Lipohypertrophy and nutritional profile among people living with HIV in Southern Brazil

Lipohipertrofia e perfil nutricional de pessoas que vivem com HIV no sul do Brasil

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ABSTRACT

Introduction: People living with the human immunodeficiency virus (HIV) are generally overweight or have an altered body composition as compared to healthy individuals, showing a change in nutritional profile over time. **Objective:** The aim of the study was to characterize the nutritional status, estimate the prevalence of lipodystrophy, and examine the association between lipohypertrophy and lipid profile alterations, and other clinical data of HIV-infected individuals. **Methods:** This was a cross-sectional study on male and female subjects living with HIV, treated at a specialized outpatient clinic, aged 18 years old and over, whether using the antiretroviral therapy or not. **Results:** The sample consisted of 420 people with a mean age of 43.8 years (standard deviation 11.7). The length of time of the HIV infection averaged 74.6 months, and 91% of the respondents were on antiretroviral therapy. Lipodystrophy prevalence was 35.7%. Of these, 82 (54.7%) presented lipohypertrophy, 61 (40.7%) had lipoatrophy and 7 (4.6%) had a mixed syndrome. Female gender, body mass index, fat percentage, waist circumference and waist-hip ratio were positively associated with the presence of lipohypertrophy ($p<0.001$). High mean total cholesterol ($p=0.015$) and LDL fraction ($p=0.028$) also showed a statistically significant association with lipohypertrophy. The sampled participants had a nutritional profile compatible with overweight or obesity. No association was found between lipohypertrophy and ART and the therapy duration. **Conclusion:** Considering the consequences of overweight as a cause of various pathological conditions, preventive measures and interventions are highly recommended for this population.
Keywords: Lipodystrophy. Acquired immunodeficiency syndrome. HIV. Obesity. Nutrition assessment.

RESUMO

Introdução: As pessoas que vivem com o HIV geralmente têm excesso de peso ou composição corporal alterada em relação aos indivíduos saudáveis, apresentando uma mudança no perfil nutricional ao longo do tempo. **Objetivo:** O objetivo do estudo foi caracterizar o estado nutricional, estimar a prevalência de lipodistrofia e examinar a associação entre lipohipertrofia e alterações no perfil lipídico e outros dados clínicos de indivíduos infectados pelo HIV. **Métodos:** Estudo transversal com indivíduos dos sexos masculino e feminino vivendo com HIV, atendidos em ambulatório especializado, com idade igual ou superior a 18 anos, em uso ou não de terapia antirretroviral. **Resultados:** A amostra foi composta de 420 pessoas com média de idade de 43,8 anos (desvio padrão 11,7). O tempo de infecção pelo HIV foi em média de 74,6 meses e 91% dos entrevistados estavam em terapia antirretroviral. A prevalência de lipodistrofia foi de 35,7%. Destes, 82 (54,7%) apresentavam lipohipertrofia, 61 (40,7%) lipoatrofia e 7 (4,6%) síndrome mista. Sexo feminino, índice de massa corporal, percentual de gordura, circunferência da cintura e relação cintura-quadril foram positivamente associados à presença de lipohipertrofia ($p<0,001$). As médias elevadas de colesterol total ($p=0,015$) e fração LDL ($p=0,028$) também mostraram associação estatisticamente significante com lipohipertrofia. Os participantes da amostra apresentavam perfil nutricional compatível com sobrepeso ou obesidade. Não foi encontrada associação entre lipohipertrofia e terapia antirretroviral e duração da terapia. **Conclusão:** Considerando as consequências do excesso de peso como causa de diversas patologias, medidas e intervenções preventivas são altamente recomendadas para essa população.
Palavras-chave: Lipodistrofia. Síndrome da Imunodeficiência Adquirida. HIV. Obesidade. Avaliação nutricional.

INTRODUCTION

The anthropometric profile of people living with HIV (PLWH) has changed quite a lot in recent years[1,2]. At the beginning of the epidemic, before the introduction of the antiretroviral therapy (ART), infected patients had cachexia and numerous opportunistic infections, which directly affected their nutritional status[3]. Wasting syndrome was one of the main forms of the disease manifestation, which generally depended on the patient's age length of HIV infection[4]. The literature highlights a change in this profile over time, indicating that PLWH are becoming overweight and obese[3,5], with abdominal and dorsal adipose tissue accumulation, associated with metabolic changes and cardiovascular diseases[2,6,7].

ART has increased life expectancy of PLWH[8]. However, pharmacological therapy results in major adverse reactions, including changes in the body composition distribution, especially the adipose tissue, whose pathophysiological mechanism has not yet been fully elucidated[9,10]. Genetic, infectious, and lifestyle factors are known to affect these changes, with increased risk for cardiovascular events and other noncommunicable chronic diseases in PLWH[11,12].

Lipodystrophy syndrome of HIV is considered an important adverse effect of ART use. Lipodystrophy is characterized by changes in body-fat distribution, consisting in visceral adiposity and accumulation of subcutaneous abdominal fat, peripheral weight loss, and metabolic alterations. Despite the strong association between lipodystrophy and ART, there are cases of PLWH who show changes in body-fat redistribution, although they are not on ART[13]. The development of lipodystrophy decreases quality of life of PLWH, causing negative psychosocial impact and even compromising treatment adherence or leading to the abandonment of therapy[7,14].

OBJECTIVE

Based on the above, the objective of this study was to characterize the nutritional status and prevalence of lipodystrophy, and

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examine the association between lipohypertrophy and lipid profile alterations, as well as other clinical data of HIV-infected individuals.

METHODS

A cross-sectional design was conducted on PLWH, receiving care at a specialized outpatient clinic, in southern Brazil. This study was approved by the Research Ethics Committee of *Universidade do Sul de Santa Catarina* (under registration CEP Unisul 1,197,743), on August 24, 2015. All participants signed an informed consent form before beginning the study.

The study included male and female HIV-positive subjects, aged 18 years old and over, who agreed to participate in the study. The exclusion criteria included pregnant women, participants with severe diseases associated or not associated with HIV infection, hospitalized patients during the study period, and those with inability to tolerate the orthostatic posture. Data collection was performed weekly between 2015 and 2018, when the PLWH attended the clinic for blood collection to measure CD4 T-lymphocyte count and viral load.

The protocol consisted of individual interviews to collect sociodemographic, epidemiological, clinical, and self-perceived lipodystrophy data; review medical records to gather clinical and laboratory information; and perform anthropometric measurements. We used a standardized questionnaire to collect data on demographic characteristics (age, gender), HIV infection-related variables (use of ART, adherence to ART, time since HIV diagnosis, and signs and symptoms of lipodystrophy). Clinical aspects of HIV infection that were also obtained from medical records were the following: 12-hour fasting glucose, lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), CD4-lymphocyte counts and HIV RNA viral load for the three months prior to the interview, time elapsed since HIV diagnosis, classes of antiretroviral drugs currently used, and duration of antiretroviral therapy. Viral load lower than 50 copies of HIV RNA per milliliter of blood (<50 copies/mL) was considered undetectable.

Data were collected during routine visits, and consisted of an interview and anthropometric assessment. All anthropometric measurements followed the protocol recommended by the International Standards for Anthropometric Assessment, and were carried out by the same evaluator with experience in anthropometric assessment. A Caumaq model BP-200F Class III stadiometer with a precision of 0.1 kg and 0.5 cm was used to measure weight and height. The patients were asked to be in the orthostatic position, dress light clothing and wear no shoes. Body mass index (BMI) was calculated considering weight in kilograms divided by height in square meters or BMI=kg/m^2. BMI was categorized according to the World Health Organization standards, i.e., a BMI up to 24.9 kg/m^2 is considered normal weight, and above 25 kg/m^2 will fall into the overweight and obese categories.

An inelastic anthropometric two-meter long tape (SN4010 model, Sanny, São Paulo, SP, Brazil) was used to measure waist, hip, neck, and arm circumferences. Participants were asked to stand in an upright position with their upper limbs hanging beside the trunk facing the evaluator. Arm circumference was measured at the midpoint between the scapula acromion and the ulna olecranon. To obtain this point, the subject had his arm flexed to 90°. After measuring the arm circumference, the person was instructed to leave the upper limb pending beside the body to be surrounded by the measuring tape.

Waist circumference (WC) and hip circumference were measured in centimeters using an inelastic anthropometric tape at the midpoint between the iliac crest and the outer face of the last rib, keeping the abdomen relaxed. The hip was measured at the level of the anterior iliac spines. The waist-hip ratio (WHR) was obtained by the ratio between WC and hip measurements. The values of WC were considered for the diagnosis of abdominal fat accumulation, and values lower than 80 cm for women, and 94 cm for men were classified as low accumulation. As for the waist-hip ratio, a WHR of over 0.85 indicated obesity in women, and a WHR of over 0.90 indicated obesity in men. A waist-to-height-ratio (WTHR) cutoff point of 0.5 was used for abdominal fat accumulation and increased cardiovascular risk[15,16].

Skin folds were measured using a CescorfTM caliper with a precision of 0.1 mm. Measurements were performed in the right hemi-body of the subject, with a series of three measurements in each skinfold, taken alternately with respect to the others. The mean fold values, or duplicate measurements with equal values were computed. Skinfolds were measured at the following sites: biceps, triceps, subscapular, iliac crest, mid-axillary, abdominal, and medial calf. The Jackson & Pollock calculator was used to calculate body-fat percentage (%F). The cutoff points used for the classification of body fat were those recommended according to gender differences. Values higher than 25% for men and 32% for women were considered high[17,18].

Diagnosis of lipohypertrophy

PLWH with lipodystrophy were those who presented at least two self-perceived body alterations that were consistent with the anthropometric measurements in that body area. The anthropometric measurements were classified using the lowest and highest percentiles (25 and 75, respectively). For the purpose of this study, PLWH who had undergone liposuction, liposculpture and used polymethyl methacrylate (PMMA) to correct facial lipoatrophy were considered cases of lipodystrophy, regardless of anthropometry. Both isolated and mixed syndrome cases were used to define lipohypertrophy and its association with obesity.

Statistical analysis

A total of 1,417 PLWH were registered in the clinic. Considering the prevalence of 50% of the unknown population with a 5% margin of error and design effect of 1%, the minimum sample size required for the study was 303 subjects. Non-probability sampling was used to select the study participants.

The Open Epi software, version 2.3.1, was used to calculate the sample size. The collected data were entered into Epidata software version 3.1 (Epi Data Association, Odense, Denmark) and exported to SPSS v.21.0 (IBM Armonk, New York, USA) for statistical analysis. Quantitative variables were described as measures of central tendency and dispersion, whereas qualitative variables were reported as absolute numbers and proportions. Pearson's chi-square test was used to test for associations between the variables

of interest. The Kolmogorov-Smirnov test was used to analyze the quantitative variables and verify the normality of the data distribution. The Student's t-test was used for mean comparison of quantitative variables, through parametric statistics. In case of non-normal distribution of data, the non-parametric Wilcoxon-Mann-Whitney U test was applied.

RESULTS

During the study period, 438 PLWH were invited. Of these, 3 refused to participate and 15 did not complete all stages of the study, being excluded from the study. So, the study encompassed 420 PLWH receiving care in an outpatient clinic. The sampled participants' mean age was 43.8 years (SD 11.7), ranging from 18–77 years.

Lipodystrophy prevalence was 35.7%. Of these, 82 (54.7%) presented lipohypertrophy, 61 (40.7%) had lipoatrophy and 7 (4.6%) had a mixed syndrome. It should be mentioned that two study participants had previously undergone facial filling with polymethyl methacrylate (PMMA), and one of them had had liposuction, thus being considered PLWH with lipodystrophy. For the purpose of this study, participants with lipohypertrophy were considered those who presented it alone and in a mixed form.

Table 1 shows the distribution of epidemiological and clinical data comparing the presence or absence of lipohypertrophy. Female gender and body mass index, fat percentage, waist circumference, waist-to-hip and waist-to-height ratios were positively associated with the presence of lipohypertrophy. Age (p=0.271) and length of time since diagnosis of HIV infection (p=0.228) did not show a statistically significant association with the presence of lipohypertrophy.

Considering each antiretroviral class separately, the most commonly ART used was the nucleoside analog reverse transcriptase inhibitor class, used by 364 (86.7%) participants, followed by non-nucleoside analog reverse transcriptase inhibitors (NRTIs), used by 256 (61.0%) participants; protease inhibitors (PIs), taken by 143 (34.0%) participants; integrase inhibitors, taken by 31 (7.4%) participants, and entry or fusion inhibitors, taken by 1 (0.2%) participant.

The duration of antiretroviral therapy ranged from 0 to 278 months, with a mean of 62.3 months (SD 56.5) and a median of 45 months. There was no statistically significant association between duration of ART therapy and the occurrence of lipodystrophy (p=0.227), even when each class was examined separately.

Table 2 shows the association between antiretroviral treatment and treatment adherence and the epidemiological and clinical characteristics of PLWH. Antiretroviral treatment and treatment adherence did not show a statistically significant association with the lipid and glycemic profile in the study sample.

Table 3 displays the lipid and glycemic profile, making a comparison between PLWH with and without lipohypertrophy.

Mean values of total cholesterol and LDL fraction were higher among those with lipohypertrophy than among their counterparts.

Table 1. Comparison between the participants with and without lipohypertrophy regarding clinical and demographic variables (n=420).

	Total	Lipohypertrophy		p-value
	n (%)	Yes	No	
Gender				**<0.001**
Male	241 (57.4)	21 (23.6)	220 (66.5)	
Female	179 (42.6)	68 (76.4)	111 (33.5)	
Age				0.423
18–59	388 (92.4)	84 (94.4)	304 (91.8)	
≥60	32 (7.6)	5 (5.6)	27 (8.2)	
ART use				0.393
Yes	382 (91.0)	83 (93.3)	299 (90.3)	
No	38 (9.0)	6 (6.7)	32 (9.7)	
ARV treatment adherence (n=382)				0.629
Yes	212 (55.5)	48 (57.8)	164 (54.8)	
No	170 (44.5)	35 (42.2)	135 (45.2)	
CD4 count (cel/mm^3)				0.907
0–349	130 (31.0)	28 (31.5)	102 (30.8)	
≥350	290 (69.0)	61 (68.5)	229 (69.2)	
Viral load HIV–RNA				0.137
Indetectable	294 (70.0)	68 (76.4)	226 (68.3)	
Detectable	126 (30.0)	21 (23.6)	105 (31.7)	
BMI				**<0.001**
Normal	218 (51.9)	15 (16.9)	203 (61.3)	
High	202 (48.1)	74 (83.1)	128 (38.7)	
%F				**<0.001**
Normal	76 (18.1)	2 (2.2)	74 (22.4)	
High	344 (81.9)	87 (97.8)	257 (77.6)	
WC				**<0.001**
Normal	235 (56.0)	8 (9.0)	227 (68.6)	
High	185 (44.0)	81 (91.0)	104 (31.4)	
WHR				**<0.001**
Normal	258 (61.4)	37 (41.6)	221 (66.8)	
High	162 (38.6)	52 (58.4)	110 (33.2)	
WTHR				**<0.001**
Normal	165 (39.3)	7 (7.9)	158 (47.7)	
High	255 (60.7)	82 (92.1)	173 (52.3)	

ART: antiretroviral treatment; ARV: antiretroviral; HIV–RNA: human immunodeficiency virus – ribonucleic acid, BMI: body mass index; %F: fat percentage; WC: waist circumference; WHR: waist-hip ratio; WTHR: waist-to-height-ratio.

DISCUSSION

The present study found a prevalence of 35.7% of lipodystrophy, and 21.2% of lipohypertrophy. These findings were consistent with those of a systematic review that found a prevalence of lipodystrophy ranging from 32.4 to 88.6% in PLWH, and a prevalence of lipohypertrophy between 12.1 and 49.2%[19]. In all the anthropometric parameters evaluated (BMI, %F, WC, WHR, and WTHR) the participants presented excess body weight or abdominal fat, which are risk factors for cardiovascular diseases.

Findings revealed that 65% of PLWH have alterations compatible with lipodystrophy and are associated with the use of ART[20,21], especially when using PIs and NRTIs, including stavudine[22]. There is an association between lipodystrophy and antiretroviral therapy. Discovering the preponderant factors causing lipodystrophy and adverse reactions to antiretrovirals have been the subject of study by researchers[1]. In the present study, however, there was no association between the use of antiretrovirals and the occurrence of lipodystrophy, or lipohypertrophy, not even when analyzed by

Table 2. Comparison between the participants with and without ART regarding clinical and nutritional variables (n=420).

	ARV use		P-value
	Yes n (%)	No n (%)	
CD4 count (cel/mm³)			**<0.001**
0–349	108 (28.3)	22 (57.9)	
≥350	274 (71.7)	16 (42.1)	
Viral load HIV–RNA			**<0.001**
Undetectable	288 (75.4)	6 (15.8)	
Detectable	94 (24.6)	32 (84.2)	
BMI			0.072
Normal	193 (50.5)	25 (65.8)	
High	189 (49.5)	13 (34.2)	
%F			**<0.001**
Normal	60 (15.7)	16 (42.1)	
High	322 (84.3)	22 (57.9)	
WC			0.348
Normal	211 (55.2)	24 (63.2)	
High	171 (44.8)	14 (36.8)	
WHR			0.353
Normal	232 (60.7)	26 (68.4)	
High	150 (39.3)	12 (31.6)	
WTHR			**0.014**
Normal	143 (37.4)	22 (57.9)	
High	239 (62.6)	16 (42.1)	

ART: antiretroviral treatment; ARV: antiretroviral; HIV–RNA: human immunodeficiency virus – ribonucleic acid; BMI: body mass index; %F: fat percentage; WC: waist circumference; WHR: waist-hip ratio; WTHR: waist-to-height-ratio.

Table 3. Participants' lipid and glycemic profile and their association with the presence or absence of lipohypertrophy.

	Total	Lipohypertrophy		p-value
	n (%)	Yes	No	
Total cholesterol	191 (38.7)	202 (32.9)	187 (39.9)	**0.015***
LDL	113 (34.8)	122 (28.7)	110 (36.2)	**0.028***
HDL	42 (0.8)	42 (1.6)	41 (1.0)	0.345**
Triglycerides	141 (6.6)	164 (8.4)	135 (8.3)	0.119**
Glicemia	95 (1.5)	95 (3.4)	95 (1.7)	0.858**

LDL: High Density Lipoprotein; HDL: low-density lipoprotein; *Student's t-test (mean and standard deviation); ** Mann-Whitney U test (median and standard error).

different viral classes, ART treatment duration and adherence to therapy. ART was associated with higher levels of CD4 and undetectable viral load, as expected[23]. There was also a statistically significant association between ART therapy and body-fat percentage, and a higher waist-to-height ratio, which may indicate that ART is a risk factor for obesity. Obesity rates among PLWH are similar to those of the general population, and its prevalence is increasing day by day. Excess body fat and visceral adiposity are associated with numerous metabolic and inflammatory sequelae. HIV and ART are specific risk factors that contribute to morbidity and mortality[24].

Lipohypertrophy was positively associated with female subjects. This finding was consistent with those from other studies, given that HIV-infected women are at higher risk to develop lipohypertrophy, compared to men[13]. Moreover, the prevalence of overweight and obesity was shown to be higher among women than among men, in both the general population and among HIV-infected people[25-28]. Several studies corroborate the findings that women have higher prevalence of central lipohypertrophy or mixed lipodystrophy syndrome compared to men, whereas men have a higher prevalence of peripheral lipoatrophy than women, although at higher risk for visceral fat[13,19,22,27].

This study found that women had significantly more adiposity in the waist region than men. A study by Foulds[28] has reported that women tend to have more abdominal fat than men. This tendency may be attributed to the women's postprandial period, since estrogen reduces oxidation of acid that would break down fat[29]. Women by nature have higher adiposity and lower muscle mass than men and these changes are hormone-dependent (estrogen versus testosterone)[30]. Men are more prone to visceral adiposity (abdominal fat) even when overweight[31].

Although most PLWH who had lipohypertrophy were not taking ART in the present study, there were six participants who were not using ART. This finding indicates the need for searching other causes of lipohypertrophy in this population[24]. In addition, five participants who had lipoatrophy were not taking ART as well. A study by Guaraldi and colleagues[30], in a retrospective cohort in Italy, concluded that both lipoatrophy and lipohypertrophy were not associated with antiretroviral therapy, but occurred as a result of the aging process itself, similar to what happens in the general population. However, in the present study, there was no association between lipohypertrophy and older age and longer time from diagnosis of HIV infection or use of ART.

When comparing lipohypertrophy with the parameters for measuring obesity or overweight in the present study (BMI, %F, WC, WCR and WTHR), all five were positively associated with the occurrence of lipohypertrophy. This finding may indicate that the diagnosis of lipohypertrophy in the present study used objective measures in accordance with the participant's self-perception of the increase in body fat in specific areas of the body. Obesity or overweight measurement variables are components of the lipohypertrophy definition, which may explain the statistical association. However, it is important to highlight that lipohypertrophy may be associated with peripheral lipoatrophy, which may compromise some diagnostic methods of obesity, such as body mass index.

A Brazilian study has shown that obesity is currently the most important nutritional change among PLWH[31], differently from the beginning of the epidemic, when cachexia and malnutrition were the predominant nutritional profiles. This difference in nutritional profile shows a significant change pattern among individuals living with HIV/AIDS[32] and, consequently, an increase in the number of noncommunicable chronic diseases in this population. The general population is facing an increased prevalence of obesity among adults and children. The same fact seems to be true for PLWH. In recent years, HIV-infected people are living longer with chronic AIDS, due to pharmacological treatment. Given this scenario, it is important to take preventive, diagnostic and therapeutic measures for possible

complications arising from obesity and lipohypertrophy, considering the specificities of HIV infection, antiretroviral treatment, and vulnerability to acute and chronic diseases[24].

The mechanisms responsible for lipid alterations in PLWH are not fully understood yet, and there are factors interacting simultaneously[33]. It is not clear whether dyslipidemia occurs as a consequence of ART or if it corresponds to a multicausal outcome, resulting from the type of antiretroviral drug being used, genetic predisposition, environmental factors, or the infection itself[34]. Lipohypertrophy and obesity are directly related to the occurrence of metabolic diseases, which may cause other health issues. A study conducted by Sacilotto and colleagues did not find metabolic alterations in patients with lipodystrophy, although they did observe important anthropometric changes evidenced by bioimpedance[35]. In the present study, there was a higher mean total cholesterol and LDL-fraction blood levels among participants with lipohypertrophy than among their counterparts. Lipodystrophy leads to a reduction in adipocyte differentiation and increases apoptosis of peripheral adipocytes. The outcome will be hyperlipidemia due to reduced peripheral storage and increased release of lipids in the bloodstream[1,22,33]. As a consequence, there is a high risk for cardiovascular disease[3]. The use of antiretrovirals did not show a statistically significant association with high values of fasting glycemia and lipid profile, which may be related to the fact that the majority of participants were taking ART.

Strengths

The strengths of this study are a sufficient sample size for the analysis and comparability of data, the conference of different information in the records physicians, and the fact that the same technically qualified evaluator was responsible for anthropometry.

Limitations

The cross-sectional design that does not allow proving the causality and temporality of lipodystrophy with the other variables investigated. In addition, in order to ensure the feasibility of the study together with the service, it was necessary to use demand as the sample, which was a sample for convenience. This can generate a selection bias, as patients who do not adhere to the service or treatment may influence the data found.

CONCLUSION

Based on the findings from the present study, it can be concluded that PLWH presented a nutritional profile compatible with overweight or obesity, in different assessment parameters, all of them associated with the presence of lipohypertrophy. The use of antiretrovirals was associated with a higher body-fat percentage and waist-to-height ratio, although without a statistically significant association with lipohypertrophy. Lipohypertrophy was also associated with the female gender and high levels of total cholesterol and LDL fraction. The importance of preventive measures and interventions should be emphasized for this population, considering that overweight is associated with an increased risk for morbidity and numerous pathological conditions, especially cardiovascular diseases.

Approval by the Human Research Ethics Committee

This study was approved by the Research Ethics Committee of Universidade do Sul de Santa Catarina (under registration CEP Unisul 1,197,743), on August 24, 2015.

Participation of each author

FST: Conceptualization, Formal Analysis, Project administration, Writing – review & editing. HCGS, MAS, CEMM: Data curation, Writing – original draft. RFS: Data curation, Methodology. DJT: Writing – review & editing, Supervision.

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Conflict of interests

The authors declare no conflicts of interest.

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