Body composition changes in female adolescents with anorexia nervosa

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ABSTRACT

Background: Body weight provides limited information about nutritional status of patients with anorexia nervosa (AN).

Objectives: Our objectives were to determine body composition (BC) changes, to find clinical predictors and endocrine correlates of total body protein (TBN) depletion, and to compare results on fat mass (FM) obtained with anthropometry (skinfold measurements) and dual-energy X-ray absorptiometry (DXA) in patients with AN.

Design: Body weight, body mass index (BMI; in kg/m²), BC (with DXA and skinfold measurements), and TBPr [with in vivo neutron activation analysis (IVNAA)] was assessed in 50 AN patients (15.2 y) and 40 healthy sex- and age-matched controls. In 47 AN patients and 22 controls, hormone concentrations were measured.

Results: In AN patients, body weight (44.4 ± 5.5 kg), BMI (16.7 ± 1.6), and FMDXA (7.0 ± 3.4 kg) were lower than in controls. Lean tissue mass by DXA (LTMDXA) was similar in AN patients and controls (35.7 ± 4.3 compared with 35.8 ± 4.5 kg), but TBPr was 87% of that of controls (8.1 ± 1.0 compared with 9.2 ± 1.2 kg; P < 0.001). Cortisol was high, testosterone was unchanged, and estradiol and insulin-like growth factor I were low. Severe protein depletion measured by IVNAA seen in 17 AN patients could not be identified with simpler methods. All except 1 of 26 AN patients with a BMI > 16.5 had normal TBPr. The difference of individual percentage of body fat measured with DXA and skinfold measurements came up to 9%.

Conclusion: The severe protein depletion in 34% of AN patients was not accurately identified by LTMDXA or simpler methods, but a BMI > 16.5 indicated normal TBPr. Future studies need to compare DXA and skinfold measurements with a reference technique to assess FM in AN patients.

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder in which persons are characterized by underweight. However, even though international disease classifications of AN are based on body weight [ie, <85% of that expected (1)], weight and body mass index (BMI; in kg/m²) were shown to be of limited use when monitoring nutritional status in patients with AN (2, 3). A broad range of studies have therefore examined body composition (BC) in patients with AN, including fat mass (FM) and lean tissue mass (LTM), to better define specific nutritional deficits. Such studies of anorexic populations have shown substantial deficits in FM when assessing body fat (BF) by skinfold-thickness measurement (4–6). Interestingly, when using height-adjusted indexes that were based on skinfold measurements in adolescent patients with AN and sex- and age-matched controls, 67% of the patients with AN were <2 SDs when based on FM index, but none were when based on the fat-free mass index (4). Subsequent studies that used more sophisticated techniques, such as dual-energy X-ray absorptiometry (DXA) to measure BC, have confirmed the significant deficits in FM (6–11), but they have been inconsistent for LTM depletion, with some researchers reporting on decreased (6–8, 10) but others on unchanged (9, 11) LTMs.

A more detailed analysis of the LT component that used in vivo neutron activation analysis (IVNAA) has shown that adult patients with AN have significant deficits of total body nitrogen (TBN), which is a well-accepted surrogate indicator of body protein status (5, 12). Concomitantly, a preliminary study of 23 adolescent patients with AN and retrospective age-matched controls from our own unit with the use of IVNAA and DXA showed that both TBN and FM were lower in patients with AN, that TBN measurements correlated highly with body weight, and that FM assessed with DXA was strongly associated with triceps skinfold measurements (13). However, although body weight and triceps skinfold measurements as simpler and noninvasive surrogates might be useful to assess nutritional status in a group of patients with AN in a research setting, it remains


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unclear whether they are of sufficient validity for clinical practice. The present study was thus undertaken to find a simple clinical predictor that can be used to identify a critical protein status in individual patients with AN, to assess the relation between endocrine variables that are known to be involved in protein metabolism [estradiol, cortisol, testosterone, and insulin-like growth factor I (IGF-I)] and protein status, and to further investigate the agreement between skinfold measurements and DXA to measure FM.

**SUBJECTS AND METHODS**

**Study populations**

From July 2004 to September 2005, adolescent females \[n = 50; \text{age} \text{(mean } \pm \text{SD): 15.2 } \pm 1.5 \text{ y; range: 12–19 y)]\) with the diagnosis of AN (1) were recruited from 2 specialist eating disorder units (Departments of Adolescent Medicine, the Children’s Hospital at Westmead and Westmead Hospital in Sydney, Australia). At the time of testing, all patients were amenorrheic but medically stable. The 7 patients with AN who had a BMI > 18.5 were included into the study because they had lost >20% of their initial weight and fulfilled the remaining diagnostic criteria for AN. Eight subjects were being treated as outpatients and the remaining 42 patients were inpatients. Tanner stage and menstrual status were assessed by the treating physician. Median Tanner stage of the patients was 4, and 5 of the 50 patients had primary amenorrhea. A healthy control group was recruited from a local high school with normal weight, based on a BMI cutoff of 23.9 for 14.5-y-old girls (14). For a sum of triceps and subscapular skinfold measurements > 35 mm, the following equation was used:

\[
\%\text{BF} = 0.546 \times (\text{TSF} + \text{SSF in mm}) + 9.7 \quad (2)
\]

Midupper arm circumference was measured by using a non-stretchable steel measuring tape (Luftin W 606 PM; Cooper Industries, Lexington, SC). Whole BC (FM in kg and LTM as a percentage of body weight) was assessed by DXA with the use of a Lunar Prodigy whole-body scanner (Lunar Corp, Madison, WI) in conjunction with ENCORE software version 8.10 (Lunar Corp).

**Body composition: total body protein**

TBN was assessed by IVNAA as described previously (18, 19). Subjects were exposed to neutrons from two \(^{252}\)Cf sources so that \(^{14}\)N is converted to \(^{15}\)N, leading to 10.8-MeV \(\gamma\)-ray emission that was measured by 4 sodium iodine detectors. The scan takes <10 min and involves a radiation dose of <0.2 mSv. Total body protein (TBPr) was calculated according to the following equation:

\[
\text{TBPr}_{\text{NAA}} = 6.25 \times \text{TBPr}_{\text{NAA}} \quad (3)
\]

Protein status of patients with AN was characterized as severely depleted or normal according to a method described earlier by Borovnicar et al (20). TBPr prediction equations based on height as well as age were developed with the use of a regression equation in the normal weight control group as follows:

\[
\rho_{\text{TBNht}} (\text{in kg}) = 2.172 \times (\text{height, in m}) - 2.060 \quad (4)
\]

\[
\rho_{\text{TBNage}} (\text{in kg}) = 0.0844 \times (\text{age}) + 0.2101 \quad (5)
\]

Measurements of TBN standardized for height or age were also expressed in index form in AN as follows:

\[
\text{Nitrogen index (NI) = measured TBN/predicted TBN (from controls)}
\]

The NI represents the proportion of TBN in a patient when compared with a reference population; a value of 1.00 represents 100% of the predicted TBN. Protein status of patients with AN was determined by expressing NI as a \(z\) score defined as the following: NI of individual patient – mean NI of control group/SD of NI within control group. An NI \(z\) score represents the number of SDs the patient is above or below the reference population mean. This enables the classification of individual subjects as severely protein depleted (NI \(z\) score < –2) or protein normal (NI \(z\) score from –2 to 2).

**Hormone measurements**

In 47 of 50 patients with AN and in 22 of 40 controls, blood tests were performed between 0700 and 0900 after the subjects had fasted overnight, and the samples were sent to the hospital laboratory for immediate analysis. Estradiol was determined by radioimmunooassay (DiaSorin, Saluggia, Italy), cortisol was measured with a solid-phase chemiluminescent enzyme immunoassay (Immulite 1000; DPC Diagnostics, Los Angeles, CA), and testosterone was measured with in-house competitive binding
radioimmunoassay in duplicate, and IGF-I measurements were determined with the use of a commercial radioimmunoassay kit (Biocline Australia Pty Ltd, Marrickville, Australia).

**Statistical analysis**

Statistical analysis was performed with the use of SPSS (version 14.0; SPSS Inc, Chicago, IL). All data are presented as means ± SDs at a significance level of $P < 0.05$. Associations between variables were tested for by using Pearson’s correlation analysis, and predictors of NI were assessed with the use of multiple regression analysis. Differences between group means were tested for by using Pearson’s correlation analysis, and predictors of NI were assessed with the use of multiple regression analysis. Differences between group means were assessed with the use of an independent samples $t$ test. A sample size for each group (AN and controls) of at least 30 patients (for 80% power) and at least 45 (for 90% power) was required to detect a 20% ($\approx 1$ SD) difference in body nitrogen between the 2 groups with $x$ at 0.05. Bland-Altman analysis of agreement was performed to assess the agreement between skinfold anthropometry and DXA to assess BF (21).

**Ethics**

The Human Research Ethics Committees at the Children’s Hospital at Westmead and Westmead Hospital approved the study protocol. Assessment and analysis of data were performed according to privacy laws.

**RESULTS**

**General characteristics, hormones, and BC of patients with AN and controls**

The estimated premorbid BMI of patients with AN was 20.7 ± 3.1, and mean duration of the eating disorder at the time of testing was 12 ± 10 mo, ranging from 3 to 48 mo. Thirty-five of the patients were at least at Tanner stage 4. In the 42 inpatients, weight and BMI of patients with AN on hospital admission were 41.9 ± 5.8 kg and 15.6 ± 1.4. Time needed to medically stabilize the patients and to obtain parental consent was 12 ± 6 d, and during this time the patients had put on a mean of 2.6 kg. All 8 outpatients were medically stable at testing. General characteristics and plasma hormone concentrations of patients with AN and controls are shown in **Table 1**. When comparing patients with AN with controls, although age and height were similar, patients with AN had significantly lower body weight and BMI ($P < 0.001$). Cortisol concentrations were significantly higher, and estradiol and IGF-I concentrations were significantly lower in patients with AN ($P < 0.001$), whereas testosterone was nearly unchanged ($P = 0.05$).

**Prediction of protein status from clinical measurements**

In patients with AN, significant positive correlations were observed between TBN and weight ($r = 0.80$) and height ($r = 0.73$). The relation between TBPr and height is shown in **Figure 1**. According to the NI based on height (NI$_{ht}$), 33 patients with AN were able to maintain their body protein in the low normal range, but 17 were severely protein depleted (NI $z$ score $< -2$). In this study, several possible predictors of protein depletion were assessed in the group of patients with AN. A comparison of these possible predictors in protein-depleted and protein-normal patients with AN is shown in **Table 3**. Severely protein-depleted patients with AN had lower weight, BMI, LTM, and FM than did protein-normal patients with AN, but no significant difference was observed in duration of the disease (11 ± 7 mo compared with 13 ± 11 mo) or estimated amount of weight lost (13 ± 7 kg compared with 15 ± 6 kg). Eleven (33%) patients with AN and normal protein and 13 (77%) of the protein-depleted patients with AN were below the fifth BMI centile for age. NI$_{ht}$ was related to body weight, BMI, BMI SDS, and

**TABLE 1**

| General characteristics and hormone concentrations of patients with anorexia nervosa (AN) and controls$^a$ |
|---|---|---|
| **AN patients** | **Controls** |
| **General characteristics$^a$** | | |
| Age (y) | 15.2 ± 1.5 (12–19) | 14.8 ± 0.8 (13–16) |
| Weight (kg) | 44.4 ± 5.5 (28.6–53.7)$^f$ | 54.2 ± 8.5 (33.9–71.6) |
| Height (cm) | 163 ± 7 (145–175) | 162 ± 7 (142–174) |
| BMI (kg/m$^2$) | 16.7 ± 1.6 (13.6–20.0)$^f$ | 20.1 ± 2.2 (15.9–24.1) |
| BMI SD score | −1.7 ± 1.0 (−4.5 to −0.0)$^f$ | 0.0 ± 0.7 (−1.6 to −1.0) |
| **Hormone concentrations$^d$** | | |
| Cortisol (pmol/L) | 396 ± 190 (192–1201)$^f$ | 173 ± 59 (100–290) |
| Estradiol (pmol/L) | 79 ± 32 (32–177)$^f$ | 119 ± 43 (67–227) |
| Testosterone (nmol/L) | 1.5 ± 0.7 (0.7–4.0)$^f$ | 1.9 ± 0.7 (1.3–4.6) |
| IGF-I (nmol/L) | 36 ± 17 (11–77)$^f$ | 62 ± 13 (35–78) |

$^a$ Values are means ± SDs; ranges in parentheses. IGF-I, insulin-like growth factor I.

$^f$ $n = 50$ AN patients; $n = 40$ controls.

$^d$ $n = 47$ AN patients; $n = 22$ controls.
TABLE 2
Body composition of patients with anorexia nervosa (AN) and controls

<table>
<thead>
<tr>
<th>Protein status</th>
<th>AN patients (n = 50)</th>
<th>Controls (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBN_{NAA} (kg)</td>
<td>1.29 ± 0.16 (0.84–1.67)</td>
<td>1.47 ± 0.20 (1.03–1.80)</td>
</tr>
<tr>
<td>TBPr_{NAA} (kg)</td>
<td>8.1 ± 1.0 (5.2–10.4)</td>
<td>9.2 ± 1.2 (6.4–11.2)</td>
</tr>
<tr>
<td>NI_{age}</td>
<td>0.87 ± 0.07 (0.72–1.05)</td>
<td>1.00 ± 0.08 (0.84–1.22)</td>
</tr>
<tr>
<td>NI_{age} z score</td>
<td>−1.6 ± 0.9 (−3.5–0.6)</td>
<td>0 ± 1.0 (−2.0–2.8)</td>
</tr>
<tr>
<td>NI z score</td>
<td>0.87 ± 0.11 (0.61–1.17)</td>
<td>1.00 ± 0.13 (0.77–1.23)</td>
</tr>
<tr>
<td>NI z score</td>
<td>−1.0 ± 0.9 (−3.0–1.2)</td>
<td>0 ± 1.0 (−1.8–1.8)</td>
</tr>
</tbody>
</table>

Anthropometry

<table>
<thead>
<tr>
<th>Lean and fat</th>
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</tr>
</thead>
<tbody>
<tr>
<td>LTM_{DXA} (kg)</td>
<td>35.7 ± 4.3 (23.1–43.5)</td>
<td>35.8 ± 4.5 (25.1–45.8)</td>
</tr>
<tr>
<td>LTM_{DXA} (%)</td>
<td>80.5 ± 6.8 (63.2–94.3)</td>
<td>67.9 ± 6.7 (55.7–81.2)</td>
</tr>
<tr>
<td>FM_{DXA} (kg)</td>
<td>7.0 ± 3.4 (1.5–19.1)</td>
<td>14.8 ± 5.3 (5.3–26.3)</td>
</tr>
<tr>
<td>FM_{DXA} (%)</td>
<td>15.5 ± 6.6 (3.7–33.2)</td>
<td>27.2 ± 6.7 (13.3–38.9)</td>
</tr>
</tbody>
</table>

Hormone concentrations

| Cortisol (pmol/L) | 452 ± 264 | 358 ± 129 |
| Estradiol (pmol/L) | 62 ± 24 | 84 ± 33 |
| Testosterone (nmol/L) | 1.42 ± 0.64 | 1.63 ± 0.75 |
| IGF-I (nmol/L) | 35 ± 19 | 37 ± 16 |

Values are means ± SDs. TBN, total body nitrogen; NAA, neutron activation analysis; NI, nitrogen index adjusted for height; NI_{age}, nitrogen index adjusted for age; LTM, lean tissue mass; DXA, dual-energy X-ray absorptiometry; MUAC, midupper arm circumference; BSF, biceps skinfold; TSF, triceps skinfold; SSF, subscapular skinfold; SIF, suprailliac skinfold; SF, skinfold measurement.

1 Values are means ± SDs; ranges in parentheses. TBN, total body nitrogen; TBPr, total body protein; NAA, neutron activation analysis; NI_{age}, nitrogen index adjusted for age; LTM, lean tissue mass; FM, fat mass; DXA, dual-energy X-ray absorptiometry; MUAC, midupper arm circumference; BSF, biceps skinfold; TSF, triceps skinfold; SSF, subscapular skinfold; SIF, suprailliac skinfold; SF, skinfold measurement.

2,3,4,5 Significantly different from controls (independent sample t test): \( P < 0.001, 4 P < 0.01. \)

LTM_{DXA} (P < 0.01), but not to hormone concentrations of estrogen, testosterone, cortisol, or IGF-I. In a multiple regression analysis with NI_{age} as the dependent variable and weight, BMI, BMI SDS, and LTM_{DXA} as the independent variables, only BMI was a significant predictor of NI_{age}. To further analyze the relation between protein status and BMI, these data are also shown in Figure 2. Figure 2 shows that virtually all except 1 of 26 patients with a BMI > 16.5 had normal body protein. However, patients with AN with a BMI ≤ 16.5, 16 were severely protein depleted and 7 had normal TBPr. When we declared BMI of 16.5 as a cutoff to separate normal from depleted protein status, the negative predictive value of this test was 96%, whereas the positive predictive value of this test only came up to 69%. When comparing patients below (n = 22) and above (n = 28) a BMI of 16.5, no between-group differences were observed in either height or age.

FIGURE 1. Relation between total body protein (TBPr) measured with neutron activation analysis (NAA) and height of 50 patients with anorexia nervosa (AN) and 40 healthy controls (C). Patients with AN with height-adjusted nitrogen index z score < −2 were classified as protein depleted (n = 17).

FIGURE 2. Relation between total body protein (TBPr) measured with neutron activation analysis (NAA) and BMI of patients with anorexia nervosa (AN). Patients with AN were classified as protein depleted (d-AN) and protein normal (n-AN) based on the nitrogen index adjusted for height. With BMI > 16.5, 25 of 26 AN patients were protein normal.
Comparing methods to assess BF

BF assessed with DXA in AN patients was 15.5 ± 6.3% and by skinfold measures it was 17.1 ± 4.6%, and in controls it was 27.2 ± 6.7% and 24.0 ± 5.5%, respectively. Both measures were highly correlated (r = 0.82, P = 0.000). In addition, percentage of FM_{DXA} was significantly associated with both skinfold anthropometry (r = 0.79) and BMI (0.59). In Figure 3, the agreement between the 2 techniques is compared with a Bland-Altman analysis. On average, the %BF was overestimated by 1.7% in patients with AN and underestimated by 2.5% in controls by skinfold anthropometry compared with DXA. In patients with AN there was a systematic bias related to degree of fatness (P < 0.001), suggesting that, particularly at low fatness, FM is overestimated by skinfold measurements when compared with DXA. In both patients with AN and controls, limits of agreement were wide, ranging from −5.6 to 8.9 in patients with AN and from −13.6 to 8.7 in controls.

DISCUSSION

This study showed that despite similar LTM_{DXA}, adolescent females with AN had significantly less TBPr than did a contemporary group of sex-, age-, and pubertal status–matched controls and that 34% of patients were severely protein depleted with N_{int} ≤ −2 SDs of control average values. Patients with AN had significantly higher cortisol, lower estradiol and IGF-I, and similar testosterone concentrations than did controls, but none of these hormonal changes was directly related with protein depletion, nor could simpler surrogate variables reliably identify protein-depleted persons. However, a BMI > 16.5 indicated normal TBPr in patients with AN. BF was also low in patients with AN, and skinfold anthropometry proved comparable to DXA in the context of estimating BF in a group of patients with AN, yet the agreement between skinfold anthropometry and DXA FM measurements was low in individual patients.

TBPr depletion and its assessment in adolescent females with AN

Average TBPr in patients with AN was significantly decreased when compared with controls without evidence of stunting, which is in agreement with our previous work (13). The difference in the degree of protein depletion (75% compared with 87% of predicted TBPr for height) can be explained with more pronounced undernutrition in the first group (BMI: 15.3 compared with 16.7). Protein depletion has been shown to be predictive of chronic morbidity in adult patients with AN (5) and of linear growth retardation in younger children before pubertal maturations (18). Therefore, it would be of clear benefit to identify and specifically monitor severely protein-deficient persons with AN. With the use of IVNAA and adaptation of a previously published model to classify protein depletion (20), 17 patients with AN (34% of the currently studied patient population) showed severe protein depletion. Protein depletion did not correlate with weight, BMI, LTM_{DXA}, or hormonal measurements. However, as shown in Figure 2, patients with a BMI > 16.5, with the exception of 1 patient, had normal body protein for height, and, in contrast, those with a BMI < 16.5 had more likelihood of being protein depleted. This finding was not evident in the previous study in which all patients were protein depleted for height. Although this finding is of further interest for a clinical setting, the exact consequences of protein depletion were not evident in this cross-sectional study. As such, further research is required to determine the long-term consequences of these initial or sustained nutritional deprivations and whether they are correctable with nutritional rehabilitation.

Limitations of assessing LTM with DXA

LTM is often seen as a surrogate marker for protein status. However, in the current study DXA did not show low LTM in anorexic patients compared with healthy controls. This finding is contrary to our previous work (13). The present study shows that information on nutritional status of patients with AN derived from DXA measurements of LTM might be misleading and that patients who present with only a moderate reduction in LTM assessed with DXA can be severely protein depleted. This discrepancy is at least partly caused by the nature of a 3-compartment model on which the DXA technique relies and fits in with our previous study on healthy adolescent females showing that FFM assessed with DXA was not a good predictor of individual protein status in this group (19). Starvation-induced changes of BC often include an increase in total body water which can in turn mask low TBPr. With the

FIGURE 3. Comparison of dual-energy X-ray absorptiometry (DXA) and skinfold anthropometry (SF) to assess body fat (BF) in patients with anorexia nervosa (AN; left panel) and healthy controls (C; right panel) with the use of the Bland-Altman analysis of agreement. %BF, percentage body fat.
use of IVNAA and deuterium oxide dilution along with skinfold anthropometry and bioimpedance analysis, an expansion of fluid at depleted TBPr has been shown in patients with chronic liver disease (22), and the researchers concluded that an early detection of protein depletion in this situation requires the use of direct methods to assess BC.

BF depletion in adolescent females with AN

In our current patient population, DXA showed a significant reduction of BF by 51% compared with sex- and age-matched normal weight controls, which is comparable to the results of our previous work (13). The use of skinfold anthropometry as a noninvasive test to assess BF is common in clinical practice. Our findings indicate that, when compared with DXA, skinfold anthropometry can produce an acceptable result for groups in research settings. However, Bland-Altman analysis of agreement showed that %BF estimated by skinfold measurements may, in the case of an individual patient, be 9% higher or 6% lower than when measured with DXA, which is an unacceptable difference for clinical purposes. This lack of agreement is by no means obvious from the correlation between the 2 methods, which was highly significant. To adequately interpret these results, we need to keep in mind that first the algorithms underlying skinfold measurement estimations were generated from densitometric assessment of BF (17) and second that DXA is not a “gold standard” technology to assess FM. An earlier study assessing BC in anorexic patients has already described that the accuracy of DXA measurements of fat and lean masses cannot be taken for granted and that a bias can be produced that, although numerically small at average degree of adiposity, is large enough in anorexic subjects to affect physiologic or clinical interpretation (23). This potentially large individual bias of DXA in comparison with a reference 4-compartment model when assessing BF was also shown in 141 healthy adolescent females (24). In addition, the different direction of the bias between AN patients and controls in the current study suggests that nutritional status per se has an influence on the BC data when measured with these indirect techniques. Therefore, to obtain more reliable information about the validity of skinfold anthropometry or DXA in an anorexic population in the future, these methods need to be compared with a reference 4-compartment model.

In conclusion, this study showed that one-third of the patient population was severely protein depleted, but as yet there is no simple clinical tool that can reliably identify these protein-depleted persons, and the consequences of sustained protein depletion have not been determined. Of interest for clinicians, LTM assessed with DXA does not reflect protein status in this population was severely protein depleted, but as yet there is no simple clinical tool that can reliably identify these protein-depleted persons, and the consequences of sustained protein depletion have not been determined. Of interest for clinicians, LTM assessed with DXA does not reflect protein status in this situation requires the use of direct methods to assess BC.

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The authors’ responsibilities were as follows—VKH: data collection and analysis and preparation of the manuscript; MRK and SCD: data collection and advice; JRA: data collection; SM: advice; MJM: interpretation and discussion of data and preparation of the final manuscript; and KJG: study design and preparation of the manuscript. None of the authors had a conflict of interest.

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