 

**ORIGINAL ARTICLES/PRACE ORYGINALNE**

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# BODY WEIGHT CHANGES IN CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME

## ZMIANA MASY CIAŁA U DZIECI Z IDIOPATYCZNYM ZESPOŁEM NERCZYCOWYM

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**Abstract**

***Background:*** *Aim of the study was to evaluate factors affecting body mass change in children with idiopathic nephrotic syndrome (INS) during 6-months treatment of initial disease bout with glucocorticoids (GC).*

***Material and methods:*** *We studied 31 children with INS (22♂, 9♀, 3.6±1.8 years) treated during 6 months with GC due to initial INS bout and 31 control healthy children (18♂, 13♀, 4.0±1.8 years). Following factors were evaluated: body mass, body mass index (BMI), BMI Z-score, gender, age, gestational age at birth, birth weight, GC dose, parental age and BMI, time spent for TV/computer, physical activity, place of residence.*

***Results:*** *Mean initial BMI Z-score was 0.35±1.1 in children with INS and -0.11±1.5 in the control group, after 6 months 0.8±1.2 (P=0.049) and 0.07±1.5 (P=0.629), respectively. Δ0-6 BMI Z-score correlated with initial BMI Z-score (r=-0.45, P=0.001), maternal age (r=0.38, P=0.04), and paternal BMI (r=0.51, P=0.0037).*

***Conclusions:*** *1. Initial 6-month GC therapy may result in body mass increase in children with INS. 2. Risk factors for body mass increase in children with INS during the first 6 months of therapy include low initial BMI, older maternal age and paternal obesity.*

**Key words:** nephrotic syndrome, children, obesity, risk factors, glucocorticoids

**Streszczenie**

***Cel:*** *Celem badania była ocena czynników wpływających na zmianę masy ciała u dzieci z idiopatycznym zespołem nerczycowym (IZN) w okresie 6 miesięcy leczenia glikokortykosteroidami (GKS) pierwszego rzutu.*

***Materiał i metody:*** *Badaniem objęliśmy 31 dzieci (22♂, 9♀, 3,6±1,8 lat) leczonych przez 6 miesięcy GKS z powodu pierwszego rzutu IZN oraz 31 zdrowych dzieci z grupy kontrolnej (18♂, 13♀, 4,0±1,8 lat). Przeanalizowano następujące czynniki: masę ciała, wskaźnik masy ciała (BMI), BMI Z-score, płeć, wiek, czas trwania ciąży, urodzeniową masę ciała, dawkę GKS, wiek i BMI rodziców, czas spędzany przed telewizorem/komputerem, aktywność fizyczną i miejsce zamieszkania.*

***Wyniki:*** *Średnia początkowa wartość BMI Z-score wynosiła 0,35±1,1 u dzieci z IZN i -0,11±1,5 w grupie kontrolnej, po 6 miesiącach odpowiednio: 0,8±1,2 (P=0,049) i 0,07±1.5 (P=0,629). Wartość Δ0-6 BMI Z-score korelowała z początkowym BMI Z-score (r=-0,45, P=0,001), wiekiem matki (r=0,38, P=0,04), BMI ojca (r=0,51, P=0,0037).*

***Wnioski:*** *1. Początkowa 6-miesięczna terapia glikokortykosteroidami może wpływać na przyrost masy ciała u dzieci z idiopatycznym zespołem nerczycowym. 2. Czynnikami ryzyka wzrostu masy ciała u dzieci z IZN w pierwszych 6 miesiącach terapii są: niska początkowa wartość BMI, starszy wiek matki i otyłość u ojca.*

**Słowa kluczowe:** zespół nerczycowy, dzieci, otyłość, czynniki ryzyka, glikokortykosteroidy

## INTRODUCTION

Due to recurrent nature of the disease, children with idiopathic nephrotic syndrome (INS) often require long-term glucocorticoid (GC) therapy to maintain disease remission. Obesity is one of the most common complications of systemic GC therapy, found in 35-43% of children with steroid-sensitive nephrotic syndrome [1-3]. On the other hand, the prevalence of obesity is known to increase among healthy children and adolescents in developed countries, reaching 17.3% in the United States [4], and as much as 5% among young children (age 5-7 years) [5]. In European studies, the prevalence of obesity among children was reported to range from 2.7 to 10.2% [6, 7, 8]. Risk factors for overweight and obesity in the general population include low socioeconomic status [9], poor dietary habits [9, 10], low physical activity [9, 10, 11], and increased parental body mass index [BMI] [12]. Data on children with nephrotic syndrome are scarce [13]. Identification of risk factors for obesity in this group would allow targeting care and preventive efforts to those patients who are at the highest risk of this complication.

## AIM

Aim of the study was to evaluate factors affecting body mass change in children with idiopathic nephrotic syndrome (INS) during 6-months treatment of initial disease bout with glucocorticoids (GC).

## MATERIAL AND METHODS

We studied 31 children (22 boys, 9 girls) aged 1.9 to 11.5 years (mean 3.6±1.8 years) with the initial INS bout. Nephrotic syndrome was defined as proteinuria >50 mg/kg/24h or ≥300 mg/dL in a spot urine sample or urinary protein-to-creatinine ratio ≥2000 mg/g in a spot urine sample with associated hypoalbuminemia (serum albumin level ≤2.5 g/dL) and edema [14]. All studied patients had normal renal function as evaluated by the glomerular filtration rate (GFR>90 mL/min/1,73 $m^2$) estimated using the Schwartz formula [14], normal levels of complement C3 and C4 components, normal blood pressure, and had no permanent erythrocyturia. None of the patients had severe concomitant disease that might affect body mass.

All patients were treated with GC prednisone (Encorton, Polfa Warszawa, Warsaw Poland) at the dose of 60 mg/$m^2$/24 h, up to 60 mg/24 h, for the first 4 weeks, followed by 40 mg/$m^2$/48 h, up to 40 mg/48 h, for the next 4 weeks, with gradual dose tapering during the next 4 months. No other immunosuppressive drugs were used in any of the patients. During 6-months follow-up, nephrotic syndrome recurred in 19 (61.3%) patients. INS recurrences were treated with GC at the dose of 60 mg/$m^2$/24 h, up to 60 mg/24 h, until 3 days after resolution of proteinuria, followed by 40 mg/$m^2$/48 h, up to 40 mg/48 h, for the next 4 weeks, with gradual dose tapering during the next 4 months [15]. Before initiation of prednisone therapy patients were instructed by a professional dietetician to follow a low-carb, low-sodium, rich in vegatables, normal protein, and normal calorie diet.

In all patients, the following parameters were evaluated before initiation of GC treatment and at 6 months: height [cm], body mass (after resolution of edema) [kg], and BMI expressed in absolute values, percentiles, and as the Z-score using percentile charts [16]. Overweight was defined as BMI ≥85th percentile and <95th percentile, and obesity as BMI ≥95th percentile for age and gender. Δ0-6 BMI Z-score was defined as difference between BMI Z-score after 6 months and at onset and was calculated for both study and control group.

The following variables were evaluated as factors potentially affecting body mass change in the study group: gender, age, gestational age at birth [week], birth weight [g], parental age [years], parental BMI [kg/$m^2$], time spent for TV/computer and physical activity before and after disease onset [hours/day], and place of residence (rural area, urban area of <100,000 or >100,000 inhabitants), Based on patient medical records, we calculate the daily GC dose during 6 months [mg/kg/24 h].

In all patients, blood pressure was measured using oscillometric devices. Hypertension was diagnosed when three blood pressure measurements were ≥95th percentile [17].

The control group included 31 healthy children.

Statistical analysis was performed using the STATISTICA 9.0 software. Normal variable distribution was evaluated using the Shapiro-Wilk test. Normally distributed variables were reported as mean values ± standard deviation, and non-normally distributed variables as medians and ranges. For normally distributed variables the Student *t* test for dependent variables was used to compare the same data in different time points and the Student *t* test for independent variables to compare data in different groups in the same time point. For non-normally distributed variables the Wilcoxon test was used to compare the same data in different time points and the Mann Whitney U test to compare data in different groups in the same time point. Differences in the rates of overweight and obesity were compared using the Fisher test. Correlations of Δ0-6 BMI Z-score with quantitative data were evaluated using the Pearson correlation coefficient for normally distributed variables, and the Spearman correlation coefficient for non-normally distributed variables. $P<0.05$ was considered statistically significant.

## RESULTS

Baseline clinical characteristics of children with INS and controls are shown in table I. The two groups did not differ significantly in regard to the reported variables.

In the study group, overweight was present at baseline in one child (3.2%) and obesity in 4 (12.9%) children, and at 6 months in 5 (16.1%) and 4 (12.9%) children, respectively. In the control group, overweight was present at baseline in 2 (6.5%) children and obesity in 2 (6.5%) children, and at 6 months in 3 (9.7%) and 3 (9.7%) children, respectively. We did not find significant differences in the number of children with overweight and obesity between the two groups.

Figure 1 and table II show BMI and BMI Z-score values in both groups during 6 months of follow-up. At 6 months, BMI and BMI Z-score showed significant changes (P=0.029 and P=0.049, respectively) in the study group but did not change significantly in the control group. BMI Z-score values did not differ between the two groups at baseline, and at 6 months, the mean BMI Z-score was significantly higher in the INS group compared to the control group (P=0.042). We showed that both in the INS and the control group, Δ0-6 BMI Z-score values did not differ between genders, and also between boys and girls in both groups. However, BMI Z-score at 6 months in girls with INS was significantly (p=0.042) higher than in girls from control group.

We did not find either significant differences in the 6-month increases in body mass, BMI, and BMI Z-score between children with or without INS recurrence (1.72±1.26 vs. 2.12±1.38 [kg], p=0.409; 0.59±1.44 vs. 0.66±1.65 [kg/m$^2$], p=0.904; 0.37±1.12 vs. 0.53±1.27, p=0.718, respectively). Also no effect of the place of residence (rural area, urban area with <100,000 or >100,000 inhabitants) on the increase in Δ0-6 BMI Z-score value was seen in the INS group (0.34±1.04 vs. 0.78±1.17 vs. 0.26±1.26, P=0.571). Hypertension developed during 6 months in 6 (19.4%) patients. Patients who developed hypertension were characterized by higher Δ0-6 BMI Z-score compared to normotensives (1.9±1.0 vs. 0.09±0.9, P=0.0003). They also received significantly higher daily GC dose during 6 months of treatment (1.4±0.4 vs. 1.1±0.3 [mg/kg/24h], P=0.048).

Correlations of Δ0-6 BMI Z-score with analyzed parameters in the study and control groups were

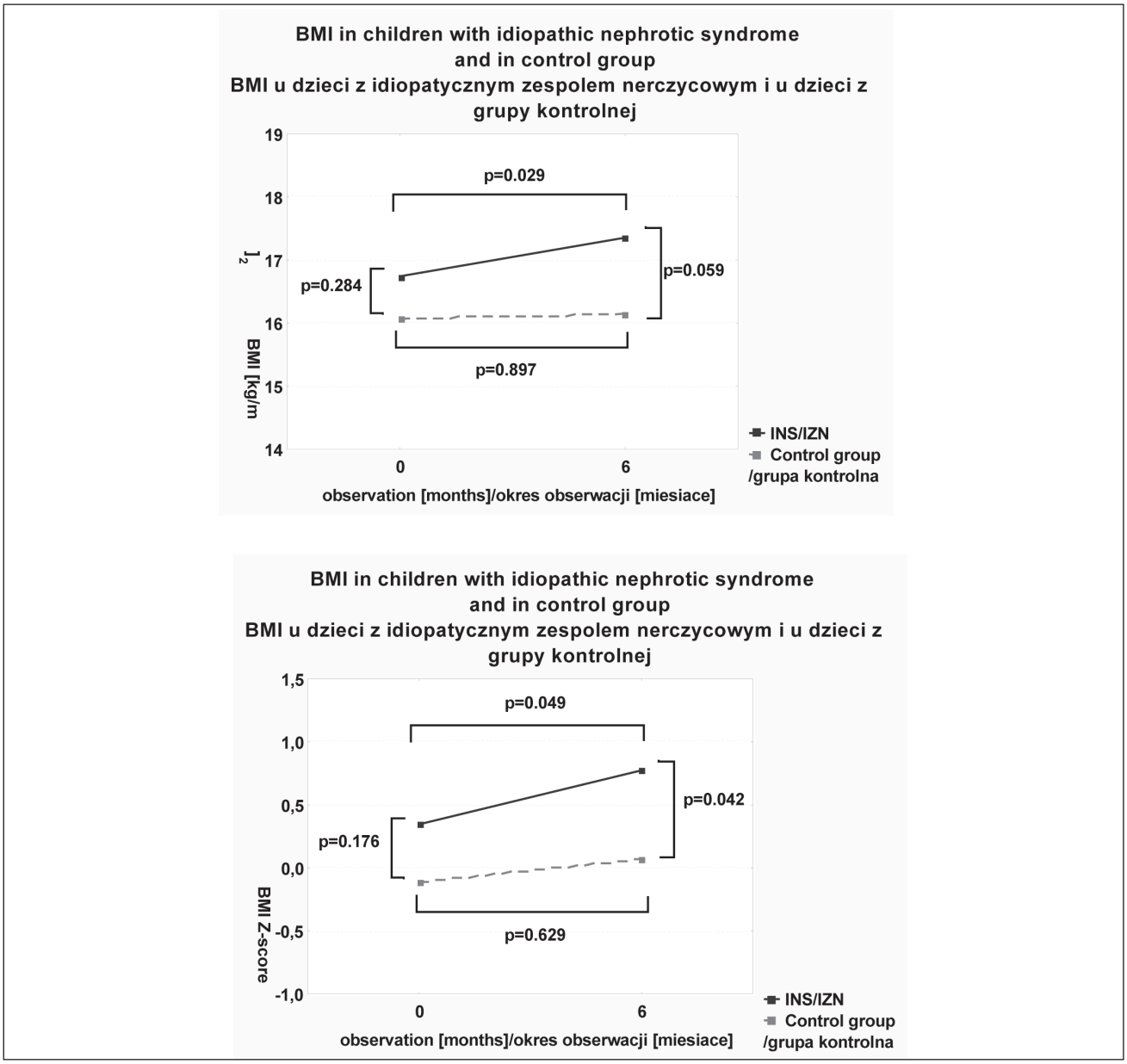


Fig. 1. BMI and BMI Z-score in children with idiopathic nephrotic syndrome (INS) and children in the control group.

*Ryc. 1. BMI i BMI Z-score u dzieci z idiopatycznym zespołem nerczycowym (IZN) i u dzieci z grupy kontrolnej.*

Table I. Clinical characteristics of children with idiopathic nephrotic syndrome (INS) and children in the control group.

*Tabela I. Dane kliniczne dzieci z idiopatycznym zespołem nerczycowym oraz dzieci z grupy kontrolnej.*

| **Variable** ***Zmienna*** | **Patient group/*Grupa pacjentów*** | | **P** |
|---|---|---|---|
| | **INS** ***IZN*** | **Control** ***Grupa kontrolna*** | |
| Number of children: n *Liczba dzieci: n* | 31 | 31 | - |
| Gender boys/girls: n Płeć chłopcy/dziewczynki: n, % | 22/9 71/29 | 18/13 58/42 | NS (P=0.30) |
| Age [years]/*Wiek [lata]* | 3.6±1.8 | 4.0±1.8 | NS (P=0.18) |
| Body mass [kg]/ *Masa ciała [kg]* | 16.93±7.82 | 18.48±7.14 | NS (P=0.42) |
| BMI [kg/m$^2$] | 16.74±2.30 | 16.07±2.59 | NS (P=0.28) |
| BMI Z-score | 0.35±1.10 | -0.11±1.48 | NS (P=0.18) |
| Gestational age [weeks]/ Wiek urodzeniowy [tygodnie] | 38 (36-41) | 39 (34-42) | NS (P=0.05) |
| Birth weight [g] Urodzeniowa masa ciała [g] | 3425 (2150-4400) | 3515 (2150-4520) | NS (P=0.63) |
| Paternal age [years] *Wiek ojca [lata]* | 33.5 (25.0-46.0) | 35.0 (28.0-54.0) | NS (P=0.22) |
| Maternal age [years] *Wiek matki [lata]* | 33.0 (22.0-41.0) | 33.0 (28.0-43.0) | NS (P=0.56) |
| Paternal BMI [kg/m$^2$] *BMI ojca [kg/m$^2$]* | 27.8 (20.8-38.5) | 26.9 (21.1-36.8) | NS (P=0.66) |
| Maternal BMI [kg/m$^2$]/ *BMI matki [kg/m$^2$]* | 24.0±4.3 | 22.9±3.3 | NS (P=0.28) |

BMI – body mass index
BMI – (ang. body mass index)/*wskaźnik masy ciała*

Table II. BMI Z-score in the study and control groups.

*Tabela II. BMI Z-score w grupie badanej i kontrolnej.*

| **Variable** ***Zmienna*** | **Patient group/*Grupa pacjentów*** | | **P** |
|---|---|---|---|
| | **INS** ***IZN*** | **Control** ***Grupa kontrolna*** | |
| BMI 0 Z-score | 0.35±1.10 | -0.11±1.49 | P=0.176 |
| BMI 6 Z-score | 0.78±1.19[1] | 0.07±1.46 | **P=0.042** |
| Δ0-6 BMI Z-score | 0.43±1.16 | 0.18±0.66 | P=0.304 |
| BMI 0 Z-score in boys/*u chłopców* | 0.38±1.16 | 0.02±1.66 | P=0.427 |
| BMI 6 Z-score in boys/*u chłopców* | 0.62±1.20 | 0.14±1.72 | P=0.304 |
| Δ0-6 BMI Z-score in boys/*u chłopców* | 0.24±1.05 | 0.12±0.59 | P=0.658 |
| BMI 0 Z-score in girls/*u dziewczynek* | 0.27±1.01 | -0.29±1.26 | P=0.284 |
| BMI 6 Z-score in girls/*u dziewczynek* | 1.16±1.12 | -0.02±1.07 | **P=0.022** |
| Δ0-6 BMI Z-score in girls/*u dziewczynek* | 0.88±1.35 | 0.26±0.77 | P=0.186 |

BMI – body mass index
BMI – (ang. body mass index)/*wskaźnik masy ciała*
[1]study group: BMI 0 Z-score vs. BMI 6 Z-score: p=0.049
*[1]grupa badana: BMI 0 Z-score vs. BMI 6 Z-score: p=0.049*

Table III. Correlations of Δ0-6 BMI Z-score in the study and control groups.
*Tabela III. Korelacje Δ0-6 BMI Z-score w grupie badanej i kontrolnej.*

| **Variable** *Zmienna* | **Patient group/*Grupa pacjentów*** | |
|---|---|---|
| | **INS Δ0-6 BMI Z-score** *IZN Δ0-6 BMI Z-score* | **Control Δ0-6 BMI Z-score** *Grupa kontrolna Δ0-6 BMI Z-score* |
| Age [years] *Wiek [lata]* | R=-0.22, p=0.236 | R=-0.33, p=0.064 |
| Gestational age at birth [week] *Wiek ciążowy [tygodnie]* | R=0.15, p=0.412 | R=-0.39, p=0.028 |
| Birth weight [grams] *Urodzeniowa masa ciała [gramy]* | R=-0.07, p=0.717 | R=0.02, p=0.929 |
| Paternal age at birth [years] *Wiek ojca przy urodzeniu dziecka [lata]* | **R=0.38, p=0.004** | R=0.06, p=0.749 |
| Maternal age at birth [years] *Wiek matki przy urodzeniu dziecka [lata]* | R=0.30, p=0.105 | R=-0.10, p=0.59 |
| Paternal BMI [kg/m$^2$] *BMI ojca [kg/m$^2$]* | R=0.07, p=0.690 | R=-0.00, p=0.983 |
| Maternal BMI [kg/m$^2$] *BMI matki [kg/m$^2$]* | **R=0.51, p=0.0037** | R=-0.02, p=0.933 |
| Initial BMI Z-score *Początkowa wartość BMI Z-score* | **R=-0.45, p=0.001** | R=-0.26, p=0.157 |
| Time spent for TV /computer before disease onset *Czas spędzony przed TV /komputerem przed początkiem choroby* | R=0.09, p=0.628 | - |
| Time spent for TV /computer after disease onset Czas spędzony przed TV /komputerem w trakcie choroby | R=0.25, p=0.181 | R=0.28, p=0.123 |
| Time spent for physical activity before disease onset *Czas spędzony na aktywności fizycznej przed początkiem choroby* | R=-0.26, p=0.158 | - |
| Time spent for physical activity after disease onset *Czas spędzony na aktywności fizycznej w trakcie choroby* | R=-0.16, p=0.397 | R=0.26, p=0.156 |
| Mean daily GC dose during 6 months *Średnia dobowa dawka GC w okresie 6 miesięcy [mg/kg/24h].* | R=0.30, p=0.096 | - |

BMI – body mass index, GC – gluococorticoid
*BMI – (ang. body mass index) wskaźnik masy ciała, GC (ang. glucocorticoid) – glikokrotykosteroidy*

presented in table III. In the study group we found negative correlations of Δ0-6 BMI Z-score with initial BMI Z-score and positive with maternal age at birth and paternal BMI. In the control group, Δ0-6 BMI Z-score showed a negative correlation only with gestational age at birth.

## DISCUSSION

In our study group of children with INS, we did not find a significant increase in the number of children with overweight and obesity during 6 months of GC treatment of the initial bout of the nephrotic syndrome. However, BMI, and BMI Z-score increased significantly during this period in the study group, with a significant difference at 6 months compared to healthy controls.

Our findings indicate that GC therapy may be a risk factor for body mass increase. Thus, it becomes even more important to identify other risk factors for body mass increase in this patient group so as to appropriately target care and preventive efforts to those patients who are at the highest risk. One approach to treat or prevent obesity is the use of other drugs that allow GC dose reduction. For example, in a study reported recently by

Sato et al., initiation of rituximab therapy in children with steroid-dependent INS reduced the rate of obesity from 16.9% to 3.1% [18].

There are no data in the literature regarding treatment duration needed for the development of obesity in children with INS exposed to GC. In pediatric kidney transplant recipients who are also treated with GC, obesity developed much faster compared to our group but frequently regressed following prednisone dose reduction [19]. Similarly, in a group of 130 children with inflammatory rheumatoid disease, the largest increase in BMI Z-score was seen during the first 4 months of GC therapy [20].

In our study group, obesity was present in 12.9% of patients after six months of GC therapy. In the studies by Foster et al. and Leonard et al., obesity was found in 41.0% and 38.0% pediatric INS patients with recent exposure to GC, respectively [13, 21]. In both these studies, unlike in our study group, disease and treatment duration was variable, often much longer than half year.

In our study group, risk factors for body mass increase included low initial BMI Z-score, older maternal age, and higher paternal BMI. In the study by Foster et al. cited above, identified risk factors for obesity in children with INS were higher maternal BMI, female gender, and non-Caucasian race [13].

During 6-months treatment we did not find significant association between the mean GC dose and BMI increase. Foster et al. also did not show such a relationship but they analyzed only steroid doses at specific time points and not time-averaged doses [13]. On the opposite, in the study by Shiff et al. who evaluated the effect of steroid on body mass in 130 children with rheumatologic conditions, the change in BMI Z-score correlated with the mean steroid dose [20]. Nakamura et al. showed, in children with a history of INS who were not treated with steroids at the time of the evaluation, that both the total GC dose and duration of GC therapy significantly increased long-term risk of obesity and hypercholesterolemia [22]. In contrast, Kyrieles and Rüth did not show a relation between BMI in adults with a history of INS in childhood and the number of disease bouts and GC dose [23, 24].

Higher paternal BMI which was identified as a risk factor for body mass increase in our study may be a marker of a sum of multiple genetic (e.g., GC receptor gene polymorphisms) and environmental (e.g., diet at the family home) factors acting on young subjects exposed to GC. A similar relation between obesity and parental BMI was found in a population of healthy children [12, 25]. Lack of an identified effect of maternal BMI in our study, unlike in the study by Foster et al. [13], might have resulted from cultural differences. Studies published recently indicate a role of genetic factors in the development of obesity in the pediatric population. Barat et al. showed an effect of GC receptor and GC-binding protein gene polymorphisms on the development of simple obesity in children [26], and Nakamura showed the importance of angiotensinogen gene polymorphisms in the development of obesity in children with INS treated with GC [27].

In contrast to studies performed in the general population [9, 10, 11], we were unable to show a relation between body mass increase and time spent for TV/computer. Similarly, Shiff et al. did not show an effect of physical activity on body mass change in children with rheumatologic conditions treated with GC [21]. Our findings might have been affected by the nature of data regarding activity during leisure time, which were collected using a questionnaire.

The limitations of the study are: small number of patients in both study and control group, and lack of analysis of body compostion analysis (bioimpedance) in the patients. Relatively small sample sizes precluded using multivariate analysis to assess most important factors affecting weight changes in children with idiopathic nephrotic syndrome.

## CONCLUSIONS

1. Initial 6-month GC therapy may result in body mass increase in children with INS.
2. Risk factors for body mass increase in children with INS during the first 6 months of therapy include low initial BMI, older maternal age and paternal obesity.

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