Changes in Total Body Fat and Body Mass Index among Children with Juvenile Dermatomyositis Treated with High-dose Glucocorticoids

Amer Khojah (KHOJAH.A@GMAIL.COM)
Ann and Robert H Lurie Children's Hospital of Chicago https://orcid.org/0000-0003-3357-4863
Victoria Liu
Wellesley College
Gabrielle Morgan
Ann and Robert H Lurie Children's Hospital of Chicago
Richard M. Shore
Ann and Robert H Lurie Children's Hospital of Chicago
Lauren M. Pachman
Northwestern University Feinberg School of Medicine

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Abstract

Objective High-dose glucocorticoids (GC) remain the primary therapy to induce remission in Juvenile Dermatomyositis (JDM). Studies of the natural history of GC associated weight gain in children are very limited, especially in the JDM population. This study aims to measure BMI changes in a cohort of JDM subjects over 60 months and to examine the changes in body composition by DXA. Methods We included all subjects with JDM who had five years of follow up data and serial DXA. BMI and total body fat (TBF) percentiles were calculated based on the CDC published percentile charts. To study the natural history of weight gain and TBF, we assessed the data at four-time points (T0 = baseline, T1 > 1.5 years, T2= 1.51-3.49 years, T3 = 3.5-5 years). Results 96 subjects (78% female, 70% white) were included. Paired T-test showed a significant increase in the mean BMI percentile by 17.5 points (P=0.004) after the initiation of medical treatment, followed by a gradual decrease over the study period. However, the TBF percentile did not change over the study period. TBF in the last visit had a strong correlation with T1 BMI (P <0.001) and muscle weakness Disease Activity Score (P=0.002) Conclusions Although the BMI percentile decreased throughout the study, the TBF percentile remained high until the end of the study (60 months). This finding raises the concern that some of the reduction in the BMI percentile could reflect a drop in the lean body mass from muscle wasting rather than actual fat loss.

Introduction

Juvenile Dermatomyositis (JDM) is a multisystem pediatric disease characterized by chronic inflammation of muscle and skin (1). Despite the recent advances in the treatment of JDM, high dose corticosteroid remains the primary therapy to induce remission (2). Typically, JDM patients need either intravenous or oral corticosteroid therapy for around two years (1). Although previous studies showed that untreated JDM subjects have lower weight and height than age and gender-matched controls, (3) weight gain and cushingoid features are among the most common side effects observed in children after glucocorticoid initiation in various clinical trials (4). Excessive weight gain has a negative impact on affected children's physical and psychological well-being (5). Youth obesity has been shown an increased risk of hypertension, type 2 diabetes mellitus, and hyperlipidemia, which are significant risk factors for future cardiovascular diseases(6). Cardiovascular diseases are an important cause of mortality and morbidity in patients with inflammatory myopathy(7).

Besides corticosteroid therapy, there are other possible mechanisms of obesity in JDM subjects, such as; the lack of physical activity due to muscle weakness and metabolic changes from chronic inflammation (8, 9). Long term studies of the natural history of corticosteroid associated weight gain in children are very limited, especially in the JDM population. Loss of muscle mass due to muscle inflammation and muscle ischemia may complicate the assessment of obesity and mask total gain in adipose tissue.

Dual-energy X-ray absorptiometry (DXA) has been used to measure various body composition, including body fat with high-precision and relatively low X-ray exposure (10, 11). JDM patients typically undergo routine DXA to measure the bone density due to their increased risk of pathological fractures from active

inflammation, decrease mobility, and the chronic use of steroids (12). The same DXA scan can be used in this study to assess body composition, including total body fat, without additional financial burden to the patients or extra radiation. This study aims to measure body mass index BMI changes in a cohort of JDM subjects over 60 months duration and examine the body composition changes (fat vs. lean body mass) by DXA.

Methods

This was a retrospective chart review study conducted at The CureJM Center of Excellence in Juvenile Myositis Research and Care, Ann & Robert H. Lurie Children's Hospital between 2000 and 2017 (IRB# 2012–14858). We included all JDM subjects who met Bohan and Peter criteria for definite or probable JDM diagnosis and had a minimum of five years of follow up data with serial DXA and BMI assessment during the study period. Subjects with overlap syndrome were excluded from the analysis. A GE-LUNAR iDXA bone densitometer was used to perform the DXA. Encore 16 software was used to analyzed DXA results and assess fat distribution among the various body part. The TBF (total body fat) percentile was calculated based on the Centers for Disease Control and Prevention (CDC) published TBF percentile charts from National Health and Nutrition Examination Survey (NHANES) (13).

The BMI percentile was calculated based on CDC published charts (https://www.cdc.gov/growthcharts/clinical_charts.htm). Overweight was defined as a BMI at or above the 85th percentile and below the 95th percentile for age and gender-matched children. Obesity was defined as a BMI at or above the 95th percentile for age and gender-matched children. To study the natural history of weight gain and body fat changes, we assessed the patients' data at four-time point based on the duration of time between the date of first medication use and date of an assessment (T0 = baseline, T1 > 1.5 years, T2 = 1.51–3.49 years, T3 = 3.5-5 years). We also evaluated disease activity markers on presentation such as skin, muscle weakness, and total Disease Activity Score (DAS) (14).

All statistical analyses were done IBM SPSS Statistics 26 ® software. The paired T-test was used to compare the baseline BMI and TBF data and the subsequent time points. Person correlation analysis was used to assess the association between TBF percentile at the last visit of the study (3.5–5 years after medication onset) and disease activity markers and initial BMI. A P-value less than 0.05 was considered significant. The figures were generated using Graphpad Prism 8 software.

Results

96 children with definite JDM (78% female, 22% male) were included in the study. The racial and ethnic background is as follows: White, Non-Hispanic 70%, White, Hispanic 18%, African American 7%, Others 5%. The mean age at enrolment was 7 years (+/- 3.3 SD). The mean duration of untreated disease was 7 months (+/- 8.4 SD). Disease group by Myositis Specific Antibodies: 45% anti-P155/140, 12% anti-MJ, 6% anti-Mi2, 2% anti-MDA5, and 33% MSA negative. All study subjects received corticosteroid therapy, and many had multiple other immunosuppressive therapies during the study period (Table 1). BMI before the

start of treatment revealed that most JDM patients in our study had normal weight and only 20 % were either overweight or obese. Of note, 40% of study subjects had BMI assessment before starting medications because the rest of the patients has received therapy before their initial assessment in our center. The mean duration of treatment for study visits was 0.95 +/- 0.4 years, 2.59+/- 0.4 years, and 4.42 +/- 0.5 years for T1, T2, and T3, respectively. The majority of the children had a significant weight increase after treatment, with near 70% were either in the overweight or obese category using the CDC definitions, and 30 % of them were more than 98th percentile BMI for their age (Supplement Fig. 1). The baseline BMI Paired T-test showed a significant increase in the mean BMI percentile by 17.5 points ($P = 0.004$) after the initiation of medical treatment (Fig. 1). The average weight gain at the T1 time point was around 7.5 kg. Unfortunately, most JDM subjects did not have DXA at baseline; therefore, assessing the change in the TBF from pretreatment was not done. Although the BMI percentile had a significant gradual decrease over the study period (Fig. 1), the TBF percentile did not change over the study period (Fig. 2, Supplement Fig. 2). TBF in the last visit (T3) had a strong correlation with the T1 BMI, and T1 TBF percentile (correlation coefficients 0.63, 0.56 $P < 0.001$, 0.002 respectively) (Supplement Fig. 3). Interestingly, there is a positive correlation (correlation coefficients 0.39, $P = 0.002$) between the TBF percentile and muscle DAS but not the skin DAS.

Table 1
Demographic and disease characteristics of study cohort.

	Frequency (n)	Percentage
Sample size	96	
Gender		
Female	75	78.1%
Male	21	21.9%
Race/Ethnicity		
White	67	69.8%
Hispanic	17	17.7%
African American	7	7.3%
Others	5	5.2%
Treatment status at 1st visit		
Untreated	37	38.5%
Treated	59	61.5%
Myositis specific antibodies		
P155/140	42	43.8%
MJ	12	12.5%
Mi2	6	6.3%
MDA5	2	2.1%
Others or multiple MSAs	2	2.1%
Negative	32	33.3%
Treatment		
Oral steroid	96	100%
Intravenous steroid	83	86%
Methotrexate	92	95.8%
Intravenous immunoglobulin	30	31.3%
Hydroxychloroquine	48	50%
Cyclosporin	34	35.4%

	Frequency (n)	Percentage
Mycophenolate	64	66.7%
Lipodystrophy (ever)		
Present	30	31%
Absent	66	68.8%
Calcification (ever)		
Present	17	82.3%
Absent	79	17.7%

Discussion

Although most JDM patients in our study started with normal BMI, 70% met the CDC definition of overweight or obese in the first data point of the study (0.95 +/- 0.4 years after treatment initiation). This rapid increase in the patient's weight is likely due to corticosteroid therapy, physical inactivity, and changes in adipokine levels due to inflammatory status (4, 8, 15). Although BMI percentile improves over the study period, it did not reach pretreatment level even after 4.5 years of therapy. This highlights the importance of preventing excessive weight gain as soon as a patient gets started on chronic steroids with early institution of exercise and healthy eating habits. Unfortunately, in our study, we did not assess physical activity and adipokine due to the study's retrospective nature. Although we did not measure the exact accumulative dose of corticosteroid, most patients in our study were treated similarly. The typical treatment plan of JDM patient in our center involves a minimum of 3 days of IV methylprednisolone pulse (30 mg/kg with maximum dose 1000mg) on admission followed by weekly IV methylprednisolone pulses with small oral doses of oral steroids (0.5 mg/kg/day), which is weaned over time base the disease's activity. Even though steroid-sparing agents such as methotrexate, mycophenolate, and IVIG are typically started early on, our JDM patients generally are treated with glucocorticoids for at least 1–2 years. This significant steroid exposure leads to an increased risk of side effects such as weight gain, glaucoma, cataracts, and vertebral fracture. Our patients usually get DXA annually to monitor bone density. The same DXA scan was used in this study to assess body composition, including total body fat, without additional financial burden to the patients or extra radiation. Assessing body composition by DXA revealed a higher percentage of total body fat than the age-matched peers evident by high total body fat percentile based on the NHANES(13), in addition to the significant weight gain after starting steroids. Furthermore, the mean TBF percentile did not show a statistically significant change over the study period despite decreasing the mean BMI percentile. This finding raises the concern that some of the reduction in the BMI percentile could reflect a drop in the lean body mass from muscle wasting rather than actual fat loss.

This study has some limitations, including lack of baseline DXA scan, 60 % of the subject received treatment before getting referred to our center, and the lack of physical activity and adipokine measurement. Despite these limitations, the study sheds light on the risk of childhood adiposity after chronic corticosteroid exposure. We hope this study will inspire more research in this area and eventually lead to more intervention-based research to prevent weight gain and excess body fat gain when treating patients with autoimmune diseases.

Conclusion

Children with Juvenile Dermatomyositis treated with high-dose corticosteroid develop significant weight gain in the first year of therapy, evident by the sharp increase in the BMI percentile. Although the BMI percentile decreased throughout the study after the initial spike, the TBF percentile remained high until the end of the study (60 months).

Abbreviations

GC: glucocorticoids, JDM: Juvenile Dermatomyositis, BMI: Body Mass Index, TBF: total body fat, DXA: dual-energy X-ray absorptiometry, CDC: Centers for Disease Control and Prevention, NHANES: National Health and Nutrition Examination Survey, DAS: Disease Activity Score, IBM SPSS: International Business Machines Corporation Statistical Package for the Social Sciences

Declarations

Ethical Approval and Consent to participate: authors have obtained the required ethical approvals and have given the necessary attention to ensure the integrity of the work. IRB# 2012-14858 at Ann & Robert H. Lurie Children's Hospital

Consent for publication: The final manuscript has been reviewed and approved by all the authors

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Authors' information: Amer Khojah M.D: akhojah@luriechildrens.org or khojah.a@gmail.com, Victoria Liu: vliu@wellesley.edu , Gabrielle Morgan M.A: gamorgan@luriechildrens.org , Richard M. Shore M.D: rshore@luriechildrens.org , Lauren M. Pachman M.D: pachman@northwestern.edu

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Figures

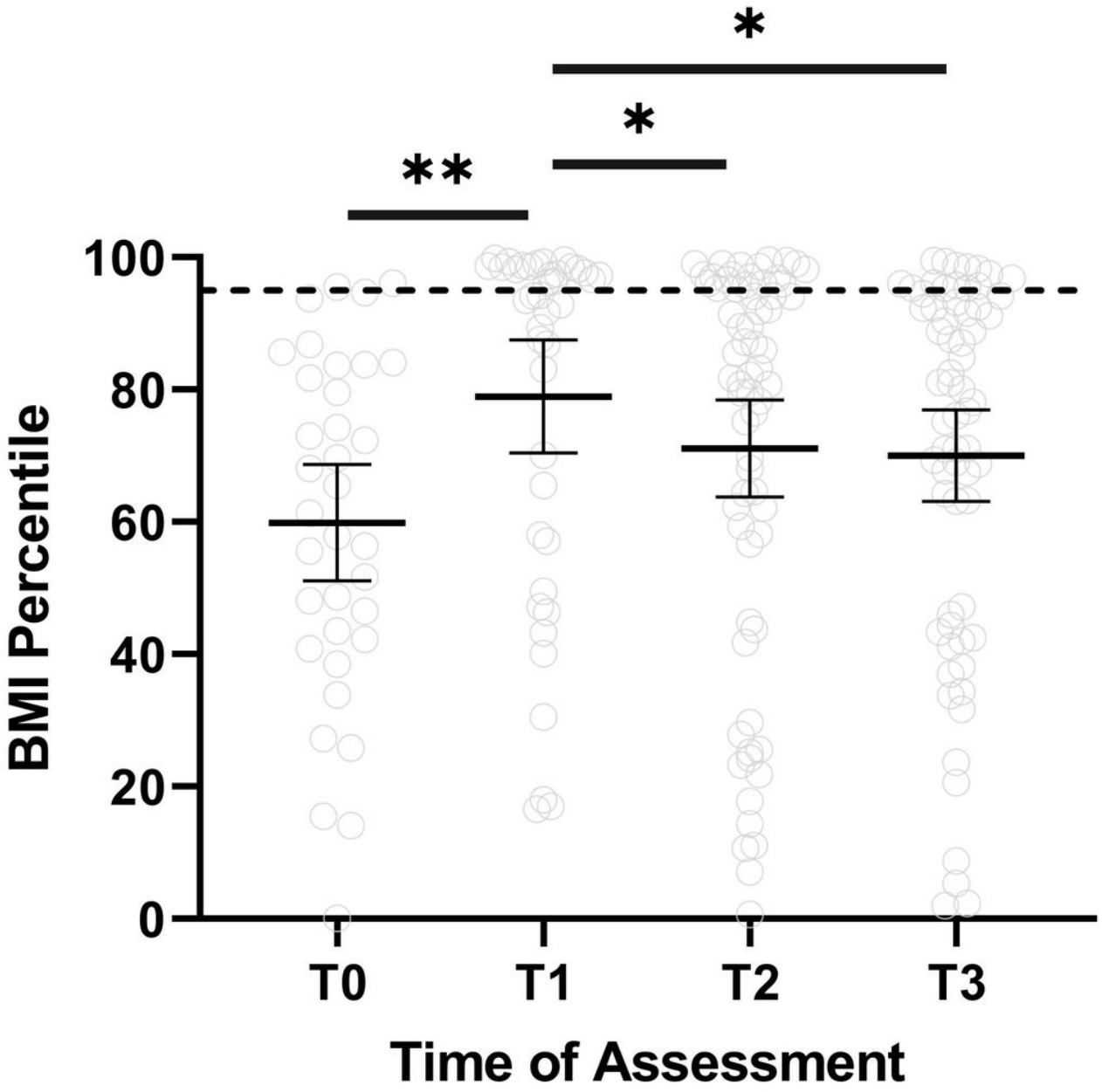

Figure 1

Changes of BMI percentile in JDM patients. T0 represented baseline date (before initiation of treatment), note data available for around 40% of the study subject. Other time point are T1 > 1.5 years, T2= 1.51-

3.49 years, and T3 = 3.5-5 years. The dotted line represents the 95th percentile; children with BMI above the 95th percentile meet the CDC definition of childhood obesity. Paired T-test showed a significant increase in the mean BMI percentile by 17.5 points (P = 0.004) after the initiation of medical treatment. BMI percentile gradual decrease over the study period. Of note, * means P value between 0.05-0.01 and ** means P value between 0.01-0.001

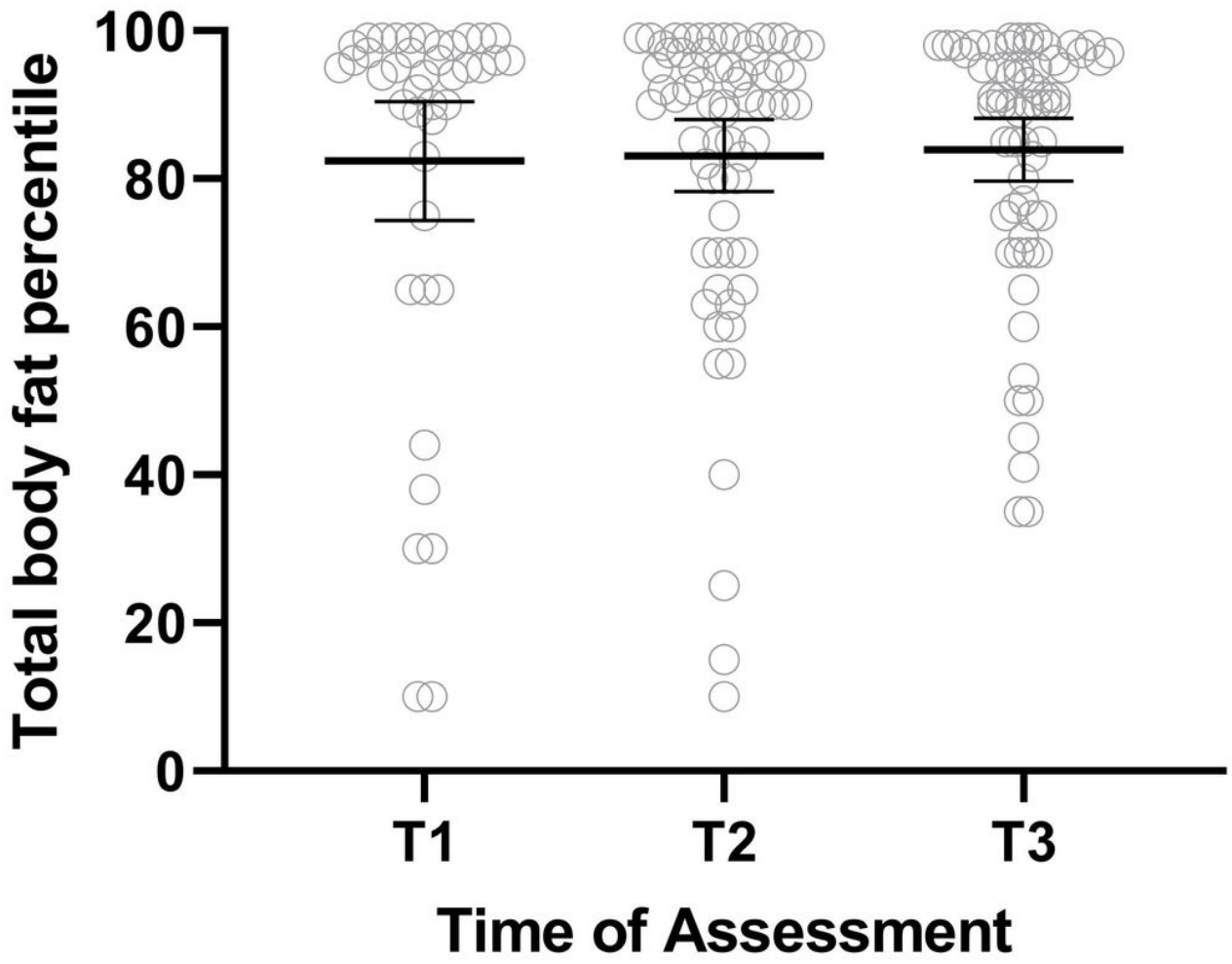

Figure 2

Changes of Total body fat (TBF) percentile in JDM patients. T1 > 1.5 years, T2= 1.51-3.49 years, and T3 = 3.5-5 years. Paired T-test did not show a significant change in the TBF over the study period.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BMIPercentilesup.jpg
- TfatPercentileSup.jpg

- XYBMlandTBFsup.jpg