

# Effects of Growth Hormone Secretion on Body Composition in Patients with Crohn's Disease

LAURENCE KATZNELSON, WESLEY P. FAIRFIELD, NEBRAS ZEIZAFOUN, BRUCE E. SANDS, MARK A. PEPPERCORN, DANIEL I. ROSENTHAL, AND ANNE KLIBANSKI

*Neuroendocrine Unit and General Clinical Research Center (L.K., W.P.F., N.Z., A.K.), Gastrointestinal Unit (B.E.S.), and Department of Radiology (D.I.R.), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; and Gastroenterology Department, Beth Israel Deaconess Medical Center (M.A.P.), Boston, Massachusetts 02215*

Crohn's disease is a multisystem disorder characterized by chronic intestinal inflammation. Accumulation of mesenteric fat occurs in patients with Crohn's disease, although the mechanisms underlying site-specific changes in adipose deposition are unclear. To investigate whether there are alterations in site-specific adipose deposition in patients with Crohn's disease and to determine hormonal influences that may underlie such changes, we investigated body composition and serum hormone levels in 20 men with Crohn's disease (mean age,  $45 \pm 2$  yr) and 20 age-, gender-, and body mass index-matched normal controls (mean age,  $43 \pm 3$  yr). None of the Crohn's patients was receiving glucocorticoid therapy. Subjects underwent hourly GH sampling for 12 h beginning at 2000 h and fasting serum IGF-I and testosterone measurements. Body composition was assessed by quantitative computed tomography of the abdomen and bioelectrical impedance analysis. In the Crohn's disease and control subjects, mean serum GH levels were  $1.07 \pm 0.2$  and  $1.7 \pm 0.2$  ng/ml ( $P = 0.06$ ), serum IGF-I levels were  $162.7 \pm 10.5$  and  $194.8 \pm 15.7$  ng/ml ( $P = 0.1$ ), and serum testosterone levels were  $489 \pm 33$  and  $514 \pm 38$  ng/ml ( $P = \text{NS}$ ), respectively. Percentage body fat was significantly higher in the Crohn's patients ( $21 \pm 0.8\%$  vs.  $17.7 \pm 0.9\%$ , respectively;  $P = 0.013$ ). Intraabdominal fat (IAF) was significantly higher in the Crohn's subjects vs. controls

( $115 \pm 11$  vs.  $69 \pm 7$  cm<sup>2</sup>, respectively;  $P = 0.001$ ). The ratio of intraabdominal to total body fat was higher in the Crohn's subjects than in the controls ( $0.4 \pm 0.1$  vs.  $0.3 \pm 0.1$ , respectively;  $P = 0.025$ ). Subcutaneous fat area was similar in the two groups. IAF was higher in Crohn's patients even when controlling for testosterone and mean serum GH. Mean serum GH contributed independently to the differences in IAF ( $P = 0.001$ ). The ratio of IAF to total body fat remained higher in the Crohn's subjects when controlling for serum testosterone, but was no longer significant in a model that also included IGF-I and mean serum GH. GH levels contributed independently to the differences in the intraabdominal to total body fat ratio ( $P = 0.02$ ). In the Crohn's patients, serum GH correlated negatively with intraabdominal and total body fat and the ratio of intraabdominal to total body fat. Crohn's disease is associated with an increase in central fat accumulation, with more IAF and a higher ratio of intraabdominal to total body fat compared with controls. Although serum GH levels were similar in the two groups, GH contributed significantly to the abdominal fat measurements. These data show that GH has an important role in modulating visceral fat distribution in patients with Crohn's disease. (*J Clin Endocrinol Metab* 88: 5468–5472, 2003)

CROHN'S DISEASE IS a multisystem disorder characterized by chronic intestinal inflammation. This disorder usually begins during adolescence or early adulthood and often leads to catabolism and protracted nutrient losses. There have been few investigations into changes in adiposity in adult patients with Crohn's disease. Some studies have demonstrated that Crohn's disease is associated with a reduction in fat mass with maintenance of lean mass (1, 2). However, such findings may be in part attributed to the lower body weight of the subjects with Crohn's disease. In addition, accumulation of mesenteric fat has been detected in patients with Crohn's disease, although the mechanisms underlying site-specific changes in adipose deposition are unclear (3). Changes in the production of local inflammatory factors have been hypothesized to explain altered adiposity in such patients. The contribution of hormonal effects to adipose deposition in Crohn's disease is unknown.

Both GH and testosterone have been shown to modulate

adiposity. Patients with GH deficiency typically have increased central adiposity, and GH treatment of patients with GH deficiency leads to a reduction in intraabdominal fat (IAF) (4). Similarly, serum testosterone levels correlate negatively with visceral fat deposits, and testosterone administration to both hypogonadal and eugonadal men leads to a reduction in central fat (5). Because both GH and testosterone mediate adipose deposition, we hypothesize that changes in serum GH and testosterone may contribute to altered body composition in patients with Crohn's disease. We therefore investigated the relationship between body composition and serum hormone levels in patients with Crohn's disease.

## Subjects and Methods

Twenty male patients with Crohn's disease (age range, 27–60 yr) were enrolled. The duration of disease was approximately  $19.9 \pm 2.6$  yr. All subjects had normal thyroid and adrenal function and had not received prednisone therapy for at least 18 months before the study. Subjects were otherwise generally healthy, and exclusion criteria included disorders known to affect bone density, muscle mass, and adipose metabolism, including rheumatoid arthritis, liver, renal, thyroid, or parathyroid disease; alcoholism; and diabetes. Exclusion criteria also included any use of antiepileptic medications, medical therapy for hyperlipidemia, initiation or discontinuation of gonadal steroid therapy, or change in gonadal

Abbreviations: AUC, Area under the curve; BMI, body mass index; CDAL, Crohn's disease activity index; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; HOMA, homeostasis model assessment; IAF, intraabdominal fat; SCF, sc fat; TF, total fat.

status within the past 6 months. For the Crohn's disease group, 4 subjects had never received glucocorticoid therapy, whereas 16 subjects had received glucocorticoid therapy in the past (median, 11.5 yr; range, 2–38 yr before the study).

Twenty healthy normal men (age range, 21–64 yr) were admitted to the General Clinical Research Center at Massachusetts General Hospital and were subjected to the same exclusion criteria. The study was approved by the subcommittee on human studies at Massachusetts General Hospital, and written informed consent was obtained from all subjects.

After completing a screening visit to determine eligibility, subjects returned for an in-patient admission to determine hormonal and body composition parameters. The Crohn's disease activity index (CDAI) was administered to assess Crohn's disease activity.

### Clinical end points

**Hormonal assessment.** Hormonal assessments were performed after a 3-d meat-free diet. The GH/IGF-I axis was assessed by frequent GH sampling performed every 60 min from 2000–0800 h. The samples were pooled for calculation of the mean overnight serum GH concentration. Subjects were allowed to eat dinner at 1800 h on the day of sampling. Fasting serum IGF-I and GH levels were determined in all subjects at 0800 h. After the overnight sampling, subjects underwent a fasting standard 75-g oral glucose tolerance test at 0800 h, with insulin and glucose determined at baseline, 30, 60, 90, and 120 min after the glucose load. The insulin area under the curve (AUC), glucose AUC, and homeostasis model assessment (HOMA) scores were calculated.

**Nutritional assessment and body composition analysis.** Dietary intake was assessed by a 5-d food diary. Body height was measured to the nearest centimeter using a stadiometer, and body weight was measured after an overnight fast. Body mass index (BMI, weight in kilograms divided by the square of the height in meters) was calculated. Percentage body fat was assessed in the morning after an overnight fast, except for water *ad libitum*, by a research dietitian using bioelectrical impedance analyzer (bioelectrical impedance analyzer model 101, body composition software, RJL System, Clinton Turnpike, MI). Bioelectrical impedance analysis is based on the principle that the resistance to an electric current is proportional to the fat-free mass. Percentage body fat is then calculated from the resistance to the electric current. Bioelectrical impedance analysis was also used to calculate total body water and intra- and extracellular water contents.

Site-specific intraabdominal adipose deposition was determined using single slice quantitative computed tomography (CT) scans through the umbilicus using 10-mm-thick axial images (RP High Speed Helical CT Scanner, General Electric Corp., Milwaukee, WI). Using graphical analysis software provided by the scanner manufacturer (General Electric Advantage Windows Workstation version 2.0, General Electric Corp.), the cross-sectional areas of total fat (TF), sc fat (SCF), and IAF were determined. All measurements were made in duplicate. The region of interest within trabecular bone was compared with a phantom containing serial dilutions of  $K_2HPO_4$ . Equivalent density was expressed in milligrams of  $K_2HPO_4$  per deciliter. Technical factors for the scan included 80 kVp, 70 mA, and a 2-sec scan time. Skin dosage with this technique has been calculated to be 230 mrad.

### CDAI

Crohn's disease activity was measured using a validated instrument, the CDAI. This questionnaire uses eight variables, including stooling, abdominal pain, well-being, use of lomotil or opiates for diarrhea, presence of abdominal mass, hematocrit, body weight, and other specific symptoms. An index less than 150 is associated with quiescent disease, and an index greater than 150 is associated with active disease (6).

### Laboratory methods

Serum IGF-I was measured in duplicate by acid-alcohol extraction and RIA kit (Nichols Institute, Inc., San Juan Capistrano, CA) with a detection limit of 70 ng/ml. The assay demonstrates less than 0.05% cross-reactivity with IGF-II and less than 0.03% cross-reactivity with other peptide hormones. GH was measured by an immunoradiometric

assay kit (Nichols Institute, Inc.) with a detection limit of 0.02 ng/ml. The intraassay precision is 4.2% at 1.4 ng/ml and 2.9% at 6.0 ng/ml. Insulin was assessed by RIA (Diagnostic Products, Los Angeles, CA), with an intraassay coefficient of variation of 4.7–7.7%. Serum total testosterone was determined using RIA (Diagnostic Products).

### Statistical methods

Comparisons were made between the Crohn's group and the control group by two-tailed *t* test. Univariate regression analyses were performed, comparing indexes of body fat and composition and hormone variables. Age, BMI, TF, and IAF were tested in a multivariate regression model to determine the mean overnight GH concentration. Statistical analyses were made using JMP statistical data software (SAS Institute, Inc., Cary, NC). Statistical significance was defined as  $P < 0.05$ . Results are the mean  $\pm$  SEM unless otherwise stated.

## Results

### Comparison of body composition and metabolic parameters

Subjects with Crohn's disease and normal controls were of similar age, weight, and BMI (see Table 1). As shown in Table 2, Crohn's and control subjects had similar dietary caloric intake, including calories per kilogram and percentages of caloric intake from carbohydrates and fat sources. Percentage caloric intake from protein was significantly lower in patients with Crohn's. Resting energy expenditure and respiratory coefficient were similar between the groups. The glucose AUC, insulin AUC, and HOMA were similar between patients with Crohn's disease and controls. The oral glucose tolerance test revealed impaired glucose tolerance in 5 of 20 subjects with Crohn's disease *vs.* 1 of 20 normal subjects. Serum testosterone was similar between the groups. There were nonsignificant trends for lower mean overnight serum GH and serum IGF-I levels in the patients with Crohn's disease.

Percentage body fat was significantly higher, and total body water was significantly lower in Crohn's subjects compared with controls. Intra- and extracellular water contents were similar between the groups. CT scans showed that Crohn's subjects had significantly more TF and IAF, and the IAF/TF ratio was higher in Crohn's disease subjects. There was a nonsignificant trend for more SCF in patients with Crohn's disease.

Percentage body fat remained significantly higher in Crohn's patients when controlling for serum testosterone and serum IGF-I in a multivariate model ( $P = 0.02$ ). However, the difference in percentage body fat was no longer

**TABLE 1.** Clinical characteristics

Variable	Crohn's (n = 20)	Controls (n = 20)	P value
Age (yr)	44.95 (2.03)	42.85 (3.02)	NS
Duration of disease (yr)	19.85 (2.64)	N/A	
Weight (kg)	74.44 (1.77)	72.31 (1.54)	NS
BMI (kg/m <sup>2</sup> )	24.24 (0.50)	23.31 (0.35)	NS
WHR	0.903 (0.008)	0.884 (0.01)	NS
Serum testosterone (ng/ml)	489.20 (32.92)	513.95 (37.61)	NS
Mean serum GH (ng/ml)	1.07 (0.21)	1.69 (0.24)	NS
Serum IGF-I (ng/ml)	162.70 (10.47)	194.75 (15.66)	NS
CDAI	101.2 (12.2)		

Data are presented as the mean ( $\pm$ SEM). WHR, Waist to hip ratio; NS, not significant.

**TABLE 2.** Body composition and nutritional parameters

Variable	Crohn's (n = 20)	Controls (n = 20)	P value
<b>Metabolic status</b>			
REE (kcal/d)	1,382.25 (36.94)	1,343.45 (34.67)	NS
RQ	0.977 (0.02)	0.935 (0.01)	NS
Glucose AUC (mg/dl·120 min)	11,301.0 (444.30)	10,686.8 (375.57)	NS
Insulin AUC (mIU/liter·120 min)	3,677.4 (404.02)	3,812.32 (351.35)	NS
HOMA	1.13 (0.12)	1.11 (0.10)	NS
<b>Dietary intake</b>			
Energy (cal)	2,314.6 (119.6)	2,311.6 (90.08)	NS
Cal/kg body weight	31.48 (1.81)	31.91 (0.95)	NS
Alcohol	5.47 (2.31)	9.89 (3.96)	NS
% Cal from fat	32.30 (1.55)	30.30 (1.07)	NS
% Cal from carbohydrates	53.44 (1.93)	53.02 (1.49)	NS
% Cal from protein	14.04 (0.56)	17.04 (1.19)	0.03
% Cal from alcohol	1.64 (0.73)	2.65 (1.00)	NS
% Body fat	21.0 (0.82)	17.70 (0.94)	0.013
<b>CT scan values</b>			
TF (cm <sup>2</sup> )	288.44 (19.42)	214.94 (15.29)	0.005
IAF (cm <sup>2</sup> )	115.12 (11.13)	68.46 (6.92)	0.001
IAF/TF ratio	0.39 (0.02)	0.32 (0.02)	0.03
SCF (cm <sup>2</sup> )	173.31 (12.10)	146.48 (11.29)	NS
% Total body water	58.00 (0.62)	60.55 (0.69)	0.01
% Intracellular water	60.50 (0.74)	60.70 (0.68)	NS
% Extracellular water	39.50 (0.74)	39.30 (0.68)	NS

Data are presented as the mean ( $\pm$ SEM). REE, Resting energy expenditure; RQ, respiratory quotient; NS, not significant.

**TABLE 3.** Correlation of hormone parameters and body composition measurements in subjects with Crohn's disease

	IAF	TF	IAF/TF	SCF	% Body fat	BMD	BMD z-score
Mean GH	-0.72 <sup>a</sup>	-0.55 <sup>a</sup>	-0.67 <sup>a</sup>	0.22	0.31	0.03	0.2
IGF-I	0.03	0.02	0.01	0.06	0.37	0.28	0.17
HOMA	0.58 <sup>a</sup>	0.44 <sup>a</sup>	0.48 <sup>a</sup>	0.18	0.42	0.14	0.03
Insulin AUC	0.34	0.41	0.11	0.33	0.5 <sup>a</sup>	0.28	0.34

Percentage body fat was measured by bioelectrical impedance analysis. BMD, Bone mineral density.

<sup>a</sup>  $P < 0.05$ .

significant between the groups when controlling for mean serum GH levels ( $P = 0.06$ ). The difference in IAF remained significant when controlling for diet, serum testosterone, mean serum GH, and serum IGF-I ( $P = 0.03$ ). Mean overnight serum GH contributed independently to the differences in IAF ( $P = 0.001$ ).

Using quantitative CT, TF area remained significantly higher in patients with Crohn's when controlling for serum testosterone and serum IGF-I ( $P = 0.01$ ), but did not remain significant in a model that additionally included mean serum GH. In fact, mean serum GH contributed independently to the differences in TF ( $P = 0.01$ ). The ratio of IAF to TF remained higher in the subjects with Crohn's disease when controlling for serum testosterone ( $P = 0.03$ ), but was no longer significant in a model that additionally included serum IGF-I and mean serum GH. Mean serum GH contributed independently to the differences in the ratio of IAF/TF ( $P = 0.02$ ). GH did not correlate with IGF-I values in either group of patients.

Bone mineral density and bone mineral density z-score were similar between the groups. There was no difference in levels of bone markers between the groups.

#### Relationship of hormone parameters to body composition in Crohn's patients (Table 3)

Mean serum GH levels correlated negatively with IAF, TF, and the IAF/TF ratio. Mean serum GH did not correlate with

SCF or percentage body fat. Serum IGF-I and testosterone did not correlate with any site-specific body composition parameters. Serum GH was compared with body composition parameters stratified for values above and below the mean. For both IAF and IAF/TF ratio, serum GH was significantly higher in the subjects with lower IAF or IAF/TF ratio [ $1.72 \pm 0.3$  vs.  $0.48 \pm 0.1$  ( $P = 0.001$ ) and  $1.88 \pm 0.31$  vs.  $0.48 \pm 0.1$  ( $P = 0.0001$ ), respectively].

Serum IGF-I, mean GH, and testosterone levels did not correlate with CDAI scores. The CDAI scores did not correlate with IAF, SCF, or IAF/TF ratio. Insulin AUC correlated positively with percentage body fat. Glucose AUC did not correlate with any site-specific body composition parameters. HOMA correlated positively with IAF, TF, and the ratio of IAF/TF. Serum hormone levels did not correlate with bone mineral density or markers of bone turnover. Disease duration did not correlate with body composition measurements.

#### Crohn's disease activity

Patients with Crohn's disease were separated by disease activity based on the CDAI ( $<150$ ,  $n = 15$ ;  $>150$ ,  $n = 5$ ). Mean GH and IGF-I values were similar between these groups. IAF, IAF/TF ratio, and SCF were similar between patients with CDAI less than 150 vs. those with CDAI greater than 150.

#### Relationship of hormone parameters to body composition in controls (Table 4)

Mean serum GH, IGF-I, and testosterone did not correlate with any of the site-specific adipose deposition measurements by CT. Insulin AUC correlates positively with percentage body fat, IAF, and TAF, but not with SCF or the IAF/TF ratio. Glucose AUC and HOMA did not correlate with TF, IAF, SCF, or the IAF/TF ratio. Serum GH was compared with body composition parameters stratified for values above and below the mean. For IAF (but not the IAF/TF ratio), serum GH was significantly higher in subjects with less IAF ( $2.19 \pm 0.3$  vs.  $1.01 \pm 0.3$ , respectively;  $P = 0.01$ ).

### Discussion

Crohn's disease is a chronic inflammatory disease characterized by changes in nutritional status and metabolism (7). We have shown that compared with controls, Crohn's disease is associated with significant alterations in body composition, including enhancement of IAF deposits. This is the first assessment of the contribution of serum hormone levels to body composition, and we have shown that in Crohn's disease, serum GH correlates strongly in a negative fashion with IAF and correlates with insulin as assessed by HOMA as well. These data demonstrate the alterations in fat deposition in Crohn's disease and the role of GH in modulating these changes.

Previous studies of body composition in patients with Crohn's disease have shown variable alterations in body composition. In patients with active Crohn's disease, reductions in fat mass using dual energy x-ray absorptiometry have been described (8). However, Tjellesen *et al.* (9) assessed body composition with dual energy x-ray absorptiometry in 31 patients with Crohn's disease and showed similar fat mass compared with controls. In this study, when analyzed as a percentage of body weight, fat mass was higher in the patients with Crohn's. We measured body fat mass with bioelectrical impedance analysis and showed that percentage body fat was higher in patients with Crohn's disease. These data demonstrate that depending on multiple factors, which may include nutritional status and medication use, Crohn's disease may be associated with variable changes in overall fat mass, including central fat accumulation.

We showed that patients with Crohn's disease have more IAF than controls. Submucosal, mesenteric fat accumulation has been described in patients with inflammatory bowel disease. This effect appears to be independent of steroid use (10). Desreumaux *et al.* (3) assessed adiposity in 21 subjects with Crohn's disease and showed that IAF area was similar to that in controls, but that the IAF to total abdominal fat area was higher in the Crohn's patients. Compared with normal

subjects, there was an overexpression of peroxime proliferator-activated receptor- $\gamma$  and TNF $\alpha$  in the mesenteric adipose tissue of patients with Crohn's. This suggests that peroxime proliferator-activated receptor- $\gamma$  expression may have a pathogenic role in the mediation of adipose deposition, possibly through the synthesis of TNF $\alpha$  in the inflammatory response. Of note, 5 (25%) of the patients with Crohn's disease in this study were treated with glucocorticoids, potentially confounding study results (3).

In the present study patients with Crohn's disease had more IAF and total abdominal fat area than controls of similar BMI. These patients were not receiving glucocorticoid therapy, so glucocorticoids did not contribute to the altered fat deposition. These findings could be attributed to Crohn's disease itself, although GH contributed to these findings as well. We did not demonstrate a difference in mean overnight GH levels compared with normal controls. However, GH contributed independently to the IAF differences. Additionally, the differences in total body fat between the patients with Crohn's disease and normal subjects were no longer significant in a multivariate model including GH, and GH contributed independently and significantly to the TF differences. GH did not correlate with body composition in the normal subjects, despite a clear correlation of GH with IAF similar to that seen in other normal populations (11). Because of the significant correlation of GH and body composition in this relatively small number of patients with Crohn's, these data strongly suggest that GH contributes to adipose deposition in Crohn's and plays an important role in central, site-specific fat deposition in Crohn's patients. Serum testosterone did not contribute to the findings.

The effects of GH on body composition corroborate earlier findings on the correlation of GH/IGF-I in children with Crohn's disease. Serum IGF-I is lower in children with Crohn's disease and may increase after treatment (12). Reduced GH and IGF-I levels have been detected in children with Crohn's disease and correlate with growth in these children (13, 14). In children, GH responsiveness to provocative testing may be blunted, suggesting reduced GH reserve in such patients (15). These studies suggest that GH/IGF-I dynamics may be altered in children with Crohn's disease, although it is unclear whether GH plays an important modulatory role in the pathogenesis of Crohn's disease or is a marker of chronic inflammatory illness. We did not detect differences in serum GH and IGF-I levels between Crohn's and control subjects, although there was a nonsignificant trend for lower GH and IGF-I values in the Crohn's patients. It is possible that GH provocative testing would have demonstrated differences in GH dynamics in Crohn's disease.

Serum testosterone levels were similar between the

**TABLE 4.** Correlation of hormone parameters and body composition measurements in normal subjects

	IAF	TF	IAF/TF	SCF	% Body fat	BMD	BMD z-score
Mean GH	0.3	0.26	0.2	0.14	0.2	0.01	0.14
IGF-I	0.4	0.3	0.24	0.2	0.07	0.05	0.56 <sup>a</sup>
HOMA	0.06	0.006	0.14	0.04	0.17	0.3	0.47 <sup>a</sup>
Insulin AUC	0.45 <sup>a</sup>	0.5 <sup>a</sup>	0.1	0.4	0.71 <sup>a</sup>	0.1	0.21

Percentage body fat was measured by bioelectrical impedance analysis. BMD, Bone mineral density.

<sup>a</sup>  $P < 0.05$ .

groups, and testosterone did not correlate with differences in body composition. There is limited literature concerning serum androgens in patients with Crohn's disease. In a study by Straub *et al.* (16), serum dehydroepiandrosterone sulfate (DHEAS) was significantly lower in 47 male patients with Crohn's disease than in controls. In this study DHEAS levels correlated negatively with humoral markers of inflammation, including IL-6, sedimentation rate, and clinical disease activity. These data suggest that DHEAS may have a pathogenic role in Crohn's disease. Serum testosterone levels have been shown to be in the low normal range in a study of 19 men with Crohn's disease (median age, 29 yr) (17). In our study of patients with Crohn's disease not receiving glucocorticoid treatment, serum testosterone levels were similar between the groups. Our data do not support a clear role for testosterone in the pathogenesis of Crohn's disease.

In summary, we have shown that Crohn's disease is associated with enhanced central adiposity, with a predominance of IAF deposition. This finding may represent an effect of immunomodulatory imbalances associated with Crohn's disease. Our data suggest a role for GH as well. Future studies are needed to delineate the effects of GH on body composition in patients with Crohn's disease.

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Address all correspondence and requests for reprints to: Laurence Katznelson, M.D., Neuroendocrine Unit Massachusetts General Hospital, 55 Fruit Street, Bulfinch 457, Boston, Massachusetts 02114. E-mail: lkatznelson1@partners.org.

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