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# Long-term Experience of Subcutaneous Immunoglobulin Therapy in Primary Immunodeficient Patients with Low and Normal Body Weight

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# Abstract

**Purpose:** The aim was to review the compliance, side effects and effectiveness of SCIG supplementation in patients with PID who had previously received IVIG therapy and subsequently switched to SCIG, as well as to compare these parameters in patients while considering body weight.

**Methods**: Demographic data, clinical and laboratory findings, SCIG dose and side effects of 87 patients were retrospectively obtained from patient files.

**Results**: Of the 87 patients aged between one and 22 years, 50 were male (57.5%) and 37 were female (42.5%). The serum IgG levels of the SCIG group were higher and more stable than those of the IVIG group. The number of hospitalizations and infections decreased significantly after initiation of SCIG**.** Thirteen patients (14.9%) had low body weight (LBW) for their age, seven of whom were male (53.8%). Serum IgG levels of the LBW cohort were significantly elevated and more stable during the SCIG period than the IVIG period. Mild, local side effects were detected in 153 administrations (3.3%) in 30 patients with normal body weight, while no local reactions were recorded in the patients with LBW.

**Conclusion**: SCIG supplementation has become an effective treatment modality for pediatric patients and can be administered safely in LBW children with PID. The number of hospitalizations and family visits were reduced, allowing patients and their parents to continue their normal lives.


# Introduction

Primary immunodeficiencies (PID) are hereditary diseases that occur due to a functional impairment of the cells and/or the components of the immune system. Although the underlying molecular mechanisms are different in PID, infections should be treated aggressively with anti-infectious agents and recurrence should be prevented using the appropriate prophylaxis and/or immunoglobulin replacement therapy (IGRT) [1]. Immunoglobulin therapy is currently used not only as PID replacement therapy but also as an anti-inflammatory and immunomodulatory drug [2]. This treatment can be given either intravenously (IVIG) or subcutaneously (SCIG). The method of IGRT administration should depend on the patient's preference, age, weight, conditions for access to hospital, and patient/family compliance [1].

IVIG replacement therapy has been used in children and adults with PID for many years [3]. The undesirable features of IVIG therapy include systemic side effects, gradual reduction of serum levels within 3 weeks, and the requirement for it to be administered in a hospital setting. This has led to the need for a new administration method that will reduce systemic side effects, provide more stable serum levels, and increase the patient's quality of life by allowing administration in the home environment. For this reason, SCIG replacement therapy is becoming the preferred method for PID treatment in recent years [4–7]. Studies have shown that SCIG replacement therapy is as effective as IVIG [8,9]. Also, the incidence of systemic side effects is low compared to that of IVIG administration [5,10]. Another

advantage of SCIG administration is the provision of higher physiological serum IgG levels compared to IVIG [11].

SCIG therapy is an effective treatment that can be used in both children and adults [4,5,12]. However, none of the studies have evaluated the efficacy of SCIG therapy in immunodeficient patients with low body weight (LBW). In this study, we evaluated compliance to therapy, side effects, complications, and the effectiveness of SCIG supplementation in the patients with PID who previously received IVIG therapy and subsequently switched to SCIG, and compared these parameters in patients according to their body weight.

# Methods

Records from 87 patients with PID (1–22 years old) who initially received IVIG and then SCIG for 12 months between April 2015 and March 2018 and underwent PID follow-up were retrospectively evaluated. The demographic data, clinical and laboratory findings, as well as SCIG dose and side effects of the patients were obtained from patient files. Patients with a weight-for-age z-score of < -2 SD were defined as the low body weight (LBW) group. Baseline IgG levels before IVIG, IgG levels at one, three, six, and 12 months after IVIG treatment (Group 1), and IgG levels at one, three, six and 12 months after SCIG treatment (Group 2) were assessed. The study was approved by the local Ethics Committee (Decision No: 2020/2821). All patients and/or parents were informed of the study and their written consent was obtained.

SCIG was administered in our clinic at a frequency and dosage previously stated. Briefly, the monthly SCIG dose was calculated as 1.37-fold the IVIG dose the patient received every month [1]. The total monthly SCIG dose was given in three or four doses per month, with injections every seven or 10 days. SCIG administration was performed by a rapid infusion (rapid push) technique with a disposable syringe and butterfly needle suitable for subcutaneous fat tissue [1]. The preferred infusion area was the lower abdomen and thigh. Approved immunoglobulin preparations for SCIG at a concentration of 10% were used for administration (Kiovig® 10% (n = 72) and Gamunex-C® 10% (n = 15)), and the infusion rate was determined to be 30–60 mL/hour. SCIG administration training was provided by a specialized nurse and the first three administrations were practiced in the hospital. After training was complete, the subsequent administrations were performed by the patient or their parents at home. All patients received 12 months IVIG treatment followed by SCIG treatment. A form containing possible side effects was prepared for the patients and they were asked to record when they experienced side effects.

### Statistical Analysis

Graphs were plotted using GraphPad Prism 6.0 and SPSS for Windows version 25.0 (Chicago, Illinois, USA) was used to evaluate the collected data. For non-normally distributed data, nonparametric tests were used. For comparison of independent groups, the Mann-Whitney U test was used, whereas the Wilcoxon test was used for comparisons of dependent groups. Continuous variables were expressed as the median (interquartile range, IQR).

IgG levels were compared between Group 1 (one, three, six, and 12 months after IVIG) and Group 2 (one, three, six, and 12 months after SCIG) using the Wilcoxon test. For in-group comparisons, the IgG levels within Group 1 (1, 3, 6, and 12 months) were compared ın itself, and the IgG values of Group 2 (one, three, six, and 12 months) were compared ın itself..Following an initial Friedman test, significant groups were analyzed using the Wilcoxon test with Bonferroni adjustment. IgG levels of patients undergoing weekly immunoglobulin administration were compared to patients undergoing administration every 10 days using the Mann-Whitney U test.

# Results

Of the 87 patients, 50 were male (57.5%) and 37 were female (42.5%), with a median age of 9.6 years (range 1–22 years). There were 13 patients (14.9%) with LBW and seven of the LBW patients were male (53.8%) and six were females (46.2%). All patients were receiving IVIG every three weeks at a dose of 400-600 mg/kg/dose before switching to SCIG. Every 10 days, 74.7% of the patients received SCIG, while 22 patients received SCIG every seven days. The characteristics of patients with NBW and DDA are summarized in Table 1.

The diagnoses of the patients are summarized in Table 2. Most patients (60.9%) had a predominant antibody deficiency (n = 53). Six patients underwent bone marrow transplants for combined immunodeficiency (n = 5) and GATA2 deficiency (n = 1) while undergoing immunoglobulin therapy.

Comparisons of serum IgG levels from the same PID patients undergoing IVIG treatment (Group 1) and SCIG therapy (Group 2) at one, three, six, and 12 months indicated a statistically significant difference between at the beginning of the therapies and during follow-up ($p < 0.001$) (Table 1E). Additionally, IgG levels of Group 2 patients were higher and more stable than those of Group 1 (Figure 1). A statistically significant difference ($p < 0.001$) was also found in the number of hospitalizations between the two groups, with 3.58 ± 4.6 hospitalizations recorded during IVIG therapy and 0.70 ± 1.4 hospitalizations recorded during SCIG therapy in a 12-month period. Serum IgG levels of patients on weekly SCIG therapy were higher compared to patients receiving SCIG every 10 days; however, no significant difference in serum IgG levels was found between the groups.

Patients with LBW weighed between 4.87 kg to 9.6 kg, with a weight-for-age z-score of < -2 SD. Most patients (76.9%) had SCIG therapy every 10 days, while three patients had treatment every seven days**.** Most patients with LBW had syndromic combined immunodeficiencies (Table 2). The site of SCIG therapy administration was the lower abdominal area (n = 11) and the thigh area (n = 2). The underlying causes of LBW were as follows: congenital heart defects, meningomyelocele, intrauterine growth retardation, prematurity and chronic diarrhea. Diagnostic features and comorbidities of 13 patients are shown in Table 2E. IgG levels in Group 2 of the LBW patients were more stable than in Group 1 ($p < 0.001$) (Figure 2, Table 3E). Among the LBW patients, comparison of IgG levels within Group 1 and Group 2 were found to be statistically significant. However among the low-body-weight patients, comparison of IgG levels in the 1st group and 2nd group in itself was not found to be statistically significant.

The reasons for switching from IVIG to SCIG in our patients included problems with venous access (n = 5), systemic side effects (n = 3), family preference (n = 21), and in response to our suggestion among the others. Infections were controlled after initiation of IVIG for most patients (n = 67), although 10 patients had recurrent infections with a serum IgG level under 600 mg/dL despite increasing IVIG doses. Three of these 10 patients had a weight-for-age z-score of < -2 SD (LBW). The diagnoses of these three patients included transient/prolonged hypogammaglobulinemia (n = 2) and LRBA deficiency (n = 1). A significant increase was observed in serum IgG levels in eight of 10 patients after SCIG therapy (p = 0.01). Two patients undergoing SCIG therapy had serum IgG levels below 600 mg/dL, although the levels were higher than those observed during IVIG therapy. These two patients were receiving SCIG every 10 days. One of these patients had a weight-for-age z-score of < -2 SD and was diagnosed with transient/prolonged hypogammaglobulinemia, while the other had an NBW and was undergoing follow-up for a diagnosis of Artemis deficiency.

A total of 4,540 administrations were performed in 87 patients over 35 months. Mild local side effects, including redness (1.2%), swelling (1%), pain (0.9%) and anxiety/fatigue/weakness (0.2%), were observed in 153 administrations (3.3%) of 30 patients. Most of the local side effects occurred during the first administration, but not in subsequent administrations. During the follow-up period, a total of five patients switched back to IVIG from SCIG. Three were due to non-compliance to therapy, and two were due to the development of thrombocytopenia. Acute severe bacterial infection was not observed in any of the patients undergoing immunoglobulin replacement therapy and there were no complications related to SCIG administration in the patients with LBW.

# Discussion

IGRT is widely used to treat PID, as IVIG or SCIG and its use has been increasing. IGRT is also used as an anti-inflammatory and immunomodulatory medication. However, there are insufficient data on the frequency of administration of SCIG therapy in children. Furthermore, there are no data on use of this therapy in children with LBW. This is one of largest studies in the literature on the effects of SCIG administration in pediatric patients with PID and reveals that SCIG can be safely used in children with LBW.

IVIG therapy has been used globally, including in our country, for a long period of time, while SCIG therapy has been safely used as a treatment modality in both adults and children since 2006 in Europe and the U.S. There are two main routes of administration for SCIG. In recent years, SCIG therapy has become a preferred route of administration that utilizes an infusion pump or rapid push method at home. While it is possible for IGRT to be initially administered as IVIG and then continued as SCIG therapy, there are some patients who begin treatment with the SCIG method. However, SCIG therapy requires 6–12 weeks to reach stable IgG levels compared to IVIG therapy. Therefore, intravenous administration of the first few doses is recommended for patients undergoing initial IGRT [13]. To evaluate family compliance in our patients, IVIG therapy was initiated in all our patients, and SCIG administration was started 12 months later. With

this method, we hypothesized that higher serum IgG values would be observed in patients undergoing SCIG administration at the beginning and during follow-up.

The monthly SCIG dose used in our study was the same for both IVIG and SCIG in European countries [14]. However, it was recommended we multiply the IVIG dose by 1.37, as per studies in the U.S. [15,16], and administer the monthly dose subcutaneously every week [15]. In contrast to the peaks and low levels of serum IgG observed during IVIG infusions, SCIG therapy has been shown to provide levels that are more stable and closer to physiological serum IgG levels [11]. Karakoç-Aydıner et al. reported no significant difference in the stability of serum IgG levels, reactions, and infection incidence when patients were administered the monthly total SCIG dose over three or four partial doses [17]. After recalculating the monthly immunoglobulin dose by using the coefficient of 1.37, we administered the total dose in three or four partial doses in 75% and 25% of the patients, respectively. While no significant difference in the infection incidence was detected, higher serum IgG levels were observed in patients administered the total SCIG dose over four divided doses, although this was not statistically significant. This indicates that weekly SCIG administration leads to serum IgG levels that are closer to physiological levels. However, we suggest considering long-term compliance to therapy when deciding on either a weekly or 10-day administration regime.

The incidence of infections has been shown to decrease linearly with increasing IgG levels during SCIG therapy [18]. Therefore, regular measurement of serum IgG levels is an important marker in evaluating clinical efficacy. While most infections in our patients were controlled after initiation of IVIG, 10 patients had a high incidence of infections despite increasing IVIG doses, and serum IgG levels could not be increased above 600 mg/dL. Three of these patients had LBW. Eight of the 10 patients produced serum IgG levels > 600 mg/dL after switching to SCIG therapy. Although the IgG levels of the other two patients also increased, the serum IgG levels persisted below 600 mg/dL. After switching to SCIG administration, infections in all our patients were controlled and hospitalizations decreased significantly. We believe that switching to SCIG treatment improved the clinical follow-up of our patients by providing an incremental increase in serum IgG levels.

The side effects observed during IVIG administration are more severe and frequent than those of SCIG therapy. Side effects that may be seen during SCIG administration are mainly local and include pain, swelling, and redness at the site of injection. While these findings are often temporary, the frequency of local side effects decreases with repeated infusions [19,20]. Local tissue reactions were reported in 2.1–20% of patients, while the rate of systemic side effects in patients receiving SCIG is between 0.3% and 3.3% [21]. A Scandinavian retrospective study evaluated more than 33,000 subcutaneous infusions in PID patients and reported 100 mild and less moderate systemic reactions, with no serious or anaphylactic reactions observed [22]. In this study, 4,540 subcutaneous administrations were performed, and no systemic side effects were observed. However, mild side effects were observed in 153 administrations (3.3%). The rate of side effects after SCIG administrations in our study was found to be consistent with the literature.

Our study shows that SCIG administration on a weekly or 10-day interval increased serum IgG levels, making it more stable than IVIG therapy. It also indicates that SCIG therapy can be administered safely in younger age groups, especially in children with LBW. Using this approach, hospitalizations and family visits were also reduced, allowing for less interruptions in the daily lives of patients and their parents, and resulting in improved quality of life. For this reason, we believe that it is beneficial to switch to SCIG therapy, especially for those patients undergoing IVIG therapy whose IgG levels do not increase or those with uncontrolled infections, even if they have LBW.

# Abbreviations

PID: Primary immunodeficiencies

IGRT: Immunoglobulin replacement therapy

IVIG: Intravenous immunoglobulin

SCIG: Subcutaneous immunoglobulin

LBW: Low Body Weight

NBW: Normal Body Weight

# Declarations

**Acknowledgments**: None.

### Contributions

Dr. XXXXXX: Analyzed and interpreted the data and wrote the paper.

Dr. XXXXXX, Dr. XXXXXX: Drafted the manuscript, as well as analyzed/interpreted the study data.

Dr. XXXXXX: Analyzed and interpreted the data, and additionally provided statistical support.

Dr. XXXXXX, Dr. XXXXXX, Ms. XXXXXX: Acquisition of data.

All authors read and approved the final manuscript.

### Funding

No funding was received.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Ethical Approval

This research study was conducted retrospectively from data obtained for clinical purposes. The study was approved by Necmettin Erbakan University Meram Medical School Ethics Committee (Date: 09.18.2020/No: 2020/2821).

## Consent to Publish

Not applicable

### Consent to participate

Not applicable

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# Tables

**Table 1: The characteristics of NBW patients and LBW patients**

| | Patients with NBW (n = 74) | Patients with LBW (n = 13) | P |
|---|---|---|---|
| Age (months)* | 150.9 ± 67.5<br>146.6 (37−266) | 50.9 ± 10.2<br>52.7 (26−67) | < 0.001 |
| Age at initiation of SCIG (months)* | 120.2 ± 64.7<br>114.5 (14−223) | 25.9 ± 9.7<br>25.4 (14−47) | < 0.001 |
| Administration period (months)* | 30.7 ± 10.7<br>29.9 (13−50) | 24.9 ± 11.2<br>23.1 (12−43) | 0.108 |
| Female/male | 31/43 | 6/7 | |

*Data are presented as mean ± standard deviation. Statistical significance was taken as $p < 0.05$.

SCIG: Subcutaneous immunoglobulin, LBW: Low Body Weight

NBW: Normal Body Weight

**Table 2: Diagnostic features of the patients**

| Diagnosis | Gender (n) Female/male | Total number (n) (%) |
|---|---|---|
| **Predominantly antibody deficiencies** | 19/34 | 53 (60.9) |
| Transient/prolonged hypogammaglobulinemia | 14/19 | 33 (37.9) |
| Agammaglobulinemia (Bruton's disease) | 0/6 | 6 (6.9) |
| Common variable immunodeficiency (CVID) | 3/6 | 9 (10.3) |
| Specific antibody deficiency | 2/3 | 5 (5.7) |
| **Combined immunodeficiency with a syndrome** | 6/12 | 18 (20.7) |
| Down syndrome | 1/5 | 6 (6.9) |
| Ataxia Telangiectasia (A-T) | 3/2 | 5 (5.7) |
| Di George syndrome | 1/2 | 3 (3.4) |
| Kabuki make-up syndrome | 1/1 | 2 (2.3) |
| PGM3 deficiency | 0/1 | 1 (1.1) |
| ICF syndrome | 0/1 | 1 (1.1) |
| **Immune dysregulation diseases** | | |
| LRBA deficiency | 1/0 | 1 (1.1) |
| **Congenital defects of phagocytes** | | |
| GATA 2 deficiency | 1/0 | 1 (1.1) |
| **Combined immunodeficiencies** | 10/4 | 14 (16.1) |
| ***A) Severe combined immunodeficiencies (SCID)*** | 8/2 | 10 (11.5) |
| ADA deficiency | 2/0 | 2 (2.3) |
| Artemis deficiency | 5/1 | 6 (6.9) |
| SCID (mutation unspecified) | 1/0 | 1 (1.1) |
| IL-2 receptor deficiency | 0/1 | 1 (1.1) |
| ***B) Combined immunodeficiency (CID)*** | 2/2 | 4 (4.6) |
| CD3γ deficiency | 1/0 | 1 (1.1) |
| Polymerase deficiency (POLD1) | 1/0 | 1 (1.1) |
| STK4 deficiency | 0/1 | 1 (1.1) |
| Unidentified CID | 0/1 | 1 (1.1) |
| DIAGNOSIS OF PATIENTS WITH LBW | | |
| **Combined immunodeficiency with a syndrome** | 2/4 | 6 (46.2) |
| Di George syndrome | 1/2 | 3 (23.1) |
| Down syndrome | 1/1 | 2 (15.4) |
| PGM3 deficiency | 0/1 | 1 (7.7) |
| **Predominantly antibody deficiencies** | | |
| Transient/prolonged hypogammaglobulinemia | 1/3 | 4 (30.7) |
| ***Severe combined immunodeficiencies (SCID)*** | | |
| ADA deficiency | 2/0 | 2 (15.4) |
| **Immune dysregulation diseases** | | |
| LRBA deficiency | 1/0 | 1 (7.7) |

**Table 1E.** IgG levels before and after IVIG and SCIG

| | IVIG group median (IQR) | SCIG group median (IQR) | P |
|---|---|---|---|
| Before IVIG/SCIG * | 587 (863–385) | 933 (1240–707) | < 0.001 |
| After IVIG and SCIG | | | |
| 1st month* | 847 (1190–700) | 1080 (1360–860) | < 0.001 |
| 3rd month* | 912 (1130–723) | 1050 (1422–926) | < 0.001 |
| 6th month* | 892 (1170–707) | 1120 (1410–961) | < 0.001 |
| 12th month* | 933 (1240–707) | 1100 (1340–897) | < 0.001 |

*Data are presented as IgG mg/dL median (IQR = Q3-Q1). Statistical significance was accepted as $p < 0.05$.

SCIG: Subcutaneous immunoglobulin, IVIG: Intravenous immunoglobulin

**Table 2E.** Diagnostic features and comorbidities of patients with LBW

| | Diagnosis | Gender | PM | IUGR | CHD | Other Comorbidity |
|---|---|---|---|---|---|---|
| **P1** | Di George syndrome | F | + | - | + | Meningomyelocele |
| **P2** | Di George syndrome | M | - | + | + | - |
| **P3** | Di George syndrome | M | - | - | + | - |
| **P4** | Down syndrome | F | - | - | + | - |
| **P5** | Down syndrome | M | - | + | + | - |
| **P6** | PGM3 deficiency | M | - | - | - | - |
| **P7** | Transient/prolonged hypogammaglobulinemia | M | + | | + | hypothyroidism, epilepsy |
| **P8** | Transient/prolonged hypogammaglobulinemia | F | - | - | - | chronic diarrhea, FMF |
| **P9** | Transient/prolonged hypogammaglobulinemia | M | - | - | - | chronic diarrhea |
| **P10** | Transient/prolonged hypogammaglobulinemia | M | + | - | - | SMA tip-2 |
| **P11** | ADA deficiency | F | - | - | - | - |
| **P12** | ADA deficiency | F | - | - | - | - |
| **P13** | LRBA deficiency | F | - | - | - | chronic diarrhea |

PM: Prematurity, IUGR: Intrauterine growth restriction, FMF: Familial Mediterranean Fever, CHD: Congenital heart disease

**Table 3E.** IgG levels before and after IVIG and SCIG in LBW patients

| | IVIG group median (IQR) | SCIG group median (IQR) | P |
|---|---|---|---|
| Before IVIG/SCIG * | 511 (693–216) | 707 (976–592) | < 0.001 |
| After IVIG and SCIG | | | |
| 1st month* | 830 (1029–677) | 924 (1290–789) | < 0.001 |
| 3rd month* | 770 (879–704) | 1060 (1350–876) | < 0.001 |
| 6th month* | 732 (936–631) | 1100 (1395–867) | < 0.001 |
| 12th month* | 707 (976–592) | 1100 (1392–913) | < 0.001 |

*Data are presented as IgG mg/dL median (IQR = Q3 - Q1). Statistical significance was accepted as $p < 0.05$.

SCIG: Subcutaneous immunoglobulin, IVIG: Intravenous immunoglobulin

# Figures

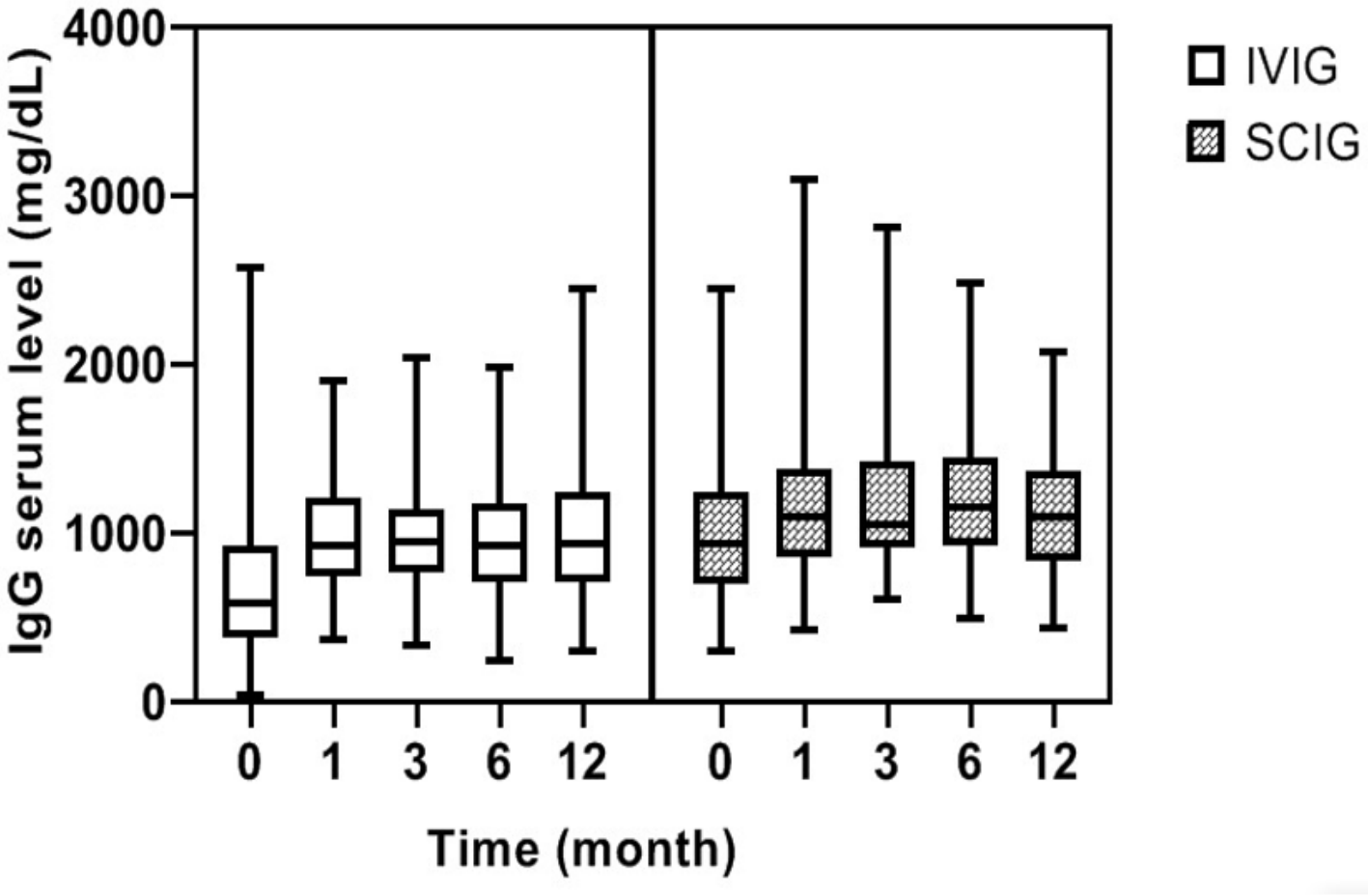


**Figure 1**

Serum IgG levels of the same patients while on IVIG and SCIG

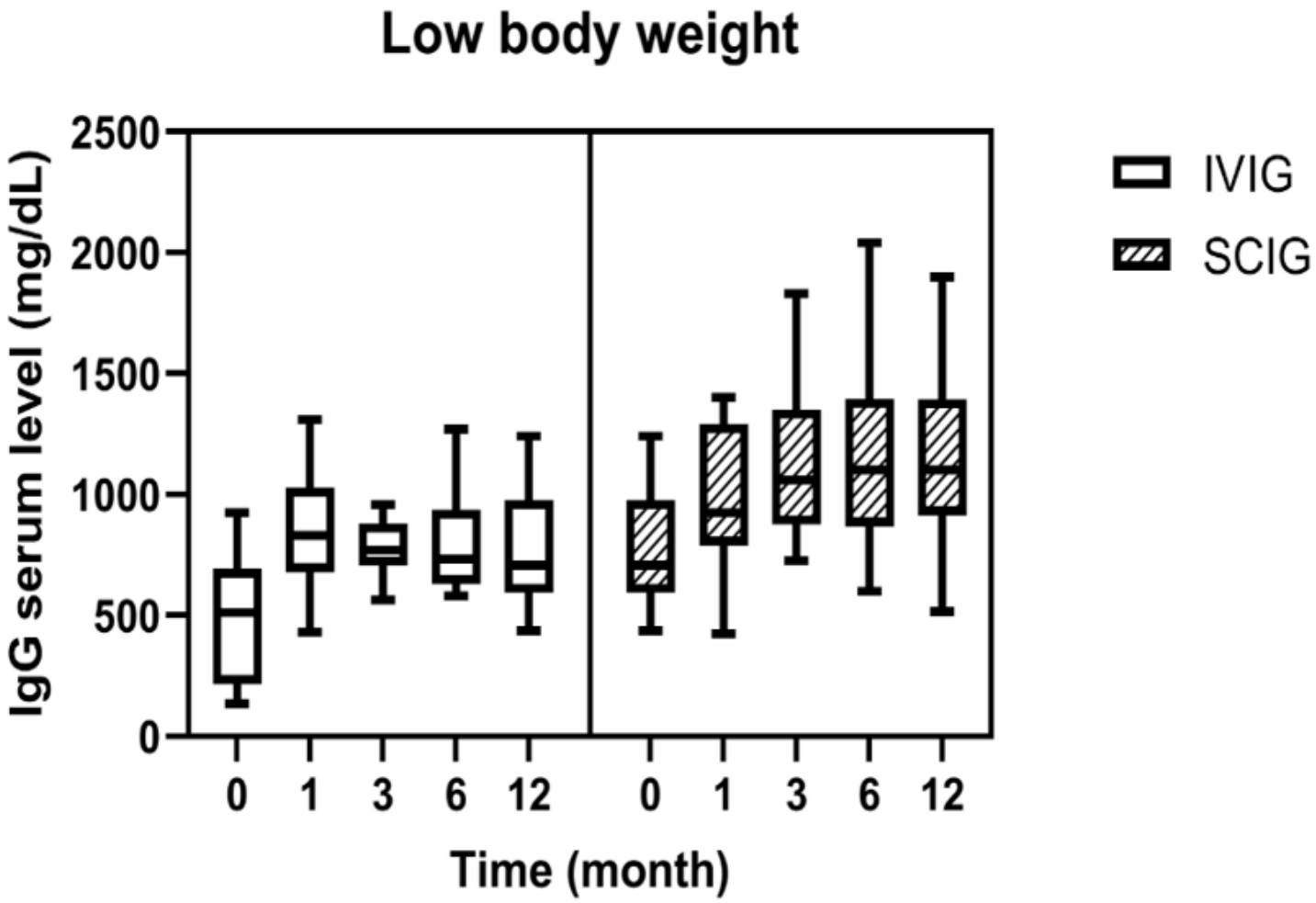


Figure 2

Serum IgG levels of the patients with LBW during IVIG and SCIG supplementation