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Clinical Research Article

Leptin Increase During Dexamethasone and Its Association With Hunger and Fat in Pediatric Acute Lymphoblastic Leukemia

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Abstract

Context: During treatment, children with acute lymphoblastic leukemia (ALL) receive high doses dexamethasone, which induce acute side effects.

Objective: To determine the influence of a 5-day dexamethasone course on changes in leptin, fat mass, BMI, hunger, sleep, and fatigue and to explore associations between these changes.

Methods: Pediatric ALL patients were included during maintenance treatment. Data were collected before (T1) and after (T2) a 5-day dexamethasone course (6 mg/m^2/day). At both time points, BMI, fat mass (bioelectrical impedance analysis), and leptin were assessed, as well as parent-reported questionnaires regarding hunger, fatigue, and sleep problems. Changes between T1 and T2 were assessed using paired tests. Correlation coefficients were calculated to assess associations between these changes (Delta scores: T2-T1). Univariable regression models were estimated to study associations between covariates and elevated leptin.

Results: We included 105 children, with median age 5.4 years (range, 3.0-18.8). Leptin and fat mass, as well as hunger scores, fatigue, and sleep deteriorated after 5 days of dexamethasone ($P < .001$), in contrast to BMI ($P = .12$). No correlations between delta leptin and delta fat mass, BMI, hunger, fatigue, or sleep were found. Elevated leptin on T1 was associated with older age (odds ratio [OR] 1.51; 95% CI, 1.28-1.77), higher fat mass (OR 1.19; 95% CI, 1.07-1.33), and earlier maintenance week (OR 0.96; 95% CI, 0.92-0.99).

Conclusion: Five days of high-dose dexamethasone treatment led to direct and significant changes in leptin, hunger scores, and fat mass. Since children with ALL are at increased risk for metabolic adverse events, understanding underlying mechanisms is important, and a dexamethasone-induced state of acute leptin resistance might play a role.

Key Words: dexamethasone, leptin, acute lymphoblastic leukemia, hunger score, fat mass

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; PedsQL, Pediatric Quality of Life Inventory; SDS, standardized deviation scores; SDSC, Sleep Disturbance Scale for Children.

Since survival rates of pediatric acute lymphoblastic leukemia (ALL) have increased to over 90% in high-income countries, more attention is given to acute and late toxicities (1). These toxicities are due to the disease itself, but also to the intensity and type of treatment. Dexamethasone is an important component of ALL treatment, but it is notorious for its numerous side effects (2, 3). Dyslipidemia and adiposity are well-known side effects of dexamethasone, as are increased fatigue and sleep problems (4-6). Additionally, increased appetite and consequent unhealthy eating behavior are reported acute side effects of dexamethasone treatment (7-9). Previous pediatric ALL studies showed that merely 4 or 5 days of glucocorticoid treatment increased blood pressure as well as fasting glucose and lipid levels, and significantly induced insulin resistance (6, 10). This illustrates that high-dose glucocorticoid pulses, which are frequently administered in ALL treatment, trigger significant metabolic changes, which in turn may precede long-term metabolic side effects with their attendant health consequences (11).

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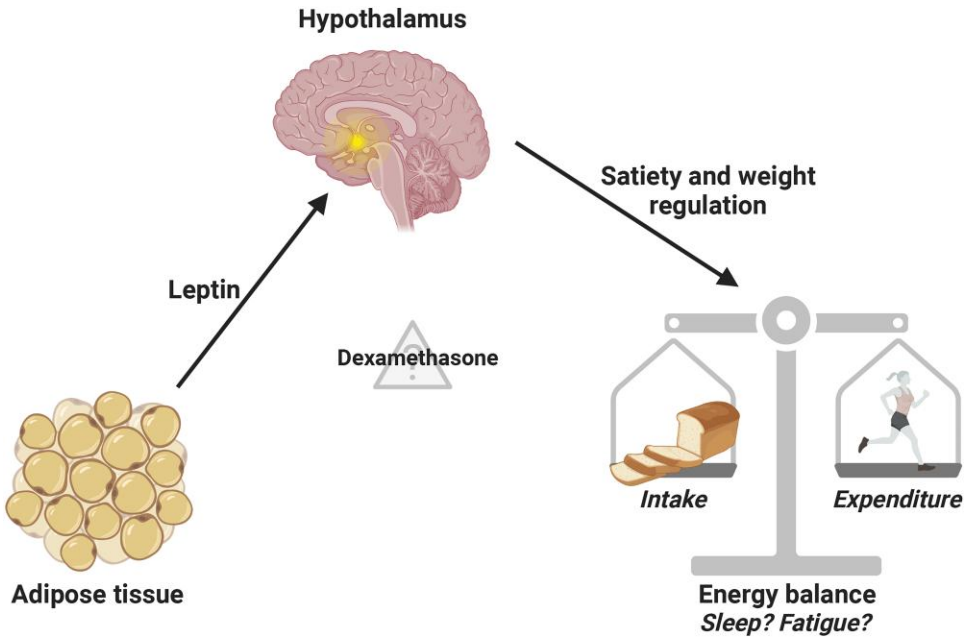

Figure 1. Regulation of energy balance through leptin pathway. Leptin is produced by adipose tissue and exerts its effect on both intake and energy expenditure through the hypothalamus. Low levels of leptin induce a physiological response, including a feeling of hunger, and decreases energy expenditure. High leptin levels reduce food intake and increases energy expenditure. The exact effect of dexamethasone and sleep and fatigue is unknown. Created with BioRender.com.

In physiological conditions, regulation of food intake and weight homeostasis is regulated by leptin (Fig. 1) (12-14). Leptin is an adipokine that is mainly produced by adipose tissue, and circulating leptin concentrations are highly correlated with fat mass. It is known that in obese individuals, hyperleptinemia occurs without an adequate response that reduces these high levels of leptin, suggesting a state of leptin resistance (14). A previous study in ALL patients showed that leptin levels increased almost 2-fold after 4 days of dexamethasone (8), similar to findings reported in healthy adults after 2 days of dexamethasone (15, 16). It may be possible that the short-term side effects of dexamethasone are mediated through (partial) leptin resistance. Furthermore, sleep deprivation is known to decrease leptin levels and increase hunger and appetite (17), and leptin is associated with cancer-related fatigue in adults (18). However, the associations between dexamethasone-induced side effects and leptin remain unclear.

Therefore, the aims of the current study were to determine the influence of a 5-day dexamethasone course on changes in leptin, as well as fat mass, hunger, sleep, and fatigue and to assess correlations between these changes. Furthermore, we aimed to explore contributing factors to high leptin levels before and during a dexamethasone course.

Materials and Methods

This study was conducted within the framework of the DexaDays-2 study: a national randomized clinical trial on dexamethasone-induced neurobehavioral problems in ALL patients at the Princess Máxima Center for Pediatric Oncology in the Netherlands, between 2019 and 2021. The design of this trial has been published previously (19, 20). This study was approved by the Medical Ethical Committee of Rotterdam (NL62388.078.17) and was performed in compliance with the ethical standards of the Princess Máxima Center as well as with the Declaration of Helsinki. All parents and/or patients provided written informed consent to participate.

Patients and Treatment

Patients between 3 and 18 years treated according to the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol were eligible for study inclusion during maintenance treatment phase, after cessation of doxorubicin, as previously described (19). Dexamethasone (6 mg/m^2/day) was administered for 5 consecutive days at the start of each 3-weekly cycle. Data and venous blood samples were collected on the first day of a 5-day dexamethasone course (T1) and on the morning after the same course (ie, after 5 full days of dexamethasone treatment) (T2). Weight (kg) and height (cm) were measured at these time points and body mass index (BMI) was calculated. Parents completed several questionnaires at T1 and T2 (Fig. 2).

Measurements

Hunger scores

Parents were asked to indicate how hungry their child was at T1 and T2 by completing an 11-point Likert-type hunger scale (Eating Thermometer), and where possible, to do so together with the child. Four different hunger scores were generated, with 0 indicating not hungry at all, and 10 indicating the hungriest possible. These 4 scores specified the average, most, least, and fasting hunger score, with a recall over the past 24 hours. Such Likert-type hunger scales have not been validated but have been used previously to assess feeling of hunger in adults and children (21, 22).

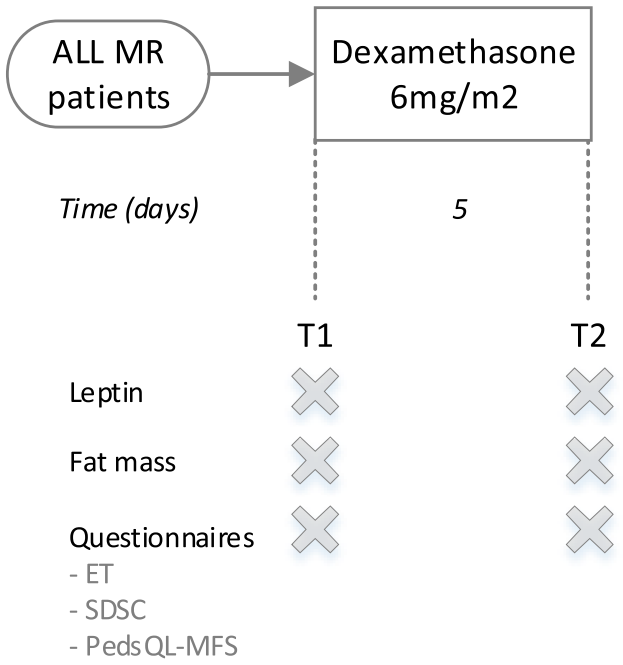

Figure 2. Study design. Acute lymphoblastic leukemia patients were included during maintenance therapy. Assessments took place before (T1) and after (T2) a 5-day dexamethasone course. Leptin and fat mass were measured, and parents completed 3 questionnaires on both time points. Abbreviations: ALL, acute lymphoblastic leukemia; ET, Eating Thermometer (hunger scores); MR, medium risk; PedsQL-MFS, Pediatric Quality of Life Inventory—Multidimensional Fatigue Scale; SDSC; Sleep Disturbance Scale for Children.

Fatigue and sleep

Parents completed the validated Pediatric Quality of Life Inventory (PedsQL)—Multidimensional Fatigue Scale (MFS) to assess fatigue. Parental versions for 4 different age groups were used: 3-4, 5-7, 8-12, and 13-18 years. The total scores were compared to Dutch reference values to generate standardized deviation scores (SDS) (23).

We used the parent-reported validated Sleep Disturbance Scale for Children (SDSC) to assess sleep. The SDSC contains 26 items, which combined generate a total sleep score: a higher score represents more sleep problems (24). Furthermore, we used the first item of the SDSC to explore whether children slept more/the same or less during a dexamethasone course. This question asks parents to indicate how many hours their child slept on average per night over the last week: 9-11 hours, 8-9 hours, 7-8 hours, 5-7 hours, or less than 5 hours.

Fat mass

Total body fat mass (kg) was estimated using a multifrequency segmental bioelectrical impedance analyzer (BIA) (Tanita MC-780, Tanita Corporation, Tokyo, Japan). Unadjusted values were reported, since no normative values for fat mass are available for Dutch children under the age of 5.

Leptin

Serum, from peripheral blood samples obtained on T1 and T2, was stored at −80 °C and leptin levels were jointly assessed after study closure to avoid variability in laboratory conditions. Leptin was quantified by ELISA (Mediagnost E07, RRID:AB_2813737, Mediagnost, Tübingen, Germany) in an ISO15189 accredited laboratory. Kit controls were within range for all measurements.

Since leptin values are highly variable between patients and are known to depend on sex, BMI, and puberty stage, they are presented as SDS using previously described normative values taking these factors into account (25). Since we did not document the puberty stage of our cohort, for this study, puberty stage was approximated per patient using the median age of reaching the stages of secondary sex characteristics in the general Dutch population, using reference values of the 1997 Dutch Growth Study (26).

Statistical Analyses

Patient characteristics and measurement results were reported as mean with SD or median with interquartile range (IQR) depending on the distribution of the variables. Delta values were calculated by subtracting T1 values from T2 values.

The changes in leptin SDS, fat mass, hunger scores, fatigue, and sleep after 5 days of dexamethasone (T2 vs T1) were assessed using paired tests: a paired *t* test in case of normally distributed measures or a Wilcoxon signed rank test in case of skewed distribution.

To explore correlations between delta leptin and delta fat mass, hunger scores, fatigue, and sleep, Spearman correlation coefficients were estimated together with the 95% CI. A correlation between 0.0 and 0.3 is negligible, between 0.3 and 0.5 low, between 0.5 and 0.7 moderate, between 0.7 and 0.9 high, and >0.9 very high (27). To explore possible contributing factors (patient demographics and treatment characteristics) for a high leptin value on T1, univariable logistic regression models were estimated: a cutoff of SDS >1.5 was used to define high leptin values at T1. Furthermore, linear regression models were estimated to explore potential influencing factors for change in leptin levels after 5 days of dexamethasone (delta leptin), with correction for T1 leptin values. All analyses were performed using IBM SPSS Statistics version 26.0.

Results

During the inclusion period, 163 medium-risk ALL patients were eligible, of whom 105 gave informed consent and therefore were enrolled in our study (Fig. 3). The median age of the included patients was 5.3 years (range, 3.0-18.8 years) and 61% were boys. The mean week of maintenance treatment phase in which patients were enrolled was week 35 (± 14 weeks) (Table 1).

For each measurement there were missing values (Fig. 3). The baseline characteristics of the patients who completed measurements and the patients with missing values were similar, except for fat mass measurement: bioelectrical impedance analysis was obtained in fewer boys than girls: 19/64 boys (30%) refused this measurement, as opposed to 3/41 girls (7%).

Changes After 5 Days of Dexamethasone

At T1, before the start of a 5-day dexamethasone course, mean leptin SDS was −0.09 (± 2.1), which increased to 1.8 (± 1.5) ($P < 0.001$) at T2 (Table 2, Fig. 4A, Supplementary Fig. S1 (28)). Fat mass increased significantly as well, from 5.1 kg (IQR 3.8 to 8.5) at T1 to 5.6 kg (IQR, 4.3 to 9.6) at

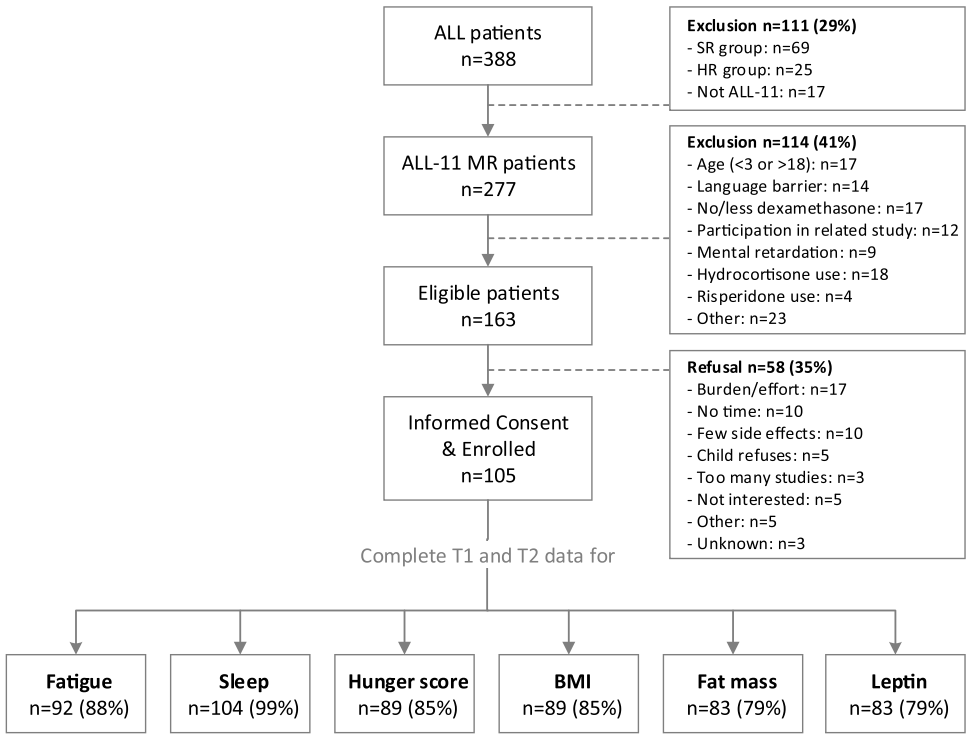

Figure 3. Flow diagram. After screening on inclusion and exclusion criteria, 163 eligible patients were asked to participate, of whom 105 were enrolled in the study. Complete data for both time points (ie, measurement before the start of a 5-day dexamethasone course (T1) and after this course (T2) is depicted. Abbreviations: ALL, acute lymphoblastic leukemia; HR, high risk; MR, medium risk; SR, standard risk.

Table 1. Baseline characteristics

Characteristic	
Age, years	
Median (range)	5.3 (3.0; 18.8)
Sex, n (%)	
Boy	64 (61)
Girl	41 (39)
Puberty stage,[a] n (%)	
Tanner 1-2	91 (87)
Tanner 3-4	4 (4)
Tanner 5	10 (9)
Type ALL, n (%)	
B-cell	93 (89)
T-cell	11 (10)
BPDCN	1 (1)
CNS involvement, n (%)	
Yes	20 (19)
No	85 (81)
Maintenance week	
Mean (SD)	35 (14)

Abbreviations: ALL, acute lymphoblastic leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CNS, central nervous system.
[a]Approximated using the median age of reaching the stages of secondary sex characteristics in the general Dutch population.

T2 ($P < 0.001$) (Fig. 4B), whereas BMI remained stable (17.3 kg/m^2 [IQR, 16.3 to 19.1]) at T1 to 17.7 kg/m^2 (IQR, 16.5 to 19.0) at T2 ($P = 0.112$) (Fig. 4C).

The median hunger scores at T1 were 5 (IQR, 3 to 6) for average hunger, 6 (IQR, 5 to 7) for most hunger, 2 (IQR, 0 to 4) for least hunger, and 5 (IQR, 2 to 6) for fasting hunger. All hunger scores had increased significantly ($P < 0.001$) at T2 to 7 (IQR, 6 to 8), 8 (IQR, 7 to 10), 4 (IQR, 2 to 6), and 7 (IQR, 5 to 9), respectively (Fig. 4D).

Median fatigue SDS was −0.5 (IQR, −2.2 to 0.5) at T1, which decreased to −3.5 (IQR, −4.6 to −2.0) at T2, indicating a significant increase in fatigue ($P < 0.001$) (Fig. 4E). The SDSC Total sleep score increased from 37 (IQR, 32 to 46) at T1 to 48 (IQR, 38 to 59) at T2 ($P < .001$) (Fig. 4F), indicating significantly more sleep problems. Sleep duration, based on the first question of the SDSC, decreased in 42 (40%) of patients, whereas in 62 (60%) sleep duration stayed the same or increased at T2.

Correlations Between Leptin Changes and Other Side Effects

No significant correlations between delta leptin SDS and changes after 5 days of dexamethasone in fat mass or the different hunger scores were found (Table 3, Supplementary Fig. S2 (28)). Furthermore, there was no correlation between delta leptin SDS and delta fatigue or sleep problems (SDSC total score) (Table 3).

Potential Influencing Factors for High Leptin

To explore which patient and treatment factors may contribute to a high leptin level (SDS > 1.5) on T1, we estimated univariable logistic regression models (Table 4). An older age increased the odds of a high leptin level at T1 with 1.51 per year (95% CI, 1.28 to 1.77). A higher fat mass at T1 increased the odds with 1.19 per kg (95% CI, 1.07 to 1.33). Earlier

Table 2. Measurements at 2 timepoints along with delta scores

	N	T1	T2	Delta	*P* value
Leptin SDS, *mean (SD)*	83	−0.1 (2.1)	1.8 (1.5)	1.9 (1.5)	<.001
Fat mass, kg, *median (IQR)*	83	5.1 (3.8; 8.5)	5.6 (4.3; 9.6)	0.7 (0.3; 1.1)	<.001
BMI (kg/m^2), *median (IQR)*	89	17.5 (16.3; 19.4)	17.7 (16.5; 19.0)	0.1 (−0.2; 0.3)	.112
Hunger score, *median (IQR)*	89				
- Average		5 (3; 6)	7 (6; 8)	2 (1; 4)	<.001
- Most		6 (5; 7)	8 (7; 10)	2 (1; 3)	<.001
- Least		2 (0; 4)	4 (2; 6)	1 (0; 3)	<.001
- Fasting (morning)		5 (2; 6)	7 (5; 9)	2 (1; 5)	<.001
Fatigue PedsQL SDS, *median (IQR)*	92	−0.5 (−2.2; 0.5)	−3.5 (−4.6; −2.0)	−2.3 (−3.4; −0.5)	<.001
Sleep time (SDSC), *n (%)*	104				
- 9-11 hours		80 (77)	53 (51)	≥sleep	<.001
- 8-9 hours		18 (17)	19 (18)	62 (60)	
- 7-8 hours		2 (2)	13 (13)		
- 5-7 hours		4 (4)	13 (13)	<sleep	
- <5 hours		0	6 (6)	42 (40)	
Sleep Score (SDSC), *median (IQR)*	104	37 (32; 46)	48 (38; 59)	8 (3; 16)	<.001

≥sleep or <sleep is based on the first question of the SDSC.
Abbreviations: IQR, interquartile range; PedsQL, Pediatric Quality of Life Inventory; SDS, standardized deviation score; SDSC, Sleep Disturbance Scale for Children.

weeks of maintenance treatment (ie, how far along a patient was in his/her treatment) revealed higher leptin values: every week further in maintenance gave a 0.96 lower odds (95% CI, 0.92 to 0.99) of high leptin. Fatigue, sleep problems, and hunger scores at T1 were not associated with a high leptin at T1.

Linear regression models were estimated to study the effect of possible explanatory variables on the change in leptin SDS during a dexamethasone course, with a correction for T1 leptin values (Table 5). Age at measurement was associated with the change in leptin: 1 year older age increased delta leptin SDS with 0.08 (95% CI, 0.02 to 0.15). Week of maintenance was also negatively associated with delta leptin values: −0.02 (95% CI, −0.04 to −0.01). Whether a child received asparaginase during the study was also associated with the increase in leptin: if a child received asparaginase, delta leptin SDS was 1.09 higher (95% CI, 0.39 to 1.79). Of note, only 11 children received asparaginase during the study measurements.

Discussion

In this national cohort of children with All, we showed that leptin SDS increased from −0.09 (± 2.1) to 1.8 (± 1.5) after merely 5 days of high-dose dexamethasone. Fat mass, hunger scores, fatigue, and sleep problems increased significantly as well, whereas BMI remained stable. No correlations between delta leptin and delta fat mass, hunger scores, fatigue, or sleep problems were found.

Our results are in line with previous studies in ALL patients, which also established an increase in leptin during glucocorticoid treatment (8, 29-35). However, none of these studies adjusted leptin values for BMI, sex, or age. The current study showed that adjusted leptin values increased considerably after 5 days of dexamethasone. The feeling of hunger, measured with 4 different hunger scores, also increased significantly during these days. Under physiological circumstances, an increase in leptin is accompanied by reduced feeling of hunger (12-14). In obese patients, elevated leptin levels also do not exert their usual anorexigenic effect, which may imply leptin resistance (36). The combination of increased leptin levels and feeling of hunger in our cohort may suggest a state of acute leptin resistance in the participants. In addition, dexamethasone is known to upregulate leptin expression and release, but also leptin receptors (37-39). It is conceivable that the increase in leptin during glucocorticoid treatment has another role than solely appetite control, but to truly determine the regulating role of leptin signaling deficits during or after dexamethasone treatment, other assessments, such as new quantitative biomarkers, are needed (40). Still, since patients with ALL frequently receive high doses of glucocorticoids for at least 1.5 years during their treatment, it is possible that the elevated leptin levels may precede certain long-term side effects in survivors, such as obesity (41-43). A study to longitudinally evaluate leptin and other appetite-regulating hormones, in combination with anthropometric measurements, feeling of hunger, and caloric intake may be of value to shed more light on underlying metabolic pathways. Furthermore, interventions designed to mediate the risk of metabolic adverse events should begin in a timely manner to diminish late toxicities.

Even though leptin is mainly produced by adipocytes and is considered as a marker of fat accumulation (34), we did not find a correlation between delta leptin SDS and delta fat mass. This may be due to the fact that bioelectrical impedance analysis tends to underestimate fat mass and is sensitive to changes in fluid balance (44). We measured an average increase of 0.5 kg in fat mass in 5 days, which may also reflect increased fluid retention. Ideally, a dual-energy x-ray absorptiometry (DXA) scan would be used to analyze body composition (45). However, DXA use is limited in children due to logistic issues, the radiation burden, and need for sedation in very young children. Besides the most appropriate measurement tool, the question arises whether adipocyte hyperplasia

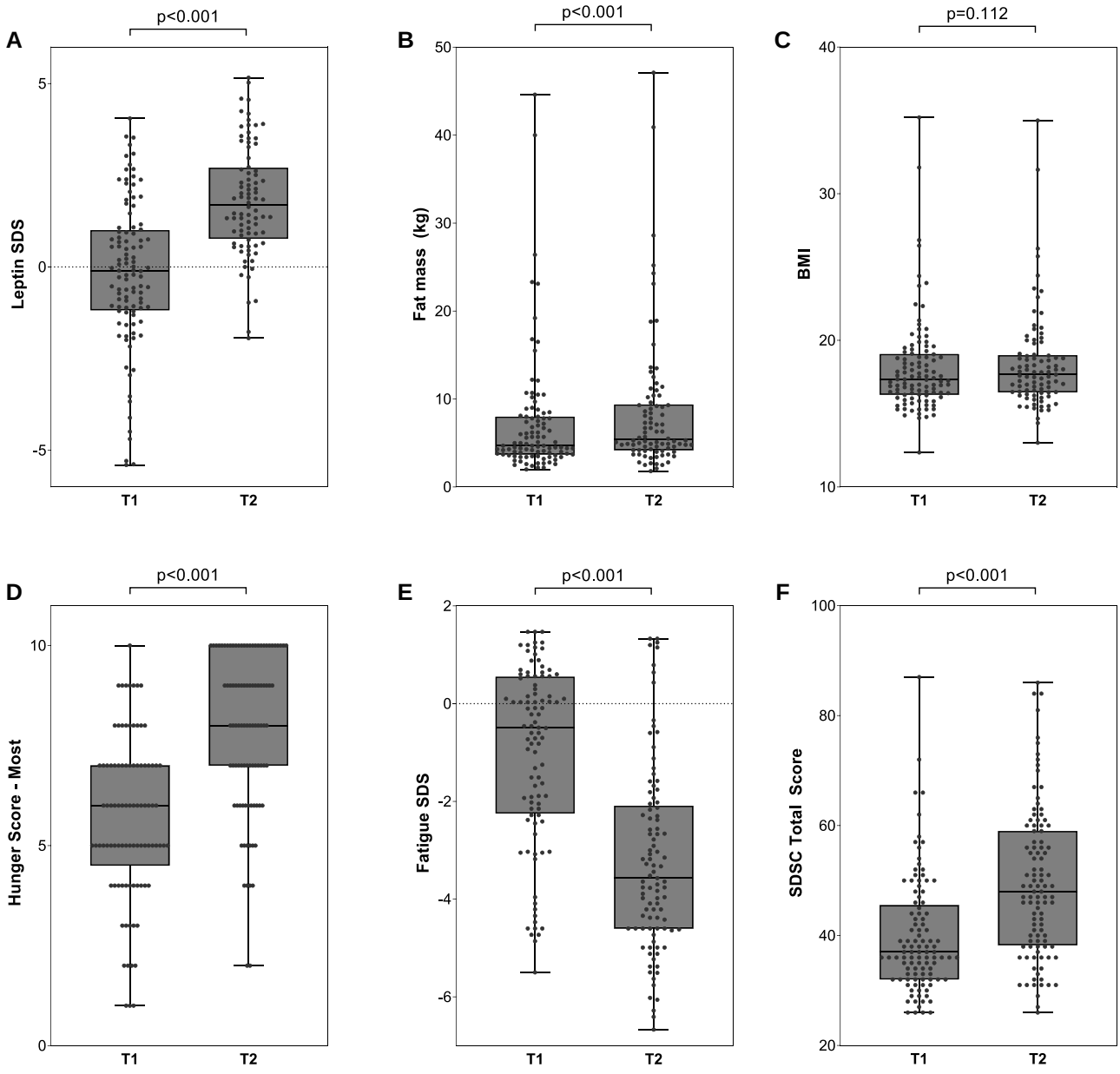

Figure 4. Boxplots before (T1) and after (T2) a 5-day dexamethasone course. Boxplots visualize measurements before (T1) and after (T2) a 5-day dexamethasone course. Abbreviations: BMI, body mass index, SDS, standardized deviation score, SDSC, Sleep Disturbance Scale for Children.

or hypertrophy occurs. Due to the rapid increase in fat mass, the latter seems more plausible. Hypertrophic adipocytes seem to secrete less leptin than normal adipocytes (46). It would be interesting to evaluate fat mass and leptin longitudinally and in a standardized way during multiple dexamethasone courses to gain better understanding of the interplay between both.

Even though we observed a significant rise in leptin levels and hunger scores after 5 days of dexamethasone, we could not establish the expected association between both. This may be due to the fact that parents reported the feeling of hunger for their child, and it was not always possible to ask children to participate in these questions because of their young age. Validated questionnaires that measure feeling of hunger or eating behavior are scarce, not available in every language, and often are only parent-reported or as self-report commencing from the age of 7 or older (8, 47). Thus, measuring the feeling of hunger in young children remains challenging and this may have influenced our results. Still, previous research showed a dexamethasone-induced increase in food intake, including increased total protein, fat, saturated fat, carbohydrate, as well as sodium intake, after 4 days of dexamethasone treatment (8). This undesirable increase in quantitative and qualitative food intake may be a direct effect of dexamethasone, independent of leptin signaling.

Parents reported that fatigue and sleep problems increased during the dexamethasone course, as was previously reported by us and others (5, 48-51). In the general population, sleep deprivation is known to decrease leptin levels and to increase hunger and appetite (17). In our cohort, we did not find an association between the change in leptin values and sleep problems, nor between changes in sleep problems and hunger scores. Interestingly, previous studies showed that, when measuring sleep objectively with actigraphy, sleep duration increased during dexamethasone administration (49, 50). Furthermore, one study in healthy children (n = 37) showed that increased sleep duration was associated with decreased

leptin values (52). In our cohort, 60% of the parents indicated that their children slept the same or more during dexamethasone, but this was not associated with the change in leptin values. However, we based our results on a single item of the SDSC questionnaire, which is a limited substitute for true sleep duration. There are no studies in children linking fatigue and leptin. Leptin has been linked to pathological inflammatory fatigue in adults, possibly through the release of proinflammatory cytokines (53-56). Dexamethasone suppresses inflammatory responses and may therefore moderate the association between fatigue and leptin in our cohort. In addition, it is conceivable that in children with ALL, other factors such as chemotherapy, immobilization, and hospital visits may influence sleep, fatigue, and leptin values independently, influencing possible associations between the changes that occur during dexamethasone.

At T1 (before start of the dexamethasone course), we observed a large variation of leptin SDS (range, −5.4 to +4.1). We explored possible contributing factors for this variation and found that older age and a higher fat mass were associated with increased leptin level at T1, even for leptin values adjusted for age, sex, pubertal stage, and BMI. The cause is not known but could indicate an increased risk of leptin resistance in children during ALL treatment. A possible contributor to this phenomenon could be concomitant asparaginase treatment, which was associated with delta leptin in our study. Asparaginase is known to influence dexamethasone pharmacokinetics, as well as to cause hypertriglyceridemia, and may therefore mediate the association between higher dexamethasone and increased leptin (57, 58). Also, we found that

Table 3. Spearman correlation coefficients for delta leptin values and delta fatigue, sleep, hunger score, and fat mass

	Delta leptin SDS			
			95% CI	
	N	r_s	Lower bound	Upper bound
Delta fat mass (kg)	78	−0.18	−0.38	0.05
Delta BMI	83	0.13	−0.09	0.33
Delta Hunger score	71			
Average		0.18	−0.06	0.40
Most		0.05	−0.19	0.28
Least		0.08	−0.16	0.31
Fasting		0.04	−0.20	0.27
Delta Fatigue SDS	73	0.04	−0.20	0.26
Delta Sleep SDSC Total score	82	−0.14	−0.35	0.08

Abbreviations: SDS, standardized deviation score; SDSC, Sleep Disturbance Scale for Children.

Table 4. Descriptive statistics for patient demographic, disease, and treatment characteristics; odds ratio along with 95% CI estimated from a univariable logistic regression model for high leptin at T1

	Normal leptin levels (<1.5 SD)	High leptin levels (≥1.5 SD)		
	Median (IQR) or n (%)	Median (IQR) or n (%)	OR	95% CI
Patient demographics	n = 83	n = 21		
Age, years	4.8 (4.0-6.5)	12.1 (9.5-15.8)	*1.51*	*1.28-1.77*
Sex				
Boy	48 (58)	15 (71)		
Girl	35 (42)	6 (29)	0.55	0.19-1.56
Fatigue T1, SDS	−0.6 (−2.3 to 0.6)	−0.1 (−0.9 to 0.2)	1.26	0.90-1.76
SDSC total score T1	36 (32-45)	39 (35-45)	1.00	0.96-1.05
Hunger scores T1				
Average	5 (3-5)	5 (4-7)	1.27	0.92-1.74
Most	6 (5-7)	6 (4-7)	1.00	0.76-1.30
Least	2 (0-4)	3 (0-4)	0.99	0.74-1.32
Fasting	5 (2-6)	4 (2-5)	0.93	0.74-1.16
Fat mass T1, kg	4.4 (3.5-5.9)	9.6 (8.2-16.7)	*1.19*	*1.07-1.33*
Disease and treatment characteristics				
Week maintenance	37 (25-49)	27 (19-37)	*0.96*	*0.92-0.99*
Asparaginase during study				
No	74 (89)	19 (91)		
Yes	9 (11)	2 (9)	0.87	0.17-4.34
CNS involvement[a]				
No	69 (83)	15 (71)		
Yes	14 (17)	6 (29)	1.97	0.65-5.97

Numbers are depicted as median (interquartile range) or number (%). Italicized values are statistically significant (P value <0.05).
Abbreviations: CNS, central nervous system; IQR, interquartile range; OR, odds ratio; SDS, standardized deviation score; SDSC, Sleep Disturbance Scale for Children.
[a]Patients with CNS involvement defined as CNS-3 or other CNS manifestations at diagnosis, or TLP+) receive 2 additional intrathecal therapy administrations and are considered as "CNS involvement yes." Medium risk group (MRG) patients without CNS involvement receive 13 intrathecal administrations, with CNS involvement 15.

Table 5. Estimated regression coefficients (β) along with 95% CI from a multivariable linear regression models for delta leptin (corrected for leptin T1)

	Leptin SDS delta		
Patient characteristics			
	β	95% CI	
		Lower bound	Upper bound
Age, years	0.08	0.02	0.15
Leptin T1	−0.60	−0.73	−0.47
Intercept	1.18		
Sex			
Boy			
Girl	−0.32	−0.78	0.14
Leptin T1	−0.49	−0.60	−0.38
Intercept	1.96		
Fat mass T1	0.01	−0.03	0.40
Leptin T1	−0.48	−0.60	−0.35
Intercept	1.76		
Fatigue SDS T1	0.07	−0.05	0.20
Leptin T1	−0.53	−0.65	−0.41
Intercept	1.82		
SDSC total scoreT1	−0.01	−0.03	0.01
Leptin T1	−0.50	−0.61	−0.39
Intercept	2.25		
Disease and treatment characteristics			
	β	95% CI	
		Lower bound	Upper bound
Week maintenance	−0.02	−0.04	−0.01
Leptin T1	−0.50	−0.60	−0.40
Intercept	2.65		
Asparaginase			
No			
Yes	1.09	0.39	1.79
Leptin T1	−0.47	−0.58	−0.37
Intercept	1.71		
CNS involvement			
No			
Yes	0.29	−0.29	0.86
Leptin T1	−0.49	−0.60	−0.38
Intercept	1.77		

Abbreviations: SDS, standardized deviation score; SE, standard error; SDSC, Sleep Disturbance Scale for Children.

children who were further along in their maintenance treatment had lower leptin levels. This is surprising, since children further in maintenance have had a higher cumulative dose of administered dexamethasone. For some dexamethasone-inducedside effects, such as osteonecrosis, a higher (cumulative) dose is associated with more physical problems (59). Moreover, lipid accumulation in hepatocytes is associated with higher cumulative doses of (endogenous) glucocorticoids (60). The reversed phenomenon in our study may be due to a longer time since asparaginase, which is only administered in the beginning of maintenance. Additionally, physical activity increases in the course of treatment and exercise may exert a protective role on metabolic adverse events and leptin resistance (61). Longitudinal studies that include physical activity in combination with leptin and body composition are needed to get more insight in the effect of multiple dexamethasone courses on these outcomes.

The current study is the first, and largest, to evaluate leptin SDS in ALL patients, before and after a dexamethasone course. Furthermore, we were able to study leptin SDS in combination with feeling of hunger, as well as fat mass and sleep and fatigue, which has not been evaluated previously.

Some limitations may be worth mentioning. The reference cohort for the leptin SDS values was based on children from the age of 5.8 years. Our study also included younger children, which may have influenced the SDS values. However, the standardized values are calculated based on Tanner stage and BMI, which will not differ greatly for younger children. Additional analyses excluding children <5.8 years did not show dissimilar results. Furthermore, we approximated puberty stage based on age and even though most children were pre-pubertal, this may have influenced our results. Also, no data regarding (the influence of dexamethasone on) gonadotropins or sex hormones was available. Since we know that leptin and various endocrine parameters are correlated (25), future studies should include a more complete panel of both metabolic and endocrine markers. The use of the unvalidated hunger scales is another limitation. However, no other validated measurement tools that assess hunger in (very) young children exist. Furthermore, the relatively small number of patients prohibited larger multivariable analyses to investigate associations between leptin and other measurements.

To conclude, standardized leptin levels increase significantly after merely 5 days of dexamethasone, as do fat mass, hunger scores, fatigue, and sleep problems. Since children with ALL are at increased risk for metabolic adverse events, it is important to understand the underlying mechanisms, and a dexamethasone-induced state of leptin resistance might play a role.

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Author Contributions

A.v.H. and E.V. included patients and collected data. E.A., M.v.d.H.E., and M.G. conceptualized the study and acquired funding. A.v.H. and M.F. performed statistical analyses. S.B. performed laboratory analyses. A.v.H. wrote the manuscript. E.V., S.B., R.L., M.G., M.F., S.N., M.v.d.H.E., and E.A. provided critical input and wrote the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Clinical Trial Information

Netherlands Trial Register NTR6695/NL6507 (https://trialsearch.who.int/)

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