

CHRONIC COMPLICATIONS OF TYPE 1 DIABETES MELLITUS IN CHILDREN

Maricela Cobuz^{1,✉}, Claudiu Cobuz²

¹ “Gr. T. Popa” University of Medicine and Pharmacy Iasi

² Center of Diabetes, Nutrition and Metabolic Diseases Suceava

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Abstract

Objectives: To evaluate the frequency of chronic complications and identify the predicting factors that may be used for their early detection. **Material and Method:** The research group included 144 T1DM children with disease duration > 5 years or disease onset during puberty. Complication screening included: full ophthalmologic examination, UAE level determination, diabetic neuropathy assessment. **Results:** Retinopathy prevalence was 12.5 %. Factors associated with retinopathy were: hyperglycemia, duration of diabetes and dyslipidemia. Microalbuminuria was detected in 23 patients (15.97%) and correlated with HbA1c or insulin therapy regimen. Diabetic neuropathy prevalence (45.8%) was studied in relation to UAE. Peripheral somatic neuropathy was significantly correlated with the diabetic nephropathy stage. Autonomic neuropathy was detected only in 13.8% patients, yet its prevalence increased with the increase in UAE. **Conclusions:** Chronic diabetic complications are relatively less frequent as compared to adults, yet their evolution is distinct due to the age-specific characteristics.

key words: T1DM, children, chronic complications

Background and Aims

The increasing prevalence of type 1 diabetes mellitus (T1DM) in children and its associated micro- and macro-vascular chronic complications are one of the major public health issues. The medical, social and economic impact of this disease is huge. T1DM complications are triggered by chronic hyperglycemia – the main cause – accompanied by non-specific risk factors, either associated with diabetes or independent

of it, as well as by a very likely genetic predisposition, which has not been sufficiently elucidated yet.

T1DM in children is a serious condition, which radically changes the life of the family, and requires special attention, considerable expenses, and physical and emotional efforts from the child, his/her parents, healthcare units and the society as a whole. The physiological and psychological specificity of growing children, their low immunity or the changes occurring during their puberty

✉ PhD Candidate in Pediatrics, Mobile phone: +40748 373140;
corresponding author e-mail: maricelacobuz@yahoo.com

determine the severity of evolving diabetes mellitus and render disease compensation efforts difficult.

T1DM in children and adolescents has a much more severe evolution and faster chronic complication development [1]. The quality of life of a T1DM patient diagnosed during childhood depends on the proper diagnosis, treatment and complications prophylaxis.

The importance of specific chronic complications monitoring and prophylaxis in T1DM children and adolescents indicates the need for a more thorough analysis of this matter.

Given the specificity of T1DM evolution in children, our research aimed to evaluate the frequency of chronic complications in a group of T1DM children as well as to identify the main predicting factors that may be used for the early detection of these specific complications.

Material and Method

The research was conducted on 144 T1DM children, who were registered in the Diabetes, Nutrition and Metabolic Diseases Centers of Iași and Suceava, with diabetes duration longer than 5 years or in whom the disease onset occurred during puberty regardless of the disease duration. The screening of specific T1DM chronic complications consisted of:

- **full ophthalmologic examination** – including: visual acuity testing; intraocular pressure determination (in order to detect a possible glaucoma); iris examination (for rubeosis iridis), lens examination (for cataract), pupil dilation and fundus ophthalmoscopy. The International Clinical Diabetic Retinopathy and Diabetic

Macula Edema (DME) Disease Severity Scale proposed five levels of DR severity – none, mild, moderate, severe and proliferative; in the presence or absence of DME [2].

- **urinary albumin excretion (UAE) level** determination. The first step in the screening and diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample, collected either as the first urine in the morning or at random, for example, at the medical visit. This method is accurate, easy to perform, and recommended by American Diabetes Association guidelines [3]. If a urinary infection was excluded, the urine sample was sent to the laboratory for the quantitative determination of UAE using the albumin/creatinine ratio method, in order to prevent any errors due to urine dilution or concentration. Albumin/creatinine ratio determination in a urine sample prevents errors due either to diuresis variations or to physical effort. The method sensitivity varies between 88% and 100%, with a very good correlation between the results of this method and those of 24h urine sampling [4]. All abnormal tests were confirmed in two out of three samples collected over a 3- to 6-month period, due to the known day-to-day variability in UAE [5]. Diabetic nephropathy has been categorized into stages based on the values of urinary albumin excretion (UAE): microalbuminuria and macroalbuminuria. In this study we used the cutoff values adopted by the American Diabetes Association for the diagnosis of micro- and macroalbuminuria [3].

- **diabetic neuropathy** is the most common diabetes mellitus complication and it occurs early in the evolution of the disease. About 20% of T1DM patients suffer from neuropathy with clinical manifestations after 10 years of evolution of the disease [6]. In our study group, diabetic neuropathy assessment tests consisted of determining pain sensitivity – using a needle, tactile sensitivity – using a cotton swab, and vibratory sensitivity – using a calibrated tuning fork. The tests were bilateral and symmetric, comparing proximal and distal areas. Osteotendinous reflexes were also measured. The presence of autonomic diabetic neuropathy was extracted from anamnesis data (children's charts).

In addition, we determined the following biochemical parameters:

- **HbA1c** – The determination was made using a gas chromatography Analyzer DiaSTAT cation exchange capacity of low pressure combined with gradient elution separation of hemoglobin subtypes. Separate fractions of hemoglobin are monitored by measuring the absorption at 415 nm.
- **HDL and LDL/VLDL Cholesterol** – The assay is based on the enzyme driven reaction that quantifies both cholesterol esters and free cholesterol. Cholesterol esters are hydrolyzed via cholesterol esterase into cholesterol, which is then oxidized by cholesterol oxidase into the ketone cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide is then detected with a highly specific fluorescence probe.

Statistical analysis

Processing of medical data obtained has been performed with the SPSS 17 specialized software. The Student t-test was used to compare two groups if the distribution was approximately normal and the variances equal. The Mann-Whitney U-test was used when the distribution was skewed and Fisher's exact test to compare categorical data. In the correlation analyses, Pearson's or Spearman's correlation coefficient was given. A p -value <0.05 was considered significant.

Results

Of the 144 patients, 80 were female (55.55%) and 64 male (44.44%); 88 came from the urban area (61%) and 56 from rural areas (39%). The diabetes onset age was: 0-1 years in 6 cases (4.16%); 2-6 years in 38 cases (26.38%); 7-10 years in 39 cases (27.08 %); 11-16 years in 61 cases (42.36%).

Retinopathy prevalence was 12.5 % (18 cases). Non-proliferative *diabetic retinopathy* lesions – small aneurisms, haemorrhage, big or small exudates – were detected in 16 of the 144 patients under survey. In 2 of the 18 cases, retinopathy was found to be proliferative. All retinopathy patients had a poor glycemic control as expressed by the HbA1c levels: 5 cases HbA1c = 8.5–9.5 %; 9 cases HbA1c = 9.5-10.5 % and in 4 cases HbA1c > 10.5 %

The parameters associated with diabetic retinopathy are presented in [Table 1](#).

Microalbuminuria was identified in 23 patients (15.97%) as shown in [Figure 1](#).

The HbA1c values differed significantly according to the UAE levels ($F=3.62$, $p=0.0277$, 95%CI). Thus, its value is considerably higher in macroalbuminuria

cases ($p=0.044$) and microalbuminuria ($p=0.037$) cases (9.6% and 9.5% respectively), as compared to the values recorded in normal albuminuria cases (8.9%). No significant

HbA1c differences were found between macroalbuminuria and microalbuminuria cases ($p=0.9109$, 95% CI). (Figure 2)

Table 1. Clinical and paraclinical parameters in patients with diabetic retinopathy.

Parameter	Group 1 (without retinopathy)	Group 2 (with retinopathy)	P
Disease duration	5.7±1.3 years	8.3±2.5 years	P<0.05
HbA1c	7.25 ± 1.35%	9.62 ± 1.48%	P<0.05
Total cholesterol	188±11.7 mg/dl	212±22.5 mg/dl	P<0.05
Triglycerides	98±16.7 mg/dl	160±21.7 mg/dl	P<0.05
Gender (male %)	55%	58%	ns

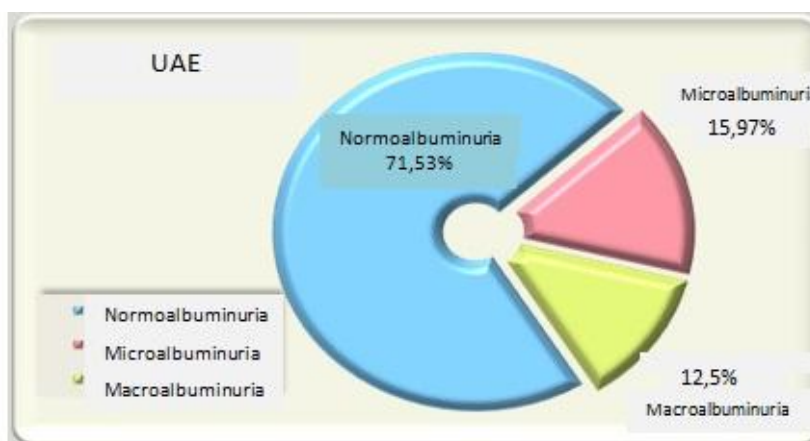


Figure 1. Case distribution according to UAE levels.

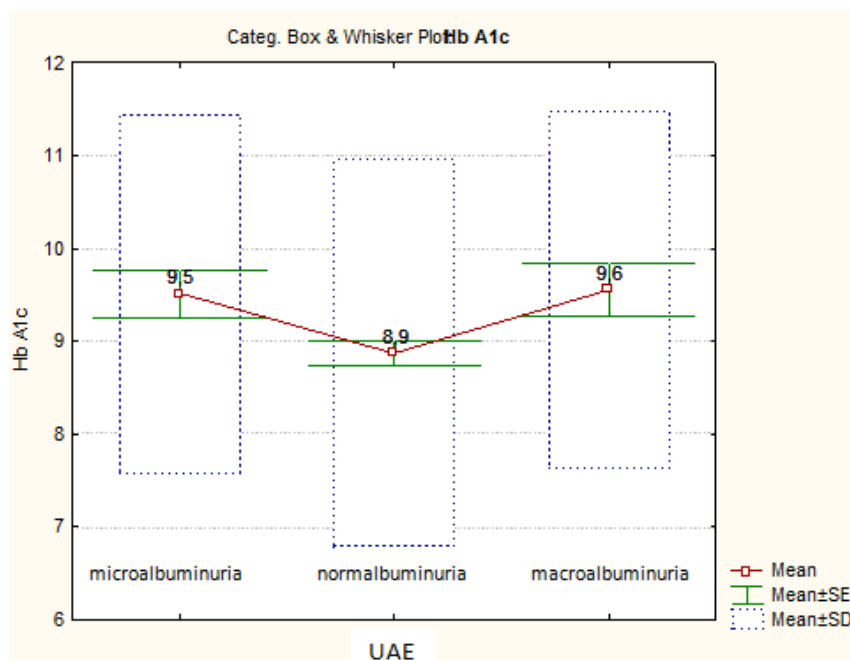


Figure 2. Mean HbA1c in different UAE groups.

In order to determine the influence of the insulin therapy regimen on UAE, we divided the patients in two groups depending on the number of insulin shots per day:

- **group 1** – 2 shots of insulin/day, including 30 patients
- **group 2** – 3-4 shots of insulin/day, including 114 patients

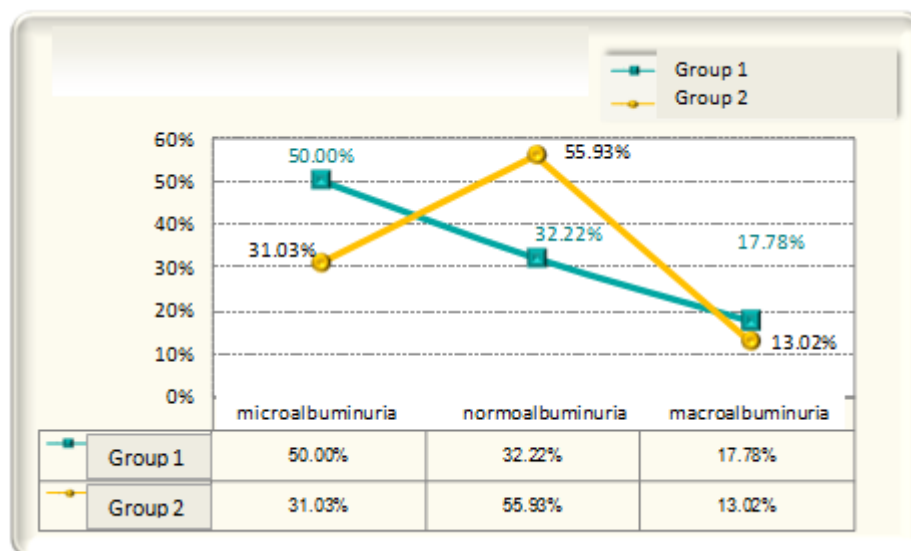


Figure 3. UAE according to the insulin treatment scheme.

Table 2. Peripheral diabetic somatic polineuropathy prevalence according to UAE.

Urinary protein excretion	Peripheral neuropathy	
		P value
Normoalbuminuria	36.8 %	ns
Microalbuminuria	65.3 %	P<0.05
Macroalbuminuria	76.2 %	P<0.05

The level of UAE in the two groups is reported in [Figure 3](#). Comparison of the UAE levels according to the insulin therapy regimen enabled us to conclude that there is a significant association ($\chi^2=9.7$, $p=0.0075$, $p<0.05$, 95%CI) between the level of UAE and the number of insulin shots. This is also supported by the result of the Spearman rank correlation testing ($r=0.54$, $p=0.029$, 95%CI), which reveals significant microalbuminuria in patients undergoing 2 shots of insulin/day insulin therapy.

Diabetic neuropathy screening was conducted on the same group of patients and its prevalence was analyzed according to the

UAE levels. On the whole study group, the prevalence was 45.8% (66 patients). In the cases we analyzed, we found that peripheral somatic polineuropathy exhibited a statistically significant correlation with the diabetic nephropathy stage ($\chi^2=27.92$, $p<<0.05$, 95%CI), being diagnosed in 76.2% of patients with macroalbuminuria in comparison with 36.8% of normoalbuminuria patients. ([Table 2](#))

The analyzed data revealed an increase in the number of patients suffering from peripheral polineuropathy cases with the increase of the UAE, being more common in patients with more advanced renal conditions.

Autonomic neuropathy is less common than peripheral neuropathy in children with diabetes mellitus and microalbuminuria and it usually occurs after a long evolution of diabetes. Autonomic neuropathy was detected in only a small number of selected patients – 20 (13.9%). Please note that several forms of autonomic neuropathy were often detected in the same patient. Cardiovascular neuropathy

(tachycardia at rest), followed by hypoglycemia unawareness and digestive neuropathy occurred most frequently. (Table 3)

Autonomic neuropathy was found to occur more frequently in microalbuminuria patients, the differences being statistically significant. (Table 4)

Table 3. Autonomic neuropathy prevalence in the study group.

Autonomic neuropathy	The number of patients
Cardiovascular	8
Digestive	3
Hypoglycemia unawareness	7
Bladder	2
Total	20

Table 4. Autonomic neuropathy prevalence according to UAE.

Urinary protein excretion	Autonomic neuropathy	
		P value
Normoalbuminuria	5.1 %	ns
Microalbuminuria	26.5 %	P<0.05
Macroalbuminuria	16.6 %	P<0.05

We found that the higher the UAE, the higher the number of autonomic neuropathy patients. Nevertheless, as compared to retinopathy and somatic peripheral neuropathy, the association of autonomic neuropathy with UAE is weaker.

Discussions

Many international studies, such as the Diabetes Control and Complications Trial (DCCT) in T1DM, or the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes mellitus, have established that chronic hyperglycemia leads to tissue damage in diabetic patients. This phenomenon is modulated both by genetic determinants of individual susceptibility, and by independent

enhancing factors such as hypertension and hyperlipidemia.

Diabetic retinopathy is the most severe ocular manifestation of diabetes. Its prevalence depends on the disease duration as it occurs in very few patients with diabetes for less than 10 years, whereas almost all patients with a history of diabetes longer than 20 years exhibit some degree of retinopathy [7]. In addition retinopathy incidence is ~50% in patients in whom diabetes onset occurred before the age of 30, and to ~90% in those with onset after the age of 30. Complication occurrence after less than 5 years of disease evolution or before puberty is extremely uncommon [7]. In our study retinopathy prevalence was 12.5 % (18 cases). The parameters associated with diabetic

retinopathy were disease duration, HbA1c and dyslipidemia. Duration of diabetes is the strongest factor determining retinopathy prevalence. The most important systemic factor associated with increased risk of DR is glycemic control, followed by control of blood pressure and blood lipids. Adequate glycemic control, i.e. HbA1c value below 7%, delays diabetic retinopathy occurrence by years, whereas patients with inadequate glycemic control are exposed to retinopathy risks shortly after diagnosis setting [8].

Diabetic renal disease is a major health problem. Thus, actually 44.9% of hemodialysis patients are diabetic nephropathy patients. Their survival rate to 3 years is only 40%, and diabetes-related renal diseases kill 600.000 patients each year [9]. Diabetic nephropathy patients are detected based on UAE rates (microalbuminuria / albumin/creatinine ratio). Microalbuminuria occurrence marks the irreversibility of the renal damage.

In our study prevalence of microalbuminuria was 15.97%. The mean incidence of microalbuminuria mean T1DM patients is higher after 5 years from diagnosis, increasing by 3-6% per year [10], thus reaching a prevalence of 30-44% after 10 years. Clinical proteinuria is rare during the first 10 years of T1DM evolution, then its incidence increases and reaches a peak of 2-3% per year after 13-20 years of evolution; after more than 20 years of T1DM evolution, proteinuria incidence drops again and remains about 0.5% per year [11-14]. Insulin therapy itself may influence the evolution of the glomerular filtration rate (GFR) by retention of sodium as some studies have suggested [15].

It has been recently shown that microalbuminuria is an important independent risk marker of both proliferative diabetic retinopathy [16] and hypertension (mean increase by 3 mmHg/year). Also, microalbuminuria values exceeding 100mg/24 hours are associated with the progressive decrease of the GFR (by 3-4 ml/min/year) and they become strongly predictive for proteinuria and chronic kidney failure occurrence [17].

Diabetic neuropathy is only partially caused by vasa nervorum damage and hence it cannot be included in the category of pure microangiopathic diabetic complications [18]. The most common form of diabetic neuropathy is distal symmetric sensitive polyneuropathy. Most of its manifestations are chronic and progressive. Since diabetic micro- and macroangiopathic complications cluster in patients, it is the patient with diabetic nephropathy who is particularly in need of treatment for neuropathic pain. In this study there was a statistically significant correlation between neuropathic symptoms (mostly pain) and nephropathy.

One major finding of this study is that diabetic nephropathy and autonomic neuropathy frequently coexist in children with T1DM. The epidemiology and natural history are still uncertain, largely because of confusion regarding the definition and measurement of this disorder. The best evidence suggests that near normal control of blood glucose in the early years after onset of diabetes may delay the development of clinically significant nerve impairment, and therefore, children and adolescents with diabetes are critical targets for primary prevention of this complication [19].

Conclusions

This study demonstrated that chronic diabetes mellitus complications in children are relatively less numerous as compared to the adults, yet their evolution is distinct due to the age-specific physiologic characteristics. The frequency of these complications is high in patients with precarious metabolic control. Thus, secondary prevention is vital in the care

provided to these patients. Also, the study has shown that a significant proportion of patients with diabetic nephropathy are free of neuropathy, but the full explanation for their protection from neuropathy is unclear.

Active screening should be performed according to standard recommendations and accompanied by an adequate therapeutic approach designed to support attaining the recommended HbA1c targets.

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