Functional Medicine & Clinical Nutrition for Nephrotic Syndrome

Nephrotic Syndrome is a kidney disease characterized by proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. Hypertension and hematuria also occur in some cases. Nephrotic syndrome may occur as a primary disorder or secondary to various systemic diseases. Most cases of primary nephrotic syndrome are idiopathic. The most common form of idiopathic nephrotic syndrome (INS) is minimal change nephrotic syndrome (MCNS; also called nil disease or minimal change glomerulonephritis), which constitutes more than 95% of cases in children and 25% of cases in adults. MCNS is so named because the glomerular morphology on microscopic examination is close to normal. Children with untreated MCNS have a high risk of dying from infection.

Glucocorticoids are the mainstay of conventional therapy for MCNS. Most patients have substantial improvement with glucocorticoid therapy, and such treatment has significantly reduced the mortality rate. However, glucocorticoids have numerous adverse effects; therefore, a safer treatment would be preferable if an effective one was available. Diuretics and antihypertensive medications are also used in some cases. In the studies reviewed below, some patients were described as having MCNS, whereas others were said to have INS or simply nephrotic syndrome.

Dietary Factors

General Considerations

Adequate protein intake is necessary to replace urinary protein losses. However, a high-protein diet is not recommended, because eating large amounts of protein does not significantly increase serum albumin levels and it may accelerate renal damage by increasing urinary protein excretion. Optimal protein intake is said to be 1.0–1.1 g/kg of body weight per day in patients with MCNS and 0.8 g/kg/day in those with other types of nephrotic syndrome. Protein intake should be lower than these levels when renal dysfunction is present.1 Moderate sodium restriction is often recommended, and fluid intake is restricted in some cases.

Food Allergy

The potential role of allergy in the pathogenesis of INS is suggested by a higher-than-normal prevalence of asthma, eczema, urticaria, and positive allergy tests in patients with this condition.2,3 In case reports 4–7 and clinical trials, 8–13 food allergy was found to be a frequent cause or exacerbating factor in children, and to a lesser extent in adults, with INS. Both glucocorticoid-responsive and glucocorticoid-resistant patients improved or went into remission after identification and avoidance of allergenic foods, and many patients were able to discontinue glucocorticoid treatment. Cow's milk was the most commonly implicated food, but other allergens such as wheat, gluten, egg, pork, fish, beef, and chicken were involved in some cases. Many children with INS were sensitive to more than one food.

A 4-year-old female with repeated relapses of nephrotic syndrome requiring prednisone was placed on a diet free of milk and eggs. Control of environmental allergens was recommended, and desensitization was also initiated. Sustained and striking improvement occurred on this regimen, and the patient was weaned off of prednisone over a period of 10 months.4

An 8-year-old female had nephrotic syndrome that had been treated with glucocorticoids for 5 years. After pork and fish were removed from her diet, glucocorticoids were reduced and eventually withdrawn. The patient had no proteinuria for 4 months, but then developed massive proteinuria after consuming a meal that contained pork.7

One group of investigators studied 6 children (aged 10–13 years) with steroid-responsive INS. Kidney biopsies performed in 5 patients showed MCNS. The patients were withdrawn from glucocorticoids and fed a hypoallergenic elemental diet. Proteinuria, which had been present in 5 patients at the start of the study, resolved in 4 patients and decreased to 300–350 mg/day in 1 patient. The improvement in proteinuria usually occurred after 3–10 days on the diet. Challenge with cow's milk resulted in a return of proteinuria (5.6–29.2 g/day) and edema and a decrease in serum IgG levels in 4 patients. In a fifth patient, urinary protein excretion increased to 2.0 g/day after cow's milk challenge. When milk was again removed from the diet, protein excretion returned to pre-challenge levels within 4–15 days. One patient had a similar response to wheat.8,9

In further studies by the same group of investigators, 17 of 24 glucocorticoid-responsive children with INS became symptom-free off of prednisone after they removed allergenic foods from their diet and received desensitization therapy (injections of food antigens). Most children were found to be sensitive to more than one food. Of the remaining 7 patients, 3 discontinued their diet and resumed prednisone, 3 were lost to follow-up, and 1 had a progression of the disease.10

Twenty-six adults with glucocorticoid-responsive INS were investigated for food allergy by means of skin tests, IgE RAST, and the human basophil degranulation test. Avoidance of suspected allergenic foods resulted in complete and sustained remission in 6 patients, all of whom were able to discontinue glucocorticoid treatment. With continued diet therapy for periods of 1–4 years, the patients remained free of relapses.11

Seventeen children (aged 1–15 years) with glucocorticoid-resistant nephrotic syndrome eliminated cow's milk from their diet for at least 14 days, without changing their previously ineffective prednisone dosage. In 6 patients with MCNS or mesangial proliferation, proteinuria disappeared after 3–8 days on the diet. Reintroduction of cow's milk after 2–3 weeks of remission resulted in a recurrence of proteinuria in 3 of 3 cases. After 1 year on a cow's milk-free diet, 2 of the 6 responders became tolerant to milk and remained in remission, 2 were still unable to tolerate milk but were in remission on a milk-free diet, 1 became steroid-dependent, and 1 was lost to follow-up.12

Thirteen adults (mean age, 35 years) with MCNS who had not responded consistently to glucocorticoids were fed an oligoantigenic diet for 10 days. The diet consisted of 1 meat, 1 carbohydrate, 1 vegetable, 1 fruit, and water. Proteinuria disappeared in 5 patients and decreased by more than 50% in an additional 4 patients. Of the 9 patients who improved, 8 relapsed after returning to their usual diet and the other patient achieved long term remission by avoiding beef.11,13

Of 26 patients (mean age, 32 years) with glucocorticoid-resistant INS, 6 had a complete remission after identifying and avoiding allergenic foods and, when possible, avoiding suspected inhalant allergens. Of the 5 responders who had been on glucocorticoids, all were able to discontinue them.14

One study found that avoidance of suspected allergenic foods was not beneficial for 84 children with glucocorticoid-responsive MCNS. However, food allergies were diagnosed in that study by IgE RAST, which is frequently unreliable. It was not stated whether the children removed cow's milk, wheat, and other major allergens from their diet.2

Most of the patients who responded to allergen avoidance in the studies described above presumably had MCNS. However, one patient who went into remission and was able to discontinue glucocorticoids was 62 years old with a diagnosis of focal and segmental glomerulosclerosis. Therefore, an allergy investigation should be considered for all patients with INS, regardless of the type. The evaluation and treatment of food allergy is discussed in chapter 7.

Some patients with INS have been found to be sensitive to environmental chemicals, house dust, and other inhalant allergens.3,10 While food allergy appears to be a far more common trigger of symptoms than environmental allergy, some patients with INS may require comprehensive allergy treatment in order to achieve the best results.

Nutritional Supplements

Vitamin D

Patients with nephrotic syndrome may develop vitamin D deficiency as a result of increased urinary excretion of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D.15–17 An inverse correlation has been found between blood levels of 25-hydroxyvitamin D and the degree of proteinuria.18 Vitamin D deficiency is probably responsible for the abnormalities of calcium metabolism that have been observed in patients with nephrotic syndrome. Vitamin D status should be assessed in patients with nephrotic syndrome, and those who are found to be deficient should receive vitamin D in doses sufficient to normalize the serum 25-hydroxyvitamin D concentration.

Vitamin B6

Of 35 children with nephrotic syndrome in relapse, 88% had a low plasma concentration of pyridoxal phosphate (the biologically active form of vitamin B6).19 Vitamin B6 deficiency may result in impaired immune function and an increased risk of thromboembolism, both of which are known complications of nephrotic syndrome. Supplementation with vitamin B6 may therefore be worthwhile.20

Iron: note of caution

Patients with nephrotic syndrome frequently have low serum levels of iron, total iron-binding capacity, and transferrin, and increased urinary excretion of iron and transferrin. However, ferritin and hemoglobin concentrations are usually normal, indicating that these patients do not have significant iron deficiency.21–23 Urinary losses of iron and transferrin in nephrotic syndrome appear to be counterbalanced by upregulation of the soluble transferrin receptor, which might help prevent the development of iron-deficiency anemia.23

Circulating levels of iron-binding proteins (albumin and transferrin) are low in patients with nephrotic syndrome. Consequently, administration of iron to a non-iron-deficient patient with nephrotic syndrome could result in the appearance of excessive amounts of unbound iron in the blood, which might increase

oxidative stress and potentially accelerate renal damage.24,25 In addition, iron is a growth factor for bacteria, and iron supplementation of patients who lack iron-binding proteins can promote infection.26,27 For these reasons, iron supplementation should be reserved for patients who have clear evidence of iron deficiency (i.e., low serum ferritin and low percent transferrin saturation). If iron is administered, it should be given in relatively small amounts, in divided doses throughout the day.

Zinc and Copper

Low plasma or serum levels of zinc and copper have been found frequently in patients with nephrotic syndrome,21,28–31 and there is one case report of acrodermatitis secondary to zinc deficiency in a child with nephrotic syndrome.32 The low concentrations of these minerals result in part from the combination of increased urinary zinc and copper excretion and increased urinary loss of their carrier proteins (e.g., albumin and ceruloplasmin). Zinc and copper play a role in immune function, and a deficiency of either of these nutrients could contribute to the increased risk of infection seen in patients with nephrotic syndrome. Moreover, since relapses of nephrotic syndrome often follow infections, zinc and copper have the potential to prevent relapses. In a double-blind trial, supplementation with 10 mg/day of zinc reduced the frequency of relapses in children with steroid-responsive nephrotic syndrome.

Eighty-one children (aged 1–16 years) with steroid-responsive nephrotic syndrome were randomly assigned to receive, in double-blind fashion, 10 mg/day of zinc or placebo for 12 months. Patients with frequent relapses also received prednisolone. In the group as a whole, the frequency of relapses was non significantly lower by 38% in the zinc group than in the placebo group (27.5% vs. 44.7%; $p = 0.1$). Among the 52 patients with a history of frequent relapses, the proportion of patients who remained free of relapses was significantly greater in the zinc group than in the placebo group (46% vs. 16%; $p = 0.02$).33

While there have been no clinical trials using copper, long term zinc supplementation should be accompanied by a copper supplement in order to prevent zinc-induced copper deficiency (chapter 31). If zinc and copper are given to patients with nephrotic syndrome, they should probably be given in relatively modest amounts in divided doses throughout the day. As may be the case with iron, administration of large doses of zinc and copper to patients who have subnormal levels of zinc- and copper-binding proteins could result in the appearance of excessive amounts of unbound zinc and copper in the blood, with potentially deleterious consequences.

High Dose Vitamin C

Possible adverse effect. In a case report, a 58-year-old woman hospitalized for nephrotic syndrome and renal amyloidosis developed acute renal failure after receiving an intravenous infusion of 45 g of vitamin C. Postmortem examination revealed extensive deposits of calcium oxalate in renal tubules, presumably as a result of the conversion of vitamin C to oxalate in vivo.34 In another case report, a 23-month-old girl with congenital nephrotic syndrome had an unusually rapid deterioration of renal function while receiving 1.8–2.0 g/day (200–250 mg/kg of body weight per day) of vitamin C for 6 months.35 These case reports suggest that high dose vitamin C may be harmful to patients with nephrotic syndrome.

Renal Complex Formula

The formula contains highly absorbable chelated magnesium as patented TRAACS™ (magnesium lysinate glycinate chelate). Magnesium is one of the most abundant essential minerals in the human body and a key cofactor for more than 300 biological processes, including magnesium homeostasis critical for overall health and well-being.1,2

Resveratrol also has been added to the updated formula for its healthy inflammatory properties and supporting healthy kidney function and integrity.3 By supporting healthy stress response throughout the body, resveratrol promotes overall health and well-being by allowing the kidneys to function properly.4

Chinese salvia is one of the most prestigious herbs in traditional Chinese medicine due to its profile of salvianolic acids, including the potent salvianolic acid B with many health benefits.5 Further evidence suggests that Chinese salvia root extract may also help promote healthy kidneys and support blood sugar levels already in the normal range.6

NAC is a highly bioavailable modified form of the amino acid L-cysteine. Since L-cysteine is rarely found in foods and is not well absorbed, it tends to be a limiting factor of glutathione production throughout the body. Research shows that NAC has health effects on renal tissues by supporting glutathione (antioxidant) status.7

Vitamin B6 plays a key role in the health of multiple organs, including the kidneys. When the kidneys are not functioning properly or damaged, homocysteine levels may increase, contributing to cardiovascular complications.8 Vitamin B6 promotes healthy kidney function by lowering homocysteine levels.8

Renal Complex Supplementation Research cited below suggests that the nutrients in Renal Complex play pivotal roles in supporting kidney integrity and function. In turn, this formula can help promote healthy kidney-related homeostatic processes.

Benefits of Renal Complex may include:

- Helps promote healthy kidney function
- Supports kidney cell regeneration
- Supports waste material removal from the body
- Supports fluid and electrolyte balance

Potential Natural Strategies

Abstract Title: Immunomodulating and antiproteinuric effect of Hippophae rhamnoides (Badriphal) in idiopathic nephrotic syndrome.

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Abstract Author(s): Rana Gopal Singh, Parampal Singh, Praveen Kumar Singh, Usha, Aruna Agrawal, B N Upadhyay, Ashutosh Soni

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Abstract:

OBJECTIVE: The treatment of idiopathic nephrotic syndrome is still not well settled and at times is very frustrating. Number of protocols have been reported with variable results outcome in various conditions. The main pillar of treatment of idiopathic nephrotic syndrome is use of immunomodulating and suppressive drugs in various combinations. The herbal preparations have also been reported to have immunomodulating property. The study has been planned to record Immunomodulating and antiproteinuric effect of Hippophae rhamnoides.

MATERIAL AND METHODS: In the present study had 2 groups having 28 patients of idiopathic nephrotic syndrome in each group have been included. The patients were subjected to haematological, biochemical, immunological investigation at 0, 1, 2 and 3 months interval with dietic advise. Group A have been put on standard treatment, whereas group B on Badriphal in the well worked up doses. The hydroalcoholic extract of 350 mg twice daily of Badriphal was given to group B as add on treatment. Patients were followed up with definite protocol at monthly interval for 3 months.

RESULTS: At the end of 3 month patients showed improvement in the symptoms of oedema, anorexia, oliguria in the herbal group. The urinary estimation of protein showed significant decrease in Group B with elevation of S. albumin levels. The inflammatory cytokines has showed significant decrease at the end of 3 month.

CONCLUSION: Thus the pilot study showed beneficial effect of the herbal preparation Hippophae rhamnoides as add on treatment. A large perspective study is recommended to establish these findings.

Article Published Date : May 31, 2013

Study Type : Human Study

Abstract Title: Role of gut microbiota in idiopathic nephrotic syndrome in children.

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Abstract:

Nephrotic syndrome cha racterized by heavy proteinuria and edema is the most common chronic kidney disease in children. It is classified into three categories, of which the idiopathic type accounts for the vast majority of cases. As indicated by the name, the etiology of idiopathic nephrotic syndrome remains unknown though it has been suggested that impaired T cell function is involved. Recently, evidence has mounted to suggest that dysfunction in regulatory T cells plays an important role in the development of allergic disease, a recognized comorbid condition for children with idiopathic nephrotic syndrome. It is known that regulatory T cells are mainly induced by short chain fatty acids produced by gut microbiota and that children with allergy are reported to have aberrant gut microbiota. On this basis, we hypothesize that an aberrant microbiota, i.e., dysbiosis in the gut resulting in defective induction of regulatory T cells, is also involved in the etiology of idiopathic nephrotic syndrome in children. Our hypothesis can be directly tested by metagenome analysis using bacterial DNA extracted from the feces of patients with idiopathic nephrotic syndrome. Indirect evidence could be obtained by epidemiological survey, such as a comparative study of the environmental factors influencing the initial colonization of gut microbiota between patients with idiopathic nephrotic syndrome and age-matched healthy children. Factors that may disrupt this colonization include a cesarean delivery, formula feeding, excessive use of antibiotics, or the introduction of inappropriate solid foods containing a high amount of saturated fat. Based on this hypothesis, we suggest it would be clinically worthwhile to study whether administration of probiotics composed of commensal bacteria known to efficiently induce regulatory T cells in vitro could control the exacerbation or relapse of INS.

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