ACADEMIA ONE
PEER REVIEWED JOURNALS

Open Herald: Periodical of Methodical Research
Volume 3, Issue 3,March 2025
ISSN (E): 2810-6385
Website: https://academiaone.org/index.php/6

Serum Immunoglobulin A, M, and G Concentrations in Iraqi Pediatric Patients Diagnosed with Nephrotic Syndrome

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Abstract

Nephrotic syndrome (NS) represents a significant contributor to the incidence of end-stage renal disease, characterized by symptoms such as edema, proteinuria, hypoalbuminemia, and hyperlipidemia. The syndrome is intricately associated with alterations in the immune response. This research focused on analyzing the serum concentrations of immunoglobulins G (IgG), M (IgM), and A (IgA) in a cohort of Iraqi pediatric patients diagnosed with NS. Blood specimens were obtained from 75 children, aged 2 to 15 years, presenting with newly diagnosed typical NS. The study findings indicated a notable reduction in the average serum IgG level (438.18 mg/dL) among NS patients compared to healthy controls (954.09 mg/dL), alongside a significant elevation in the mean serum IgM level (185.66 mg/dL) relative to controls (111.73 mg/dL). Conversely, serum IgA levels exhibited no significant disparity between NS patients and healthy controls. In conclusion, this investigation underscores a marked association between immunological markers and nephrotic syndrome in Iraqi children. The assessment of immunoglobulin levels, coupled with clinical and biochemical parameters, plays a crucial role in the management of NS. There is increasing interest in extensive studies to demonstrate that low IgG and high IgM levels are sensitive markers of worse outcomes in pediatric patients with NS.

Keywords: Nephrotic Syndrome (NS); renal disease; Immunoglobulin G; Immunoglobulin A and Immunoglobulin M.

1. Introduction

One of the clinical features of nephrotic syndrome (NS) is a variety of symptoms such as large amounts of protein in the urine, low levels of albumin in the blood, high lipid levels and swelling that may be due to an abnormal immune response. This disease originates from kidney abnormalities or is associated with chronic diseases like diabetes mellitus. The main pathophysiological mechanism is abnormal glomerular filtration barrier's selective permeability (Bierzynska et al., 2015).

The podocyte is the principal architectural component of the glomerular filtration barrier, which guarantees its structural continuity. Nephrosis responsive to steroids (SSNS) accounts for the biggest chunk of all cases under nephrotic syndrome (NS), and about half will suffer from recurrent relapses requiring non-steroidal medication for prevention purposes. The advanced stage leads to renal failure in steroid-resistant nephrotic syndrome (SRNS), 30 – 40% are caused by mutations in genes encoding podocyte-specific proteins (Davin & Rutjes, 2011).

There are many biomarkers associated with idiopathic nephrotic syndrome; it has been related to multiple markers changes. It is important to identify these biomarkers since they significantly aid in the diagnosis, staging, prognosis, and developing treatment choices, and in assessing the efficiency

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of the treatment protocols in idiopathic nephrotic syndrome (INS). The use of biomarkers has gained increased applications in many clinical settings (Rong et al., 2017).

Nephrotic syndrome can also be identified by the excretion of immunoglobulins in urine in addition to T lymphocyte dysfunction, that hinders the conversion of immunoglobulin-M-bearing B-cells into plasma cells that secrete immunoglobulin-G and immunoglobulin-A (Roy et al., 2009).

T-cells participate greatly in the malfunction of the transition system which converts immunoglobulin M (IgM) to immunoglobulin G (IgG) leading to decreased blood levels of IgG and IgA and raised levels of IgM and IgE. This decline in IgG may possibly be caused by improved catabolism and release of IgG in urine (Pereira et al., 2014). In subjects with nephrotic syndrome, the levels of IgG may indicate the severity of glomerular membrane damage indicated by the urine protein and IgG loss. One of the key causes of bacterial infections in nephrotic syndrome patients is low blood IgG levels caused by urine loss and decreased antibody manufacturing capabilities. Immunosuppressive treatment and decreased amounts of alternative complement pathway components.

Serum IgG and IgA levels decreased significantly in minimal change nephrotic syndrome (MCNS), but serum IgM levels increased. Dysfunctional T cells, which are responsible for immunoglobulin class switching, have been recognized as a major issue in idiopathic nephrotic syndrome (Youssef et al., 2011).

The purpose of the present research was to evaluate the levels of IgG, IgM, and IgA in the blood of a sample of Iraqi pediatric nephrotic syndrome patients.

2. Patients and Methods

2.1. Sampling

Blood samples were taken from 75 pediatric subjects having an age range of 2 – 15 years old which were diagnosed with new-onset typical nephrotic syndrome (NS) between the period of September 2021 and October 2022. The study subjects were followed-up for one year at the "Children's Welfare Teaching Hospital" in the Medical City of Baghdad.

2.2. Types of cases studied

In the present research, a total of 75 pediatric subjects with nephrotic syndrome (NS) [52 males and 23 females], were diagnosed before starting treatment. After one year period of treatment and follow-up, subjects were further divided into two sub-groups: a steroid-sensitive group (SSNS), involving 50 subjects (67%, 35 males and 15 females), and a steroid-resistant group (SRNS), involving 25 subjects (33%, 17 males and 8 females). The SSNS group was further divided into two subgroups: 27 subjects (36%) were categorized as frequently relapsing (SSFR, with 18 males and 9 females) and 23 subjects (31%) as infrequently relapsing (SSIFR, with 17 males and 6 females) based on the frequency of relapses taking place during six months of follow-up. The SRNS group was also subdivided into two subgroups: 8 subjects (10%) with genetically positive steroid resistance (GPSR, with 6 males and 2 females), and 17 subjects (23%) with genetically negative steroid resistance (GNSR, with 11 males and 6 females) based on the outcomes of genetic tests. The study also included 30 healthy pediatric subjects (10 females and 20 males), with an age range of 3 – 15 years serving as a control group. An informed consent was obtained from all the parents and legal guardians of the study subjects involved in the study. The study was approved by the ethics committee of the College of Biotechnology / Al-Nahrain University.

2.3. Determination of the serum IgG, IgM, and IgA levels by RID plates

RID plates were used to measure the levels of IgM, IgG, and IgA (IgG, IgA and IgM, RID/LTA/Italy) according to the manufacturer's instructions.

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3. Statistical analysis

The analysis of the impact of different variables on the research parameters was conducted utilizing the Statistical Analysis System (SAS, 2012) software. To statistically compare percentages, chi-square analysis was employed, while the means were significantly compared using either the least significant difference (LSD) ANOVA test or the T-test, depending on the data distribution. Additionally, this study involved the calculation of the correlation coefficient to ascertain the relationship between various variables.

4. Results

4.1. Immunoglobulin G, M and A (IgG, IgM and IgA)

The findings regarding the average serum levels of immunoglobulins G, M, and A (IgG, IgM, IgA) among children newly diagnosed with nephrotic syndrome (NS) prior to therapy, as well as in the treated NS groups post-therapy (including the steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) cohorts), along with their respective subgroups (frequently relapsing SSFR; infrequently relapsing SSIFR; genetically positive steroid resistance GPSR; genetically negative steroid resistance GNSR), and the control group, are presented in Tables 1 and 2.

Table (1): Comparison of IgM, IgG and IgA levels between several groups (newly diagnosed: before therapy, treated NS group: after therapy, control).

Groups	Immunoglobulins (Mean ± SEM)		
	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)
Control	954.09 ± 4.45 a	111.73 ±1.18 c	188.72 ± 1.02 a
NDNS	438.18 ± 3.01 c	185.66 ±1.05 b	184.68 ± 0.94 a
Treated NS	457.29 ± 2.48 b	203.49 ±1.28 a	172.62 ± 0.99 b
P-value	0.0001 **	0.0001 **	0.0001 **
A significant difference was indicated by different letters in the same column (P≤0.01) for the NDNS group, which stands for newly diagnosed NS.			

Table (2): Comparison of IgM, IgG and IgA levels between treated NS groups (post therapy) (Steroid sensitivity and resistance groups).

Groups		Immunoglobulins (Mean ± SEM)		
		IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)
Treated NS (Post therapy)	SSNS	457.97 ±3.10	203.44 ±1.51	172.77 ±1.19
	SRNS	455.94 ±4.15	203.60 ±2.38	172.33 ±1.79
P-value		NS	NS	NS
A significant difference (P≤0.01). NS: Non-significant.				

4.2. Immunoglobulin G (IgG)

Glycoprotein-binding components, such as immunoglobulin G (IgG), play a pivotal role in both innate and adaptive immune responses, acting as crucial effectors. The functionality of IgG extends

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across a spectrum, influenced by its binding affinity for various Fc receptors (FcR) and complement proteins, enabling it to mediate both pro-inflammatory and anti-inflammatory responses upon antigen recognition throughout the organism (Russell et al., 2018).

In this study, the laboratory results revealed that the serum IgG levels in the healthy control group (954.09 ± 4.45 mg/dl) were significantly higher compared to those in the treated nephrotic syndrome (NS) group (457.29 ± 2.48 mg/dl) and children newly diagnosed with NS (NDNS) (438.18 ± 3.01 mg/dl) as displayed in Table 1. Additionally, the serum IgG levels between the two treated NS patient groups, steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS), showed no significant difference, as illustrated in Table 2.

These observations are in alignment with the findings of Mashhad et al., (2017) and Bahbah et al., (2015), who reported that children diagnosed with NS exhibited reduced serum IgG levels.

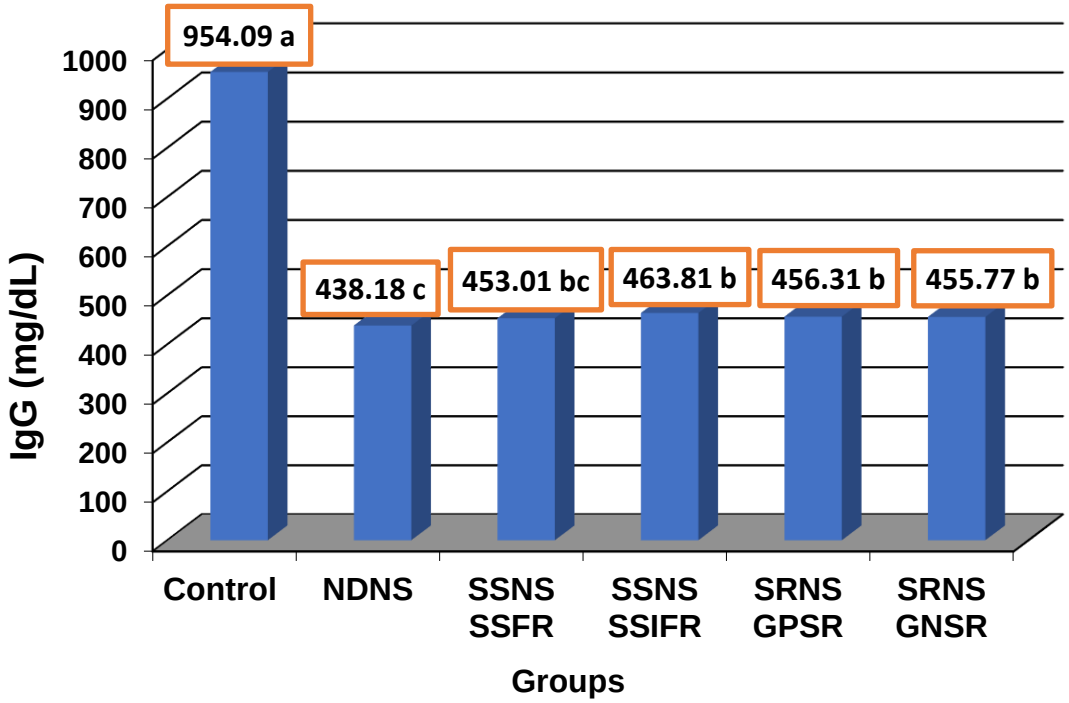

Fig. 1. Relation of serum IgG levels with clinical types of nephrotic group. A significant difference was denoted by different letters in column (P≤0.01).

Furthermore, *there were no significant differences between the different treated NS sub-groups "SSFR, SSIFR, GPSR, and GNSR" in serum IgG levels as previously shown in Figure (1).*

4.3. Immunoglobulin M (IgM)

Immunoglobulin M (IgM) serves as the primary antibody generated during the initial immune response. It exists both as a component of the B-cell antigen receptor complex on the cell surface and as a secreted glycoprotein. In the serum, IgM predominantly exists in a pentameric form, endowing it with a higher valency compared to other immunoglobulin isotypes due to its structure facilitating the formation of 10 antigen-binding sites. IgM is synthesized from germline-configured transcripts in B cells before class switch recombination (CSR) and somatic hypermutation (SHM), typically exhibiting low affinity (Notkins, 2004).

Table 1 reveals a notable reduction in serum IgM levels in the healthy control group (111.73 ± 1.18 mg/dl) when juxtaposed with children newly diagnosed with nephrotic syndrome (NDNS) (185.66 ± 1.05 mg/dl) and the treated NS cohort (203.49 ± 1.28 mg/dl).

This observation aligns with the results obtained by Bahbah et al., (2015) and El-Mashhad et al., (2017), who reported elevated serum IgM levels in children diagnosed with nephrotic syndrome. Conversely, these findings contrast with those reported by Youssef et al., (2011), who observed no significant difference in IgM levels between nephrotic syndrome patients and healthy individuals.

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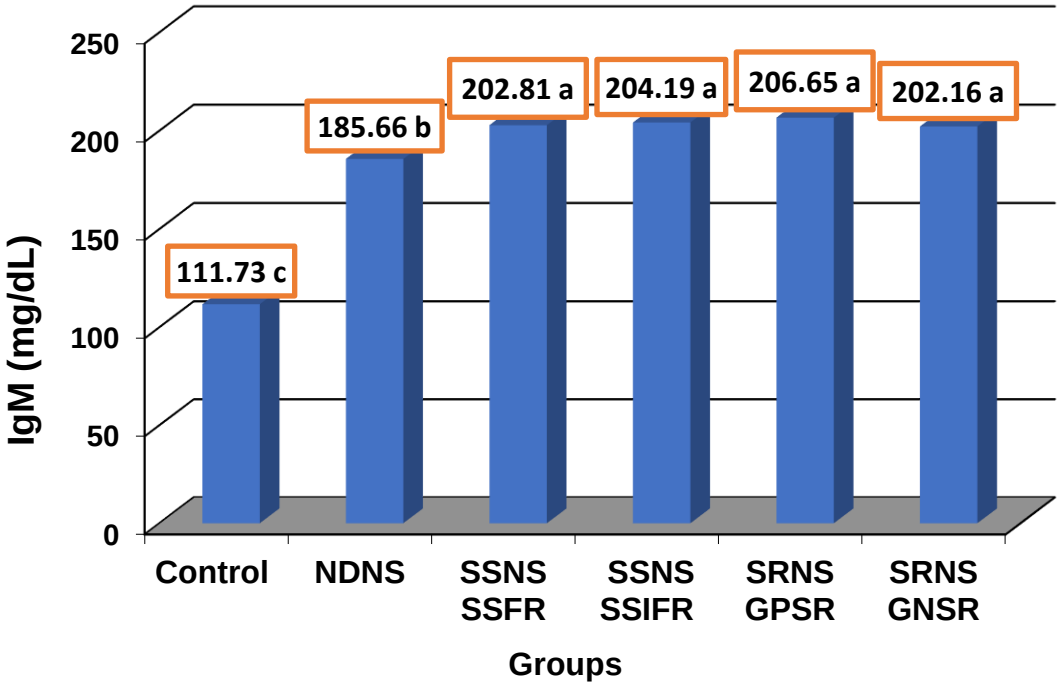

Fig. 2. Relation of serum IgM levels with clinical types of nephrotic group. A significant difference was denoted by different letters in column (P≤0.01).

Furthermore, there were no significant differences between the different treated NS sub-groups "SSFR, SSIFR, GPSR, and GNSR" in serum IgM levels as previously shown in Figure (2).

4.4. Immunoglobulin A (IgA)

In humans, Immunoglobulin A (IgA) predominantly exists as monomers in serum, with a composition of approximately 90% IgA1 and 10% IgA2. Conversely, the form of IgA observed in external secretions is primarily polymeric, referred to as secretory IgA (SIgA). SIgA plays an indispensable role in orchestrating the adaptive humoral immune defense across the mucosal surfaces of the gastrointestinal tract (GIT), respiratory tract (RT), and urogenital tracts (Woof and Russell, 2011).

Analysis presented in Table 1 indicates that there are no significant variations in serum IgA levels between the healthy control group (188.72 ± 1.02 mg/dl) and children newly diagnosed with nephrotic syndrome (NDNS) (184.68 ± 0.94 mg/dl). However, both groups exhibited significantly higher levels compared to the treated NS group (172.62 ± 0.99 mg/dl). These results align with the findings of Youssef et al., (2011) and are in contrast with those reported by El-Mashad et al., (2017), who

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observed lower concentrations of IgA in children diagnosed with nephrotic syndrome.

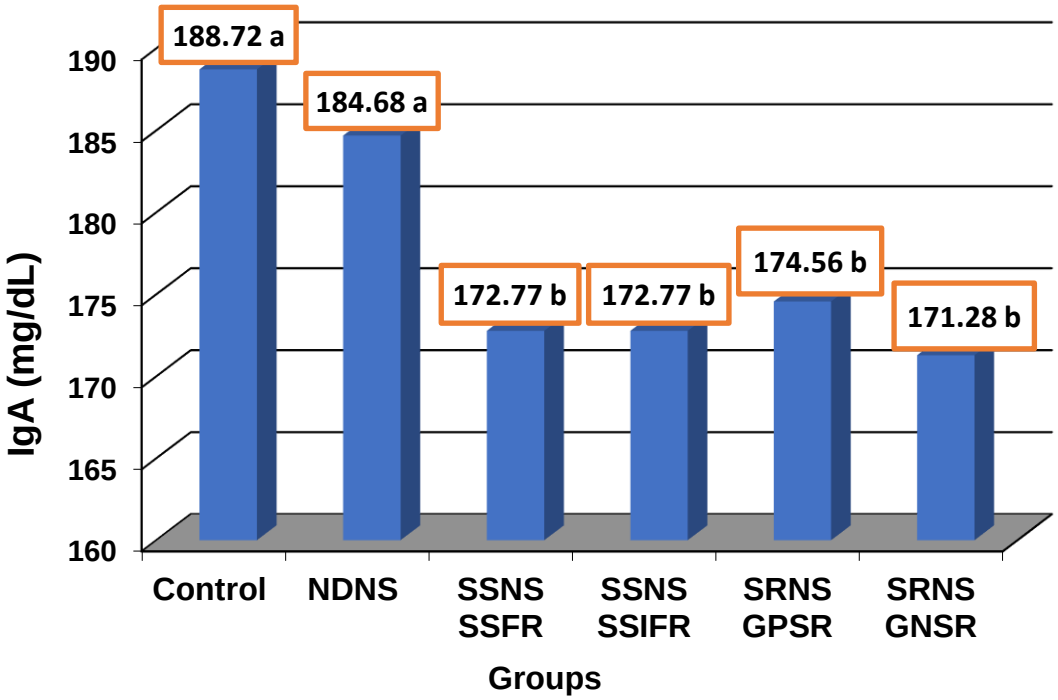

Fig. 3. Relation of serum IgA levels with clinical types of nephrotic group. A significant difference was denoted by different letters in column (P≤0.01).

Furthermore, there were no significant differences between the different treated NS sub-groups "SSFR, SSIFR, GPSR, and GNSR" in serum IgA levels as previously shown in Figure (3).

5. Discussion

The present study highlights a reduction in IgG levels and an increase in serum IgM levels among nephrotic syndrome (NS) patients in comparison to healthy controls. This observation deviates from the findings of Youssef et al., (2011), which did not demonstrate a significant difference in IgM levels between NS patients and controls. However, these results align with the studies conducted by Azat (2012) and El-Mashad et al., (2017). Additionally, the study revealed no significant differences in IgA levels between NS patients and healthy controls, corroborating the findings of Youssef et al. (2011) but contrasting with El-Mashad et al., (2017), who reported elevated serum IgM levels alongside reduced IgG and IgA levels in children with NS.

The observed alterations in IgG and IgM concentrations are associated with the pronounced proteinuria in NS patients, who also exhibit unusual susceptibility to bacterial infections, as noted by Bahbah et al., (2015). The failure to transition from surface IgM-bearing B-cells (plasma cells) to IgG and IgA-secreting plasma cells has been attributed to T-lymphocyte dysfunction, in addition to urinary loss of immunoglobulins (Roy et al., 2009).

The differences in immunoglobulin levels between pediatric subjects with NS and the controls are another piece of evidence that B-lymphocyte involvement and T-cell malfunction may play roles in the pathogenesis of the glomeruli lesions found in NS patients (Azat, 2012).

The findings of low IgG levels in this study is supported by the study results presented by El-Mashad et al. (2017). In their study, the researchers found that NS patients that exhibited albuminuria and high urine IgG levels had low serum IgG levels. The low oncotic pressure due to NS in pediatric subjects causes an elevated rate of synthesis of high molecular weight (MW) proteins, like lipoproteins, resulting in hyperlipidemia. IgG liver levels strongly correlated statistically significantly with their cholesterol levels (Azat, 2012; El-Mashad et al., 2017). The low oncotic pressure and reduced serum protein levels increase the synthesis rate of high MW IgM (Bahbah et al., 2015).

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Conclusions:

The immunological biomarkers investigated in this study were all significantly and positively correlated with each other and were also indicative of NS in a group of pediatric Iraqi subjects. Furthermore, the use of these biomarkers in conjunction with the clinical diagnosis of NS provides a useful means of differentiating the various manifestations of the disease. However, further study and investigation into these immunologic biomarkers are required in order to ascertain their value as future potential diagnostic or prognostic markers of NS in pediatric subjects.

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