril Study Group (1996), in 7.2% of the cases there was a progression of the persistent MAU during 24 months (6). Ahmad *et al.* showed that for 5-years treatment with Enalapril –7.7% of their patients developed macroalbuminuria (3).

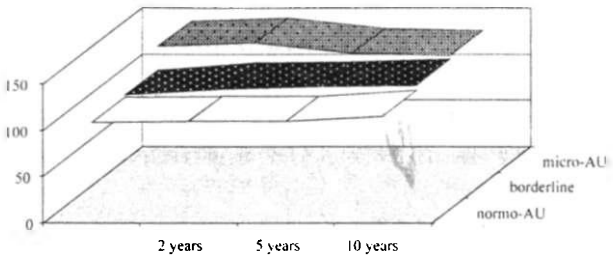

Fig. 2. Dynamics of GFR for 10 years

The data for 5.40% regression in our MAU-patients are corresponding to Ellis *et al.* (5). For a 4-year period 7 out of 124 patients (5.64%) with DNP undergone a reverse development to normal albuminuria and in 33.87% there was an improvement (5).

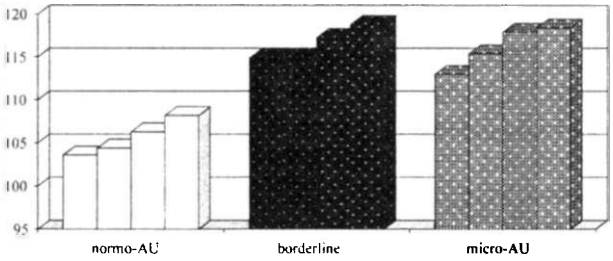

Fig. 3. Dynamics of systolic BP for 10 years

We consider that the most vulnerable and suitable for active observation is the group of adolescent diabetics with borderline albuminuria. Their evolution shows that almost 1/5 of them (21.74%) are progressors towards MAU and eventually to clinical DNP. These are patients in puberty, worse metabolic control and more often (40%) with familial predisposition to hypertension (2 out of 5 progressors in the group of borderline albuminuria). So they possess determinant risk factors like the patients with initial DNP (the MAU-group).

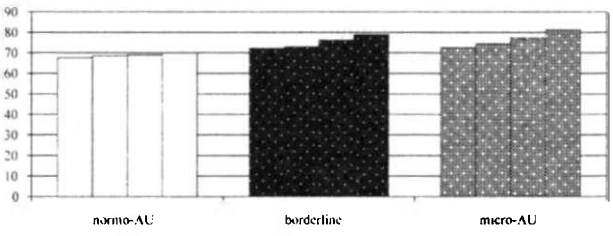

Fig. 4. Dynamics of diastolic BP for 10 years

When MAU-patients are early treated with ACEI they have a stable course of AE and in 91.89% the renal function did not get worse. We establish that there is not a significant difference in the reduction of GFR using various ACEI. Values of 2.3 ml/min/year are average referent values, mentioned in the literature (4,8,11).

Table 1. Dynamics of proteinuria for 10 years

Groups of pts:	In the beginning:	After 2 years:	After 5 years:	At the 10th year:
Normo – AU	2,1 ± 0,2	2,18 ± 0,3	2,29 ± 0,32	2,48 ± 0,42
Borderline – AU	2,42 ± 0,3	2,46 ± 0,38	2,49 ± 0,43	2,51 ± 0,56
Micro – AU	6,93 ± 0,32	9,8 ± 0,40	23,6 ± 0,36	25,2 ± 0,2

Table 2. dynamics of DFR for 10 years

Groups of pts:	In the beginning:	After 2 years:	After 5 years:	At the 10th year:
Normo - AU	108,6 ± 4,5	109,4 ± 3,9	110,0 ± 4,1	115,2 ± 4,4
Borderline – AU	110.3 ± 3.4	117,4 ± 3,9	119,3 ± 4,6	121,5 ± 3,7
hyphpar0Micro - AU	135,4 ± 4,1	139,4 ± 4,3	128,3 ± 3,9	125, 4 ± 3,8

Table 3. Dynamics of BP for 10 years

Groups of pts:	BP (mmHg)	In the beginning:	After 2 years:	After 5 years:	At the 10th year:
Normo - AU	SBP	103,6 ± 11,3	104,4 ± 13,9	106,3 ± 14,1	108,2 ± 14,4 NS
	DBP	67,6 ± 15,7	68,1 ± 11,4	69,0 ± 12,6	70,9 ± 10,8 NS
Borderline – AU	SBP	113,6 ± 14,8	114,9 ± 13,9	117,3 ± 14,1	118,8 ± 13,7 p<0.06
	DBP	72,4 ± 16,7	73,2 ± 14,8	76,3 ± 12,9	78,9 ±13,4 p<0.05
Micro - AU	SBP	114,6 ± 21,2	115,4 ± 18,3	117,6 ± 13,9	118, 4 ± 13,4 p<0.06
	DBP	72.6 ± 17,4	74,5 ± 17,3	77,4 ± 15,8	81,3 ± 14,3 p<0.01

The fact that in 8.1% of MAU-positive patients there is a progression and in 5.4% regression of the renal complication shows that DNP has not an inevitable malignant course, which justifies early therapeutic interference even in childhood.

CONCLUSIONS

1. The frequency of MAU in our patients is 24.83%
2. Some 21.1% of normoalbuminuric patients are with borderline albuminuria; in 5 of them (21.74%) it progresses for 5 years to MAU with cumulative index 0.91% per year.
3. In MAU-positive group the treatment with ACEI avoids the progression for 10 years in 86.48%, progression in 8.2% and regression to normal albumin excretion in 5.40%.
4. Diastolic BP doesn't change significantly by graded exercise, but raises significantly in MAU-positive patients and correlates with the elevated albumin excretion for the 10-year period.

REFERENCES

1. Коев, Д. Клинична ендокринология. София, 1993, 269, 308-314.
2. Цанева, В. Епидемиология на захарния диабет и неговите усложнения в детската възраст. Докт. дис. Варна, МУ-Варна, 1998.
3. Ahmad, J., M. A. Siddiqui, H. Ahmad. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic pts with microalbuminuria.- *Diabet. Care*, **20**, 1997, 1576-1581.
4. Bjorck, S., H. Mulec, S. Johnsen. Renal protective effect of enalapril in diabetic nephropathy.- *BMJ*, **304**, 1992, 339-343.
5. Ellis, D., C. Lloyd, D. J. Becker. The changing course of diabetic nephropathy: low density lipoprotein cholesterol and blood pressure correlate with regression of proteinuria.- *Am. J. Kidney Dis.*, **27**, 1996, No 6, 809-818.
6. Koeva, L., D. Koev. Epidemiology of diabetes mellitus in Bulgaria.- *Biomed. Rev.*, **5**, 1996, 57-63.
7. The Microalbuminuria Captopril Study Group. Captopril reduces the risk of nephropathy in IDDM

patients with microalbuminuria.- *Diabetologia*, **39**, 1996, No 5, 587-593.

8. Penno, G., N. Chaturvedi, et al. Effect of ACE gene polymorphism on progression of renal disease and the influence of ACE inhibition in IDDM patients. Findings from the EUCLID randomized controlled trial.- *Diabetes*, **47**, 1998, 1507-1511.
9. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.- *Diabet. Care*, **20**, 1997, 1183-1197.
10. Rudberg, S., R. Osterby. Decreasing glomerular filtration rate-an indicator of more advanced diabetic glomerulopathy in the early course of microalbuminuria in IDDM adolescents?- *Nephrol. Dial. Transplant.*, **12**, 1997, No 6, 1149-1154.
11. Yip, J. M., S. L. Jones, M. J. Wiseman. Glomerular hyperfiltration in the prediction of nephropathy in IDDM: a 10-year follow-up study.- *Diabetes*, **45**, 1996, No 12, 1729-1733.