Acute Phase/Relapse of Nephrotic Syndrome

Subjects: Pediatrics

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Nephrotic syndrome (NS) is a common pediatric disease characterized by a dysfunction in the glomerular filtration barrier that leads to protein, fluid, and nutrient loss in urine. Corticosteroid therapy is the conventional treatment in children. Long-term complications of NS and prolonged exposure to steroids affect bones, growth, and the cardiovascular system. Diet can play an important role in preventing these complications, but there is a scarcity of scientific literature about nutritional recommendations for children with NS.

nephrotic syndrome nutrition pediatrics

1. Fluid Balance

Patients with NS experience fluid retention and edema, and this leads to an overall water imbalance in the body [1]. Nevertheless, fluid restriction for edema is usually not recommended, as it may cause hypotension and acute kidney injury (AKI), worsening intravascular volume depletion and dehydration [2][3]. However, moderate fluid restriction can be advised with caution in selected cases, such as in patients who develop significant hyponatremia, massive anasarca, or oliguric renal failure [3][4][5]. The management of edema in NS first requires the assessment of the euvolemic state of the patient. In the case of normal intravascular volume, moderate edema should be treated only with a low-salt diet, without fluid restriction. Severe edema requires fluid restriction with loop diuretics in hospital settings. In case of reduced intravascular volume with normal blood pressure, albumin should be administered intravenously, followed by furosemide once euvolemia is restored. Hypovolemic shock should be treated following specific resuscitation guidelines [6]. All foods that are liquid at room temperature, such as milk, juice, yogurt, ice cream, soup etc., should be counted upon evaluation of fluid intake [1]. A few strategies can be implemented to control fluid intake in children, such as using small glasses filled to look like they contain a greater amount of fluid, avoiding salty foods that increase thirst, offering frozen pieces of fruit or chewing gum to quench thirst, and avoiding warm environment.

2. Macronutrients Intake

2.1. Carbohydrates

Although corticosteroids are the cornerstone of treatment for NS, their prolonged and repeated use may lead to significant adverse effects, such as hyperglycemia and insulin resistance [4]. Corticosteroids can also cause weight gain, and subsequently obesity, due to behavioral changes, including increased appetite [7][8]. Obesity affects

patients' quality of life and could seriously impact emotional health and social relationships in the future as adults [8]. Because of this, the short- and long-term effects of steroid therapy on body weight must be discussed with patients and their families [7]. Children and their parents need to be instructed to follow a healthier diet [5], with a focus on a reduced intake of simple sugars [9], while an adequate intake of high-complex carbohydrates should be ensured to maximize the utilization of proteins [10][11].

2.2. Proteins

NS causes protein loss through the damaged glomerular filtration barrier in the urine. Early management of the NS recommended an increased protein intake to replace losses and avoid the development of protein malnutrition [4]. However, recent studies demonstrate that increased dietary protein intake does not improve serum albumin concentrations [4]. The higher dietary protein intake results in increased urinary protein losses without a net gain of protein, due to the altered glomerular permselectivity. In addition, a high-protein diet leads to changes in glomerular hemodynamics that may accelerate the progression of renal disease [11]. On the contrary, protein restriction can positively impact kidney function in adult patients with decreased renal function, but a very low-protein diet should be avoided for the risk of malnutrition [2]. Intake of high-quality proteins is recommended in patients with proteinuria, as it is recommended for the general pediatric population [5][6]. Vegetable sources of protein are preferred whenever possible [2].

2.3. Lipids

Dyslipidemia is a frequent metabolic complication in patients with active NS. It is caused by compensatory protein and lipoprotein synthesis in the liver in response to urinary protein loss, reduced transport of cholesterol in the bloodstream due to hypoalbuminemia, and an acquired deficiency of enzymes involved in the regulation of lipid metabolism, which are lost in urine. Additionally, corticosteroid use may be associated with an elevation in blood lipid levels [4]. The long-term effects of dyslipidemia in pediatric NS are unclear. To date, no data support a link between dyslipidemia in these patients and an increased incidence of cardiovascular disease in adulthood. However, the acceleration of the atherosclerotic process in pediatric NS probably has multifactorial roots, as these children show other atherogenic risk factors, such as hypoalbuminemia, hypertension, hypercoagulability, and obesity [4]. On the other hand, dyslipidemia is involved in the progression of renal disease [11]. Measuring baseline lipid levels in children with NS may be useful in screening for underlying secondary causes of dyslipidemia [12]. Lipids normalize following remission, so reducing proteinuria is usually sufficient to reduce hyperlipidemia [11]. Managing dyslipidemia in pediatric NS during the acute phase requires dietary optimization. Children over 2 years old should follow the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1): fats should be restricted to <30% of total daily calories, saturated fats to <10%, and cholesterol consumption to <300 mg/d [2][4][13], while simultaneously increasing the consumption of healthier fats, such as monounsaturated, polyunsaturated, and omega-3 fatty acids [4]. On the other hand, children who also present with hyperlipidemia should follow the CHILD-2 diet plan, which further limits the intake of saturated fats to <7% and cholesterol to <200 mg/d [4]. No fat intake restriction is recommended for children under the age of 2, and they can be breastfed [4]. The use of pharmacological agents to treat dyslipidemia is controversial when dietary adjustments are insufficient [11].

Evidence of benefits and safety in the use of statin therapy to reduce serum cholesterol levels in children and adolescents with NS is lacking; therefore, it is not recommended for all patients. However, it can be considered in high-risk patients with severe low-density lipoprotein (LDL) cholesterol elevation based on clinical circumstances. Specific triglyceride (TG)-lowering agents are also not recommended for children and adolescents with elevated TGs [4]. New strategies, which may induce partial or complete clinical remission of NS, are increasingly being implemented. These include bile acid sequestrants, fibrates, nicotinic acid, ezetimibe, and lipid apheresis. Because there is a dysregulation in some proteins involved in the lipid metabolism in NS, such as proprotein convertase subtilisin/kexin type 9 (PCSK9), the use of target therapy with anti-PCSK9 monoclonal antibodies or small inhibitory ribonucleic acids (RNAs) could play a crucial role for future treatments [14].

3. Micronutrients Intake

3.1. Sodium

Sodium plays a key role in regulating blood pressure and fluid retention in patients with NS. Nevertheless, there is a lack of standardized recommendations for sodium intake in children with newly diagnosed NS. In children with NS, current suggestions for sodium restriction vary from <2 mEq/kg/d to an approach based on a “no added salt diet” [6][9]. The Pediatric Nephrology Clinical Pathway Development Team proposes a one-to-one ratio of 1 mg of sodium for each calorie (kcal) in order to adequately restrict sodium intake to energy requirement [9]. During the initial nutrition consultation, emphasis should be placed on strategies to lower sodium in the diet, preferring fresh foods to processed ones [9], identifying and limiting high-sodium foods, and avoiding salt when preparing food or eating [1].

3.2. Calcium and Vitamin D

Metabolic bone disease (MBD) is a frequent complication of NS in children. The pathogenesis is multifactorial. Urinary loss of minerals and plasma proteins, including calcium and vitamin D binding protein, results in hypocalcemia and low vitamin D levels, which may lead to osteopenia and osteoporosis. Corticosteroids decrease intestinal absorption and tubular reabsorption of calcium. Hypocalcemia is usually not long-lasting and serum levels of calcium can normalize during remission, but prolonged corticosteroid therapy, especially due to frequent relapses, may cause MBD. Corticosteroids also suppress the development and function of osteoblasts, as they increase the lifetime of osteoclasts and inhibit the release of parathyroid hormone, which results in a reduced overall bone mineral density [4]. Serum vitamin D levels should be routinely monitored in children with NS starting at the time of diagnosis [15]. Periodic assessments are also indicated for serum phosphorus, ionized calcium, parathyroid hormone, and alkaline phosphatase [4]. Moreover, dual-energy X-ray absorptiometry (DXA) can be considered in patients with NS to measure bone mineral density [5]. Patients and their caregivers should be counseled to monitor calcium and vitamin D intake in order to have an age-appropriate calcium intake [9]. When dietary modification is not successful, patient-specific calcium and vitamin D supplementation should be prescribed. Daily supplementation with 500 mg of elemental calcium (250 mg twice daily) is advised [4][9]. Addressed hypocalcemia, vitamin D supplementation regimens reported in the literature range from 800–1000 IU

of cholecalciferol daily to 60,000 IU once a week [4][9]. In patients with advanced renal insufficiency, 1,25-dihydroxycholecalciferol should be used for vitamin D replacement [11]. There is insufficient evidence on the pharmacologic treatment of MBD in children with NS. The prevention and treatment of steroid-induced osteoporosis in pediatric age are currently based on the reduction or discontinuation of steroids [5].

3.3. Iron, Copper, and Zinc Deficiency and Anemia

The urinary loss of transferrin, erythropoietin, transcobalamin, ceruloplasmin, iron, and trace elements may lead to anemia. Patients with iron deficiency anemia should receive replacement therapy, and, in the case of low erythropoietin levels, therapy with erythropoietin should be considered. Transferrin levels will correct with the resolution of proteinuria [4]. Laboratory evidence of anemia that does not respond to iron or erythropoietin therapy suggests deficiencies in other micronutrients, like copper, zinc, and vitamin B12. Copper and zinc deficiencies result in reduced activity of copper and zinc superoxide dismutase, shortening the life span of red blood cells. Moreover, the addition of zinc therapy to the standard therapy of NS seems to reduce the number and the frequency of relapses, to help induce remission [4], and to reduce the proportion of infections associated with relapses, with a metallic taste as a mild adverse event [16]. The mechanism of zinc action is not fully clear, but it is probably linked to its immunoregulatory role: zinc deficiency might lead to the down-regulation of Th1 cytokines, with an increased risk of infections [16]. **Table 1** provides a summary of dietary recommendations to follow during the acute phase of NS in children, based on the literature examined.

Table 1. Summary of nutrition modifications suggested in the treatment of the acute phase of NS in children.

Fluids	In patients with maintained intravascular volume: moderate edema requires no fluid restriction; severe edema requires fluid restriction and loop diuretics in hospital settings [6]. In patients with contracted intravascular volume with normal blood pressure: administer albumin infusion, followed by furosemide [6]. In patients with hypovolemia: follow specific resuscitation guidelines [6].
Carbohydrates	Reduced intake of simple sugars [9], with an adequate intake of high-complex carbohydrates [10][11].
Protein	Daily protein intake recommended for the general pediatric population [5][6]. Prefer vegetable sources.
Dietary fat	In children >2 years old: <30% of total calories, saturated fats <7–10%, cholesterol consumption <200–300 mg/d [2][4][13], increasing the consumption of monounsaturated, polyunsaturated, and omega-3 fatty acids [4]. In children <2 years old: no fat intake restriction [4]. Children with hyperlipidemia: <7% saturated fats, <200 mg/d cholesterol [4].
Sodium	<2 mEq/kg/d [9]. “No added salt diet” approach [9]. 1 mg for each kcal [9].

Calcium and vitamin D	Elemental calcium: 500 mg daily (250 mg twice daily) [4][9]. Cholecalciferol: from 800–1000 IU daily to 60,000 IU once a week [4][9]. In patients with advanced renal insufficiency, use 1,25-dihydroxycholecalciferol [11].
Iron, copper, and zinc	In patients with iron deficiency anemia: administer replacement therapy [4]. In patients with low erythropoietin levels: consider therapy with erythropoietin [4]. In patients with anemia that does not respond to iron and erythropoietin therapy: consider and correct deficiencies in other micronutrients, like copper, zinc, and vitamin B12 [4].

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