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Role of chemerin in the metabolic regulation of type 1 diabetes in children

Rola chemeryny w regulacji metabolicznej cukrzycy typu 1 u dzieci

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Abstract

Introduction and objective: Type 1 diabetes is one of the most common chronic diseases of childhood, leading to the development of chronic micro- and macrovascular complications. Recently, many researchers have been focusing their efforts on identifying new markers for the progression of this disease. It is known that adipokines play a significant role in the regulation of lipid and carbohydrate metabolism. The aim of this study was to evaluate the level of serum chemerin in children with type 1 diabetes and assess their correlation with body mass index, glycated haemoglobin, and lipid profile. **Materials and methods:** The study group included 40 children with newly diagnosed, 40 with long-term diabetes, and 14 children without diabetes as a control group. Chemerin levels were measured using a sandwich enzyme-linked immunosorbent assay. **Results:** We did not find any statistically differences in chemerin levels in the studied groups of children. In the group of patients with long-term, metabolically well-controlled diabetes, chemerin levels were higher in girls than in boys ($p = 0.028$). Moreover, no difference in chemerin levels was observed between the studied groups of children depending on the body mass index percentiles. A negative correlation was found between chemerin level and age in children with newly diagnosed diabetes and metabolically well-controlled diabetes. **Conclusions:** Our study provides new insights into the status of chemerin among paediatric patients with varying degrees of type 1 diabetes control. However, further research is needed involving larger groups of patients with differing degrees of sexual maturation and with the presence of microvascular complications.

Keywords: diabetes mellitus, body mass index, chemerin

Streszczenie

Wprowadzenie i cel: Cukrzyca typu 1 jest jedną z najczęstszych chorób przewlekłych wieku dziecięcego, prowadzącą do rozwoju przewlekłych powikłań mikro- i makronaczyniowych. Wielu badaczy w ostatnim czasie kieruje swoje wysiłki na poszukiwanie nowych markerów zaawansowania tej choroby. Wiadomo, że adipokiny odgrywają znaczącą rolę w regulacji metabolizmu lipidów i węglowodanów. Celem pracy była ocena poziomu chemeryny w surowicy dzieci chorych na cukrzycę typu 1 i jego korelacji ze wskaźnikiem masy ciała, hemoglobiną glikowaną i profilem lipidowym. **Materiał i metody:** Grupę badaną stanowiło 40 dzieci z nowo rozpoznaną, 40 z długotrwałą cukrzycą oraz 14 dzieci zdrowych, które stanowiły grupę kontrolną. Chemerynę oznaczono za pomocą testu immunoenzymatycznego. **Wyniki:** Nie stwierdzono statystycznych różnic w stężeniu chemeryny w badanych grupach dzieci. W grupie pacjentów z długotrwałą cukrzycą, dobrze kontrolowanych metabolicznie stężenie chemeryny było wyższe u dziewcząt niż u chłopców ($p = 0{,}028$). Ponadto nie zaobserwowano różnic w stężeniu chemeryny pomiędzy badanymi grupami dzieci w zależności od percentyli wskaźnika masy ciała. Odnotowano ujemną korelację pomiędzy poziomem chemeryny a wiekiem u dzieci ze świeżo rozpoznaną cukrzycą i cukrzycą dobrze wyrównaną metabolicznie. **Wnioski:** Niniejsze badanie dostarcza nowych informacji na temat statusu chemeryny wśród pacjentów pediatrycznych z różnym stopniem kontroli cukrzycy typu 1. Konieczne są jednak dalsze badania obejmujące większe grupy pacjentów, różniących się stopniem dojrzałości płciowej i występowaniem powikłań mikronaczyniowych.

Słowa kluczowe: cukrzyca, wskaźnik masy ciała, chemeryna

INTRODUCTION

Diabetes mellitus is a global health problem, affecting populations in both developing and developed countries. Type 1 diabetes mellitus (T1DM) is the most common form of diabetes in children and adolescents, and also one of the most common chronic diseases of childhood. In 2021, an estimated 108,300 children and adolescents under the age of 15 years were newly diagnosed with T1DM, and 651,700 children and adolescents were living with the condition worldwide[1].

Long-term damage, dysfunction, and failure of various organs, especially eyes, kidneys, nerves, heart, and blood vessels are caused by chronic hyperglycaemia associated with diabetes[2]. Many recent studies have discussed the role of adipose tissue as an endocrine organ[3]. Adipokines such as adiponectin, leptin, resistin, chemerin, progranulin, and omentin are bioactive mediators secreted by adipose tissue[4]. They play a significant role in the regulation of lipid and carbohydrate metabolism, insulin sensitivity, and insulin secretion, and are involved in inflammatory responses[5]. The role of adipokines in the pathogenesis of T1DM has also been studied[6]. One of the newly identified adipokines, chemerin, plays a role in the glucose metabolism. Chemerin is expressed predominantly in white adipose tissue, with only small amounts found in brown adipose tissue[7]. It is associated with obesity and may mediate the relationship between increased fat mass and early atherogenic risk in obese children[8,9]. Chemerin influences both inflammation and metabolism, and may provide a link between chronic inflammation, obesity, and its related disorders[10]. Furthermore, in T1DM patients, chemerin may be considered a promising adipokine for the development of diabetic complications, including pathological changes in glucolipid metabolism and inflammatory factors, which may promote the development of macroangiopathy, diabetic retinopathy, and nephropathy[11]. Moreover, many studies have indicated that chemerin may be related to immune-mediated inflammatory disease, high blood pressure, and vascular endothelial function[12].

AIM OF THE STUDY

The aim of this study was to evaluate the levels of serum chemerin in T1DM children and establish their correlation with body mass index (BMI), glycated haemoglobin (HbA1c), and lipid profile.

MATERIALS AND METHODS

Ethical approval

The study protocol was approved by the Bioethics Committee at the Rzeszów University (Resolution No. 2018/03/08). All activities conducted in studies involving human participants adhered to the ethical principles set forth by the institutional and/or national research committee, in accordance with the 1964 Declaration of Helsinki and its subsequent revisions, or equivalent ethical guidelines. Written informed consent was obtained from either the legal guardians and/or the study participants themselves.

Study subjects

The study encompassed a total of 94 children, divided into four distinct groups. Among the children with diabetes, there were 40 patients with newly diagnosed T1DM (NT1DM) and 40 with long-term T1DM, defined as lasting more than one year. In the long-term T1DM group, 20 children had good metabolic control (T1DMw), while the other 20 had poor metabolic control (T1DMn). All children were of Caucasian ethnicity, and none had a family history of T1DM or any other forms of diabetes. The diagnosis of T1DM adhered to the criteria established by the International Society for Pediatric and Adolescent Diabetes[13]. Participants were recruited from the Department of Paediatrics, Paediatric Endocrinology and Diabetology, as well as the Endocrinology Outpatient Clinic, between January 2019 and April 2021. The measurement of chemerin levels was performed on the fifth day of hospitalisation, following the stabilisation of the patients' general condition. For the remaining patients, the duration of diabetes treatment exceeded one year. Patients with T1DM were treated with insulin analogues through either intensive insulin therapy using insulin pens or continuous subcutaneous insulin infusion via a personal insulin pump. Poor metabolic control was defined as an HbA1c level exceeding 7%.

Concurrent with the study, a control group of 14 healthy children was recruited from a local paediatric outpatient department. These healthy children had no medical history of illnesses and were confirmed as healthy during clinical examinations.

Children whose BMI exceeded the 85th percentile for their respective sex and age were included in both the diabetic and healthy children groups. However, having a BMI above the 85th percentile was not a criterion for exclusion from the study groups. Subsequently, the patients were categorised into three groups based on their BMI percentiles: 1) underweight – less than the 3rd percentile, 2) healthy weight – between the 3rd percentile and less than the 85th percentile, and 3) overweight and obesity – at or above the 85th percentile.

It is noteworthy that all children shared similar socioeconomic status, lifestyle, and dietary habits.

Blood collection and analysis

In the morning, following an overnight fasting period, a venous peripheral blood sample of 5 mL was drawn and collected in a standard clotting activator tube. After collection, the samples were allowed to clot and were subsequently

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		NT1DM	Long-term T1DM		Healthy controls	*p*
			T1DMw	T1DMn		
Sex (F/M)		11/29	6/14	10/10	9/5	
Age [years]	**Mean ± *SD***	9.47 ± 3.91	11.86 ± 3.94	13.37 ± 3.5	14.33 ± 4.84	0.001
	Range	2.2–16.1	2.9–17.9	5.1–17.8	3.6–17.6	
BMI [kg/m^2]	**Mean ± *SD***	16.84 ± 3.67	18.05 ± 2.69	21.64 ± 3.54	21.22 ± 3.05	<0.001
	Range	12.5–26.34	14.31–24.16	16.27–28.06	15.03–26.34	
BMI percentiles						
<3rd	***n* (%)**	7 (17.5)	0	0	0	
3rd–85th	***n* (%)**	27 (67.5)	16 (80)	13 (65)	11 (79)	
>85th	***n* (%)**	6 (15)	4 (20)	7 (35)	3 (21)	
HbA1c [%]	**Mean ± *SD***	11.78 ± 2.58	6.47 ± 0.48	10.18 ± 2.18	5.29 ± 0.19	<0.001
	Range	6.93–17.03	5.23–6.9	8–15.1	4.9–5.6	
TC [mg%]	**Mean ± *SD***	178.23 ± 55.66	170.5 ± 27.95	179 ± 47.42	176.07 ± 11.81	0.929
	Range	16–297	129–224	125–292	150–190	
HDL [mg%]	**Mean ± *SD***	54.38 ± 30.13	62.65 ± 17.9	58.45 ± 9.29	49.93 ± 7.67	0.007
	Range	19–181	29–97	40–78	40–68	
LDL [mg%]	**Mean ± *SD***	95.38 ± 44.1	92.1 ± 20.96	99 ± 35.52	82.14 ± 17.65	0.543
	Range	30–206	45–124	44–182	60–115	
TG [mg%]	**Mean ± *SD***	297.93 ± 319.63	62.65 ± 17.9	112.7 ± 72.24	99.86 ± 27.72	<0.001
	Range	53–1800	34–139	41–328	58–156	

BMI – body mass index; **HbA1c** – glycated haemoglobin A1; **TC** – total cholesterol; **TG** – triglycerides; **NT1DM** – patients with newly diagnosed diabetes; **T1DMw** – patients with long-term diabetes, metabolically well-controlled; **T1DMn** – patients with long-term diabetes, metabolically poorly controlled.

Tab. 1. General characteristics of children included in the study

centrifuged for 10 minutes at 1,000 g, maintaining a temperature of 4°C, using a centrifuge model 5702 R from Eppendorf AG (Germany). The resulting serum was then carefully transferred into cryovials and promptly frozen at –80°C for subsequent analysis. It is important to note that the serum samples were not stored for longer than one month, and they were thawed at room temperature only once during the analysis process. Additional clinical parameters were extracted from the patients' clinical records.

Chemerin assay

Chemerin was estimated with using a sandwich enzyme-linked immunosorbent assay (ELISA) (E102, Mediagnost, Germany). According to the manufactures specifications, the inter- and intra-assay coefficients of variation are below 10%. Absorptiometric measurements were performed on a Tecan Infinite 200 PRO multimode reader (Tecan Group Ltd., Männedorf, Switzerland). Serum levels of chemerin were expressed in ng/mL.

Statistical analysis

Statistical analyses were conducted using the STATISTICA software package (version 13.3, StatSoft Inc., 2017, Tulsa, OK, USA). The data were presented as the mean and standard deviation (*SD*), along with the range. It is important to note that the majority of variables did not conform to a normal distribution, as confirmed by the Shapiro–Wilk test, thus necessitating the application of non-parametric tests. Multiple comparisons were carried out using the Kruskal–Wallis ANOVA. Statistical significance was determined with a *p*-value of less than 0.05.

RESULTS

The study included 40 children with NT1DM, ages ranging from 2.2 to 16.1 years, and 40 patients with long-term T1DM (20 with T1DMw, ages ranging from 2.9 to 17.9 years, and 20 with T1DMn, ages ranging from 5.1 to 17.8 years). The control group consisted of 14 healthy children, ages ranging from 3.6 to 17.6 years (Tab. 1).

Children from the NT1DM group were statistically younger than those from the T1DMn group ($p = 0.007$) and the healthy children ($p < 0.001$). Children with NT1DM had a statistically lower BMI than those from the T1DMn group ($p < 0.001$) and the healthy children ($p = 0.002$). Moreover, children from the NT1DM group had a statistically higher level of HbA1c compared to those from the T1DMw group ($p < 0.001$) and the healthy children ($p < 0.001$). Children with long-term and well-controlled diabetes had statistically lower HbA1c levels than those from T1DMn group ($p < 0.001$). There was no statistical difference in cholesterol and LDL levels. We noted a statistical difference in the level of HDL between children from the NT1DM group and those from the T1DMw group ($p = 0.036$). Finally, children from the NT1DM group had statistically higher levels of triglycerides than those from the T1DMw group ($p < 0.001$), the T1DMn group ($p = 0.002$), and the healthy children ($p = 0.02$).

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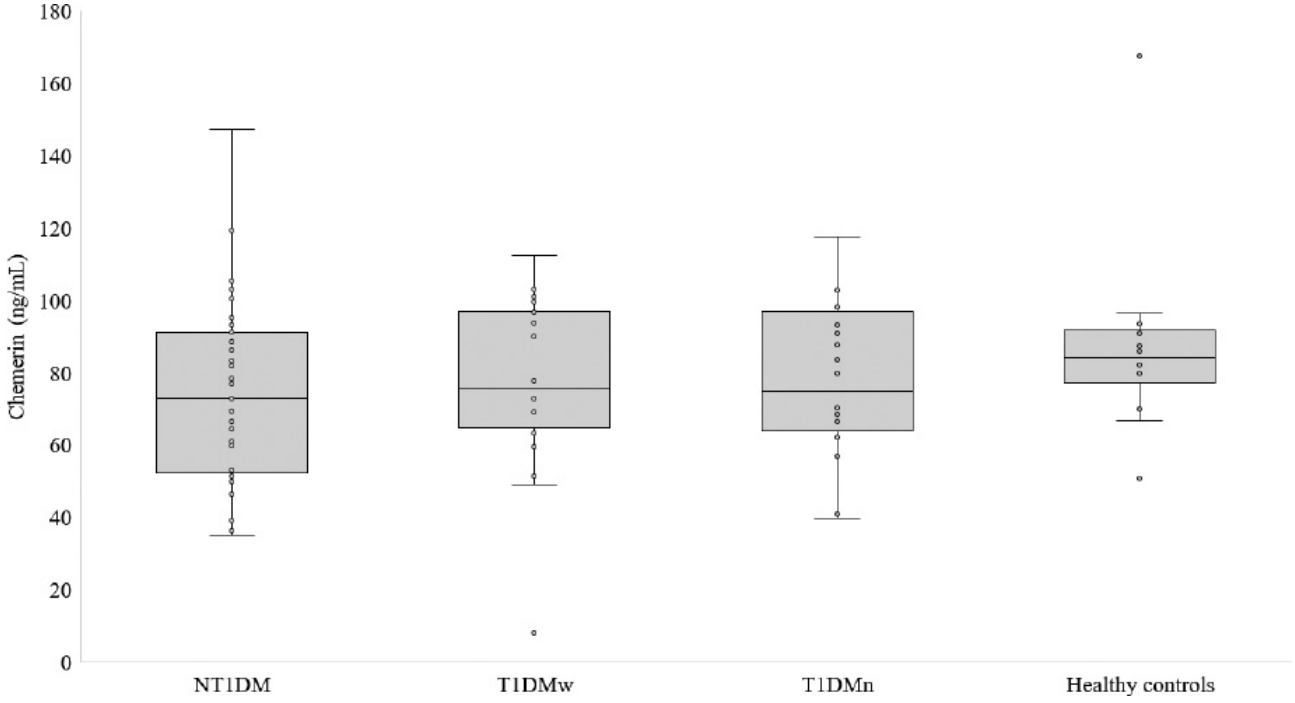

NT1DM – patients with newly diagnosed diabetes; **T1DMw** – patients with long-term diabetes, metabolically well-controlled; **T1DMn** – patients with long-term diabetes, metabolically poorly controlled.

Fig. 1. Chemerin levels in studied groups

		Chemerin [ng/mL]
NT1DM	**Boys**	73.03 ± 21.2
	Girls	73.32 ± 33.64
	p	0.628
T1DMw	**Boys**	69.71 ± 24.83
	Girls	93.88 ± 11.24
	p	**0.028**
T1DMn	**Boys**	78.93 ± 23.33
	Girls	77 ± 19.93
	p	0.791
HC	**Boys**	86.85 ± 5.68
	Girls	87.11 ± 32.95
	p	0.351

NT1DM – patients with newly diagnosed diabetes; **T1DMw** – patients with long-term diabetes, metabolically well-controlled; **T1DMn** – patients with long-term diabetes, metabolically poorly controlled; **HC** – healthy controls.

Tab. 2. Chemerin parameters depending on the sex of the study participants

Fig. 1 presents the levels of chemerin in studied groups. No statistically differences were found in the level of chemerin among the studied groups of children (NT1DM: 73.11 ± 24.84 ng/mL, T1DMw: 76.96 ± 24.17 ng/mL, T1DMn: 77.97 ± 21.14 ng/mL, and healthy children: 87.02 ± 26.04 ng/mL, $p = 0.357$).

Tab. 2 presents differences in chemerin levels depending on the sex of the study participants.

There was no statistical difference in chemerin levels among children with NT1DM, T1DMn and the healthy children. In the T1DMw group, chemerin levels were higher in girls than in boys ($p = 0.028$).

Tab. 3 presents the level of chemerin depending on BMI percentiles. Children below the 3rd percentile were present only in the NT1DM group. No difference in chemerin levels was observed between the studied groups of children.

The dependence between chemerin levels and the general characteristics of patients was estimated using Spearman correlation. Spearman's rank correlation coefficients and *p* values for each separate studied group are presented in Tab. 4. We found a negative correlation between chemerin levels and age in children with NT1DM and T1DMw ($R = -0.344$, $p = 0.029$ and $R = -0.66$, $p = 0.002$, respectively). Moreover, in the group of healthy children, there was a moderate positive correlation between the level of chemerin and Hb1Ac. A strong negative correlation was also found between chemerin levels and LDL in healthy controls. No other associations were demonstrated between chemerin concentration and the other analysed parameters.

DISCUSSION

Scientific research in recent years among children with T1DM suggests a possible role of chemerin in the development of diabetes and diabetic complications. In our study, no statistically significant differences in the concentration of chemerin were found among the studied group of children (NT1DM: 73.11 ± 24.84 ng/mL, T1DMw: 76.96 ± 24.17 ng/mL, T1DMn: 77.97 ± 21.14 ng/mL and healthy children: 87.02 ± 26.04 ng/mL, $p > 0.05$). No difference in chemerin levels between recent-onset and long-term diabetic subjects was also observed in a study by Verrijn Stuart et al.

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BMI	NT1DM	T1DMw	T1DMn	HC	*p*	*p* NT1DM/HC	*p* T1DMw/HC	*p* T1DMn/HC	*p* NT1DM/T1DMw	*p* NT1DM/T1DMn	*p* T1DMw/T1DMn
<3rd	67 ± 23.07	-	-	-	-	-	-	-	-	-	-
3rd–85th	74.94 ± 24.47	77.99 ± 19.23	79.38 ± 20.81	87.45 ± 29.37	0.657	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
>85th	71.78 ± 32.9	73.86 ± 38.27	75.34 ± 23.16	85.43 ± 9.49	0.887	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999

BMI – body mass index; **NT1DM** – patients with newly diagnosed diabetes; **T1DMw** – patients with long-term diabetes, metabolically well-controlled; **T1DMn** – patients with long-term diabetes, metabolically poorly controlled; **HC** – healthy controls.

Tab. 3. Chemerin levels depending on BMI percentile

	NT1DM		T1DMw		T1DMn		HC	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*
Age	−0.344	0.029	−0.660	0.002	−0.156	0.513	−0.205	0.481
BMI	−0.088	0.586	−0.332	0.152	0.089	0.710	0.064	0.829
Hb1Ac	−0.189	0.241	0.222	0.346	−0.056	0.815	0.582	0.029
TC	−0.164	0.311	0.179	0.450	−0.266	0.257	−0.223	0.444
HDL	0.053	0.745	0.061	0.799	−0.390	0.089	0.360	0.206
LDL	−0.189	0.244	0.259	0.270	0.421	0.065	−0.601	0.023
TG	−0.092	0.57	−0.319	0.170	−0.143	0.547	−0.106	0.719

BMI – body mass index; **HbA1c** – glycated haemoglobin A1; **TC** – cholesterol; **TG** – triglycerides; **NT1DM** – patients with newly diagnosed diabetes; **T1DMw** – patients with long-term diabetes, metabolically well-controlled; **T1DMn** – patients with long-term diabetes, metabolically poorly controlled; **HC** – healthy controls.

Tab. 4. Spearman's rank correlation coefficients and p *values for chemerin*

(220 vs. 255 ng/mL, $p > 0.05$)[14]. Similarly, among children with TDM1 and normal body weight, chemerin levels did not differ depending on the duration of diabetes[15]. This may indicate that the duration of TDM1 may not affect chemerin levels in children. On the other hand, adult patients with increased levels of chemerin had a longer duration of diabetes in a study by Gu et al.[16]. Similar observations were made among Egyptian diabetic adults in a study by Elmahdy et al.[17].

Importantly, no difference in chemerin levels was observed between children with good and poor diabetic control. Likewise, no relationship between chemerin levels and metabolic control of the disease was observed in normal weight children with TDM1[15].

In contrast, Elsehmawy et al. found a significant increase in serum chemerin in children with T1DM as compared to controls (117.12 ± 25.79 vs. 83.33 ± 5.51 pg/mL, $p < 0.001$) as well as in non-controlled and controlled diabetic children (135.36 ± 15.18 vs. 89.67 ± 4.85 pg/mL, $p < 0.001$)[11]. Chemerin was significantly higher in adolescent diabetic patients than in healthy controls[18]. Increased circulating chemerin was also observed in adult patients with type 2 diabetes mellitus[16,19]. Abnormal levels of circulating and gluteal subcutaneous adipose tissue-secreted chemerin were noted in adult patients with nascent metabolic syndrome[20].

Also, no statistical difference in chemerin levels was found depending on sex among children with NT1DM, T1DMn, and healthy children. In the T1DMw group, chemerin levels were higher in girls than in boys ($p < 0.05$). The associations between chemerin concentration and the sex of the subjects are not clearly defined - some studies indicate no sex differences, whereas others describe increased concentration of this hormone in one of the sexes[17–24].

Furthermore, no difference in chemerin levels was observed between the studied groups of children depending on BMI percentiles. In contrast, the study by Redondo et al. found that obese children had significantly higher serum chemerin levels compared with lean children (125.1 vs. 98.4 ng/mL, $p = 0.001$)[25]. Moreover, in the group with obesity, the serum levels of chemerin were significantly higher compared with the controls (130.5 vs. 113.8 ng/mL, $p = 0.006$)[26]. Similar observations have been described in other reports[9,27].

Our study showed no correlation between chemerin levels and patients' clinical parameters including HbA1c and lipid profiles. Only negative correlations were found between chemerin and age in children with NT1DM and T1DMw. A positive association of chemerin with age was observed in majority of studies on chemerin levels in adult humans[23,28]. A positive correlation of chemerin with BMI, urea, fasting blood glucose, and HbA1c was noted among diabetic children in a recent study[11]. Moreover, the results of other authors showed a relationship between chemerin and LDL levels[18]. In obese children without metabolic syndrome components, chemerin levels also positively correlated with BMI z-score ($R = 0.33$, $p < 0.01$) and the inflammatory parameter C-reactive protein ($R = 0.36$, $p < 0.01$)[26]. Furthermore, positive correlations were found between chemerin levels and BMI for age in both lean and obese children[9,27].

CONCLUSION AND LIMITATIONS

Although our study provides new information on chemerin among paediatric patients with varying degrees of T1DM

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control, several limitations of the study should be mentioned. The study is a single-centre study with a small group of children. The COVID-19 pandemic prevented us from collecting a larger group of patients. Moreover, the assessment of chemerin levels in children with long-term diabetes and the presence of nephropathy and diabetic retinopathy seems to be an interesting issue. Therefore, further research is needed involving larger groups of patients differing in the degree of sexual maturation and the presence of microvascular complications.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could adversely affect the publication's content and claim the right to this publication.

Author contribution

Original concept of study: KJK, AM. Collection, recording and/or compilation of data: KJK. Analysis and interpretation of data; writing of manuscript: KJK, SG. Critical review of manuscript; final approval of manuscript: AM.

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