THE ROLE OF “BORDERLINE ALBUMINURIA” IN THE EVOLUTION OF INITIAL DIABETIC NEPHROPATHY

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ABSTRACT

In the last few years, all scientific studies and researchers are focused on detecting the earlier manifestations of chronic diseases' complications. In diabetics with “borderline albuminuria” (BAU), the protein excretion is slightly above the upper limits of normal albuminuria. They are often neglected by general practitioners and specialists, although they represent an important group for studying the initial renal injuries and are potentially suitable for angiotensin-converting enzyme inhibitors' (ACEIs) treatment. *Aim of the study:* an assessment of the natural evolution of BAU for a 10-years period concerning its role in the initial renal injuries in diabetics. *Patients and methods:* In a long prospective study, we examined regularly 109 type 1 diabetics with normoalbuminuria at the beginning. The albumin excretion was measured by immuno-turbidometry (Cobas mira plus) with Randox tests in 6-months intervals together with HbA1c, creatinine clearance and blood pressure. *Results:* In 21,1% of diabetics we found “borderline albuminuria” and 21,74% of them after the 5th year developed microalbuminuria with cumulative index of 0,91% annually. The patients' risk factors with significant importance were: bad metabolic control, “high-normal” hypertension and familiar predisposition to hypertension. *Conclusions:* We found that the borderline albuminuria plays an important role in the initial diabetic nephropathy, because more than 1/3 of the progressive BAU patients were with DM duration less than 5 years. As the blood pressure was a significant factor for progression of borderline- to micro-AU, the problem is *not whether to start treatment with ACEIs* in such patients and *when to start treatment*. Our patients with borderline albuminuria were suitable for ACEIs, because they had also some significant risk factors for the progression into early diabetic nephropathy.

Keywords: borderline albuminuria, microalbuminuria, initial diabetic nephropathy, ACEIs

BACKGROUND

All scientific studies in the last few years are focused on detecting the earlier stages of chronic diseases' complications. Diabetes Mellitus is a metabolic disorder in man, which has a great socio-economic significance for the preventive medical cares in general practice and for the healthcare system as a whole. Sometimes, diabetic patients with so called “borderline albuminuria” are neglected by general practitioners, because their protein excretion is at the upper limits of normal albuminuria. They are a key group for studying the initial diabetic nephropathy and angiotensin-converting enzyme inhibitors' application in young diabetics.

DEFINITIONS

1. BORDERLINE ALBUMINURIA - A mean overnight albumin excretion rate of 7.2 - 20 micrograms/min on one of three consecutive timed collections

2. MICROALBUMINURIA:

A. Intermittent: overnight albumin excretion rate of 20-200 micrograms/min on one of three consecutive timed collections

AN ASSESSMENT SCALE FOR ALBUMIN EXCRETION

0 µg/min	10 µg/min	20 µg/min	200 µg/min
↓	↓	↓	↓
Normal-AU	Bordeline-AU	Micro-AU	Macro-AU
(< 20 µg/min)	(10 - 20 µg/min)	(20 - 200 µg/min)	(> 200 µg/min)

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- B. *Persistent*: a minimum of three of four consecutive overnight albumin excretion rates of greater than 20 micrograms/min.

AIM OF THE STUDY

An assessment of the clinical significance of "borderline albuminuria" for the evolution of initial diabetic nephropathy in general practice.

TASKS IN THE STUDY

1. To determine the natural history of "borderline" increases in albuminuria in adolescents with type 1 DM in a long prospective study
2. To indicate the factors which are associated with the progression to persistent microalbuminuria
3. To assess the clinical significance of "borderline" albuminuria in general practice

STUDY DESIGN

A 10-years prospective study involving 109 adolescent diabetics, 65 boys and 44 girls from 39 general medical prac-

tices with mean age 13.9 ± 2.85 years and duration of DM 4.8 ± 3.15 years. From all these patients we found 23 normotensive adolescent diabetics with borderline albuminuria and they were followed prospectively at 6-months intervals and the following indexes have been measured:

1. *Metabolic control (HbA1c)*
2. *Albumin excretion (microgram/min)*
3. *Creatinine clearance (GFR)*
4. *Mean arterial pressure (mm Hg)*
5. *Dietary factors*
6. *Smoking*

METHODS

We used in our analysis the following methods of investigation:

I. METABOLIC CONTROL

HbA1c - MEIA method

II. ALBUMIN EXCRETION

a) *Microalbuminuria (MAU) - semi-quantitative methods* (Micral, Microbumintest)

b) *Immunoturbidometry - quantitative method* (ranges: 9.7 - 206.2 mg/l)

III. GLOMERULAR FILTRATION RATE (GFR)

Tabl.1. Comparission between borderline- and normo-albuminuric young diabetics in the study

INDEXES	Patients with borderline AU - 23 of 109 (21.1%)		Patients with normal AU	P-coefficient: Pts with progressive borderline AU versus pts with normal AU
	Progressors	Non-progressors		
Number	5 / 23 (21,74%)	18 / 23 (78,26%)	86 (78,90%)	
Sex	2♂ : 3♀	10♂ : 8♀	58♂ : 28♀	P < 0. 2
Age (years)	14,9 ± 2,9	13,3 ± 2,7	13,4 ± 2,15	P < 0. 04
Duration of DM	5,8 ± 3,28	5,3 ± 3,15	3,75 ± 3,01	P < 0. 001
Normo-AU (A/C ratio)	2,42 ± 0,3	2,1 ± 0,1	2,15 ± 0,42	P < 0. 2
Normo-AU (µg/min)	19,36 ± 1,3	16,8 ± 0,99	17,2 ± 1,2	
MAP (mm Hg)	86,56 ± 5,9	80,76 ± 5,1	80,46 ± 5,4	P < 0. 01
HbA1c (%)	10,1 ± 2,25	8,45 ± 2,1	8,29 ± 1,60	P < 0. 001
Retinopathy	3 (13,04%)	1 (4,35%)	13 (15,12%)	P < 0. 06
Polyneuropathy	4 (17,4%)	9 (39,13%)	31 (36,04%)	P < 0. 2
Family history of hypertension	5 (21,74%)	3 (13,04%)	18 (20,93%)	P < 0. 001

- % is the share of the involved patients in the group
- All indexes are estimated as mean values for the whole period
- Albuminuria is estimated as albumin / creatinine ratio in urine (A/C ratio)

Abbreviation: Mean arterial pressure (MAP) = diastolic AP + 1/3 (systolic – diastolic AP) in mm Hg

- a) standard (4h) creatinine clearance
- b) Tc-99m DTPA clearance, "DIACAM", Siemens

IV. MEAN ARTERIAL PRESSURE

Diastolic + 1/3 (Systolic - Diastolic) AP in mm Hg

V. DIETARY REGIMENTS

Protein and sodium intakes

VI. SMOKING HABITS

RESULTS AND DISCUSSION

The results from the observation were structured and shown in the following tabl.1:

RESULTS

The results according to the different parameters in the study were:

1. PROGRESSION TO MICROALBUMINURIA:

- 23 of 109 patients (21.1%) with normo-albuminuria were with borderline albuminuria at the entry of the study
- 5 of them (21.74%) were "progressors" and developed persistent microalbuminuria over 31 (25-55) months

2. METABOLIC CONTROL:

- The most significant risk factor for BAU and the consequent MAU in adolescent diabetics is the poor glycemic control.
- HbA1c in diabetics with borderline AU, who are "progressors" is 10.1% versus 8.45% in non-progressors and 8.29% in patients with normoalbuminuria ($p < 0.001$).

3. DURATION OF DM:

- Duration of DM among "progressors" was higher – 5.8 years versus 3.75 years in normoalbuminuric diabetics
- No statistical significance in DM duration was found between "progressors" and "non-progressors"
- *Important finding is that over 1/3 of all patients with "borderline albuminuria" have DM duration under 5 years!*

4. MEAN ARTERIAL PRESSURE:

- All patients remained normotensive during the study
- "Progressors" to persistent microalbuminuria had higher mean arterial pressure than "non-progressors" - 86.56 mm Hg versus 80.46 mm Hg ($p < 0.01$)

5. NO DIFFERENCE WAS FOUND IN:

- Glomerular filtration rate
- Dietary protein and sodium intakes
- Smoking prevalence

DISCUSSION

The problem when or even whether to start treatment with ACEIs in young diabetics with microalbuminuria and normal blood pressure still exists in general practice of some countries!!!

In patients with borderline albuminuria a severe, regular and more frequent control of albumin excretion is needed, because after some years they become suitable even for ACEI treatment and this moment may be missed by their general practitioners.

In our study, normoalbuminuric patients have additional risk factors with great importance for progression of the initial diabetic renal involvement.

Important finding - some adolescent pts with borderline AU have DM duration less than 5 years!

The fact that 21.1% of young diabetics in our study with normal albumin excretion have a "borderline albuminuria" show that these patients *require a special attention in general practice to minimize associated factors of poor metabolic control and higher mean blood pressure in the development of incipient nephropathy!*

Our data suggest that we are right to recommend adolescent diabetics an earlier screening for borderline AU and other microvascular complications no matter the age of the patients, the beginning of puberty and DM duration!

CONCLUSIONS

1. There is a relatively high rate of progression to persistent microalbuminuria in pubertal adolescents with borderline increases in albuminuria and duration greater than 4 years!
2. 21,1% of our young normotensive normo-albuminuric diabetics have borderline albuminuria (23/109 patients)
3. Approximately 1/5 of them (21,74%) after the 5-th year of the study developed persistent microalbuminuria
4. The main risk factors for progression of borderline albuminuria to persistent microalbuminuria were:
 - A. *Bad metabolic control*
 - B. "High-normal" hypertension
 - C. Familiar predisposition to hypertension
5. We recommend an early detection of initial diabetic nephropathy in young diabetics in general practice, even in childhood and especially in puberty, which is a risk period for its manifestation.
6. We recommend to general practitioners a severe, regular and more frequent control of albumin excretion and the other risk factors in diabetics with borderline albuminuria

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