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CLINICAL RESEARCH

Effect of Combined Gluten-Free, Dairy-Free Diet in Children With Steroid-Resistant Nephrotic Syndrome: An Open Pilot Trial

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Introduction: Steroid-resistant nephrotic syndrome (SRNS) affects both children and adults and has a high rate of progression to end-stage renal disease. Although a subset of patients have well-characterized genetic mutation(s), in the majority of cases, the etiology is unknown. Over the past 50 years, a number of case reports have suggested the potential impact of dietary changes in controlling primary nephrotic syndrome, especially gluten and dairy restrictions.

Methods: We have designed a prospective, open-label, nonrandomized, pilot clinical trial, to study the effect of a gluten-free and dairy-free (GF/DF) diet in children with SRNS. The study will be organized as a 4-week summer camp to implement a GF/DF diet in a tightly controlled and monitored setting. Blood, urine, and stool samples will be collected at different time points during the study. The primary end point is a reduction of more than 50% in the urine protein:creatinine ratio. The secondary end points include changes in urine protein, kidney function, and serum albumin, as well as effects in immune activation, kidney injury biomarkers, and gut microbiome composition and function (metagenomic/metatranscriptomic).

Conclusion: This study will advance the field by testing the effect of dietary changes in patients with SRNS in a highly controlled camp environment. In addition, we hope the results will help to identify a responder profile that may guide the design of a larger trial for further investigation.

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Idiopathic nephrotic syndrome (INS) is the most common type of nephrotic syndrome in children, presenting clinically with massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Despite recent advances in identifying genetic mutations in a subset of these patients,[1] in the large majority of cases of nephrotic syndrome, the etiology is unknown.[2] The underlying lesion leading to the severe proteinuria is a defect in the glomerular filter barrier, with diffuse effacement of podocyte foot processes on electron microscopy and without glomerular deposits or inflammatory lesions. Two different histopathological patterns may be identified by light microscopy: minimal change disease (MCD),[3] without optical changes in glomeruli, and primary focal segmental glomerulosclerosis (FSGS),[4] with scar lesions visible inside glomeruli.

The clinical course and prognosis of INS is widely dependent on the response to initial treatment course with steroids, which itself is closely related to the distinct histological pattern. Although 80% to 90% of children with INS achieve complete remission with the initial course of steroid therapy and are classified as having steroid-sensitive nephrotic syndrome (SSNS),[5] about 10% to 20% present with a lack of response to steroids (steroid-resistant nephrotic syndrome [SRNS]), or experience frequent relapses after withdrawal of steroids,

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resulting in steroid-dependent nephrotic syndrome (SDNS).[6] SRNS and SDNS are predominantly associated with an FSGS pattern in more than 60% of cases, whereas SSNS is associated with an MCD pattern. Therefore, common practice is to only perform a kidney biopsy to determine the exact pathological findings after steroid treatment for 4 to 8 weeks without clinical response.

It has been proposed that MCD and FSGS are different histological patterns of the same disease, representing a spectrum, with MCD dominating the initial presentation and the continuous podocyte injury leading to FSGS, although this remains controversial.[7] In a subset of SRNS, causative genetic mutations have been discovered.[1] When no genetic mutation can be found, it is hypothesized that toxic circulating factor(s) causes podocyte injury and consequently increases glomerular permeability. This could also explain the high rate of recurrence of the disease after transplantation.[6,8] The exact nature of this circulating factor(s) is still unknown, but it is thought that the immune system could be a major culprit.[9–13]

Without response to steroids and therefore persistent proteinuria, SRNS poses an enormous therapeutic challenge. In addition to the inevitable progression to end-stage renal disease, other complications such as malnutrition, infection, and thrombotic events often occur.[5,6] Children with SRNS are usually started on a variety of immunosuppressant drugs such as calcineurin inhibitors, mycophenolic acid, and/or, in cases with difficult courses, alkylating agents and rituximab, with variable success rates and significant side effects.[14,15] Despite the use of newer immunosuppressive agents, the response rate to therapy remains low.[14,15] To find novel therapeutic strategies for SRNS, it is critical to investigate potential etiologies and biomarkers for this syndrome. Over the past 50 years, a number of case reports have suggested the potential impact of dietary changes in controlling INS, likely related to food sensitivity.[16,17] In particular, gluten and dairy restrictions have been associated with a significant decrease in proteinuria, both in SSNS/SDNS and in SRNS.[18–21] In 1977, Sandberg *et al.*[20] studied 6 children with INS and demonstrated significant reduction in proteinuria (<0.5 g/d) after the removal of cow's milk from the diet, with exacerbation of proteinuria once patients were rechallenged with cow's milk. In 1989, Laurent *et al.*[16] investigated the relation between INS and food sensitivities in pediatric and adult INS patients (age range 7–72 years). They investigated a broader collection of foods, including cow's milk, egg, chicken, beef, pork, and gluten. Among 26 participants, 6 responded to dietary interventions and achieved complete remission (CR): 2 patients after gluten avoidance and 3 after removal of cow's milk. Milk sensitivity was also reported in 6 of 17 children with INS, whose proteinuria improved after milk exclusion from the diet.[22]. Lagrue *et al.*[15] implemented an oligoantigenic diet (which included removal of milk and gluten) in 42 patients with difficult-to-manage INS. They found that 13 of these patients achieved >50% reduction in proteinuria and 5 achieved CR. In most of the patients who responded, the time onset to response was within 1 week, and INS recurred immediately when the restricted diet was stopped. More recently, Lemley *et al.*[17] reported a case series of 8 children (2–14 years of age) with difficult-to-manage INS who were started on gluten-free diet. All patients experienced a significant reduction in the relapse rate, enabling lower doses or withdrawal of steroids or immunosuppressive drugs. In this pilot study, we decided to focus on SRNS, as it is the most orphan entity in terms of therapeutic approaches and the greatest challenge among all INS varieties. In addition, the knowledge of successful responses to gluten/dairy removal in cases of SRNS, including patients of our coinvestigators, encouraged us to target this specific population first.

The exact mechanism by which dietary interventions can reduce proteinuria is unknown, but several hypotheses have been proposed (Figure 1). Different from food allergy that is mediated by an IgE response, food sensitivity is linked to immune cellular dysfunction and is difficult to diagnose, as no circulating antibodies or skin tests have shown a reliable correlation.[17–19,21,23,24] Exposure to sensitive foods may trigger the release of inflammatory factors/cytokines that could directly damage the podocytes (Figure 2).[19]

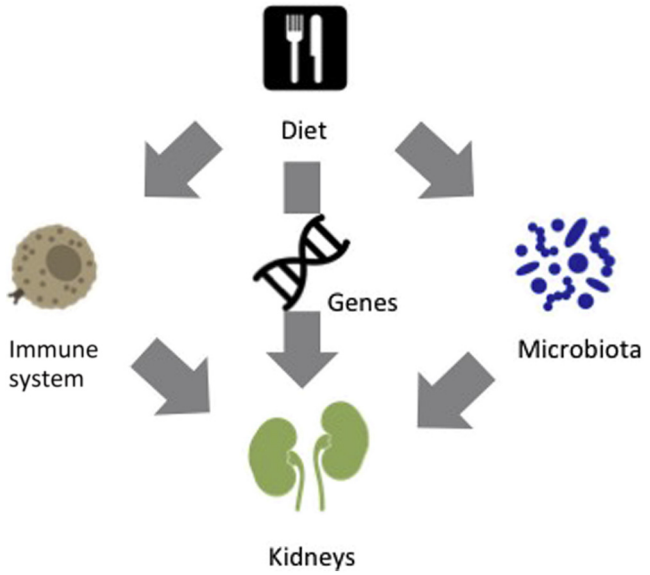

Figure 1. Illustration of the hypothesis behind a dietary intervention influencing the immune system activation, microbiota, and kidneys.

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