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► To cite this version:

Cécile Bétry, Madeleine Lauverjat, Thomas Mouillot, Charlotte Bergoin, Didier Barnoud, et al.. Hyperphagia in short bowel patients: Fat-free mass is a strong predictor. *Nutrition*, 2019, 62, pp.146 - 151. 10.1016/j.nut.2018.12.013 . hal-03486144

HAL Id: hal-03486144

<https://hal.science/hal-03486144>

Submitted on 20 Dec 2021

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1 Hyperphagia in short bowel patients: fat-free mass is a strong predictor

2

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17 **Acknowledgments**

18 We thank the staff of the Nutrition Intensive Care Unit for their helpful assistance in the data

19 collection. We thank Peter Tucker for proofreading this manuscript.

20

21 C. Bétry, T. Mouillot and C. Chambrier contributed to the conception and design of the

22 research; C. Bétry, M. Lauerjat, C. Bergoin, D. Barnoud, S. Ait and C. Chambrier

23 contributed to the acquisition of the data; C. Bétry and C. Chambrier contributed to the

24 analysis and the interpretation of the data. C. Bétry drafted the manuscript. All authors

25 critically revised the manuscript, agree to be fully accountable for ensuring the integrity and
26 accuracy of the work, and read and approved the final manuscript

27

28 **Funding source**

29 C. Bétry was funded by the FRM during the writing of this article (Grant 40184). This
30 research did not receive any other grant from funding agencies in the public, commercial, or
31 not-for-profit sectors. The funding bodies did not have any involvement in the design/conduct
32 of the research, in data analysis/interpretation, or in writing/approval of the manuscript.

33

34 **Declarations of interest:** none

35

1 **Title**

2 Hyperphagia in short bowel patients: fat-free mass is a strong predictor

3

4 **Abstract**

5 *Background:* Some short bowel syndrome patients develop hyperphagic behaviour. Such an
6 increase in food intake stimulates intestinal adaptation and limits dependence on parenteral
7 nutrition. The aim of this study was to determine the factors modulating food consumption in
8 short bowel syndrome patients.

9 *Methods:* The associations between oral energy intake and anthropometric, metabolic,
10 nutritional, and intestinal absorption-related characteristics were determined in a monocentric
11 cohort of short bowel syndrome patients on parenteral nutrition with a stable nutritional
12 status. Body composition was assessed by dual X-ray absorptiometry. Data were
13 retrospectively collected from clinical records.

14 *Results:* After screening, 38 adult patients with a short bowel syndrome **under parenteral**
15 **nutrition** ~~and without intestinal transplantation or debilitating gastrointestinal symptoms~~ were
16 included in this study. Oral energy intake ranged from 577 to 4054 kcal per day. Oral energy
17 intake correlated positively with weight, fat-free mass, hand-strength, resting energy
18 expenditure and negatively with free triiodothyronine and C-reactive protein using Spearman
19 correlation. Fat-free mass and thyroid-stimulating hormone remained positively correlated
20 with oral energy intake independently of all other parameters in a multilinear regression
21 model.

22 *Conclusions:* Fat-free mass is a strong predictor of oral energy intake in short bowel
23 syndrome patients **under parenteral nutrition and without debilitating gastrointestinal**
24 **symptoms**. Increasing fat-free mass ~~using a physical activity program~~ could be a way to

BMI, body mass index, CRP, C-reactive protein, DEXA, dual X-ray absorptiometry, FFM, fat-free mass, FFMI, fat-free mass index, FM, fat mass, FMI, fat mass index, FT3, free triiodothyronine, FT4, free thyroxine, REE, resting energy expenditure, TSH, thyroid-stimulating hormone

25 stimulate oral energy intake in short bowel syndrome patients. This assumption should be
26 assessed by further studies.

27

28 *Keywords:* parenteral nutrition; energy metabolism; body composition; fat-free mass;
29 thyrotropin; intestinal absorption

30 **Introduction**

31 In adults, short bowel syndrome is secondary to intestinal resection for gastrointestinal
32 conditions including mesenteric ischemia, inflammatory bowel diseases, occlusive syndromes
33 or bowel cancers. This syndrome is defined by a remnant bowel length inferior to 150-200
34 cm. Massive small intestine resection induces temporary or permanent intestinal failure owing
35 to malabsorption related to a reduced intestinal surface ¹.

36 The development of parenteral nutrition during the last decades has changed the prognosis
37 of short bowel syndrome patients. However, long-term parenteral nutrition induces serious
38 complications, e.g., central venous catheter-related bloodstream infections and intestinal
39 failure-associated liver disease ^{2,3}. Moreover, home parenteral nutrition is an expensive
40 treatment associated with a poor quality of life ^{4,5}. Thus, one of the main objectives of short
41 bowel syndrome patient care is to promote intestinal adaptation and to reduce dependence on
42 parenteral nutrition. Some short bowel syndrome patients present adaptive hyperphagia which
43 is critical for intestinal adaptation ^{6,7}. Stimulating food consumption could therefore be a safe
44 and inexpensive way to reduce dependence on parenteral nutrition ⁸.

45 Few studies have assessed the factors which modulate oral energy intake in short bowel
46 syndrome patients. These studies focused on the links between hyperphagia and certain
47 hormones – namely leptin, dipeptidyl peptidase-4, peptide YY and ghrelin, with inconclusive
48 results ⁹⁻¹¹. Since fat-free mass correlates with oral energy intake in healthy normal weight
49 and obese subjects, we hypothesised that body composition could at least partly determine
50 oral energy intake in short bowel syndrome patients ¹²⁻¹⁴. The aim of our study was to
51 determine the factors associated with oral energy intake in short bowel syndrome patients on
52 home parenteral nutrition and stable nutritional status.

53 **Materials and Methods**

54 **Study population**

55 This study was based on observational routinely-collected data from one home
56 parenteral nutrition referral centre in Lyon, France. Health data were recorded in
57 computerised patient records during clinical practice. In our centre, every patient, who is
58 under home parenteral nutrition for extended period, is routinely hospitalised for nutritional
59 assessment. All short bowel subjects, who were hospitalised for a nutritional this assessment
60 in our unit from January 2007 to October 2016 were screened. Clinically stable patients with a
61 short bowel syndrome for at least 1 year and on home parenteral nutrition were included.
62 Short bowel syndrome was defined as a remnant short bowel length inferior to 200 cm with or
63 without colon resection ¹. Owing to the eating difficulties of adult patients with a paediatric
64 short bowel syndrome, these patients were excluded from our study ¹⁵. Patients with intestinal
65 transplantation, and those with an oral energy intake below 500 kcal and/or frequent
66 nausea/vomiting were also excluded.

67 **Nutritional assessment**

68 All included patients received a standardised nutritional assessment during a hospital
69 stay of a few days. If a patient received several nutritional assessments, only the data from the
70 most recent hospitalisation were collected. These nutritional assessments are routinely
71 performed in the home parenteral nutrition referral centre of Lyon. The purpose is to ensure
72 that the long-term home parenteral nutrition is appropriate. Nutritional assessment includes
73 body composition analysis and anthropometry, a 3-day food diary, indirect calorimetry, blood
74 and stool tests.

75 **Body composition and anthropometry**

76 All anthropometric measurements were performed by medical practitioners. Weight,
77 height, brachial circumference at the centre of the upper limb and triceps skinfold at the same
78 site using an anthropometric calliper were determined. The device used for determination of
79 handgrip strength changed in 2012. Thus, only handgrip strength measured with a Jamar
80 dynamometer data after 2012 was considered. Fat-free mass and fat mass were estimated by
81 dual X-ray absorptiometry (DEXA). Indirect calorimetry (Quark RMR – Cosmed) was
82 performed for 30 min in fasting subjects after discontinuation of parenteral nutrition for at
83 least six hours.

84 **Determination of food intake and definition of hyperphagia**

85 Oral energy intake was assessed by a trained dietitian using a 3-day food diary filled
86 out at home prior to hospitalisation.

87 Some authors have attempted to define hyperphagia in short bowel syndrome but no
88 clear definition has yet to emerge. Based on a review of the literature, two principal
89 definitions have been retained in this paper in order to classify the subjects as hyperphagic or
90 non-hyperphagic. We defined subjects as hyperphagic if they had an oral energy intake
91 greater than either $40 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ⁹ or one and a half times their resting energy expenditure
92 ⁶.

93 **Blood and stool tests**

94 Blood tests were performed including determination of albuminemia, C-reactive
95 protein (CRP) level, thyroid function, and plasma amino acids in order to measure plasma
96 citrulline concentration. Intestinal carbohydrate absorption was determined using a blood D-
97 xylose test. Fasting subjects were given 5g of D-xylose dissolved in 200 mL water and D-
98 xylose blood concentration was measured after one hour. Stools were collected by subjects for
99 three days at home before hospitalisation in order to determine average daily stool weight.

100 **Ethics statement**

101 According to current French law, patients were individually informed that their data
102 could be used for research (MR-003 reference methodology) and did not object. Data were
103 collected during routine medical examination. Patients did not undergo any treatment or
104 examination specifically devised to collect data for this study.

105 **Statistical analysis**

106 Statistical analysis was performed using RStudio Version 1.0.136 with occasional
107 reliance on ‘prettyR’, ‘RVAideMemoire’, ‘ggplot2’, ‘car’, ‘zoo’¹⁶. Owing to the small
108 number of patients, non-parametric statistics were used. Data are presented as median and
109 95% confidence interval. All P-values below 0.05 were considered significant.

110 The relationship between oral energy intake and the following 24 variables were
111 examined: age, sex, short bowel syndrome causes, bowel anatomy, remnant small bowel
112 length, duration of short bowel syndrome, resting energy expenditure, body weight, fat-free
113 mass, fat mass, brachial circumference, skinfold, hand strength, plasma albumin, thyroid-
114 stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), CRP,
115 parenteral energy intake, number of parenteral infusions per week, volume of parenteral
116 infusion stool weight, one-hour D-xylose blood concentration and citrullinemia. In order to
117 determine the predictive factors of oral energy intake, a univariate analysis was first
118 completed using Spearman correlations and Wilcoxon-Mann-Whitney test or Kruskal-Wallis
119 test for categorical variables with more than two factors. For the Spearman correlation
120 determination, the results were expressed as Rho and 95% confidence interval. Confidence
121 intervals were determined using a bootstrap with 1000 replicates.

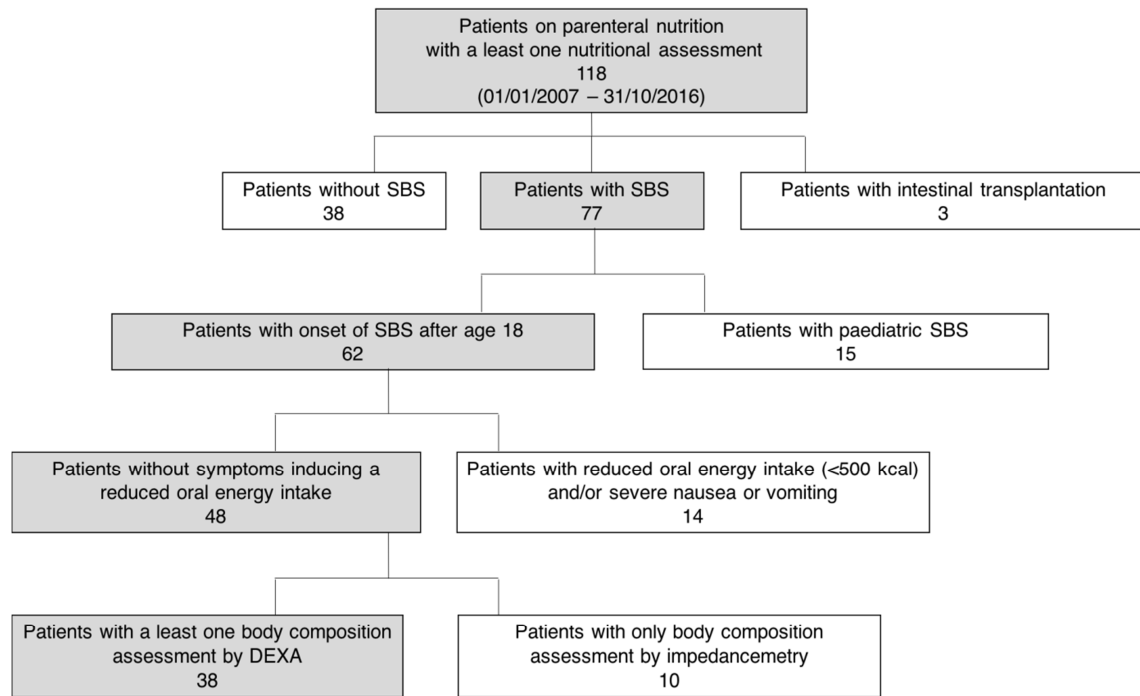
122 Subsequently, a multiple regression analysis was performed to determine the factors
123 significantly and independently associated with oral energy intake. Variables with P-value

124 below 0.1 in univariate analyses as well as age and sex were entered. Hand-strength was
125 excluded because too many values were missing. Owing to the collinearity between weight
126 and fat-free mass, assessed by variance influence factor, weight was replaced by fat mass.
127 Variance influence factor was below 5 for each factor after this adjustment. The residual of
128 multiple linear regression was normally distributed using the Shapiro-Wilk test ¹⁷.

129 **Results**

130 **Patient inclusion**

131 All patients (n = 119) on home parenteral nutrition and hospitalised for a nutritional
132 assessment between January 2007 and October 2016 were screened (Figure 1). A total of 38
133 patients were included.



134

135 Figure 1. Patient inclusion flowchart.

136 SBS, short bowel syndrome, DEXA, Dual-energy X-ray absorptiometry

137 **Patient characteristics**

138 The study population was made up of 24 males (63%) and 14 females with a median
139 age of 63 years [IC95%: 37-77]. Patients underwent intestinal resection due to mesenteric
140 ischaemia (n=24, 63%), small bowel obstruction (n=5, 13%), intestinal tumour (n=3, 8%),
141 radiation enteritis (n=3, 8%), or other causes (n=3, 8%). The median remnant small bowel
142 length was 70 cm [IC95%: 8-164]. Among the 18 patients with a stoma, 16 patients had an
143 end-jejunostomy while 2 had a colostomy with a jejunocolic anastomosis. Among the 20
144 patients without a stoma, 17 had a jejunocolic anastomosis and 3 a jejunoleal anastomosis.
145 The median period between nutritional assessment and bowel resection was 52 months
146 [IC95%: 16-214]. Table 1 shows the demographic, anthropometric, metabolic, nutritional and
147 intestinal absorption-related characteristics.

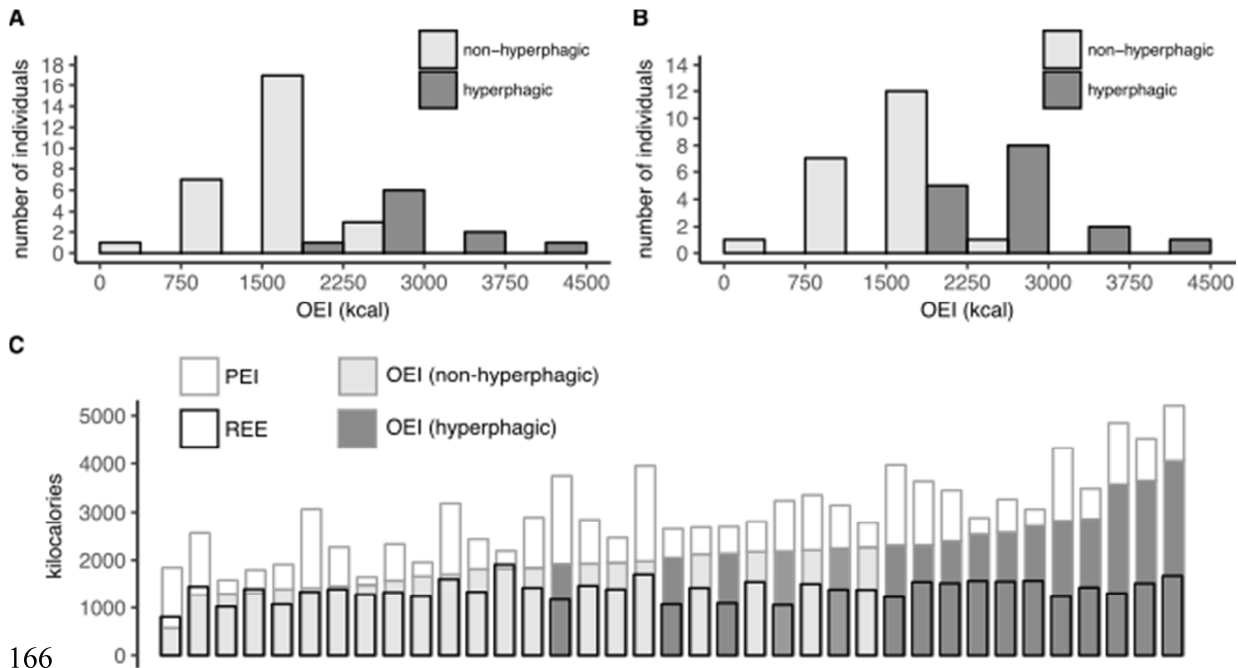
	Median [IC 95%]
age, years, n = 38	63 [37, 77]
sex, %, (M/F), n = 38	63% (24/14)
<i>Anthropometric characteristics</i>	
body weight, kg, n = 38	63.0 [48.9, 80.0]
BMI, kg.m-2, n = 38	22.0 [17.3, 26.8]
FFM, kg, n = 38	42.9 [34.9, 58.2]
FFMI, kg.m-2, n = 38	15.5 [13.4, 19.5]
FM, kg, n = 38	16.5 [7.9, 28.3]
FMI, kg.m-2, n = 38	6.2 [2.7, 11.0]
brachial circumference, cm, n = 35	27 [23, 34]
skinfold, mm, n = 35	14 [5, 33]
Hand strength, kg, n = 14	32 [17, 43]
<i>Metabolic characteristics</i>	
REE, kcal, n = 37	1394 [1053, 1685]
TSH, mUI/L, n = 36	1.29 [0.48, 3.07]
FT3, pmol/L, n = 35	4.1 [3.3, 5.2]
FT4, pmol/L, n = 35	12.8 [10.1, 17.3]
CRP, mg/L, n=38	3.3 [0.9, 15.7]
albumin, g/L, n = 38	37.3 [28.1, 44.0]
<i>Nutritional characteristics</i>	
oral energy intake, kcal/d, n = 38	2087 [1293, 3586]
parenteral energy intake, kcal/d, n = 38	840 [286, 1682]
number of parenteral infusions, per week, n = 38	4 [2, 7]
volume of parenteral infusion, L, per bag, n = 38	1142 [286, 3038]
amino acid content of parenteral infusion, g/kg/day, per bag, n = 38	0.62 [0.24, 1.22] g/kg/day
<i>Intestinal absorption-related characteristics</i>	
stool weight, g per day, n = 35	1165 [186, 2939]
one-hour D-xylose blood concentration, mmol/L, n = 31	0.60 [0.24, 1.51]
citrullinemia, mmol/L, n = 38	20 [7, 43]

148 Table 1. Anthropometric, metabolic, nutritional and intestinal absorption-related
149 characteristics of the population.

150 BMI, body mass index, FFM, fat-free mass, FFMI, fat-free mass index, FM, fat mass, FMI,
151 fat mass index REE, resting energy expenditure, TSH, thyroid-stimulating hormone, FT3, free
152 triiodothyronine, FT4, free thyroxine, CRP, C-reactive protein

153 **Oral and parenteral energy intake**

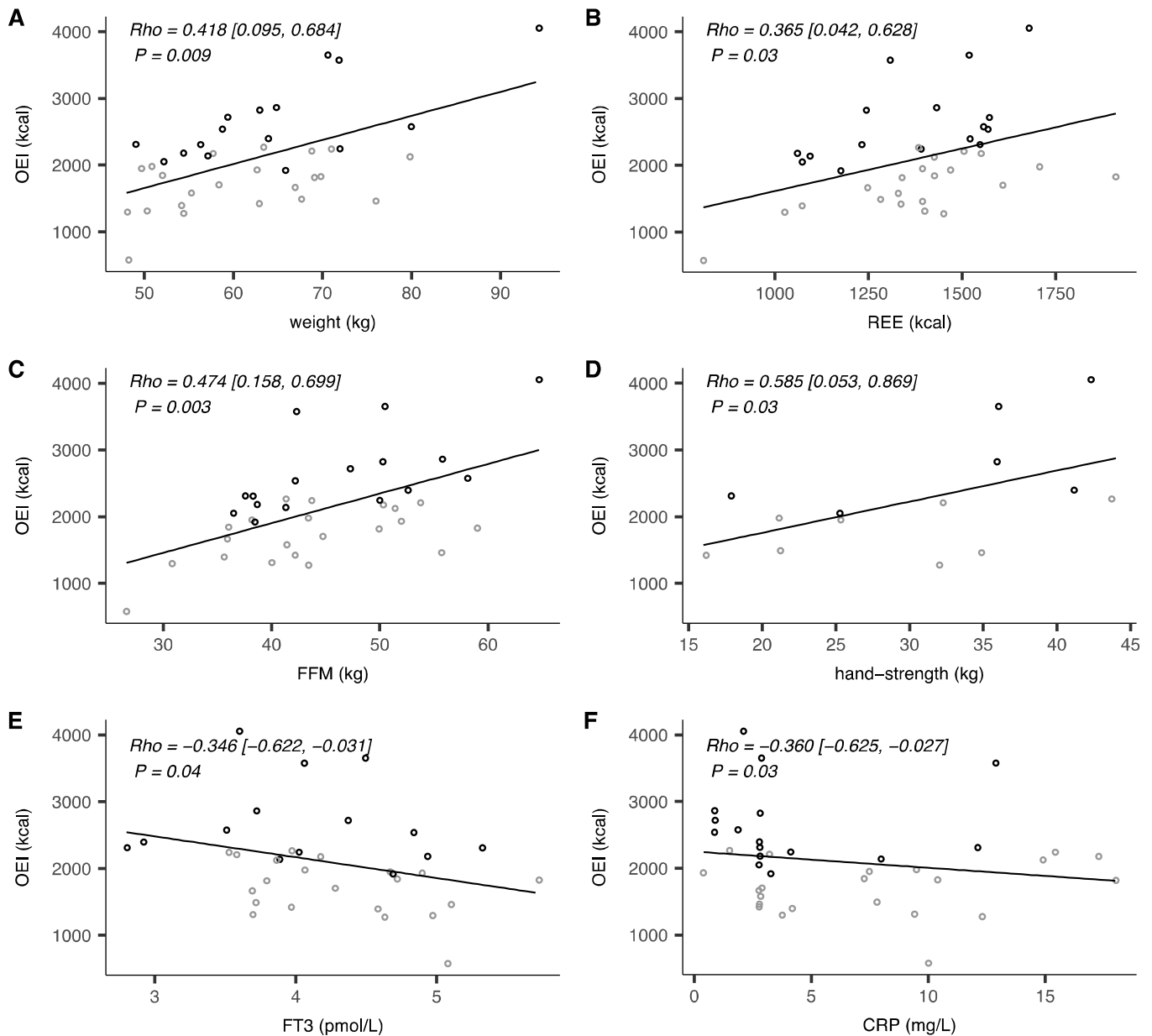
154 Patients were assigned either to the hyperphagic or the non-hyperphagic group
155 according to the two retained hyperphagia definitions, namely an oral energy intake greater
156 than $40 \text{ kcal.kg}^{-1}.\text{day}^{-1}$ (Figure 2A) or one and a half times their resting energy expenditure
157 (Figure 2B). Subjects with hyperphagia accounted for 26% (n=10) using the first definition
158 (Figure 2A) and 43% (n=16) using the second definition (Figure 2B). As illustrated in Figures
159 2A and 2B, oral energy intake had a Gaussian distribution which did not make it possible to
160 clearly distinguish the group of hyperphagic patients from the group of non-hyperphagic
161 patients. Whatever the definition of hyperphagia, the hyperphagic patients were only the
162 patients with the greatest energy intake (on the right of the curve). Given this and for further
163 analyses, the population was analysed as a whole. Oral and parenteral energy intake and
164 resting energy expenditure for each patient are given in Figure 2C. In the vast majority of
165 cases, oral energy intake provided more than resting energy needs.



167 Figure 2. Oral energy intake (OEI), parenteral energy intake (PEI) and resting energy
 168 expenditure (REE) in the cohort of 38 short bowel syndrome patients
 169 A. Distribution of the OEI in patients designated either non-hyperphagic (OEI/weight < 40
 170 kcal.kg-1.day-1, n = 28, 73.7%) or hyperphagic patients (OEI/weight \geq 40 kcal.kg-1.day-1,
 171 n=10, 26.3%)
 172 B. Distribution of the OEI in patients designated either non-hyperphagic (OEI < 1.5*REE,
 173 n=21, 56.8%) or hyperphagic patients (OEI \geq 1.5*REE, n=16, 43.2%)
 174 C. Individual variations of parenteral energy intake (PEI), oral energy intake (OEI) and
 175 resting energy expenditure (REE). The subjects were ranked according to their oral energy
 176 intake. OEI is marked in dark grey if patients are hyperphagic with either of the two
 177 definitions.
 178 One subject was not represented in Figure 2B and 2C because the REE was missing.

179 **Relationship between oral energy intake and characteristics of the population and**
180 **parenteral intake**

181 Significant univariate analyses are illustrated in Figure 3. Oral energy intake was
182 correlated with weight (Rho = 0.418 [0.095, 0.684], P = 0.009), fat-free mass (Rho = 0.474
183 [0.158, 0.699], P = 0.003) but not with fat mass (Rho = 0.021 [-0.313, 0.337, P = 0.90).
184 Despite the low numbers of subjects with a measure of hand strength (n = 14), oral energy
185 intake was significantly correlated with hand strength (Rho = 0.585 [0.053, 0.869]). Oral
186 energy intake was also positively correlated with resting energy expenditure (Rho = 0.365
187 [0.042, 0.628], P = 0.03) and negatively correlated with FT3 (Rho = -0.346 [-0.622, -0.031],
188 P= 0.04) and CRP (Rho = -0.360 [-0.625, -0.027] (Figure 3). Oral energy intake was not
189 correlated with any other parameters including age, mean remnant small bowel length, short
190 bowel syndrome duration, parameters related to parenteral nutrition and intestinal functions
191 (Table 2). The oral energy intake in subgroups of patients categorised by sex, short bowel
192 syndrome causes and bowel anatomy was not significantly different (P = 0.11, P=0.97,
193 P=0.88 respectively). Using multiple linear regression analysis with oral energy intake as the
194 dependent variable, and with age, sex, fat-free mass, resting energy expenditure, TSH, FT3
195 and CRP as independent variables, oral energy intake positively correlated with fat-free mass
196 (P < 0.05) and TSH (P < 0.01) independently of all other parameters (Table 3).



177

198 Figure 3. Significant associations between oral energy intake (OEI) and body weight, resting
 199 energy expenditure (REE), fat-free mass (FFM), hand strength, free triiodothyronine (FT3),
 200 and C-reactive protein (CRP).

201 Univariate associations were assessed using Spearman correlations. The confidence interval
 202 of the Spearman correlation coefficients was determined using a bootstrap with 1000
 203 replicates.

204 Hyperphagic patients with either of the two definitions are marked in dark grey and non-
205 hyperphagic patients are marked in light grey.

	Rho	IC95	p
age, years	-0.051	[-0.385, 0.288]	0.76
FM, kg	0.021	[-0.313, 0.337]	0.90
brachial circumference, cm	0.065	[-0.322, 0.401]	0.71
skinfold, mm	-0.169	[-0.511, 0.213]	0.33
TSH, mUI/L	0.322	[-0.002, 0.621]	0.06
FT4, pmol/L	-0.204	[-0.503, 0.146]	0.24
parenteral energy intake, kcal/d	0.154	[-0.175, 0.486]	0.36
number of parenteral infusions, per week	0.098	[-0.263, 0.421]	0.56
volume of parenteral infusion, L, per bag	0.129	[-0.217, 0.448]	0.44
albumin, g/L	0.144	[-0.213, 0.475]	0.39
duration of the short bowel syndrome, months	-0.022	[-0.367, 0.317]	0.90
remnant small bowel length, cm	-0.010	[-0.366, 0.344]	0.95
stool weight, g	0.050	[-0.340, 0.395]	0.77
one-hour blood D-xylose concentration, mmol/L	0.112	[-0.246, 0.434]	0.55
citrullinemia, mmol/L, n = 38	0.094	[-0.220, 0.408]	0.57

207 Table 2. Correlation between oral energy intake and anthropometric, metabolic, nutritional

208 and absorption parameters using Spearman's rank correlation

209 IC 95% was determined after bootstrap with 1000 replicates.

210 FM, fat mass, TSH, thyroid-stimulating hormone, FT4, free thyroxine

Predictor variables	β (Standardised coefficients)	Standard error	P-value
sex	-0.206	0.14	0.30
age	0.103	0.17	0.44
FFM	0.660	0.44	<0.01
FM	0.187	0.11	0.18
REE	0.307	0.40	0.12
TSH	0.398	0.05	<0.01
FT3	-0.044	0.29	0.74
CRP	-0.054	0.05	0.68

211 Table 3. Multivariate model with oral energy intake as the dependent variable and predictor

212 variables as the independent variables.

213 FFM, fat-free mass, FM, fat mass, REE, resting energy expenditure, TSH, thyroid-stimulating

214 hormone, FT3, free triiodothyronine

215 **Discussion**

216 ~~In short bowel syndrome patients, the development of hyperphagia is essential for~~
217 ~~intestinal adaptation and subsequently to reduce dependence on parenteral nutrition.~~ In short
218 bowel syndrome patients, luminal nutrients are essential for intestinal adaptation and
219 hyperphagia can reduce dependence on parenteral nutrition in some patients. Despite much
220 interest in this area, previous studies have failed to determine the factors that explain the
221 increase in food consumption in some short bowel syndrome patients.

222 In this observational study, we reported the correlations between oral energy intake
223 and the factors potentially involved in oral energy intake in these patients. The most striking
224 result is that oral energy intake strongly correlated with fat-free mass, both in linear and
225 multiple linear regression models. We hypothesise that fat-free mass drives oral energy intake
226 in short bowel syndrome patients. However, one may argue that in short bowel syndrome
227 patients, greater oral energy intake induces a better nutritional status leading to greater fat-free
228 mass. This hypothesis is unlikely since the correlation between fat-free mass and oral energy
229 intake is shared across many different populations, i.e. healthy normal weight, overweight or
230 obese adults and adolescents who are not expected to be malnourished^{12-14,18-20}. Furthermore,
231 all of the patients in our cohort were thoroughly monitored before their nutritional assessment
232 and the parenteral nutrition was periodically adjusted to maintain a satisfactory nutritional
233 status. A difference in nutritional status within the cohort was therefore not expected. We also
234 found a positive correlation between TSH and oral energy intake in the multivariate model.
235 One possible explanation for this result is that the subjects with the highest oral energy intake
236 tend to be overfed. Indeed, an increase in TSH was previously demonstrated in response to
237 experimental overfeeding²¹.

238 In order to understand the drivers of oral energy intake, one important and
239 controversial issue was to know if parenteral nutrition inhibits oral intake. In our study, oral

240 energy intake was not correlated with any parameter related to parenteral nutrition, namely
241 energy, number and volume of infusions in good agreement with other observational studies
242 ^{6,22}. It is also reinforced by experimental studies showing the lack of acute effect of parenteral
243 nutrition on hunger and satiety both in short bowel syndrome patients ²³ and healthy subjects
244 ²⁴ even if some other studies suggest an effect of parenteral nutrition on subsequent oral
245 energy intake ^{25,26}. Our results also showed that the duration of short bowel syndrome is not
246 associated with oral energy intake at least in the included patients, which are on parental
247 nutrition for at least one year.

248 The main limitation of our study is its retrospective design. This limitation is related to
249 the difficulty of collecting prospective data in short bowel syndrome patients owing to the low
250 population size. To limit the bias of recruitment and ensure consecutive recruitment during
251 the study period, we screened all patients with a nutritional assessment in our unit. We
252 analysed only fat-free mass data assessed by DEXA to ensure the homogeneity of the results.
253 Oral energy intake determination was based on a 3-day diary and one concern is therefore
254 possible misreporting of oral energy intake. Nevertheless, good agreement between objective
255 and subjective assessment of oral energy intake in the short bowel syndrome population has
256 been previously shown ⁷. Finally, we excluded patients with limited oral energy intake and/or
257 frequent nausea/vomiting. In our retrospective study, these gastrointestinal symptoms were
258 not precisely quantified. Thus, we were not able to include them in statistical analyses and to
259 determinate in which measure they affect oral energy intake.

260 This study has revealed that fat-free mass is an important determinant of oral energy
261 intake. One way to increase fat-free mass could be to increase physical activity. Such a
262 strategy was previously assessed with a resistance training program inducing an increase in
263 both fat-free mass and energy intake in nine short bowel patients ²⁷. This study is promising

264 and should be validated in a larger cohort. Future work should also assess, if increasing fat-
265 free mass limits dependence on parenteral nutrition

266 In conclusion, our work suggests that fat-free mass is an important determinant of oral
267 energy intake in short bowel syndrome patients **under parenteral nutrition and without**
268 **debilitating digestive symptoms.** This finding adds to a body of evidence highlighting the
269 correlation of fat-free mass and oral energy intake in other populations. Future studies are
270 therefore required to elucidate the links between oral energy intake, fat-free mass, physical
271 activity and dependence on parenteral nutrition in short bowel syndrome patients. It could
272 help to better follow up these patients in order to ensure both intestinal adaptation and
273 nutritional adequacy.

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