Effects of Glucocorticoid Pulse Therapy on Thyroid Function and Thyroid Antibodies in Children with Graves' Disease

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Abstract

Objective The purpose of this study is to observe the effects of glucocorticoid pulse therapy on thyroid function and thyroid antibodies in children with Graves' disease (GD).

Methods Twenty children who were treated by intravenous methylprednisolone pulse therapy (MPT) followed by oral prednisolone administration and antithyroid drugs were included in the pulse group. Twenty children who were treated with antithyroid drugs alone were included in the control group. Serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), thyrotropin (TSH), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyrotropin receptor antibodies (TRAb) were recorded at baseline and 10 days, 30days, and 60 days after treatment.

Results Significant differences in FT3, FT4, TSH, TPOAb, TGAb, and TRAb levels were found in both groups from baseline to follow-up time points (all $P<0.05$). On the 30th day, the TRAb level in the pulse group was significantly lower than that in the control group ($P=0.023$). However, the level of TRAb rose on the 60th day. For values of TRAb at baseline, 10 days, and 60 days after treatment, there were no significant differences respectively between the two groups (all $P>0.05$). No significant differences were observed in FT3, FT4, TSH, TPOAb, and TGAb levels between the two groups (all $P>0.05$).

Conclusion Our results suggest that the effects of intravenous MPT followed by oral prednisolone on TRAb level are temporary in children with GD. It is not helpful to the sustained recovery of thyroid function.

Introduction

Hyperthyroidism is a relatively rare disease in children compared to adults. The incidence rate of hyperthyroidism in children is increasing over the last decades [1–2]. The most common cause of hyperthyroidism in children is Graves' disease (GD). GD is an autoimmune thyroid disease caused by the production of thyrotropin receptor antibodies (TRAb). There are a wide variety of clinical manifestations of GD. The most common extrathyroidal manifestation of GD is Graves' orbitopathy. GD also has serious adverse effects on children's growth and development[3].

The purposes of treatment for GD are to reduce excessive thyroid hormone production within a safe scope, maintain normal thyroid function, relieve clinical symptoms, and prevent recurrence of hyperthyroidism. Seeking the most appropriate therapy for children is very important and urgent. Therapies for children with GD include antithyroid drugs (ATD), radioactive iodine therapy, and surgical thyroidectomy [4]. The best treatment for children with GD has been debated for many years. ATD are considered the first-line treatment, but side effects of drugs and poor long-term remission need to be solved. Radioactive iodine therapy usually should be restricted to children older than 10 years of age due to its side effects such as thyroid malignancy and hypothyroidism [5]. Thyroidectomy is the last choice for children with GD. It will lead to subsequent hypothyroidism, hypoparathyroidism, and postoperative complications. Therefore, drug therapy is usually the initial treatment for children with GD at present.

In children with GD who only use antithyroid drugs, uncontrolled symptoms, long-term remission, and high recurrence rate are often presented. How to correct thyrotoxicosis promptly and maintain euthyroidism stably for children with GD should be solved. European Group on Graves' orbitopathy (EUGOGO) recommended that glucocorticoids should be used for moderate-to-severe Graves' orbitopathy if orbitopathy is active in adults. It also recommended that thyroid function should be restored promptly for children with Graves' orbitopathy. Although glucocorticoids should be avoided in children with GD associated with orbitopathy, the avoidance of glucocorticoids still needs evidence from committee reports and/or clinical experiences of authorities [6]. At present, few studies have explored the effects of glucocorticoid pulse therapy on thyroid function and thyroid antibodies in children with GD. Accordingly, the purpose of this study was to observe the effects of intravenous methylprednisolone pulse therapy (MPT) followed by oral prednisolone administration on thyroid function and thyroid antibodies in children with GD.

Materials And Methods

Patients

The retrospective study included children who were newly diagnosed with GD between 2014 to 2018 at our Pediatric Department. The including criteria were as follows: the diagnosis of GD was based on clinical and biochemical findings, such as palpitations, fatigue, irritability, increased appetite, weight loss, diarrhoea, increased perspiration, elevated serum free thyroxine (FT4) and free triiodothyronine (FT3) levels, suppressed serum thyrotropin (TSH) level, and positive TRAb; the presence of bilateral exophthalmos according to the reference [7]. Children with peptic ulcers, severe hypertension, cardiovascular diseases, liver dysfunction, tumor, diabetic mellitus, infectious diseases, and other autoimmune diseases were excluded. We also excluded children who had received previous ATD treatment at baseline, and those who were lost to follow-up during the study. A total of 40 children fulfilled the criteria. Of these, 20 children were treated by intravenous MPT followed by oral prednisolone administration and ATD treatment, aged 7.7±3.2 (range 2.0-14.0) years, 6 boys and 14 girls, 20 children were treated with ATD alone (n=20), aged 8.9±4.0 (range 2.0-14.0) years, 4 boys and 16 girls. The control group and the pulse group had similar age and sex distribution.

Study protocol

We obtained clinical and treatment data from children's medical records. Age, sex, clinical signs, goiter size, serum concentrations of FT3, FT4, TSH, thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and TRAb, electrocardiogram (ECG), and thyroid and cardiac ultrasound were recorded at diagnosis and during follow-up. Follow-up visits occurred 10 days, 30days, and 60 days after treatment.

All children received ATD treatment (methimazole 1.0mg/kg/day) after diagnosis. The doses of methimazole were adjusted according to individual's weight and thyroid hormone levels. Metoprolol (0.5-1.0mg/kg/day) was administered orally if heart rate exceeds 100 bpm [8]. In the pulse group, high-dose methylprednisolone was infused intravenously at a dose of 5mg/kg/day for 3 successive days, and the dosage was reduced by half every 3 days. Blood pressure, blood glucose, and electrocardiogram were monitored daily. After 3 cycles of this course, oral prednisolone was administered. The dosage of prednisolone was gradually tapered off over a period of 3 weeks. Oral calcium and vitamin-D were also supplemented for children during glucocorticoid treatment.

The study was approved by the Ethics Committee of Linyi People's Hospital (approval number: YX10070). Written informed consents for anonymized data to be collated and analyzed were obtained from all patients' parents.

Methods

Fasting serum samples were collected in the morning from all subjects. Serum FT3, FT4, TSH, TPOAb, TGAb, and TRAb concentrations were measured by an automated chemiluminescence immunoassay system (Advia Center, Siemens, Munich, Germany). Normal ranges were 2.27-4.22 pg/mL for FT3, 0.88-1.75 ng/dL for FT4, 0.35-5.5 μIU/mL for TSH, 0-60 IU/mL for TPOAb, 0-60 IU/mL for TGAb, and 0-1.22 IU/L for TRAb. TPOAb, TGAb, and TRAb values above the normal ranges were defined as positive. The intra- and inter-assay coefficients of variation were all <5.0% and <4.0%, respectively. The sensitivity of FT3, FT4, TSH, TPOAb, TGAb, and TRAb were 0.19 pg/mL, 0.1 ng/dL, 0.001 μIU/mL, 0.1 IU/mL, 10 IU/mL, and 0.01 IU/L respectively.

Grading of goiter was performed by inspection and palpation, and was classified according to the World Health Organization (WHO) criteria: grade 0, no goiter; grade 1,goiter palpable but not visible; grade 2, goiter visible with neck in normal position [9]. Degree of proptosis was measured with a Hertel exophthalmometer. Physical examination of all subjects was done by one experienced investigator.

Thyroid ultrasound was performed with a 5-12 MHz linear-array transducer on a LOGIQ 9 scanner (GE Medical Systems, Milwaukee, WI, USA). Echocardiography was performed with a 2-5 MHz transducer using an IU-22 ultrasound scanner (Philips Medical System, Bothell, WA, USA). All ultrasound examinations were carried out by the same trained sonographer. ECG was recorded with an electrocardiograph (1550p; Nihon Kohden, Tokyo, Japan) at paper speed of 25 mm/s and 10 mv/mm.

Statistical analysis

Normal distribution of variables was checked with the Shapiro-Wilk test before further analyses. Values of FT3, FT4, and TRAb showed Normal distributions. Values of TSH, TPOAb, and TGAb showed skewed distributions. Therefore, normally distributed variables were expressed as mean ± standard deviation, and

skewed distributed data were expressed as the median and interquartile range. Chi-square test was used to compare clinical characteristics of the two groups. Repeated measures general linear models were used to determine whether there were changes in values of FT3, FT4, and TRAb at baseline, 10 days, 30days, and 60 days. Friedman's nonparametric test was used to analyze changes in TSH, TPOAb, and TGAb levels at different time points. The Mann-Whitney U test was used to compare nonparametric data at each moment between groups. A two-tailed P-value of less than 0.05 was considered statistically significant. The analyses were performed using statistical software SPSS version 19.0 (SPSS Inc. Chicago, USA).

Results

Baseline clinical characteristics

In the pulse group, the duration of clinical symptoms was about 0.50(0.18, 1.00) years. In the control group, the duration of clinical symptoms was about 0.50(0.27, 1.00) years. There was no significant difference in the duration of hyperthyroidism between the two groups ($P > 0.05$). At the beginning of the study, all children presented with typical symptoms of GD. All children showed exophthalmos. In the pulse group, 8 children who felt palpitations, 9 children who felt fatigue, 16 children who manifested as irritability, 11 children who had increased appetite, 3 children who had weight loss, 7 children who had diarrhoea, 11 children who showed increased perspiration, 5 children who showed goiter grade 1, and 15 children who showed goiter grade 2. In the control group, 10 children who felt palpitations, 10 children who felt fatigue, 15 children who manifested as irritability, 9 children who had increased appetite, 4 children who had weight loss, 9 children who had diarrhoea, 12 children who showed increased perspiration, 4 children who showed goiter grade 1, and 16 children who showed goiter grade 2. There were no significant differences in the symptoms of hyperthyroidism, the grading of goiter, heart rate, and blood pressure between the two groups (all $P > 0.05$). Baseline clinical characteristics are shown in Table 1.

Table 1
Baseline Characteristics of Children with Graves' Disease.

Characteristic	The pulse group (n = 20)	The control group (n = 20)	P value
Gender [male(%)/female(%)]	6(30.0)/14(70.0)	4(20.0)/16(80.0)	0.465
Age(year)	7.7 ± 3.2	8.9 ± 4.0	0.303
Duration(year)	0.50(0.18,1.00)	0.50(0.27,1.00)	0.901
Palpitations(%)	8(40.0)	10(50.0)	0.525
Fatigue (%)	9(45.0)	10(50.0)	0.752
Irritability (%)	16(80.0)	15(75.0)	0.705
Increased appetite (%)	11(55.0)	9(45.0)	0.527
Weight loss (%)	3(15.0)	4(20.0)	0.677
Diarrhoea (%)	7(35.0)	9(45.0)	0.519
Increased perspiration (%)	11(55.0)	12(60.0)	0.749
Exophthalmos(mm)	17.85 ± 4.09	18.25 ± 4.36	0.767
Goiter grade 1 (%)	5(25.0)	4(20.0)	0.705
Goiter grade 2 (%)	15(75.0)	16(80.0)	0.705
Heart rate (bpm)	114 ± 18	115 ± 17	0.873
Systolic blood pressure (mmHg)	121 ± 12	124 ± 11	0.449
Diastolic blood pressure (mmHg)	71 ± 4	74 ± 5	0.063
TPOAb(+) (%)	17(85.0)	17(85.0)	1.000
TGAb(+) (%)	15(75.0)	14(70.0)	0.723
TRAb(+) (%)	20(100.0)	19(95.0)	0.311
Data are presented as means ± SD, median (interquartile range), or number (percentage).			
Abbreviations: TPOAb, thyroid peroxidase antibodies; TGAb, thyroglobulin antibodies; TRAb, thyroid stimulating hormone receptor antibodies.			

Laboratory and imaging parameters before treatment

There were no significant differences in the values of FT3, FT4, TSH, TPOAb, TGAb, and TRAb between the two groups (all $P < 0.05$). The parameters of TPOAb, TGAb, and TRAb before treatment are shown in

Table 1. Ultrasound examinations of thyroid showed increased thyroid volume and parenchymal blood flow in all children. In the pulse group, there was one child who had thyroid nodules, and one child who had thyroid follicular cysts. Cardiac ultrasound examinations revealed that 4 children had enlarged left atrium and left ventricle and mitral regurgitation, other children showed normal results. In the control group, cardiac ultrasound examinations revealed that one child had enlarged left atrium and ventricle and mitral regurgitation, other children showed normal results. The ECG in the pulse group showed that 11 children had sinus tachycardia, one child had excessive left ventricular voltage, 3 children had T-wave changes, one child had sinus arrhythmia, and 4 children were normal. The ECG in the control group showed that 11 children had sinus tachycardia, 2 children had sinus arrhythmia, and 7 children were normal.

Clinical, laboratory, and imaging parameters after treatment

In repeated measures of values of FT3, FT4, and TRAb levels, there was significant difference from baseline to follow-up time points (all $P < 0.001$). FT3, FT4, and TRAb levels at different time points were compared respectively.

In the two groups, there were significant differences in FT3 levels between baseline and 10, 30, and 60 days after treatment (all $P < 0.001$). However, there were no significant differences among 10, 30, and 60 days after treatment (all $P > 0.05$). The time points did not differ from group to group ($P = 0.132$). There was no significant difference between the pulse group and the control group ($P = 0.414$).

In the pulse group, there were significant differences in FT4 levels between baseline and 10, 30, and 60 days after treatment (all $P < 0.01$), there were significant differences between 10 days and 30, and 60 days after treatment (all $P < 0.001$), and there was no significant difference between 30 and 60 days after treatment ($P = 0.705$). In the control group, the results showed that there were significant differences between baseline and 10, 30, and 60 days after treatment (all $P < 0.01$), and there were no significant differences among 10, 30, and 60 days after treatment (all $P > 0.05$). The time points did not differ from group to group ($P = 0.186$). There was no significant difference between the pulse group and the control group ($P = 0.549$).

In the pulse group, there were significant differences in TRAb levels between baseline and 10, 30, and 60 days after treatment (all $P < 0.01$), there were significant differences between 10 days and 30, and 60 days after treatment (all $P < 0.05$), and there was no significant difference between 30 and 60 days after treatment ($P = 0.846$). In the control group, the results showed that there were significant differences between baseline and 30, and 60 days after treatment (all $P < 0.05$), and there were no significant differences among 10, 30, and 60 days after treatment (all $P > 0.05$). The time points differed from group to group ($P = 0.001$). For values of TRAb at baseline, 10 days, and 60 days after treatment, there were no significant differences respectively between the two groups (all $P > 0.05$), but for values of TRAb at 30 days, there was significant difference between the two groups ($P = 0.023$).

There were no significant differences between the pulse group and the control group in the values of TSH, TPOAb, and TGAb (all $P > 0.05$). TSH, TPOAb, and TGAb levels at different time points were compared respectively. In the pulse group, the results showed that there were significant differences in TSH, TPOAb, and TGAb levels from baseline to follow-up time points ($P = 0.001$, $P = 0.001$, and $P = 0.002$, respectively). In the control group, there were significant differences in TSH, TPOAb, and TGAb levels from baseline to follow-up time points ($P < 0.001$, $P = 0.036$, and $P = 0.001$, respectively). The changes of thyroid function and thyroid antibodies in children with GD are shown in Fig. 1.

In the pulse group, 7 children had elevated fasting blood glucose temporarily, 5 children had mild hypertensive on the basis of hyperthyroidism. After treatment, the above symptoms returned to normal. The clinical characteristics after treatment are shown in Table 2. Our children in this study still showed exophthalmos and thyroid goiter after 60 days of treatment. The abnormal of typical symptoms of hyperthyroidism, cardiac ultrasound, and ECG were all relieved in all children.

Table 2
Characteristics of Children with Graves' Disease after Treatment.

Characteristic	The pulse group (n = 20)	The control group (n = 20)	P value
Palpitations (%)	3(15.0)	1(5.0)	0.292
Fatigue (%)	3(15.0)	2(10.0)	0.633
Irritability (%)	8(40.0)	10(50.0)	0.525
Increased appetite (%)	17(85.0)	1(5.0)	< 0.001*
Weight loss (%)	0(0)	0(0)	1.000
Diarrhoea (%)	1(5.0)	2(10.0)	0.548
Increased perspiration (%)	8(40.0)	5(25.0)	0.311
Exophthalmos(mm)	17.73 ± 3.92	18.18 ± 4.25	0.730
Heart rate (bpm)	90 ± 8	87 ± 9	0.341
Systolic blood pressure (mmHg)	100 ± 7	98 ± 5	0.426
Diastolic blood pressure (mmHg)	64 ± 3	65 ± 4	0.661
TPOAb(+) (%)	15(75.0)	16(80.0)	0.705
TGAb(+) (%)	8(40.0)	15(75.0)	0.025*
TRAb(+) (%)	20(100.0)	18(90.0)	0.147
Data are presented as means ± SD, median (interquartile range), or number (percentage).			
No change occurred in exophthalmos and thyroid goiter after 60 days of treatment.			
Abbreviations: TPOAb, thyroid peroxidase antibodies; TGAb, thyroglobulin antibodies; TRAb, thyroid stimulating hormone receptor antibodies.			
*P < 0.05			

Discussion

In this study, we observed the effects of intravenous MPT followed by oral prednisolone administration on thyroid function and thyroid antibodies in children with GD. We found no significant differences in FT3, FT4, TSH, TPOAb, and TGAb levels between the pulse group and the control group. On the 30th day, the TRAb level in the pulse group was significantly lower than that in the control group. However, the level of TRAb rose on the 60th day, and there was no difference between the two groups. Our results indicated that the intravenous MPT followed by oral prednisolone administration had a transient mitigation effect on TRAb level in children with GD.

GD is an autoimmune thyroid disease. Deficiency in suppressor T cells and loss of self-tolerance are mainly involved in the pathogenesis of GD. Antigen-presenting cells (APC) in thyroid tissue and peripheral blood can recognize autoantigens and present them to T cells. T-helper (Th) cells differentiate into Th1 and Th2 cell subsets under the action of specific cytokines. Cell-induced cytotoxicity and infiltration are associated with increased Th1 activity. Increased Th2 activity can stimulate B lymphocytes to produce TRAb, which mediates humoral immunity [10–11]. TRAb bind to TSH receptor (TSHR) to activate thyroid gland, leading to hyperthyroidism and goiter. Excess circulating thyroid hormone causes a wide range of clinical symptoms. Graves' orbitopathy is due to the autoimmune response not the result of hyperthyroidism [12]. Many patients have antibodies against TSHR and thyroid peroxidase, and about 50% of them have antibodies against thyroglobulin [13]. In our children, most of them showed positive TRAb, TGAb and TPOAb.

Glucocorticoids have immunoregulatory effects. It can decrease aggregation of macrophage, interfere with function of T cells and B cells, reduce the activity of immune cells, inhibit the release of inflammatory mediators (i.e. cytokines and prostaglandins), lower the concentration of disease relevant thyroid-stimulation immunoglobulins, and prevent antibodies from binding to receptors [14–15]. In addition, glucocorticoids have non-specific anti-inflammatory effects. It can reduce interstitial capillary dilatation, exudation and edema, inhibit the proliferation of vascular endothelial cells, alleviate interstitial congestion, and decrease thyroid gland volume. Therefore, glucocorticoids can control hyperthyroidism to some extent.

The mechanism for glucocorticoids use in GD is their immunosuppressive and anti-inflammatory effects. Glucocorticoids can be given orally, intravenously and locally [16]. Retrobulbar injection of glucocorticoids may be considered under circumstances of absolute contraindications to systemic glucocorticoids [17]. Therefore, intravenous and oral glucocorticoids were used in our study.

The effects of glucocorticoids therapy on Graves' orbitopathy has been studied in most studies. A meta-analysis of 14 clinical trials showed that glucocorticoids were more effective than other treatments for Graves' orbitopathy, especially the intravenous glucocorticoid pulse therapy [18]. A prospective, randomized, and placebo-controlled study also reported that MPT effectively improved diplopia, eye movement and proptosis for active and moderately severe Graves' orbitopathy. It was well tolerated and safe. However, the proptosis of one eye worsened in one patient. The effect of treating proptosis with MPT was not so obvious for overall outcome of both eyes [19]. A small number of paediatricians recommended the use of glucocorticoids in children with moderate-to-severe and active Graves' orbitopathy. Glucocorticoids are the choice of treatment [20]. Based on this recommendation, GD children associated with orbitopathy were treated with MPT treatment in our study. However, the difference of proptosis in children with GD was not noted after MPT treatment. This may be due to our short-term follow-up.

Few studies have been conducted on the effects of glucocorticoids therapy on thyroid function and thyroid antibodies. A study found that the level of TSH binding inhibitor immunoglobulin (TBII) in some

adult patients with GD decreased significantly after 3 to 6 months of pulse therapy, but increased again at 12 to 24 months. The effect of pulse therapy on autoimmune antibody was transient. The pulse therapy did not improve remission rate of GD [21]. However, studies of the effects of glucocorticoids therapy on thyroid function and thyroid antibodies in GD children are few. Therefore, glucocorticoids therapy on thyroid function and thyroid antibodies in GD children is our main observation. There are no clinical evidence on the optimal dosage and regimen of intravenous and oral glucocorticoids for children. Prolonged glucocorticoid administration will lead to Cushing's syndrome, hyperglycemia, hypertension, gastrointestinal ulcer, infection, osteoporosis, growth retardation, etc.[22]. Therefore, based on the above considerations, we used intravenous MPT followed by oral prednisolone administration in this study. After 9 days of MPT, oral prednisolone was administered. The dosage of prednisolone was gradually tapered off over a period of 3 weeks. Increased appetite, hyperglycemia, hypertension were found in some of children in the pulse group. After ceasing glucocorticoid therapy, these symptoms returned to normal. It can reduce the side effects of prolonged glucocorticoid administration to some extent.

In our study, the TRAb level on the 30th day in the pulse group was significantly lower than that in the control group. It was due to the immunosuppressive effect of glucocorticoids. The level of TRAb rose on the 60th day, and there was no difference between the two groups. It was due to the discontinuation of glucocorticoids after 30 days. In addition, the rate of positive TGAb in the pulse group was lower than that in the control group also due to the immunosuppressive effect of glucocorticoids. There was no difference in the level of TGAb between the two groups. It may be due to our small sample size.

There are two main limitations in this study. On one hand, different dosage and regimen of glucocorticoid administration may result in different therapeutic effects. There are no literatures which clearly specify the dosage and regimen of glucocorticoid administration for children. Considering the side effects of glucocorticoids on children, we adopted small dosage of intravenous MPT followed by oral glucocorticoids. On the other hand, this is a retrospective cohort study based on clinical practice with consents of parents and ethics committee. Our clinical practice provided initial exploration for follow-up prospective study. The sample size was small and the observation time was short in our study. In fact, GD is relatively rare in children. The half-life of glucocorticoid is relatively short.

Conclusion

In conclusion, the effects of intravenous MPT followed by oral prednisolone on TRAb level are temporary in children with GD. It is not helpful to the sustained recovery of thyroid function. In the future, the dosage and regimen of glucocorticoid administration, as well as new treatment methods which can reduce the recurrence rate and restore thyroid function promptly need to be further explored for children with GD.

Abbreviations

GD: Graves' disease; MPT: methylprednisolone pulse therapy; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; TPOAb: thyroid peroxidase antibodies; TGAb: thyroglobulin

antibodies; TRAb: thyroid stimulating hormone receptor antibodies.

Declarations

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Authors' Contributions

Medical Practices: Yanyan Hu, Yulin Man, Xuemei Sun. Concept: Yongzhen Xue. Design: Yanyan Hu, Yongzhen Xue. Data Collection or Processing: Yanyan Hu, Yulin Man. Analysis or Interpretation: Yanyan Hu, Yongzhen Xue. Literature Search: Yanyan Hu, Yulin Man, Xuemei Sun. Writing: Yanyan Hu, Yulin Man, Xuemei Sun.

Conflict of interest

The authors declare that they have no conflict of interest.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional review board of was approved by Linyi People's Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

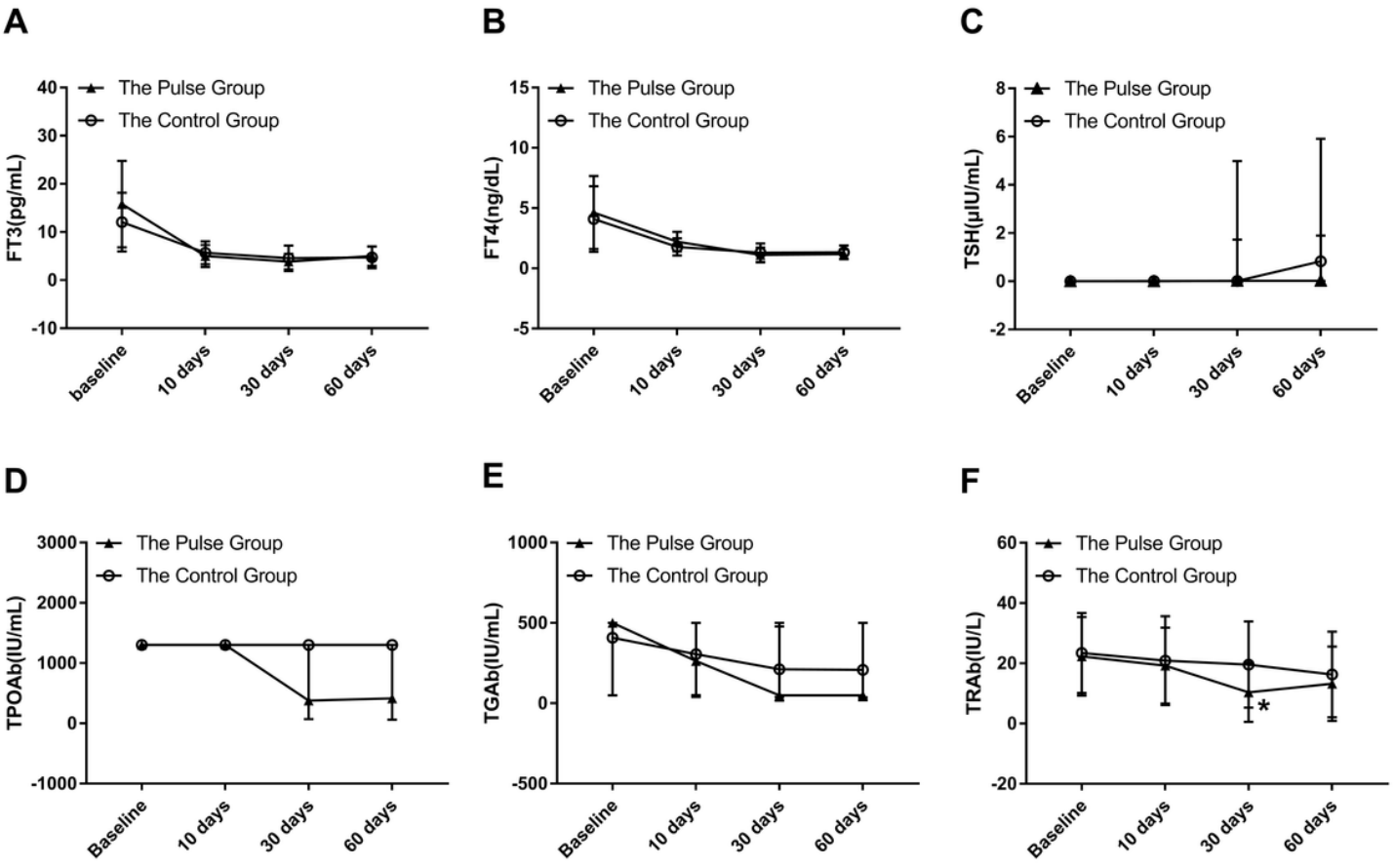

Figure 1

The changes of thyroid function and thyroid antibodies in children with GD

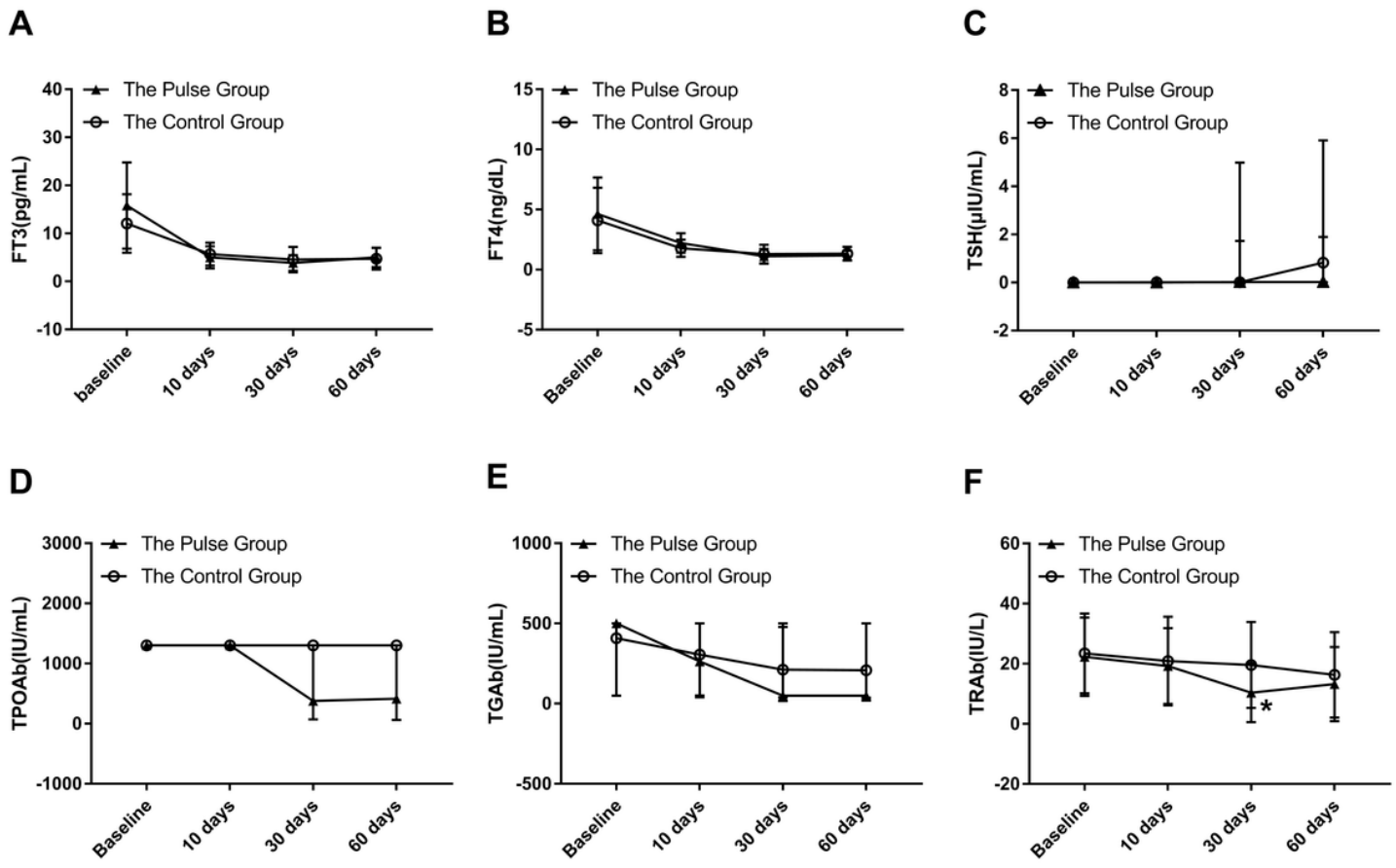

Figure 1

The changes of thyroid function and thyroid antibodies in children with GD