Metabolic control and its variability are major risk factors for microalbuminuria in children with type 1 diabetes

Kontrola glikemii i jej zmienność głównymi czynnikami ryzyka mikroalbuminurii u dzieci chorych na cukrzycę typu 1

Joanna Nazim[1], Wojciech Fendler[2], Jerzy Starzyk[1]

[1]*Paediatric Endocrinology Department, Jagiellonian University, Medical College, Kraków, Poland*
[2]*Department of Paediatrics, Oncology, Haematology and Diabetology, Medical University of Lodz, Poland*

Abstract

Introduction: To assess in a prospective study the course and the predictors of microalbuminuria in children and adolescents with type 1 diabetes.

Material and methods: 438 children and adolescents who developed diabetes in the years 1985–2004 were followed for 9.2 ± 3.4 years from the diagnosis. Microalbuminuria was assessed on the basis of timed overnight urine collections performed once per year. Variability of glycated haemoglobin was expressed as a coefficient of variation (%) calculated by dividing standard deviation (adjusted for the number of measurements) by mean of HbA_{1c}.

Results: Microalbuminuria was noted in 99 patients (22.6%) after 8.27 ± 3.3 years of diabetes. In 29 individuals (6.6%), microalbuminuria was persistent. The prevalence of microalbuminuria was not dependent on the period of diabetes diagnosis. During follow-up, 17 (58.6%) patients with persistent MA reverted to normoalbuminuria. Children without any episodes of microalbuminuria had significantly lower HbA_{1c} variability (8.44%; 95% CI 7.81–9.08%) than those with one (10.28% 95% CI 9.10–11.47%; p = 0.007). The difference of HbA_{1c} variability between patients with and without microalbuminuria persisted after correction by mean HbA_{1c} (p = 0.04). Risk factors for ever developing microalbuminuria during the observation period in multivariate analysis included: mean HbA_{1c} (HR [95% CI]: 1.17 [1.00–1.37; p = 0.05]) and its variability (1.04 [1.00–1.07]; p = 0.05), insulin dose (HR per 0.1 unit*kg^{-1}*day^{-1}: 0.87 [0.79–0.96]; p = 0.005), presence of arterial hypertension (1.63 [1.07–2.49]; p = 0.02), and age at onset of diabetes (1.15 [1.08–1.21]; p < 0.0001).

Conclusions: Children who develop microalbuminuria are characterised by poorer and more variable metabolic control, hinting at the importance of interventions aimed at both improvement and stabilisation of HbA_{1c} levels. **(Endokrynol Pol 2014; 65 (2): 83–89)**

Key words: microalbuminuria; diabetic nephropathy; glycated haemoglobin variability

Streszczenie

Wstęp: Mikroalbuminuria jest wskaźnikiem wczesnej fazy nefropatii cukrzycowej i czynnikiem ryzyka jej progresji, równocześnie obserwuje się znaczny odsetek samoistnej normalizacji albuminurii. Celem wieloletniego prospektywnego badania była ocena historii naturalnej i czynników ryzyka rozwoju mikroalbuminurii u dzieci i młodzieży z cukrzycą typu 1.

Materiał i metody: Przez 9,2 ± 3,4 lat od rozpoznania choroby obserwowano 438 dzieci, które zachorowały na cukrzycę w latach 1985–2005. Mikroalbuminurię oceniano w nocnych zbiórkach moczu wykonywanych każdego roku. Zmienność hemoglobiny glikowanej (HbA_{1c}) wyrażono współczynnikiem zmienności (%) obliczonym jako iloraz odchylenia standardowego (adjustowanego do liczby pomiarów) i średniej HbA_{1c}.

Wyniki: Mikroalbuminurię stwierdzono u 99 (22,6%) chorych po 8,27 ± 3,3 latach cukrzycy. U 29 (6,6%) dzieci mikroalbuminuria była obecna przez co najmniej 2 kolejne lata. Częstość mikroalbumiurii nie zależała od okresu rozpoznania cukrzycy. W czasie dalszej obserwacji u 17 (58,6%) badanych albuminuria uległa normalizacji. U dzieci bez epizodu mikroalbuminurii wykazano znamiennie mniejszą zmienność HbA_{1c} (8,44%; 95% CI 7,81–9,08%) w porównaniu z chorymi z mikroalbuminurią (10,28% 95% CI 9,10–11,47%; p = 0,007). Różnica ta była nadal obecna po uwzględnieniu średniej HbA_{1c} (p = 0,04). Czynnikami ryzyka rozwoju mikroalbuminurii u dzieci w okresie wieloletniej obserwacji ujawnionymi w analizie wieloczynnikowej były: średnia HbA_{1c} (HR [95% CI]: 1,17 [(1,00–1,37; p = 0,05]), zmienność HbA_{1c} (1,04 [1,00–1,07]; p = 0,05), dawka insuliny (HR dla 0,1 j.*kg^{-1}*day^{-1}: 0,87 [0,79–0,96]; p = 0,005), nadciśnienie tętnicze (1,63 [1,07–2,49]; p = 0,02) i wiek zachorowania na cukrzycę (1,15 [1,08–1,21]; p < 0,0001).

Wnioski: Dzieci, u których rozwinęła się mikroalbuminuria charakteryzowały się gorszą i bardziej zmienną kontrolą metaboliczną cukrzycy stąd w leczeniu należy zwrócić uwagę zarwyano na poprawę jak i stabilizację HbA_{1c}. **(Endokrynol Pol 2014; 65 (2): 83–89)**

Słowa kluczowe: *mikroalbuminuria; nefropatia cukrzycowa; zmienność hemoglobiny glikowanej*

Joanna Nazim M.D., Ph.D., Paediatric Endocrinology Department, Jagiellonian University, Medical College, Wielicka St. 265, 30–663 Kraków, Poland, tel.: +48 12 658 12 77, fax: +48 12 658 10 05, e-mail: jnazim@wp.pl

Introduction

Microalbuminuria was initially regarded as the early marker of incipient diabetic nephropathy — stage III of diabetic kidney disease according to the Mogensen classification, which progressed to overt proteinuria and to end stage renal disease in up to 80% of patients in older studies and in 14% in more recent publications [1, 2]. Later, after the analysis of renal biopsy specimens, it was proved that diabetic patients with microalbuminuria may have advanced glomerulopathy and demonstrate renal function impairment. In these subjects, microalbuminuria is rather the indicator of existing structural kidney abnormalities and not only the risk marker [3]. This implicated the recommendations of different diabetes societies (including ISPAD guidelines) to introduce some treatment modalities i.e. ACE inhibitors or AT2 blockers to reduce microalbuminuria and delay or stop the progression of kidney disease [4–6].

On the other hand, some studies have reported the regression of microalbuminuria in more than 50% of adults and up to 50% of adolescents even without any intervention [2, 7–13]. Such natural course of the disease brings into question the necessity of pharmacological treatment implementation, especially in diabetic children and adolescents. There is no consensus on the frequency of diabetic nephropathy and microalbuminuria, as some reports evidence decreasing prevalence, while others show no improvement despite the intensification of diabetes control and pharmacological therapy [14–17]. Another important conclusion suggested on the basis of recent studies is that microalbuminuria is reversible even without any intervention. Thus, the predictive value of microalbuminuria as the marker of incipient diabetic nephropathy in children has also been challenged.

The aim of this prospective study was to assess the prevalence and the course of microalbuminuria in diabetic children and adolescents after a long follow-up period and establish the predictors of microalbuminuria development in a paediatric population. Secondly, we planned to evaluate the impact of variability of metabolic control on the risk of developing microalbuminuria in children with diabetes.

Material and methods

The study population included children and adolescents, inhabitants of the Malopolska region in Poland, who developed type 1 diabetes mellitus in the years 1985 to 2004. All patients with newly diagnosed type 1 diabetes (according to WHO criteria) were referred to the University Children's Hospital in Cracow and remained under the care of the Endo-crinology Department of the hospital thereafter. In our routine practice, each patient visited the diabetes clinic at least four times a year. At each visit, a physical examination was performed and weight, height, BMI, blood pressure, glycated haemoglobin (HbA_{1c}) and insulin dose were recorded. Additionally, starting two years after the diabetes onset, all patients underwent lipid profile examination, urine analysis (to exclude infection), screening for retinopathy and microalbuminuria once per year. The mean time of follow-up was 9.2 ± 3.4 years. The protocol of patients' evaluation was approved by the Jagiellonian University ethics committee and informed consent was obtained from patients and their parents.

Albumin excretion rate (AER) was estimated in timed, overnight urine collections (collection time 7–9 hours). In cases of AER value above the reference range for healthy children and adolescents ($> 10\,\mu g/min$), two additional urine collections were performed within 3–6 months. Microalbuminuria was defined as $AER \geq 20\,\mu g/min$ and $< 200\,\mu g/min$ in at least two samples obtained within the period of 3-6 months. Microalbuminuria observed in two or more consecutive years, i.e. two or more samples with $AER \geq 20\,\mu g/min$ in at least two years in a row, was regarded as persistent.

We identified 438 individuals with complete data records i.e.: anthropometric measurements, albuminuria and retinopathy screening, blood pressure, HbA_{1c}, total cholesterol, LDL, HDL and TG assessment who were followed annually for at least five years. The analysed endpoint was the first episode of microalbuminuria.

Urinary albumin was measured with double antibody radioimmunoassay (Immunotech, Prague, Czech Republic). The intra-assay coefficient of variation was $\leq 6.1\%$, and the inter-assay coefficient of variation was $\leq 10\%$.

HbA_{1c} was assessed with high performance liquid chromatography (Variant II Haemoglobin Testing System, BioRad Laboratories) until 2007, and immunoturbidimetry (Vitros 5.1 FS Chemistry System, Ortho Clinical Diagnostics, Johnson and Johnson) thereafter. Comparison of both methods revealed a correlation coefficient r = 0.96. To convert values obtained by different methods, the following equation was used: Variant = 1.5685 + 0.74776 Vitros. Reference range for HPLC method was: 4.5–6.1%. The assay was DCCT-aligned.

Lipids: serum total cholesterol, LDL, HDL cholesterol and triglycerides were measured enzymatically in samples collected in fasting conditions using an autoanalyser (Vitros 5,1 FS Chemistry System, Ortho Clinical Diagnostics, Johnson and Johnson), LDL cholesterol was determined directly.

Blood pressure was measured with a standard mercury sphygmomanometer in patients seated, after

10–15 minutes of rest. Patients with blood pressure > 95th percentile for sex, height and age were diagnosed with arterial hypertension (HA). Percentile tables from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents were used [18].

BMI z-score was calculated using Polish national data [19].

Statistical analysis

Continuous variables entering the analysis were mean values of each analysed parameter computed using baseline values and all subsequent measurements until reaching the endpoint or the end of observation (transfer of the patient to an adult diabetology clinic). Variability of HbA_{1c} was expressed as coefficients of variation (CV) computed as (Average/ /Standard Deviation)*100%. In order to circumvent the dependence of SD upon the number of measurements, we used the correction [20]. The presence of HA at baseline assessment was used in the analysis due to subsequent different therapeutic approaches and an inability to determine actual compliance to pharmacological treatment. As the first line of hypertension management, nonpharmacological intervention was recommended, and in cases of no improvement ACE inhibitors were introduced. Statistical analysis was performed using a two stage approach. Initial univariate analysis was used to screen for variables likely to be associated with the endpoint (microalbuminuria) occurring for the first time during the observation period. To do so, we used univariate Cox regression analysis to select variables with a p value < 0.15. Those that met this criterion entered a multivariate backward stepwise model building procedure in search of one with a p value lower than 0.05 considered as statistically significant. Statistica 10.0 package (Statsoft, Tulsa, OK, USA) was used for statistical analysis.

Results

General characteristics of the study group are presented in Table I.

Out of 438 patients, 99 (22.6%) developed microalbuminuria after 8.27 ± 3.3 years of diabetes. Persistent microalbuminuria was found in 29 (6.6%) participants, 19 boys and ten girls. In 60 (13.7%) patients, microalbuminuria was transient and reverted to normal range after one year and in ten (2.3%) subjects microalbuminuria was intermittent (Fig. 1). During the follow-up period of 9.2 ± 3.4 years (range 5–18.6 years), 17 (58.6%) patients with persistent microalbuminuria reverted to normoalbuminuria after
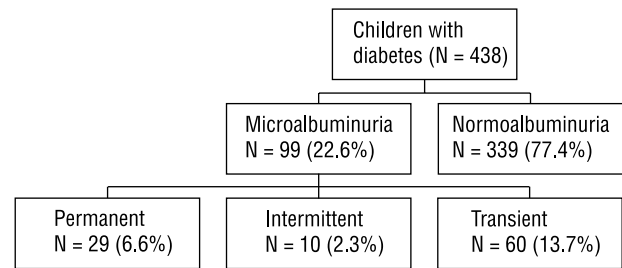

Figure 1. *The course of microalbuminuria in type 1 diabetic children*
Rycina 1. *Historia naturalna mikroalbuminurii u dzieci chorych na cukrzycę typu 1*

2–3 years and remained normoalbuminuric until the end of the observation (median 3 years, range 1–7). Of those individuals, only two patients received ACE-inhibitor because of concomitant hypertension. We found no difference in the mean HbA_{1c} before the development of microalbuminuria and during the follow-up period in patients with the normalisation of AER (8.25 ± 1.4 v. 8.28 ± 1.1%). In two subjects, microalbuminuria persisted for 4–5 years before discharge from the clinic, and in the remaining ten patients with persistent microalbuminuria there was no follow-up data available because they were transferred to an adult clinic after two years of microalbuminuria presence. None of the patients developed macroalbuminuria during the period of analysis. Background retinopathy was found in two patients with persistent microalbuminuria (including one who regressed to normoalbuminuria after two years). All but one patient with persistent microalbuminuria had low-grade values of AER (mean 39.1 ± 17.9 μg/min.). We did not observe a change in the prevalence of microalbuminuria dependent on the year of diagnosis of diabetes since 1985 (p = 0.53 for differences between patients with onset of diabetes in the years 1985–1990, 1991–1995 and 1996–2000).

Risk factors for the development of microalbuminuria

Univariate analysis allowed the authors to identify five variables potentially associated with the risk of developing microalbuminuria both in a time-dependent and time-independent manner. These variables included: age at onset of diabetes, presence of arterial hypertension at baseline, mean HbA_{1c} concentration throughout the observation period, variability of HbA_{1c} (CV), and mean insulin dose (Table I). Multivariate Cox regression analysis yielded a final model showing that factors independently associated with the risk of developing the first episode of microalbuminuria were: the presence of arterial

Table I. *General characteristics of the study group*
Tabela I. *Ogólna charakterystyka grupy badanej*

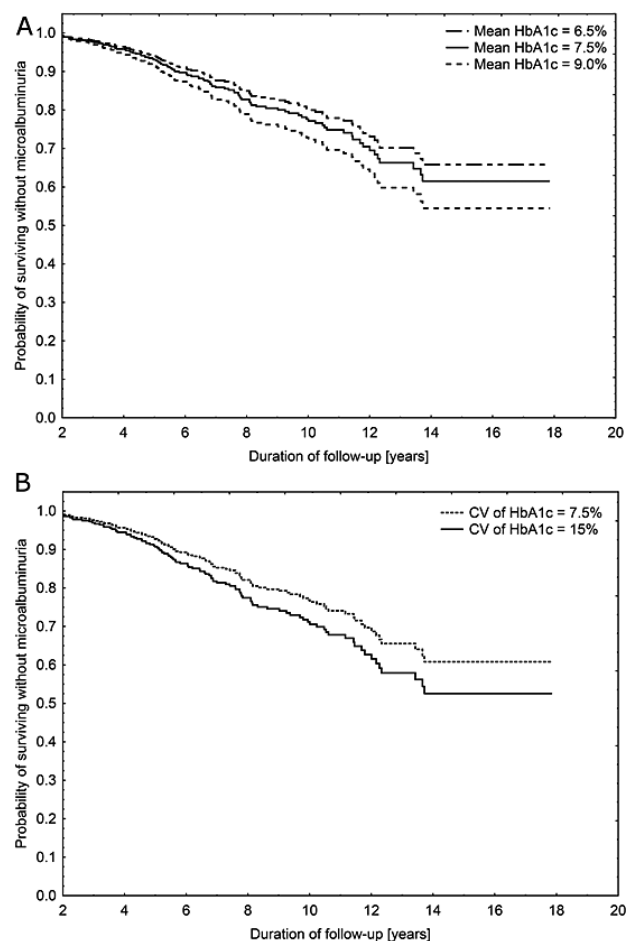| Variables	The whole study group	Children with MA	Children without MA	HR (95%CI)
Sex (M/F)	241/197	58/41	183/156	0.87 (0.58–1.29)
Age at onset (years)	8.77 ± 3.6	9.11 ± 3.63	8.68 ± 3.59	1.17 (1.10–1.23)*
Arterial hypertension at baseline (absent/367/71 present)		72/27	295/44	0.69 (0.46–1.03)*
BMI1 Z-score	−0.05 ± 0.67	−0.17 ± 0.63	−0.02 ± 0.68	0.76 (0.56–1.03)
Mean HbA$_{1c}$ (%)	7.89 ± 1.39	8.39 ± 1.71	7.95 ± 1.28	1.16 (1.00–1.34)*
CV of HbA$_{1c}$ (%)	8.86 ± 5.99	10.29 ± 5.93	8.44 ± 5.95	1.03 (1.00–1.07)*
Mean insulin dose (in 0.1 U/kg)	8.83 ± 2.21	8.47 ± 2.11	8.94 ± 2.23	0.85 (0.77–0.93)*
Mean Chol [mmol/L]	4.43 ± 0.76	4.43 ± 0.81	4.47 ± 0.74	0.92 (0.69–1.23)
Mean TG [mmol/L]	0.82 ± 0.31	0.81 ± 0.35	0.83 ± 0.30	0.79 (0.40–1.58)
Mean LDL [mmol/L]	2.46 ± 0.69	2.41 ± 0.73	2.48 ± 0.69	0.97 (0.70–1.35)
Mean HDL [mmol/L]	1.61 ± 1.96	1.49 ± 0.36	1.51 ± 0.35	1.00 (0.52–1.93)

Data is presented as means with standard deviations unless noted otherwise. MA — microalbuminuria; HR — hazard ratio; HbA$_{1c}$ — glycated haemoglobin; 95%CI — 95% confidence Interval. Variables marked with an *differed significantly with a p value < 0.15 and entered multivariate analysis

Table II. *Multivariate analysis results of factors affecting the risk of developing the first microalbuminuria episode*
Tabela II. *Wyniki analizy wieloczynnikowej czynników ryzyka rozwoju epizodu mikroalbuminurii*

	Parameter Estimate	P value	HR	HR (95% CI)
Age at onset	0.14	< 0.0001	1.15	1.08–1.21
Mean HbA$_{1c}$	0.16	0.04	1.18	1.00–1.38
Mean daily insulin dose	−0.14	0.005	0.87	0.79–0.96
CV of HbA$_{1c}$	0.04	0.049	1.04	1.00–1.08
HA	0.25	0.02	1.63	1.07–2.49

HR — hazard ratio; 95%CI — 95% Confidence Interval; HbA$_{1c}$ — glycated haemoglobin

Figure 2. *Estimated Kaplan-Meier curves for specific values of risk factors associated with microalbuminuria: glycated hemoglobin (**A**) and HbA$_{1c}$ variability (**B**)*
Rycina 2. *Krzywe Kaplana-Meiera dla wybranych wartości czynników ryzyka mikroalbuminurii: Hemoglobina glikowana (**A**) i zmienność HbA$_{1c}$ (**B**)*

hypertension, age at onset of diabetes, HbA$_{1c}$ level and its CV and insulin dose per kg (Table II). Kaplan-Meier curves computed for three HbA$_{1c}$ thresholds are presented in Figure 2A and the effect of HbA$_{1c}$ variability is shown in Figure 2B. Sex-standardised BMI did not maintain statistical significance in the multivariate model. Children without any episodes of microalbuminuria had significantly lower HbA$_{1c}$ variability (8.44%; 95% CI 7.81–9.08%) than those with one (10.28% 95% CI 9.10–11.47%; p = 0.007). The difference in HbA$_{1c}$ variability between patients with and without microalbuminuria persisted after correction by mean HbA$_{1c}$ (p = 0.04), regardless of the number of microalbuminuria episodes. No significant differences were noted between patients with one or more episodes of microalbuminuria (p = 0.95).

Discussion

We analysed the results of a long term prospective study of AER in a cohort of type 1 diabetic children and adolescents treated in a tertiary paediatric diabetes centre in Poland. The prevalence of microalbuminuria and persistent microalbuminuria in our patients was comparable to that reported in the current literature. The cumulative prevalence of any microalbuminuria in children was 9% to 25.7% and persistent microalbuminuria from 4.5% to 18% after up to ten years of diabetes [11–13, 21–23].

The data concerning the change in the frequency of microvascular complications in diabetic children during the previous 20 years is not consistent. Downie et al. [24], after analysing complications in adolescents stratified by four time periods, reported an initial declining rate of microalbuminuria from 1990 to 2000 which remained unchanged from 2000. This observation however was not confirmed by others [25]. According to Amin et al. [25], no change was shown in the frequency of any microalbuminuria in long term follow-up. These differences cannot be explained only by the change in the quality of diabetes control. In both the reports of Downie et al. and Amin and al., HbA_{1c} of their patients had unsatisfactory metabolic control (HbA_{1c} levels above 8%). But in the cohort described by Amin et al. no significant improvement was achieved during the follow-up, while Downie documented an initial significant decline of HbA_{1c} after the intensification of insulin therapy regimen. In our data, no change was found in the prevalence of any microalbuminuria and persistent microalbuminuria dependent on the year of diabetes diagnosis. Analysis of metabolic control in our centre expressed by HbA_{1c} values showed significant improvement during the last 15 years. Yearly mean HbA_{1c} decreased from 10.4% in 1990 to 7.4% in 2005 [26], which may partially explain the low frequency of persistent microalbuminuria in our patients which was mainly low-grade and the high rate of microalbuminuria regression compared to our previous observations [27].

Many factors, some of them potentially modifiable, may influence the development of microalbuminuria in children. The most important one is glycaemic control. Suboptimal values of HbA_{1c} are indicated in many papers as a risk factor of persistent microalbuminuria and diabetic nephropathy [11–13, 22, 28–30] and patients with microalbuminuria have usually worse diabetes control than subjects without this condition. Our data confirms the importance of diabetes control in the process of the development of microalbuminuria. Striving to achieve the best possible control of glycaemia from the onset of diabetes in children irrespective of age is fully justified. The availability of better tools for therapy and monitoring of diabetes enables attainment of this goal without the increased risk of hypoglycaemia [24]. Other predictive factors with conflicting data on their significance include: age at onset of diabetes [11, 12, 21, 22], duration of diabetes [12, 13, 22, 23], gender [13, 21], arterial hypertension [21, 22], dyslipidemia [22] and puberty [11, 13, 29, 31, 32]. In our patients, factors that significantly influenced the risk of microalbuminuria development, besides HbA_{1c}, were modifiable variables like the presence of hypertension at baseline and daily insulin dose. Higher insulin requirement is frequently linked to insulin resistance and accompanied by a higher BMI. The explanation of the beneficial effect of higher insulin supply in our patients may represent better adjustment of insulin doses to individual needs, all the more as our patients were not overweight.

The important finding is the high rate of the regression of persistent microalbuminuria in our cohort (at least 60%). We were not able to estimate the real reversibility rate of microalbuminuria because in the remaining 40% of our microalbuminuric patients, persistent microalbuminuria developed just before the transfer to the adult clinic and they were lost to longer follow-up. It should be underlined however, that the normalisation of AER did not depend on pharmacological intervention (data not shown). Only two patients were treated with ACE inhibitors because of concomitant increase of blood pressure. There is limited evidence that the use of ACE inhibitors in adolescents and children decreases the albumin excretion rate and reverses structural changes within the kidney [33]. The normalisation of increased AER in microalbuminuric patients may not correspond to the improvement of renal structural lesions [34]. On the other hand, decreased GFR rarely occurs in diabetic patients without preceding microalbuminuria [35].

There are several reports of a high rate of microalbuminuria regression in type 1 diabetic patients but a direct comparison of the results is not possible because of different durations of follow-up, definitions of microalbuminuria, and the inclusion into the analysis of patients with transient elevation of AER [7, 11, 12, 21]. Microalbuminuria in our patients was characterised by rather low intensity (below 100 μg/min) and short duration, which may explain the high rate of the normalisation. In some of them, elevation of AER might be triggered by puberty and regression of microalbuminuria was the consequence of the end of the pubertal period. Age at onset of diabetes was an independent risk factor for the development of microalbuminuria in our cohort of patients, which

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additionally underlines the importance of endocrine changes during the puberty period for the manifestation of microalbuminuria, even in diabetics with very short disease duration [36]. Factors which showed significant association with the odds of developing microalbuminuria additionally included BMI and variability of HbA_{1c}. BMI did not retain significance after multivariate analysis, although earlier reports have shown that patients with higher BMI Z-scores were protected from developing microalbuminuria with the underlying mechanism still unknown [37]. With regard to variability of HbA_{1c}, the effect was surprisingly pronounced, particularly considering the adjustment for mean HbA_{1c} level. In view of the available data, we hypothesise that variability of HbA_{1c} may represent a 'breakthrough' effect of a sudden deterioration of metabolic control with the associated episode of microalbuminuria, both of which are subsequently resolved. If this is the case, protection from such events may be offered by interventions aimed at reducing the variability of HbA_{1c}, such as the introduction of insulin pump therapy [38]. The significance of HbA_{1c} variability as a risk factor of microalbuminuria development in patients with type 1 and type 2 diabetes has been confirmed recently [39, 40].

The limitation of this study is a lack of longer follow-up in some patients after the development of persistent microalbuminuria. This may have resulted in an underestimated effect of metabolic control and its variability, as fewer measurements could lead to a lower CV in children with persistently high HbA_{1c} and truncated observations. We also did not use Tanner stage to indicate the onset of puberty, but the significance of age at onset of diabetes explained the influence of puberty on the risk of microalbuminuria.

In conclusion, the results of this long-term clinic-based study indicate that microalbuminuria in type 1 diabetic children and adolescents is frequently low grade and reversible in the majority of patients even without pharmacological intervention. Major risk factors for developing microalbuminuria in diabetic children are modifiable by therapeutic actions not necessarily focused on nephrologic treatment, underlining the significance of metabolic control and adequate insulin dosage. Children who develop microalbuminuria are characterised by poorer and more variable metabolic control, hinting at the importance of interventions aimed at both improvement and stabilisation of HbA_{1c} levels.

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