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Diabetic microangiopathy in capillaroscopic examination of juveniles with diabetes type 1

Mikroangiopatia cukrzycowa w badaniu kapilaroskopowym dzieci z cukrzycą typu 1

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: The aim of this work was a quantitative and qualitative assessment of a selected part of the microcirculation in children with diabetes type 1 using videocapillaroscopy technique.

Material/Methods: The authors tested a group consisting of 145 children (70 boys, 75 girls) diagnosed and treated for diabetes type 1 in the Diabetic Clinic of GCZD in Katowice for at least one year. The study included history, clinical examination (including dermatological examination) and videocapillaroscopy. Capillaroscopy, a non-invasive, painless and easily repeatable test, was performed using videocapillaroscopy with digital storage of the obtained images. All nailfolds were examined in all children using videocapillaroscopy, and the obtained images were assessed quantitatively and qualitatively for changes in capillary loops in the tested children according to the defined diagnostic procedure.

Results: The analysis of capillaroscopic images described selected quantitative and qualitative characteristics. The conducted analysis showed an increase in the number of capillaries and their elongation, the presence of megacapillaries and Raynaud loops, which were accompanied by an intensive red background, indicating possible neoangiogenesis. The increase in the number of capillaries, disturbances in distribution of capillaries and the presence of abnormal capillaries were correlated with the longer duration of diabetes. Raynaud loops were more frequently found in the cases of increased mean values of HbA1c. Higher values of HbA1c influenced the capillaroscopic images, mainly the number of vessels, including Raynaud loops.

Conclusions: Videocapillaroscopy technique could be a useful tool to detect the early changes of microangiopathy in children with diabetes type 1.

Key words: **capillaroscopy • diabetes mellitus type 1 • children**

Streszczenie

Wstęp: Celem pracy była ocena ilościowa i jakościowa wybranej części mikrokrążenia u dzieci z rozpoznaną cukrzycą typu 1 za pomocą wideokapilaroskopii.

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Materiał/Metody: Przebadano grupę 145 dzieci (70 chłopców, 75 dziewcząt) leczonych z powodu rozpoznanej cukrzycy typu 1 w Poradni Diabetologicznej GCZD w Katowicach, od co najmniej roku.

Badanie składało się z zebrania wywiadu, przeprowadzenia badania klinicznego (w tym oceny dermatologicznej) oraz wykonania badania wideokapilaroskopowego. Kapilaroskopia zaliczana jest do nieinwazyjnych, bezbolesnych, łatwo powtarzalnych metod diagnostycznych, a w wariancie wideokapilaroskopowym pozwala dodatkowo na nagrywanie i przechowywanie obrazów w wersji cyfrowej. U dzieci zbadano wszystkie wały paznokciowe za pomocą wideokapilaroskopu, a wszystkie uzyskane obrazy oceniono pod kątem zmian jakościowych i ilościowych w mikrokrążeniu według przyjętej w pracy metodyki.

Wyniki: W przeprowadzonej analizie statystycznej stwierdzono zwiększenie liczby kapilar naczyniowych wraz z ich wydłużeniem, obecność megakapilar i pętli Raynauda rozmieszonych w obrębie intensywno-różowego pola widzenia wskazującego na neoangiogenezę. Wzrost liczby kapilar naczyniowych, zaburzenia ich rozmieszczenia oraz obecność nieprawidłowych kapilar korelowało z czasem trwania cukrzycy. Pętle Raynauda występowały częściej u dzieci z podwyższonymi wartościami HbA1c. Wyższe wartości HbA1c miały wpływ na obrazy kapilaroskopowe, przede wszystkim w aspekcie liczby kapilar, a zwłaszcza liczby pętli Raynauda.

Wnioski: Wideokapilaroskopia należy do przydatnych metod diagnostycznych w wykrywaniu wczesnych zmian o charakterze mikroangiopatii u dzieci z cukrzycą typu 1.

Słowa kluczowe: **kapilaroskopia • cukrzyca typu 1 • dzieci**

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Introduction

Capillaroscopy is a non-invasive diagnostic technique allowing for microscopic viewing of capillary loops belonging to skin microcirculation within its trophic layers as well as for the structural and morphological assessment of a selected fragment [1].

Videocapillaroscopy is a modern form of traditional capillaroscopy, in which examination of capillary loops is performed using a special probe connected with a video-optical terminal sending the image to the color monitor of a computer. The examination is easy to perform, safe (non-invasive), painless and is characterized by good repeatability and easiness of performance. A disadvantage of capillaroscopy is a possibility to assess only a selected part of the microcirculation, related to the restricted area of examination: the microcapillary circulation (trophic) comprises only 15% of the total cutaneous circulation [2]. Capillaroscopy is used mostly for diagnosis of Raynaud's phenomenon in the course of connective tissue diseases and constitutes a "gold standard" [5]. It is also used for assessment of microcirculation in diabetic patients [4,14].

Chronic diabetic complications (retinopathy, nephropathy, neuropathy) in developed form appear in children comparatively rarely. Flow disturbances in skin microcirculation may precede development of typical diabetic complications. Lack of data on disturbances of skin microcirculation in children with diabetes type 1 prompted the authors to perform an assessment of microcirculation in patients with diabetes type 1.

Objective

The aim of this work was a quantitative and qualitative assessment of a selected part of the microcirculation in children with diabetes type 1 using the videocapillaroscopy technique.

Material and Methods

The tested group consisted of 158 children aged 4 to 18 years, suffering from diabetes type 1 for at least one year, treated in the Diabetic Clinic of GCZD in Katowice. Capillaroscopy was performed in all patients, but results useful for statistical analysis and interpretation were obtained from 145 of the tested children (70 boys, 75 girls).

The following descriptive statistics were obtained for each of the analyzed parameters: group size (N), mean value of a parameter and standard error of mean (SEM), median (M) as well as upper and lower quartile (Q_1 and Q_3). The values were described graphically in the form of box plots. Detection of differing variables was performed using the criterion abs(X) > Q + 1.5 IQR, where IQR means inter-quartile range, and Q is the upper or lower quartile of distribution of variable X. These values are depicted on box plots by *. Normality of distributions was tested using Lilliefors' parametric test. The hypothesis of homogeneous variation

was verified using Fisher's F statistic. If distributions showed divergence from the normal distribution and/or lack of variance homogeneity, the hypothesis of convergence of distribution between the sub-groups was verified using a non-parametric rank Kruskal-Wallis ANOVA test and Mann-Whitney U test. Comparative analysis of the variable groups with normal distributions was performed using standard ANOVA algorithm and Student's t-test.

Discrete variables consisting of abstract classes were analyzed using χ^2 independence test or its modification in the form of credibility quotient G together with an appropriate correction due to the discontinuity of small class numbers. An appropriate multidistribution table was prepared for each case. Multi-factor logistic regression with a stage algorithm allowed us to perform a correction of risk levels defined in one-dimension analysis. AIC Akaikeg's informative criterion was used for choosing a model. The values of coefficients, their standard deviations and p values for rejection of the hypothesis of a lack of correlation were calculated. The analysis results were recognized as statistically significant if the p value was lower than 0.05. No Bonferroni correction was performed.

Capillaroscopy was performed in standardized conditions: each child spent 15 minutes before examination in a room with the temperature of 20–22°C [19]. Examinations were performed using a Fotofinder TeachScreen Software videodermatoscope equipped with a capillary probe allowing image magnifications of 70 to 160× to be obtained. Examination was performed by the same person. All nailfolds of both hands were examined, after treating the cuticula with ultrasonographic gel; the latter increased transparency of the corneal layer. The final assessment included capillaroscopy images obtained from well-visible test areas, such as nailfolds of the third and fourth finger. Assessment was performed only for good images of microcapillaries.

The following capillaroscopy parameters were described and analyzed: numbers of vessels (decreased, increased, normal), distribution of vessels, morphology of vessels, background (pink, pale pink, red), visibility of subpapillary venous plexus.

Thirty capillaries for 5 mm of length was recognized as a normal number of capillaries counted in a distal row of capillaries of a nailfold [6], meaning 5 to 7 for 1 mm of length [10]. Fewer than 5 capillaries in 1 mm was recognized as a decreased number, while above 7 capillaries in 1 mm was recognized as an increased number of capillaries.

Disturbances in capillary distribution define their improper morphology, frequently together with a decrease in the numbers. Disturbances in capillary loop distribution include disturbance of normal configuration (distribution in different directions), presence of single avascular fields, and avascular fields with one dominating megacapillary.

The following morphological types of capillary loops were found [2,6,17,19]: hair-pin capillaries, bushy capillaries, Raynaud loops, megacapillaries.

Visibility of the subpapillary venous plexus (SVP) was defined according to Wertheimer's criteria, modified by Terreri et al. [19,21].

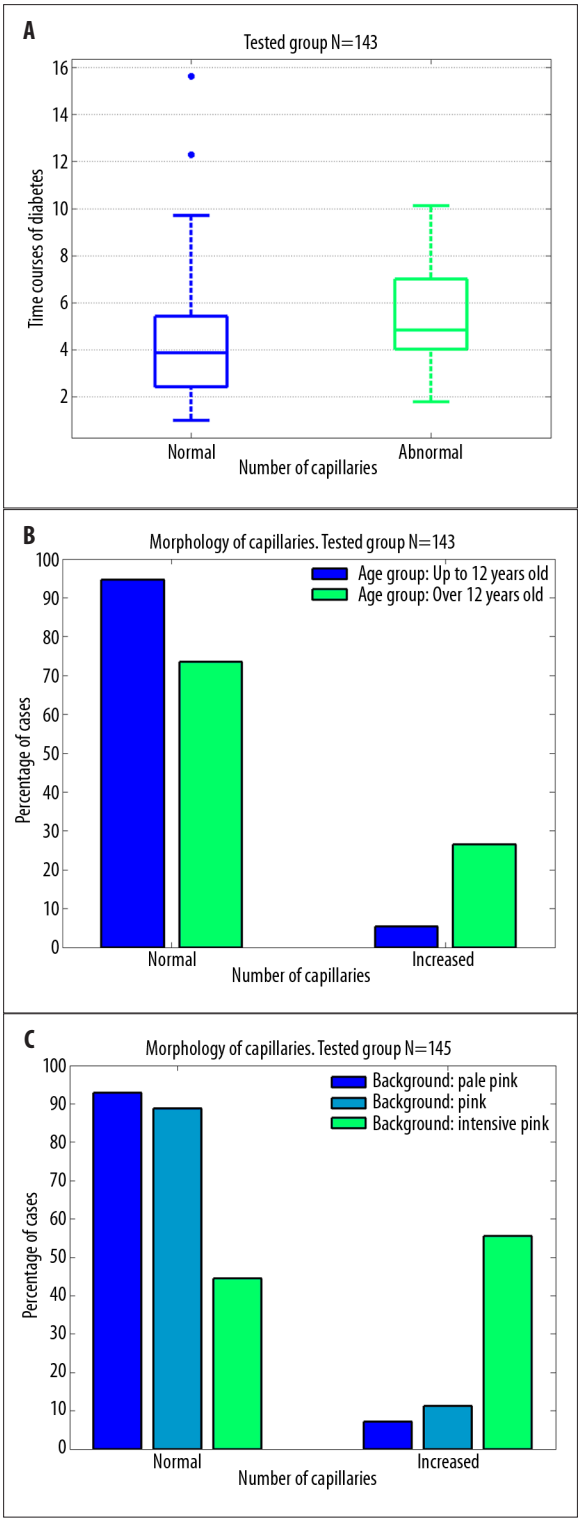

Fig. 1. Number of capillaries; **A** – diabetes duration, **B** – age of children, **C** – background

Results

Characteristics of the tested group

The mean time of diabetes was 4.45 years (SD: 2.39), the minimal time was 1.0 year, and the maximal time was 15.63

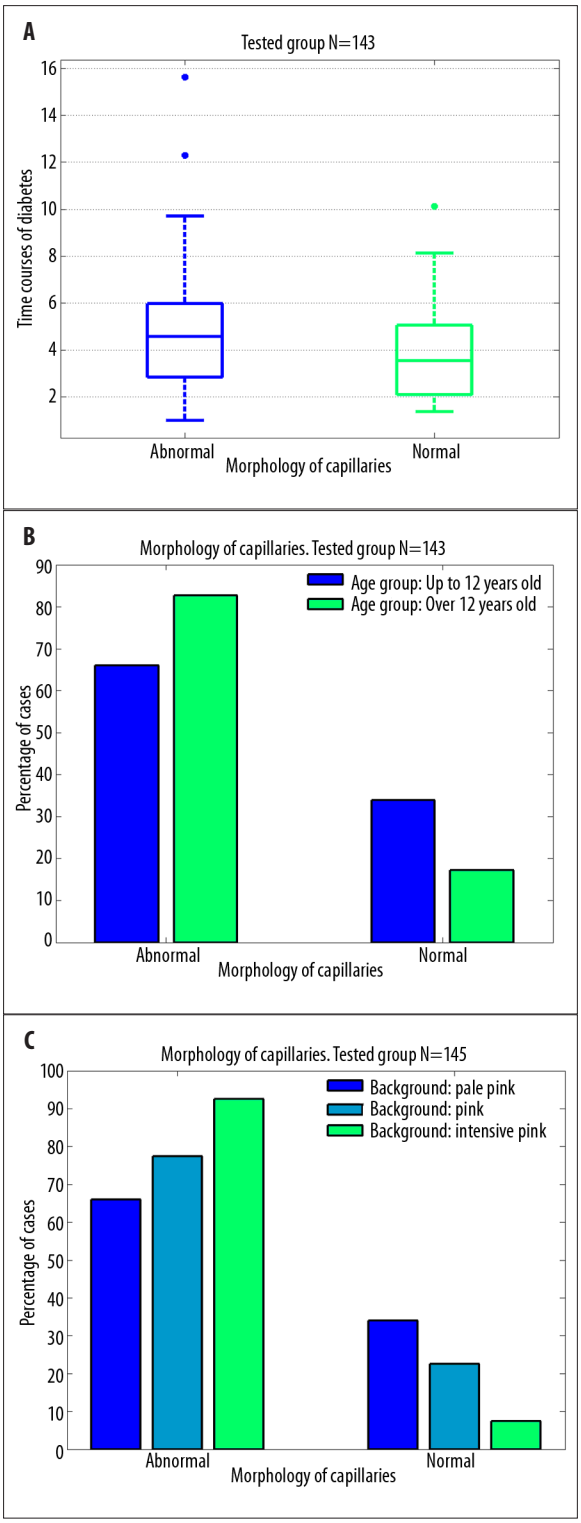

Fig. 2. Irregular capillaries and; **A** – diabetes duration, **B** – age of children, **C** – background

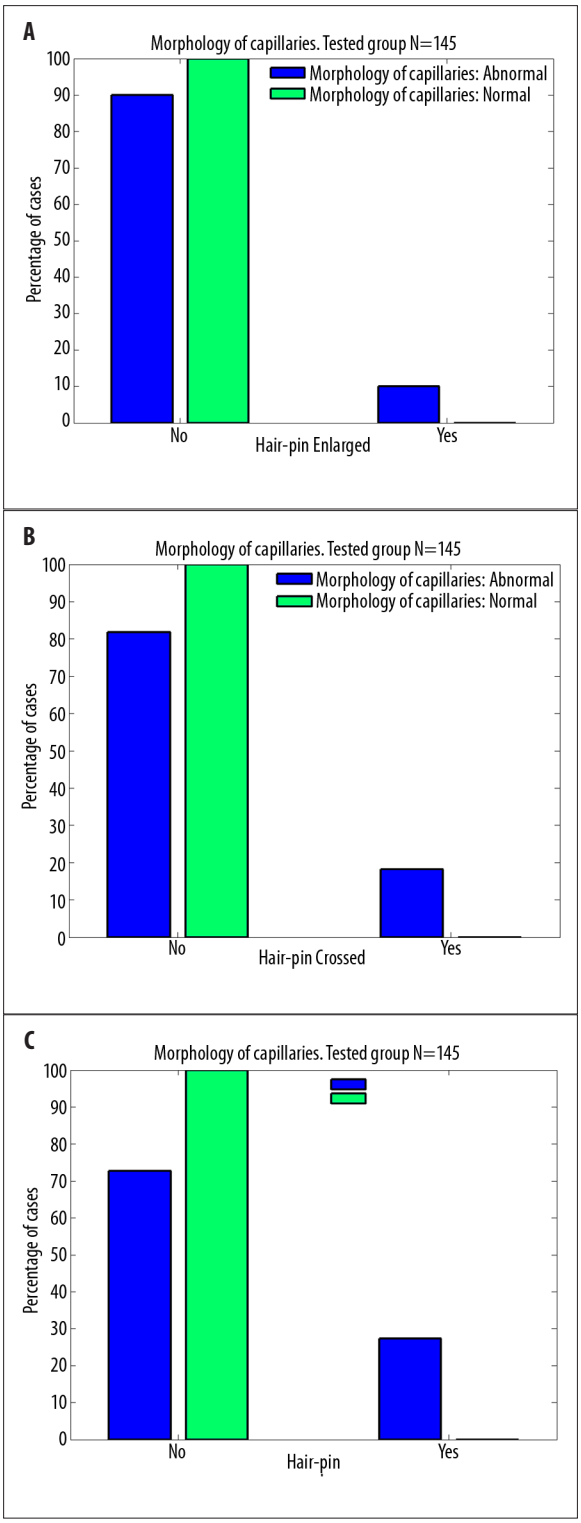

Fig. 3. Irregular capillaries; **A** – enlarged hair-pin, **B** – crossed capillaries, **C** – basic hair-pin

years. The mean dose of insulin per day was 0.79 iu/kg of b.m. (SD: 0.28).

The mean time of diabetes in the group of children aged up to 12 years was 3.89 years (SD: 2.00); the mean time of diabetes in the group of children aged above 12 years was longer and was 4.81 years (SD: 2.57) (p=0.0344). The mean daily dose of insulin in the group of younger children was 0.73 (SD: 0.27) and was lower than the mean value in the group of older children (0.83; SD: 0.28) (p=0.0117).

An increase in the number of vessels together with the longer time of diabetes course was found (p=0.0050) (Fig. 1A).

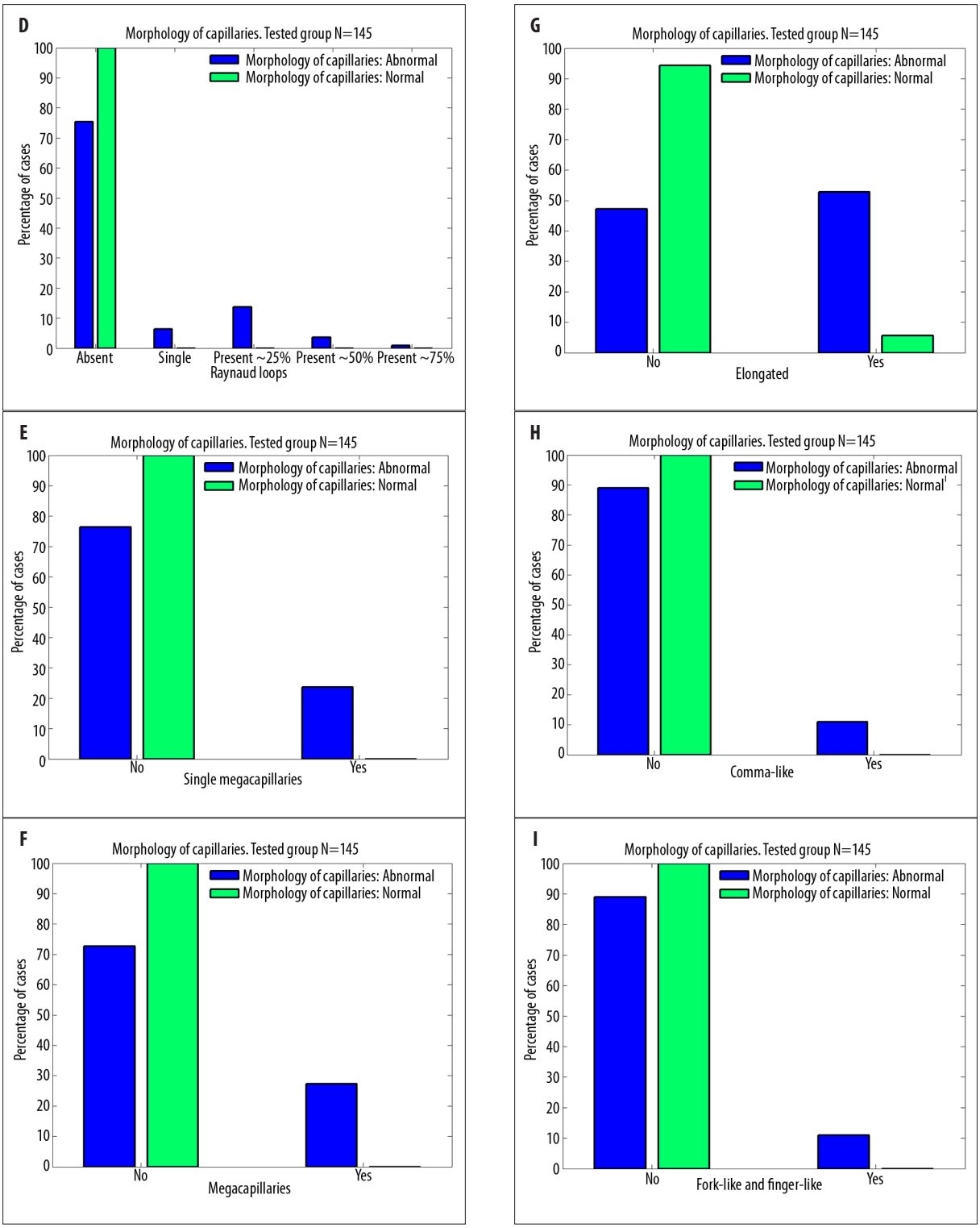

Fig. 3. Irregular capillaries; **D** – Raynaud loops, **E** – single megacapillaries, **F** – megacapillaries, **G** – elongated, **H** – comma-like, **I** – bushy capillaries

A significant statistical difference was also observed between the children's age and the numbers of vessels. Among children with normal numbers of vessels 45% (53) were younger children and 55% (64) were older ones. The group of children with the recognized improper number of vessels was dominated by older children (above 12 years of age): 88% (23), in comparison to 12% (3) of younger children (p=0.0030) (Fig. 1B).

The increase in the numbers of vessels was accompanied by the intensive red background (p<0.0001) (Fig. 1C). An increased number of vessels was more frequently found in girls (18; 69%) (p=0.0792). More frequent occurrence of irregular capillaries was observed together with the longer course of diabetes (4.6; SD: 2.4) (p=0.0683) (Fig. 2A).

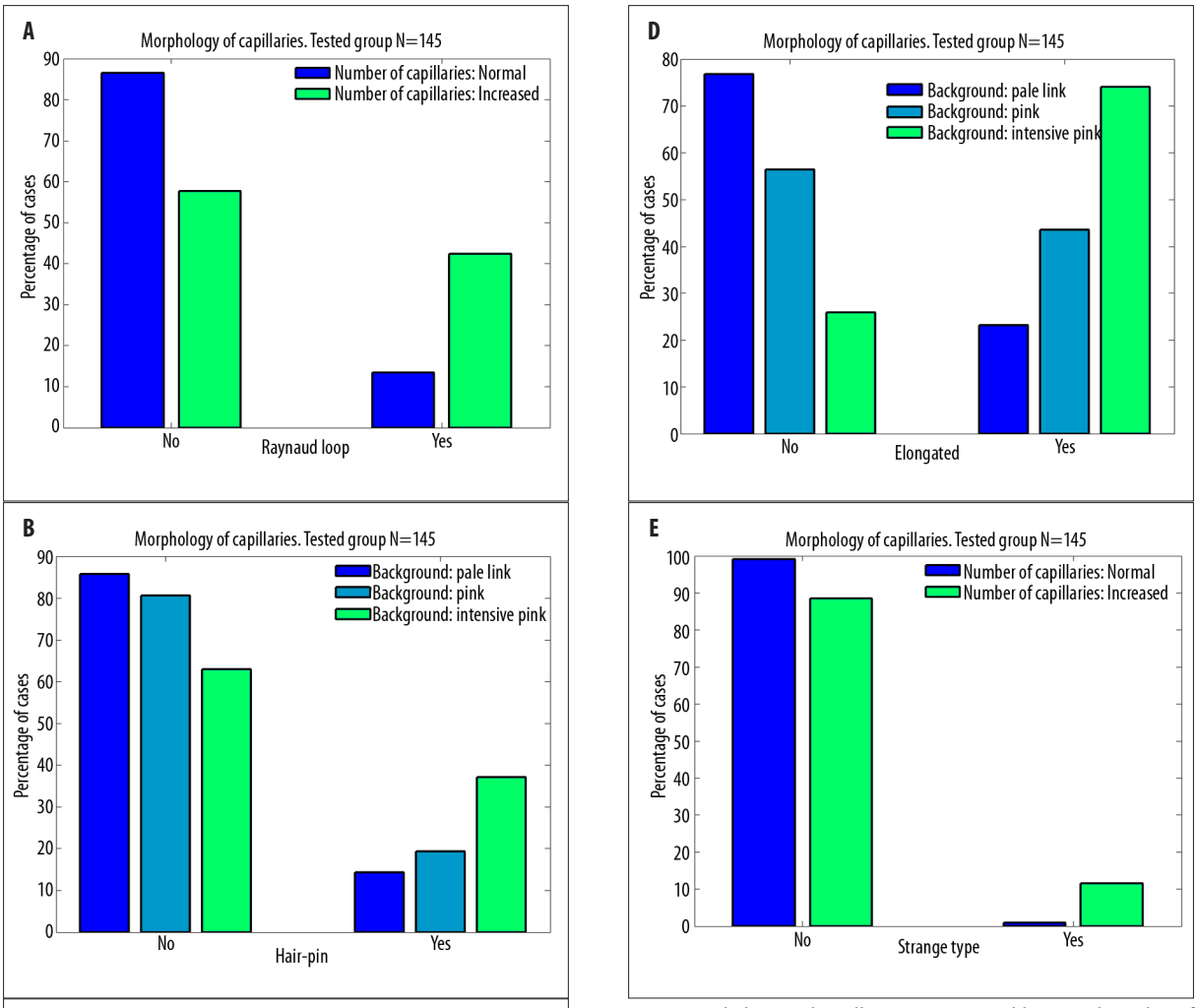

Fig. 4. Morphology and capillaries; **A** – raynaud loops and number of capillaries, **B** – hair pin capillaries and background, **C** – elongated capillaries and number of capillaries, **D** – elongated capillaries and background, **E** – strange capillaries and number of capillaries

A significant statistical correlation was found between the age and irregular morphology of capillaries (p= 0.0200). In the group of children aged up to 12 years, irregular capillaries were found in 37 children (66%); they were more frequently found in older children aged above 12 years (72 patients, 82%) (Fig. 2B). The presence of capillaries with irregular morphology was more frequently found in the intensive red background (25; 92%) (p=0.028145) (Fig. 2C). Within the category of irregular morphology of capillaries, the following were statistically significant: enlarged type of hair-pin capillaries (11; 10%), p=0.0500 (Fig. 3A); crossed capillaries (20; 18%), p = 0.0060 (Fig. 3B); basic type of hair-pin capillaries (30; 27%), p=0.0005 (Fig. 3C); Raynaud loops (27; 24%), p=0.0012 (Fig. 3D); single megacapillaries (26; 23%), p=0.0015 (Fig. 3E); megacapillaries (30; 27%), p=0.0005 (Fig. 3F); elongated (58; 52%), p<0.0001 (Fig. 3G); comma-like (12; 10%), p=0.0413 (Fig. 3H); fork-like and finger-like capillaries, consisting of a form of bushy capillaries (12; 11%), p=0.0413 (Fig. 3I).

The incidence of Raynaud loops was most frequently found together with the increased number of vessels (11; 42%) (p=0.0006) (Fig. 4A). Similarly, the presence of hair-pin capillaries was most frequently found within the intensive red background (10; 37%) (p = 0.0533) (Fig. 4B).

The incidence of elongated capillaries accompanied the increased number of vessels (18; 69%) (p=0.0015) (Fig. 4C), and they were most frequently found within the intensive red background (20; 74%) (p<0.0001) (Fig. 4D). The incidence of strange capillaries was most frequently found

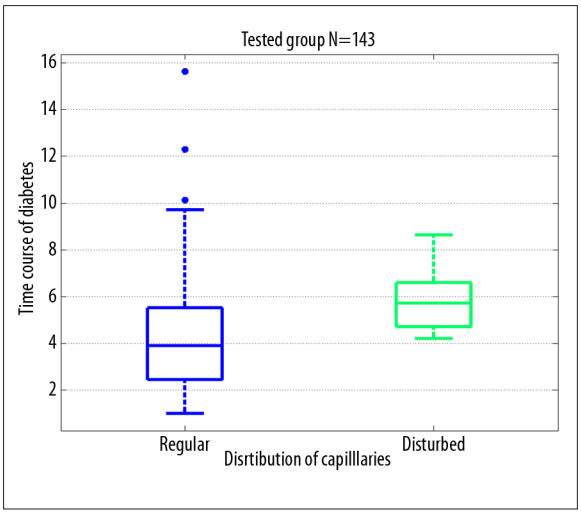

Fig. 5. Distribution of capillaries and diabetes duration

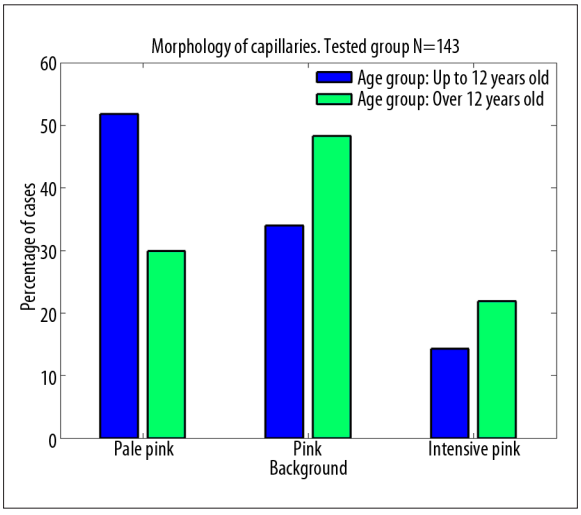

Fig. 6. Type of background and number of capillaries

together with the increased number of capillaries (3; 11.5%) (p=0.0026) (Fig. 4E).

The longer the course of diabetes, the more frequent were disturbances in distribution of capillaries (5.8 years; SD: 1.36) (Fig. 5) (p=0.0381).

A statistically significant correlation was found between the type of background and the children's age (p=0.0314). The pale-pink background was more frequent in the group of children aged up to 12 years (51%; 29), then the pink one (30%; 26) and the intensive red one (21%; 19). The pink (48%, 42), pale-pink (32, 22%, 29) and intensive red background (21, 11%, 19) was observed in the group of children aged above 12 (Fig. 6). The intensive red background was accompanied by the increase in the number of capillaries (15; 55%, p=0.000000). It was found that the visibility of the subpapillary venous plexus depends on the acuity of the vision field; the plexus was invisible in 100% (44) of the cases with a decreased acuity of vision (p=0.0446). Fig. 7 shows capillaroscopic changes in diabetes type 1.

A tendency (without statistical significance) for annual HbA1c mean value to increase with age was found in

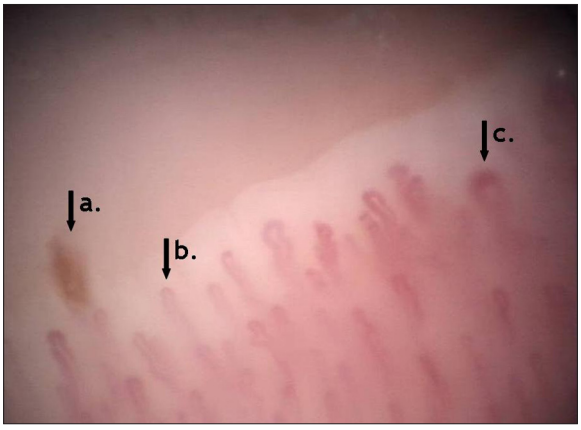

Fig. 7. Capillaroscopy in diabetes: megacapillaries (c), enlarged capillaries (b) and extravasations (a)

girls. The increased annual HbA1c values may influence the increase in the number of capillaries (p=0.0592) (mean 6.93 versus 7.42). The hair-pin capillaries occur more frequently in children with lower mean annual HbA1c values (p=0.0411).

The presence of Raynaud loops was correlated with increased annual HbA1c values (p=0.0108).

The following parameters influenced the increase in the numbers of capillaries when constructing a logistic model: age (β=0.3590, p=0.0123), presence of Raynaud loops (β=2.7091, p=0.006) and elongation of capillaries (β=2.3155, p=0.0081).

The output statistical parameters were statistically significant. Age, time course of diabetes, mean values of HbA1c, presence of Raynaud loops, elongated capillaries, BMI, and background color (pink, intensive pink) were taken into account at p<0.05.

Discussion

Capillaroscopy examinations of healthy persons, including children and adolescents, show a homogeneous, ordered distribution of capillaries, which are located in parallel, at regular distances, displaying narrow distances between ascending and descending arms. The shape of regular capillaries resembles the letter "U" upside-down, with a narrower arterial arm, an upper part and a venous arm, the latter larger than the arterial one. The focused character of the decrease in the number of capillaries can be found in 7% of healthy persons [19]. An important diagnostic goal is to define the decreasing number of capillaries, if there is any tendency to develop avascular areas – below 30 at 5 mm of length in the distal row of capillary loops observed using capillaroscopy [6]. Areas with a decreased number of capillaries are defined as a lack of two or more capillaries, and the avascular areas should cover at least 3 mm in width [19]. Our own study showed an increase in the number of capillaries, corresponding to the prolonged time course of diabetes, especially in older children, most frequent in girls. Megacapillaries possess an "aneuric" shape of capillary loops, whose arms are at least ten times larger in relation to the neighboring normal capillaries [15] and which are characteristic for systemic scleroderma and

scleroderma-like syndromes [7]. Zaug-Vesti et al. found significantly more frequent presence of aneuric-like dilated capillaries in patients with diabetes type 1, regardless of the presence of retinopathy [22]. Presence of atypical capillaries, such as enlarged or strange ones, is observed in one third of healthy persons [19]. In our study atypical capillaries were without statistical significance. Hair-pin capillaries look like a hair-pin; they can be found even in healthy persons. Our study showed statistically significant occurrence of the basic type of hair-pin capillaries (30; 27%), enlarged hair-pin capillaries (11; 10%) and crossed capillaries (20; 18%). Bushy capillaries are defined as small branches going in different directions. They are most frequently found in systemic and focal lupus erythematosus, systemic scleroderma [6], in patients with mixed-type diseases of connective tissue [7] or cutaneous-muscular inflammation [6], and they can also indicate neoangiogenesis [5]. They can appear in a finger-like and a fork-like form. In our study, capillaries such as fork-like and finger-like capillaries, consisting of a form of bushy capillaries (12; 11%), were statistically significant. Elongation of capillaries may indicate neoangiogenesis and inflammation of vessels, such as the one found in the course of systemic lupus erythematosus [11]. In our observation the incidence of elongated capillaries accompanied the increased number of vessels (18; 69%), and they were most frequently found within the intensive red background. Atrophic and aneuric-like enlarged capillaries are more frequently found in children with diabetes in comparison to the control group [20]. Enlarged capillaries are characterized by at least 4-fold enlargement of a descending and an ascending arm, a transverse and a descending one in comparison to the neighboring capillary loops [19]. Similarly, the study of Meyer et al. [16] showed an increased frequency of twisted and enlarged capillaries, indicating microangiopathy in patients with diabetes type 1 and 2. Such capillaries are most frequently found in systemic scleroderma, cutaneous-muscular inflammation and in non-differentiated diseases of connective tissue [6].

Within the category of irregular morphology of capillaries, Raynaud loops (27; 24%), single megacapillaries (26; 23%), megacapillaries (30; 27%) and elongated (58; 52%) capillaries were the most frequently found. The incidence of Raynaud loops was most frequently found together with the increased number of vessels (11; 42%). In our study the increase in the number of vessels and their elongation, the presence of megacapillaries and Raynaud loops was mostly correlated with the intensive red background, which may indicate neoangiogenesis. Capillaroscopic images obtained from diabetic patients show the presence of atypical capillaries, or of capillaries difficult to define according to the recognized criteria of morphological assessment. Cicco and Cicco [3], performing videocapillaroscopy in patients with diabetes type 1 and 2, found the presence of abnormal capillaries resembling horns in 50% of cases ("*deer horns*"), "*elephant nose*"" in 72% of cases, and twisted, corkscrew-like capillaries in 44% of cases. Additionally, videocapillaroscopic images in diabetes were characterized by decreased density of capillaries, which was found in 28% of the tested cases [3]. Hair-pin capillaries can be found in healthy children, as well as strange, meandering or bushy capillaries [9].

Subpapillary venous plexus (SVP) is usually described in children [19]. In the healthy population it is found in approximately 30% of persons, and it is more frequently found in patients with systemic lupus erythematosus, sometimes with systemic scleroderma [7,10]. In our observations, the visibility of the subpapillary venous plexus depended on the acuity of the vision field; the plexus was invisible in 100% (44) of the cases with a decreased acuity of vision. Among the authors working with capillaroscopy in diabetic children, Kurilyszyn et al. [14] showed that twisted and enlarged capillaries are significantly more frequently found in the venous part together with a decrease in the density of capillaries. Spiral capillaries with a tendency of shortening and enlargement together with a pink background accompanied by neovascularization were found in the cases of advanced diabetic microangiopathy [14]. No correlation between changes in capillaroscopic images and age, BMI and the time course of diabetes were found [14]. The level of HbA1c above 6.1% of HbA1c was found in more than 90.9% of patients with advanced capillary changes [14]. Capillaroscopic images are dominated by changes resembling atherosclerosis: the number of capillaries is decreased, the course of capillaries is twisted, capillaries are of different thickness and length, and they sometimes possess butt-like enlargements [4]. The study of Cisło et al. [4], which consisted of capillaroscopic assessment of nailfolds in children with diabetes type 1, showed most frequently capillaries of a snail-like, twisting shape with narrowing and elongation. The described capillaroscopic changes can be already present in small children and they do not depend on the period of disease manifestation. However, they can intensify depending on the severity of the disease in a directly proportional manner [4]. In this study, capillaroscopic changes were correlated with a longer course of diabetes. However, no changes such as a decrease in the number of vessels proportional to the severity of the disease were found. On the contrary, the higher the annual values of HbA1c, the higher the numbers of capillaries, including Raynaud loops. In our observations, Raynaud loops were more frequently found in the cases with an increase in the mean values of HbA1c. The study of Tubiana-Rufi et al. [20] also confirmed differences in the capillaroscopic images from the children with diabetes type 1, which were significantly more frequent (61.4%) in comparison with the control group of healthy children (20%; $p<0.001$). Atrophic and aneuric-like capillaries were significantly more frequently found in the group of children with diabetes type 1. The incidence of aneuric-like capillaries did not correlate with the time course of diabetes, the level of HbA1c, or sex. In our study, higher values of HbA1c influenced the capillaroscopic images, mainly the number of vessels, including Raynaud loops.

The latest observations of Kuryliszyn-Moskal et al. [12,13] proved that abnormalities in nailfold capillaroscopy reflect the extent of microvascular involvement. In this study the morphological changes were observed with nailfold capillaroscopy in 86 (81%) diabetics patients. Severe capillaroscopic changes were found in 32 out of 54 (59%) diabetic patients with microangiopathy and in only 7 out of 52 (13%) patients without microangiopathy. The capillaroscopic score was significantly higher in diabetic patients with microangiopathic complications in comparison to patients without microangiopathy ($p<0.001$). Scardina et al. [18] proved that capillary alterations can occur also in

the oral mucosa of diabetics. The loop density decrease is probably a symptom of peripheral microangiopathy [18].

Skin microvascular dysfunction in type 1 diabetes precedes symptoms of end-organ microvascular disease [8], so knowledge of nailfold capillaroscopy abnormalities in diabetes mellitus type 1 is useful in the clinical approach.

Limitations

The study consists of a description of capillaroscopic findings in children with diabetes. The findings are defined as abnormal based on cut-offs which are derived from the literature, but they concern age-matched groups. In order to define the utility of capillaroscopic findings as a screening tool for vascular complications, it would be necessary to perform a longitudinal study. This is a pilot study in which many disturbances were described and they may be evaluated in the future.

Conclusions

1. The increase in the number of vessels and their elongation, the presence of megacapillaries and Raynaud loops was mostly correlated with the intensive red background, which may indicate neoangiogenesis.
2. The increase in the number of capillaries, disturbances in distribution of capillaries and the presence of abnormal capillaries were correlated with the prolonged time course of diabetes.
3. Raynaud loops were more frequently found in the cases with an increase in the mean values of HbA1c.
4. Higher values of HbA1c influenced the capillaroscopic images, mainly the number of vessels, including Raynaud loops.
5. Videocapillaroscopy technique could be a useful tool to detect the early changes of microangiopathy in children with diabetes type 1.

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