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Research Article

# Characteristics of adverse side effects of corticosteroid therapy in children with nephrotic syndrome and methods of pharmacological correction

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## Abstract

**Introduction:** The article discusses the issues of the long-term glucocorticosteroid therapy in children with nephrotic syndrome that results in severe adverse side effects.

**Methods:** This retrospective study included 89 case reports of patients with nephrotic syndrome, aged 1–18, who received treatment at Voronezh Regional Pediatric Hospital №1 in 1999–2014. The children's BMI Z-score was calculated from neasured height and weight. The authors considered therapeutical complications revealed through clinical-laboratory and instrumentation examination.

**Results and discussion:** Long-term administration of glucocorticosteroids in patients with steroid-dependent nephrotic syndrome caused overweight and obesity. The patients who had received glucocorticosteroids for 6 months prior to the examination were overweight or obese (78%), had reactive pancreatitis (72%), leukemoid reactions (67%), liver damage (50%), Cushing's syndrome (44%), chronic gastroduodenitis (33%), hyperglycemia (11%), arterial hypertension (6%), or infectious diseases (6%). The children observed during the period of prolonged remission of nephrotic syndrome had neither overweight, nor obesity or growth failure; signs of chronic gastroduodenitis were observed in 15% of the children.

**Conclusion:** The long-term glucocorticosteroid therapy in children with nephrotic syndrome caused the excess body weight or obesity and gastro-intestinal disorders. So, proton pump inhibitors should be applied simultaneously with glucocorticosteroids to prevent gastro-intestinal disorders.

## Keywords

adverse side effects, children, glucocorticosteroids, nephrotic syndrome.

## Introduction

Nephrotic syndrome is a clinical symptom complex characterized by proteinuria of >40 mg/m$^2$/h, a decreased blood albumin level to <25 g/l, hyperlipidemia and swelling development (Obukhova and Dlin 2014). The incidence of this diseases in the pediatric population is 2–7 primary cases per 100 000 children a year; this disease may be idiopathic or secondary (in the presence of systemic diseases of the connective tissue, drug administration

and other pathologies) (Clinical recommendations on medical care for children with nephrotic syndrome).

The idiopathic nephrotic syndrome (INS) is the most common in children. The onset of the disease at the age of 4–6 is characterized by the most favourable course and an adequate response to the steroid therapy. Minimal glomerular alterations, when light microscopy detects insignificant changes or lack of any, appear to be a morphological substrate of this clinical course. Focal-segmental glomerular sclerosis is more common in children experiencing the first occurrence of nephrotic syndrome at the age of 6 (up to 45% of cases); other types of the disease are less common (Clinical recommendations on medical care for children with nephrotic syndrome).

According to the International Study of Kidney Disease in Children (ISKDC) recommendations, administration of glucocorticosteroids (GCS) is indicated to all children with INS (Beck et al. 2013). The standard regimen of the glucocorticosteroid therapy includes administration of prednisolone at a dose of 60 mg/m$^2$/day (no more than 60 mg/day) for 4–6 weeks, followed by a hormone prescribed in the alternating regimen, every other day, at a single dose of 40 mg/m$^2$ (maximum 40 mg/48 h) for 4–6 weeks with gradual dose reduction by 5 mg (10 mg/m$^2$) once a week until total discontinuation of the drug. The entire duration of the glucocorticosteroid therapy should be of no less than 4–5 months (Lombel et al. 2013, Pasini et al. 2015). The alternating regimen (administration of the drug every other day) is suggested to support remission, since this regimen has a less negative impact on the child growth and extends the remission of the disease (Broyer et al. 1992).

The nephrotic syndrome is divided into steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) depending on the response to the conventional therapy. In SSNS, the remission is usually achieved within 2–4 weeks, in some patients – by the 6$^{th}$-8$^{th}$ week, and only in 4% of children – in 12 weeks after the onset of treatment. If there is no remission in 8 weeks after the start of prednisolone administration, then SRNS is diagnosed (Obukhova and Dlin 2014). Approximately 80–90% of children respond to the corticosteroid therapy appropriately and have a favourable prognosis; but 50–60% of patients have either frequent disease recurrences, or develop a steroid-dependent variant of the SSNS, which is termed steroid-dependent nephrotic syndrome (SDNS) (Obukhova and Dlin 2014). Most children with the relapsing course of the disease will afterwards respond with a complete remission to corticosteroids, and a long-term prognosis in this group of patients is favourable (Hjorten et al. 2016). The recurrent attacks, steroid-dependence and steroid-toxicity appear to be indications for administration of the immunosuppressive therapy with cytostatics, alkylating agents or preparations of monoclonal antibodies (rituximab) (Obukhova and Dlin 2014).

Children with frequently relapsing nephrotic syndrome (FRNS) and SDNS require a long-term corticosteroid therapy, which results in the development of severe side effects, including growth failure, behavioral disorders, obesity, Cushing's syndrome, hypertension, visual impairment, impaired glucose tolerance, decreased bone mineral density and other disorders (Obukhova and Dlin 2014). The number of adverse side effects (ASE) is considered to be the highest when administering glucocorticosteroids at high doses considerably exceeding physiological doses (Landyshev 2014). Moderate and high doses of corticosteroids administered for anti-inflammatory and immunosuppressive purposes are stated to be >0.5–0.75 mg/kg/day relating to prednisolone (Landyshev 2014, Simmonds et al. 2010).

Side effects of the glucocorticosteroid therapy depend on both – dosage and duration of treatment, and an individual patient's sensitivity. The impact of various schemes of the glucocorticosteroid therapy on the risk of the development of nephrotic syndrome and the adverse event detection frequency have been studied in Hahn et al. (2015), and no significant differences in the risk of adverse events were found between long-term treatment and 2–3-month courses of prednisolone administration (Hahn et al. 2015).

# Methods

This retrospective study included 89 case reports of patients with nephrotic syndrome, aged 1–18; all the patients received treatment at Voronezh Regional Pediatric Hospital №1 in 1999–2014.

To perform the comparative evaluation of the parameters of body length, body weight and body mass index (BMI), Z-score was calculated following the method suggested by the World Health Organization (WHO) using WHO AnthroPlus software (WHO growth reference 5–19 years).

NS and a clinical variation of the disease were determined as defined in the current clinical recommendations (Clinical recommendations on medical care for children with nephrotic syndrome). The children having NS were given therapy in compliance with the protocol of the ISKDC and Federal Clinical Recommendations (Beck et al. 2013, Clinical recommendations on medical care for children with nephrotic syndrome). Relapses of the disease were treated with a course of prednisolone (60 mg/m$^2$/day, three times a day) until 3 normal urinary test results were obtained; prednisolone therapy was then continued in the alternating regimen (40 mg/m$^2$/48h in a single dose for 4–6 weeks) with further dose reduction by 5–10 mg/week until complete withdrawal of the preparation (Beck et al. 2013). When complications of the GCS therapy were revealed, the treatment was performed according to the clinical recommendations on the management of patients (Clinical recommendations on medical care for children with nephrotic syndrome).

Statistical analysis was performed using STATISTICA v. 6.0. software (StatSoft, США). Mean values (MV) were presented together with the standard deviation (SD). The two-tailed Student's t-test was used to reveal signif-

icant differences between two independent groups; the test was performed under the following condition – the compliance between the empirical distribution of Gaussian samples and dispersion equality in the groups. Dispersion equality in the groups was tested by F-test. When the Gaussian assumption for the values under study were rejected, the non-parametric Mann-Whitney U test was applied to analyze differences in two groups. These parameters were described using the median value ($25^{th}$; $75^{th}$ percentiles). The probability of statistical hypotheses was accepted to be at a 5% level of significance.

## Results and discussion

The impact of glucocorticosteroids on the physical development of children was assessed on the case reports of 28 patients who had been receiving the glucocorticosteroid therapy during the last 6 months before the examination. Twelve patients included in the study had non-frequently relapsing steroid-sensitive nephrotic syndrome (SSNS), 6 patients had frequently relapsing nephrotic syndrome (FRNS), and 10 patients had steroid-dependent nephrotic syndrome (SDNS). Table 1 presents the characteristics of the patients of different groups.

Groups of patients with various clinical forms of NS did not differ in age (Table 1). The median age in different groups was 6–8.3 years. The children with FRNS, especially, those with SDNS, had a statistically longer duration of the disease, duration of GCS therapy and total cumulative GCS dose compared to the children with non-frequently relapsing nephrotic syndrome. The most significant differences were obtained in patients with SDNS. Those children received long-term treatment with low doses of corticosteroids. The patients with frequently relapsing nephrotic syndrome received repeated courses of high doses of GCS. No differences were revealed between the groups of patients regarding the dose received by the children during the last 6 months of the therapy (p=0.306).

All the atients with nephrotic syndrome had body length parameters within the normal values of healthy children (the mean value of Z-score being 0 and standard deviation equalling 1). Mean values of the body length were lower in the group of patients with steroid-dependent nephrotic syndrome compared to the children with non-frequently and frequently relapsing nephrotic syndrome (Fig. 1).

The mean values of BMI were higher in the patients with frequently relapsing and steroid-dependent nephrotic syndrome compared to the patients with non-frequently relapsing nephrotic syndrome. The most significant deviations of Z-score from the mean values were obtained in the group of children dependent on steroids. Long-term administration of GCS resulted in overweight and obesity in these patients (BMI Z-score >1) (Fig. 2).

A retrospective analysis of other adverse side effects (ASE) of the glucocorticosteroid therapy was performed in 31 patients with steroid-sensitive nephrotic syndrome. The analysis included 16 boys (51.6%) and 15 girls (48.4%), aged 3–18; median age (standard deviation, SD) was 8.2 (SD - 4.0). Group 1 included 18 children who had been receiving GCS for 6 months prior to the hospital admission; this number also included 4 children with FRNS and 3 patients with SDNS. Group 2 included 13 patients who had not received GCS for 6 months and longer. All the patients of group 2 had non-frequently relapsing nephrotic syndrome, with remission periods up to 13 years.

Most children (21 patients, 68%) were admitted to the hospital repeatedly; the total number of hospitalizations was 87, 4.1 hospitalizations per one child (Table 2).

Thirty-seven patients (43%) were admitted to the hospital in the relapsing period, 50 patients (57%) – in the remission period. Duration of the remission in patients from different groups is given in Table 2. Hospital admission during the period of remission was accompanied by a course of GCS therapy in patients of group 1. Patients of group 2 admitted during the period of remission did not receive GCS. Over the three years of observation, two

**Table 1.** Clinical Variations of the Disease and Administered Doses of Glucocorticosteroids in Pediatric Patients with Nephrotic Syndrome.

| Parameters | SSNS n=12 | FRNS n=6 | SDNS n=10 | p |
|---|---|---|---|---|
| Age of children, years | 6.0 | 7.8 | 8.3 | |
| Median value (25; 75) | (5.2; 9.6) | (5.3; 8.1) | (4.6–13.3) | 0.515 |
| min–max | 4.0–14.0 | 4.2–14.5 | 3.1–17.4 | |
| Duration of the disease, months (mos) | 16.0 | 39 | 60 | |
| Median value (25; 75) | (8.8; 32.3) | (19.0; 70.0) | (29–124.3) | 0.021 |
| min–max | 4.0–43.0 | 19.0–74.0 | 7.0–177.0 | |
| Duration of GCS therapy, days | 270 | 670 | 1266 | |
| Median value (25; 75) | (183; 491.3) | (630; 730) | (562.3; 2450) | 0.005 |
| min–max | 90–760 | 518–1185 | 220–3592 | |
| Cumulative dose of GCS, mg/kg | 202.6 | 333.8 | 518.7 | |
| Median value (25; 75) | (154.8; 230.3) | (294.2; 361.3) | (423.1; 594.7) | <0.001 |
| min–max | 92.8–316.1 | 286.5–487.7 | 230–706.4 | |
| Dose of GCS during 6 mos, mg/kg | 52.3 | 48.3 | 55.3 | |
| Median value (25; 75) | (35.1; 67.9) | (35.6; 51.9) | (28.3; 130.2) | 0.306 |
| min–max | 13–118.6 | 26.9–72.7 | 15–266.5 | |

**Table 2.** Hospitalization of Patients with Steroid Sensitive Nephrotic Syndrome.

| Parameters | Group1 (n=18) | | Group 2 | p |
|---|---|---|---|---|
| | Non-FRNS (n=11) | FRNS and SDNS (n=7) | Non-FRNS (n=13) | |
| Total number of hospitalizations, abs. | 43 | 28 | 16 | |
| Number of hospitalizations per one patient | 3.9 | 4.0 | 1.2 | 0.033 |
| Number of hospitalization in the relapsing period, abs. (%) | 21 (49) | 14 (50) | 2 (15) | |
| Duration of remission, months M (SD), months min – max | 3.1 (2.4) 1–10 mon | – | 60.8 (51.5) 11 mon–150 mon | 0.000 |

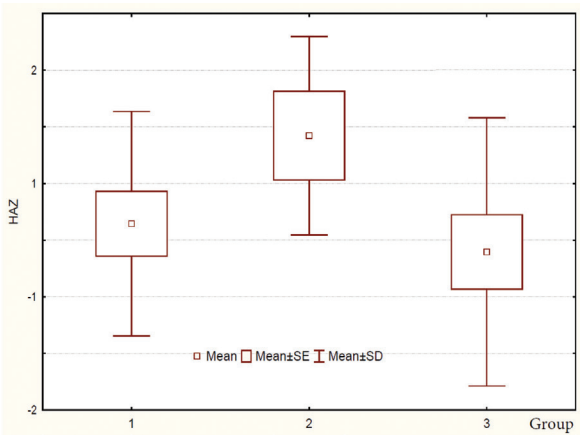


**Figure 1.** Z-score of the body length in patients with different clinical variations of nephrotic syndrome (1 – SSNS, 2 – FRNS, 3 – SDNS; HAZ – height for age Z-score).

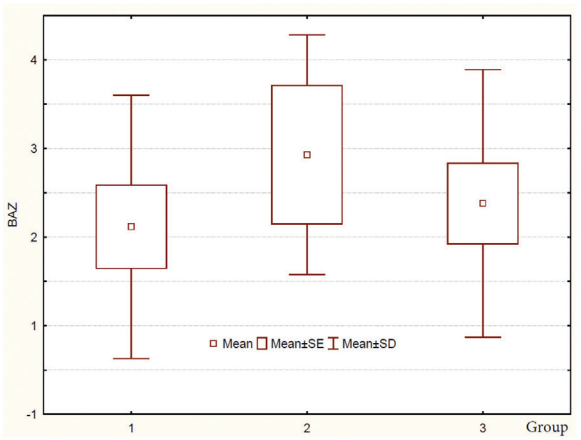


**Figure 2.** Z-score of the body weight in patients with different clinical variations of nephrotic syndrome (1 – SSNS, 2 – FRNS, 3 – SDNS; BAZ – BMI for age Z-score).

patients of group 2 had had one relapse of nephrotic syndrome – after remission of 24 and 37 months.

The side effects of the GCS pharmacotherapy were assessed in the patients in all the periods of hospitalizations. The following parameters were considered for assessment of the adverse side effects: complaints, physical signs of Cushing's syndrome, blood pressure findings, full blood count and biochemical assay findings, urinary test findings, results of the kidney and abdominal US examination, fibrogastroduodenoscopy, and the results of the ophthalmological examination. The following parameters were assessed: the changes in the general health, deviations from the normal values of the physical development parameters and findings of the laboratory and instrumentation tests, which appeared in in patients when administering the GCS therapy and were observed after its completion. Before GCS administration, the children had neither gastro-intestinal pathologies, nor obesity; their blood pressure did not exceed the 90$^{th}$ percentile of the age norm; there were no pathological changes in either laboratory, or instrumentation test findings. No other pathologies were revealed in the patients included in the study, they were not taking other preparations that might result in the observed conditions.

Most of the children had several hospitalizations regarding nephrotic syndrome; the incidence of ASE was considered during all the hospitalizations; the level of physical development, the cumulative dose of GCS and the clinical variation of the disease were assessed based on the findings of the last hospitalization.

The children of group 1 and 2 with non-FRNS received lower a cumulative dose of prednisolone and had a shorter duration of GCS administration than the patients with FRNS and SDNS.

ASEs of the corticosteroid therapy were recorded in 17 patients of group 1 (94.4%). Several ASEs were observed in all the patients of group 1. Two children of group 2 were diagnosed with diseases that might have resulted from the previous GCS therapy; the other children of group 2 had no delayed complications of the GCS administration.

Overweight and obesity – either as an autonomous complication after the GCS therapy or as a sign of Cushing's syndrome – were most frequently observed in children of group 1. Some children had body weight gain within the normal values typical for this age and gender. Cushing's syndrome was diagnosed in cases of specific Cushing-type distribution of adipose tissues (in the neck, facial, abdominal regions), the thinning of the limbs, skin changes, and striae appearance.

No children of short or shorter than medium height were revealed (body length Z-score <2). Two patients of group 1 in repeated hospitalization during the relapsing period of NS had a decreased Z-score of the body length within the normal values typical for this age and gender. In the further observation period, the body length Z-score recovered to reach the previous parameters.

Leukemoid reactions (evident leukocytosis with an increased content of neutrophilic leukocytes) were reported in 12 children of group 1 against the administration of the maximum prednisolone dose.

Corticosteroid therapy frequently resulted in the gastro-intestinal events in the patients under study: there were signs of reactive pancreatitis, in the children of group 2 – exacerbation of pancreatitis with pain syndrome and an increase in the serum amylase. Exacerbation of chronic gastroduodenitis was observed in 33.3% of patients of group 1; gastric erosion was diagnosed in one case. Half of the children had liver damage (diffuse hepatic changes in ultrasound examination, an increase in transaminases in blood serum).

Arterial hypertension, disturbances of the carbohydrate metabolism and infections were less frequently diagnosed complications in the patients with nephrotic syndrome during their stay in the hospital (Fig. 3).

Obesity and overweight, reactive pancreatitis, chronic gastroduodenitis and liver damage were more often diagnosed in the children with non-frequently relapsing nephrotic syndrome (Fig. 3).

Unlike them, the patients with FRNS and SDNS more frequently developed arterial hypertension and Cushing's syndrome. There were no statistically significant differences between the groups.

The performed study showed the incidence of adverse side effects in the children receiving the GCS therapy and the structure of pediatric morbidity patterns after its completion. Long-term administration of high doses of GCS resulted in the development of Cushing's syndrome. The incidence of these adverse side effects was higher than in other studies (Hahn et al. 2015, Ishikura et al. 2015); this is probably due to the fact that the occurrence of the adverse side effects was analyzed during administration of the maximum dose of prednisolone. The children of group 2, who were monitored during the period of the prolonged remission of nephrotic syndrome, were neither overweight, nor obese; they had no growth failure. The study of the adverse side effects depending on whether GCS were or were not administered allowed assessing the prognostic value of therapeutic side effects and their impact on the child's health.

Gastro-intestinal disorders were frequently diagnosed in the patients of group 1; they included development of reactive pancreatitis, chronic gastroduodenitis, and hepatic disorders. The incidence of the above disorders was higher compared to the data of other researchers (Bekmurzayeva and Poleshchyuk 2012, Hahn et al. 2015). The complaints of a child and all the changes revealed in clinical-laboratory and instrumentation tests were taken into account. Pancreatic and hepatic disorders were transient and were corrected after the end of the GCS therapy. Two patients had signs of chronic gastroduodenitis after the end of GCS therapy. This fact was one of the reasons for developing a criterion of the early diagnostics of adverse side effects in GCS therapy to perform targeted pharmacological correction of the conditions described above.

Leukemoid reactions detected in the children of group 1 against the GCS administration appeared during the administration of the maximum hormone dose and disappeared after the dose reduction; which did not require additional correction.

According to the clinical records, one child of group 1 did not reveal complications of the GCS administration despite the "standard" dose of GCS. Though there was body weight gain in this case as well, it fell within the range of values normal for the given age and gender.

Foster et al. (2006) specified influence of the immediate (within 6 months) and long-term (over 6 months)

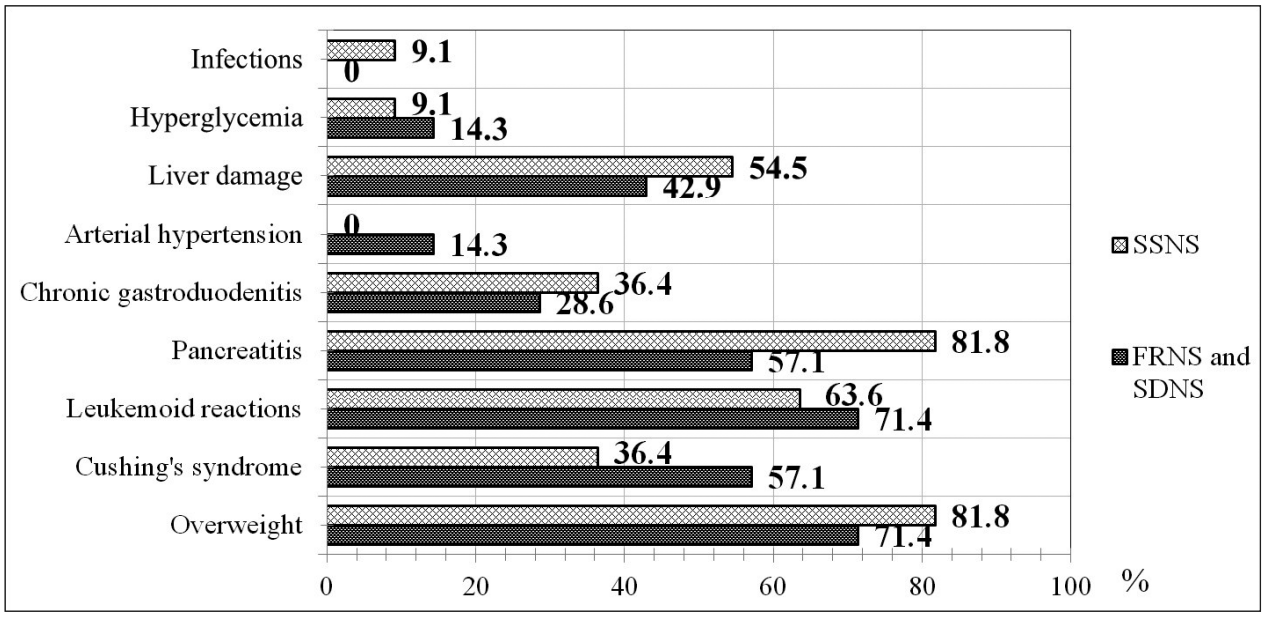


**Figure 3.** The incidence of the adverse side effects of corticosteroid therapy in patients with clinical variations of nephrotic syndrome.

administration of GCS on the development of obesity in children with steroid-sensitive nephrotic syndrome (Foster et al. 2006). According to the present study results, non-administration of GCS for 6 months and over resulted in the normalization of the body weight of a child. In long-term monitoring (up to 13 years), children with non-frequently relapsing nephrotic syndrome had neither excess body weight nor growth failure.

Blood pressure was measured and a blood glucose test was performed regularly in all children. Deviations of these parameters were detected only in a small number of patients.

In adults, GCS administration often results in steroid diabetes mellitus (Landyshev 2014, Strachunsky and Kozlov 2001). In the performed studyб the episodes of hyperglycemia during the administration of high doses of GCS were reported only in 2 children.

There was a retrospective study of the adverse side effects of the GCS therapy by analyzing the clinical records findings, that is why the study did not include behavioral and sleep disorders that might also occur in children during the GCS administration. All the children were examined by the ophthalmologist, but this examination did not involve intraocular pressure measurement. All the children with nephrotic syndrome were given calcium and vitamin D preparations to prevent osteoporosis; an X-ray examination was performed if medically required, but no targeted examination was performed to reveal osteoporosis in the patients.

The general recommendations on the management of patients receiving GCS orally include application of the minimal effective doses compliant with the therapeutical regimen (the alternating regimen, circadian rhythm of administration). If possible, it is necessary to reduce the dose of the preparation until the drug withdrawal (Beck et al. 2013). Rational nutrition with the sufficient protein content, increased intake of products rich in potassium (1.5–2 g/day), calcium and vitamin D, reduced intake of chlorides, maintenance of the normal body weight, regular physical exercise, depending on the general health status, are of great importance (Tsygin et al. 2006).

Potassium preparations (potassium chloride, potassium and magnesium aspartates) should be administered to correct hypokalemia arising when administering high doses of corticosteroids.

Cholecalciferol (vitamin D3) (dosage 1000–30000 IU/day) in combination with calcium preparations (dosage 1000–1500 mg/day) should be prescribed to correct osteopenia and osteoporosis in children receiving corticosteroids (Clinical recommendations on medical care for children with nephrotic syndrome). This therapy should be administered simultaneously with prescribing GCS that are to be taken for a long term – for 3 months and over (Toroptsova 2014).

To prevent damage to the gastro-intestinal tract , proton pump inhibitors should be applied (Beck et al. 2013).

When GCS are administered for more than 10 days, the preparation should be withdrawn with the gradual dose reduction. Withdrawal regimens depend on the duration of CS administration. It is possible to reduce intake of prednisolone by 2.5–5 mg every 3–5 days (Beck et al. 2013). Special care should be taken in reducing a prednisolone daily dose to 10 mg and less. If the preparations have been applied for 2 weeks and longer throughout 1.5–2 years, the patient's status should be monitored under stress after withdrawal of the preparations, and, when necessary, a protective therapy with GCS should be performed (Beck et al. 2013).

There are no evidence-based data relating the ASE of GCS therapy specific for treatment of glomerulonephritis, but there is evidence relating to immunosuppression in kidney transplantation. Application of antibiotics to minimize opportunistic infections and proton pump inhibitors to prevent peptic ulcers are the examples of the most common preventive measures (Beck et al. 2013).

## Conclusion

Thus, glucocorticosteroid therapy of nephrotic syndrome in children resulted in the development of a large number of side effects. Adverse side effects, including the most commonly observed obesity and overweight, reactive pancreatitis, liver damage, Cushing's syndrome, were reported in 94.4% of patients receiving glucocorticosteroid therapy for 6 months prior to the examination. After completion of the corticosteroid therapy (for 6 months and more), the signs of chronic gastroduodenitis were recorded in 15.4% of children; which might be ASE of the GCS therapy.

In addition to potassium and cholecalciferol preparations, proton pump inhibitors are recommended for use to prevent adverse side effects of GCS on the gastro-intestinal tract in patients receiving the corticosteroid therapy.

## Conflict of interests

The authors have no conflict of interest to declare.

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