Brief report

Abnormal plasma peptide YY$_{3-36}$ levels in patients with liver cirrhosis

Luzia Valentini Ph.D. [a,*], Tatjana Schuetz Ph.D. [a], Ajmal Omar M.D. [a], Silja Gläser M.D. [a], Esmatollah Kasim M.D. [a], Peter Nowotny Ph.D. [b], Thomas Kroencke M.D., Ph.D. [c], Johann Ockenga M.D., Ph.D. [a,d]

[a] Department of Gastroenterology, Hepatology and Endocrinology, Charité-Universitätsmedizin Berlin, Berlin, Germany
[b] Clinic for Internal Medicine III, Medical University Vienna, Vienna, Austria
[c] Institute for Radiology, Charité-Universitätsmedizin Berlin, Berlin, Germany
[d] Department of Gastroenterology, Hepatology, Endocrinology, and Nutritional Medicin, Klinikum Bremen Mitte, Bremen, Germany

ARTICLE INFO

ABSTRACT

Objective: Peptide YY$_{3-36}$ (PYY$_{3-36}$) is a gut hormone with anorectic action that also affects energy expenditure. Anorexia and malnutrition are often observed in patients with decompensated liver cirrhosis (LC), whereas patients with LC after insertion of transjugular portosystemic stent shunts (TIPS) show normal eating behavior. The underlying mechanism of anorexia in decompensated LC and its resolution in patients with TIPS is still unclear. We thus investigated fasting and postprandial PYY$_{3-36}$ serum levels in patients with decompensated LC, patients with compensated LC with in situ TIPS, and healthy controls.
Methods: We analyzed fasting PYY$_{3-36}$ levels in six patients with decompensated LC (four men and two women, 55 ± 11 y of age), nine patients with TIPS (seven men and two women, 48 ± 11 y of age), and 10 controls (eight men and two women, 43 ± 9 y of age) postprandially after a standardized meal of 300 kcal and during 1-h continuous parenteral nutrition. Energy expenditure was determined by indirect calorimetry.
Results: At baseline PYY$_{3-36}$ was comparable in controls and patients with TIPS (91 ± 10 and 89 ± 25 ng/L) but was increased in patients with decompensated LC (165 ± 44 ng/L, $P < 0.01$). Although the cumulative postprandial PYY$_{3-36}$ increase was similar in controls (mean 2089 ng/240 min per liter) and patients with decompensated LC (mean 1735 ng/240 min per liter), no postprandial PYY$_{3-36}$ increase was observed in patients with TIPS (mean -579 ng/240 min per liter). Parenteral nutrition did not significantly affect PYY$_{3-36}$ levels in any group. Fasting PYY$_{3-36}$ values were negatively related to resting energy expenditure ($r = -0.443$, $P = 0.030$). PYY$_{3-36}$ was not associated to liver parameters (e.g., bilirubin, alanine aminotransferase).
Conclusion: Our results demonstrate an abnormal neuroendocrine regulation of PYY$_{3-36}$ in patients with decompensated LC and those with TIPS.

Introduction

Peptide YY (PYY) [1] is a 36–amino acid hormone related to neuropeptide Y (NPY) [2]. It is synthesized predominantly in the L-cells of the distal gastrointestinal tract. PYY is secreted into the circulation in proportion to meal size, similar to CCK and GLP-1 [3].

PYY$_{3-36}$, which was investigated in the present study, is the truncated 34–amino acid form produced from PYY by cleavage of the N-terminal tyrosine and proline residues. In healthy humans PYY$_{3-36}$ constitutes 40% and 54% of total PYY in the fasted and fed states, respectively [4]. The long form of PYY acts through Y-receptor subtypes Y1, Y2, Y4, and Y5. Because degradation of the N-terminus of PYY interferes with Y1, Y4, and Y5 but not with Y2, PYY$_{3-36}$ is a specific agonist for the Y2 receptor subtype [5]. PYY$_{3-36}$ acting through Y2 receptors apparently decreases appetite, as shown first in 2002 with the peripheral administration of PYY$_{3-36}$ leading to decreased food intake [6]. The anorectic effect has since been widely [3] but not uniformly [7] confirmed. PYY$_{3-36}$ also negatively relates to energy expenditure [8].

Anorexia is an important problem in patients with decompensated liver cirrhosis (LC) [9], contributing up to an 80%

prevalence of malnutrition in this group [10]. Malnutrition puts patients at higher risk of complications [10] and death. Patients with LC after insertion of transjugular intrahepatic portosystemic shunts (TIPS), however, show improved nutritional status and normal appetite behavior [11,12]. The underlying mechanism for the development and reversal of anorexia or malnutrition in LC not fully understood. Furthermore, aberrations in energy expenditure are often seen in patients with LC. Muller et al. [13] reported an 18% and 31% prevalence of hypermetabolism and hypometabolism, respectively, in a mixed group of patients with compensated and decompensated LC.

The technique of transjugular intrahepatic portosystemic shunts (TIPS) was introduced as a clinical procedure to decrease portal hypertension in advanced cirrhosis, mostly to treat associated complications such as recurrent variceal bleeding or refractory ascites [14]. It then was observed that the procedure is frequently associated with marked nutritional improvement [11,12] and increased voluntary food intake [12], leading sometimes to involuntary weight gains beyond the predisease weight. Identifying the mechanism would be important for improving the pathophysiologic understanding of the metabolic consequences of portal hypertension [15]. This, for example, could result in pharmacologic treatment options for malnourished cirrhotic patients for whom TIPS is contraindicated.

We hypothesized that PYY_{3-36} might contribute to the often observed anorexia in patients with decompensated liver disease. Thus we compared two groups of cirrhotic patients with regard to circulating PYY_{3-36} and energy metabolism at baseline, postprandially after a standardized meal, and during parenteral nutrition. One group consisted of patients with decompensated LC and portal hypertension and thus prone to develop malnutrition and the other consisted of patients with compensated LC and without portal hypertension due to the previous insertion of TIPS and thus not prone to develop malnutrition. A group of healthy subjects served as controls.

Materials and methods

Subjects

All subjects gave written informed consent before entering the study and the study protocol was approved by the local ethics committee. The decompensated LC group consisted of six patients (four men and two women, 55 ± 11 y of age) with decompensated LC of alcoholic etiology with signs of portal hypertension (ascites, esophageal varices >I°, encephalopathy). The TIPS group consisted of nine patients (seven men and two women, 48 ± 11 y of age) with stable and compensated LC of alcoholic etiology on average 33 ± 31 mo after TIPS insertion (range 5.7–83.4 mo). Portosystemic pressure gradients were measured during routine TIPS portography immediately before the study, as previously described [14]. Ten age-matched healthy subjects (eight men and two women, 43 ± 9 y of age) constituted the control group.

In all subjects blood was drawn from the right cubital vein at baseline and 15, 30, 45, 60, and 120 min after oral stimulus. After 240 min from baseline the infusion of parenteral nutrition started and blood was drawn in 15-min intervals during the infusion. Measurements of energy expenditure were started 15 min before oral or parenteral nutrition. Measurements continued in 1-min intervals until 60 min after nutritional intake or parenteral nutrition. After blood sampling at 0 min, subjects drank 200 mL of an oral supplement (300 kcal, 12.0 g of protein, 36.8 g of carbohydrates, and 11.6 g of fat; Biosorb, Fresenius-Kabi). Alternatively, a 60-min infusion of parenteral nutrition (Trimix perikal, Fresenius-Kabi) was started immediately after blood sampling at 240 min of the study protocol. The energy supplied was 150% of a previously measured resting energy expenditure (REE) divided by 24 h to determine the requirements for 1 h (90–150 kcal).

We analyzed PYY_{3-36} using a radioimmunoassay method (PYY-67HK, LINCO Research, St. Charles, MO, USA) and measured REE and respiratory quotient (RQ) by indirect calorimetry (Deltatrac, Datex Instruments, Helsinki, Finland). Body composition was determined by bioelectrical impedance analysis using a BIA 2000-M (Data Input, Darmstadt, Germany). Body cell mass comprises the oxygen-consuming and metabolically active part of the fat-free mass, mainly consisting of body organs and muscle mass.

Statistics

The data were analyzed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant when two groups were compared. When more than two groups were compared, the Bonferroni adjustment for multiple testing was used. Data are presented as mean $\pm$ standard deviation unless indicated otherwise. The Mann-Whitney U test was used to compare means, and the Spearman correlation coefficient was used to evaluate associations between two parameters. Areas under the curve (AUCs) were calculated using the trapezoidal rule.

Results

Baseline characteristics

Disease-associated classification and blood values were significantly deteriorated in patients with decompensated LC compared with patients with TIPS. Body weight and body mass index were comparable among groups. However, body cell mass was decreased in the two patients groups compared with controls, whereas fat mass was similar (Table 1).

The REE was similar in the control and TIPS groups but significantly lower in the decompensated LC group. When REE values were divided by body cell mass, controls had significantly lower REE/body cell mass values (megajoules per kilogram per day, $P < 0.05$) than patients with TIPS or patients with decompensated LC.

In patients with TIPS the portosystemic pressure gradient was below the intended range of 10 to 15 Torr (7.6 ± 3.7 Torr, range 1–13 Torr, reference <15 Torr).

Peptide YY_{3-36}

Basal venous PYY_{3-36} concentrations were elevated in patients with decompensated LC (165 ± 44.5 ng/L) compared with controls (91 ± 9.7 ng/L, $P = 0.002$) and patients with TIPS (89 ± 24.6 ng/L, $P = 0.007$). After the oral nutritional stimulus, PYY_{3-36} increased in controls after 30 min (106 ± 19 ng/L, $P < 0.05$) and remained elevated until 120 min. The PYY_{3-36} increase in patients with decompensated LC was attenuated and started only 60 min after the nutritional stimulus (Fig. 1A). It

Table 1
Patient characteristics

	TIPS	dLC	Controls
Child-Pugh Score (n)	7A/2B/0C	0A/4B/2C	
Ascites (n)	0	4	
Encephalopathy (n)	0	4	
Serum albumin (mg/dL)	3.9 ± 0.33	$3.0 \pm 0.71^*$	NA
Total bilirubin (mg/dL)	1.42 ± 0.76	$4.2 \pm 3.8^*$	$0.56 \pm 0.31^{\ddagger,\parallel}$
INR	1.2 ± 0.11	$1.4 \pm 0.11^*$	NA
ALT (U/L)	22.5 ± 8.0	28.3 ± 8.4	21.3 ± 6.4
AST (U/L)	29.0 ± 14.1	$60.8 \pm 26.5^*$	36.1 ± 10.3
Height (cm)	174 ± 10	175 ± 8	180 ± 8
Weight (kg)	77 ± 6.9	70 ± 16.5	85 ± 9.6
BMI (kg/m^2)	25.1 ± 2.4	24.1 ± 3.5	26.4 ± 3.6
Fat mass (kg)	19.4 ± 7.7	19.6 ± 5.3	19.5 ± 8.1
BCM (kg)	28.2 ± 4.6	21.3 ± 6.2	$35.4 \pm 4.9^{\dagger,\ddagger}$
REE (MJ/d)	7.4 ± 0.7	$6.0 \pm 1.2^*$	7.1 ± 1.1
REE/BCM (MJ · kg^{-1} · d^{-1})	0.27 ± 0.05	0.29 ± 0.08	$0.21 \pm 0.03^{\dagger,\S}$

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCM, body cell mass; BMI, body mass index; dLC, decompensated liver cirrhosis; INR, international normalized ratio; NA, not analyzed; REE, resting energy expenditure; TIPS, transjugular portosystemic stent shunts

* $P < 0.05$, TIPS versus dLC.
† $P < 0.05$.
‡ $P < 0.05$, TIPS versus controls.
§ $P < 0.05$.
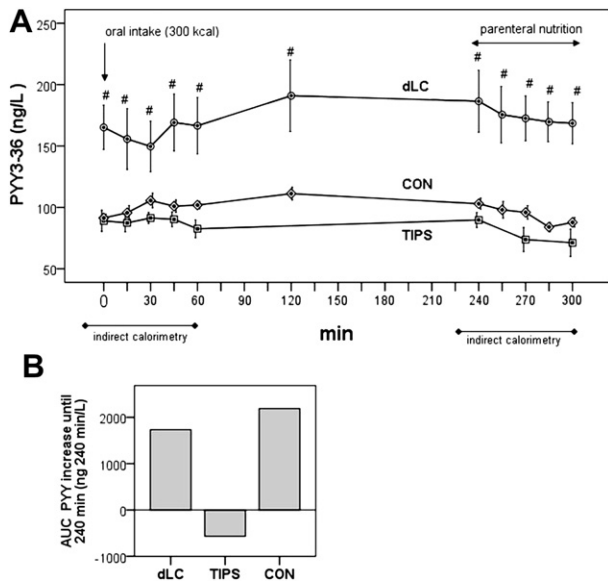$^\parallel$ $P < 0.01$, dLC versus controls.

Fig. 1. (A) PYY3–36 serum levels over the time course and (B) area under curve of nutrition-induced increase until 4 h after nutritional intake. #$P < 0.01$ compared with CON and patients with TIPS. CON, controls; dLC, decompensated liver cirrhosis; PYY3–36, peptide YY_{3-36}; TIPS, transjugular portosystemic stent shunts.
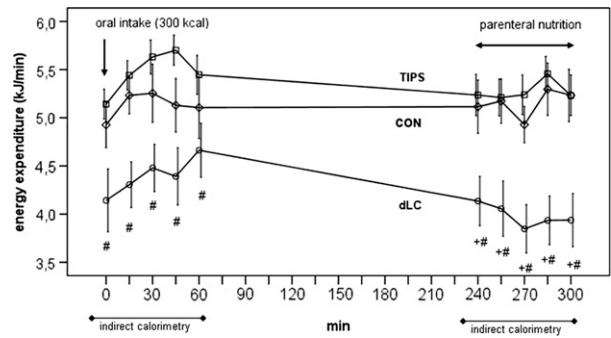
Fig. 2. Energy expenditure (kilojoules per minute) at baseline, after oral intake, and during parenteral nutrition. # $P < 0.05$, dLC versus TIPS; + $P < 0.05$, dLC versus CON. CON, controls; dLC, decompensated liver cirrhosis; TIPS, transjugular portosystemic stent shunts.

reached a peak value 120 min after the nutritional intake (191 ± 65 ng/L, not significant). In patients with TIPS, PYY_{3-36} remained similar to baseline throughout the investigation (Fig. 1A). Parenteral nutrition did not significantly affect PYY concentrations in any study group, although trends for continuously decreasing values could be observed in all groups (Fig. 1A). Postprandial changes in PYY over 240 min were similar in patients with decompensated LC (AUC 1735 ± 4223 ng/240 min per liter) and controls (AUC 2089 ± 2315 ng/240 min per liter); however, no increases were seen in patients with TIPS (AUC −579 ± 4922 ng/240 min per liter; Fig. 1B).

Energy expenditure

After the oral nutritional stimulus, energy expenditure significantly increased in all groups and reached its peak value sooner in controls (30 min) followed by patients with TIPS (45 min) and those with decompensated LC (60 min). Parenteral nutrition had no effects on energy expenditure (Fig. 2).

Correlations

Baseline REE negatively correlated to baseline PYY_{3-36} in the entire group ($r = -0.433$, $P = 0.030$), but the postprandial increase of energy expenditure was not related to the postprandial increase of PYY_{3-36} ($r = 0.091$, $P = 0.737$). Relations to RQ were found only in patients ($r = 0.767$, $P = 0.001$) but not in controls. We found no significant associations of PYY_{3-36} to liver parameters (alanine aminotransferase, $r = 0.539$, $P = 0.051$; bilirubin, $r = 0.380$, $P = 0.180$). Hepatic venous portosystemic pressure gradients in the TIPS group were not related to PYY_{3-36} ($r = -0.145$, $P = 0.73$).

Discussion

We found increased fasting serum levels of PYY_{3-36} in patients with decompensated LC, who are at high risk of

developing malnutrition. Baseline PYY_{3-36} was normal in patients with compensated LC and in situ TIPS, who have no or a very low risk of developing malnutrition [11,12]. After the oral nutritional stimulus, PYY_{3-36} increased in controls and patients with decompensated LC but not in patients with TIPS.

To our knowledge, we are the first to report on PYY_{3-36} levels in patients with LC. One group [9] recently demonstrated insignificantly increased total PYY values in a mixed group of patients with compensated and decompensated LC. Unfortunately, we cannot compare the results because of differences in samples and the use of total PYY instead of PYY_{3-36}

Decompensated LC and anorexia

There are many studies that have confirmed that PYY_{3-36} has anorectic effects in rodents, primates, and humans [3] and that PYY_{3-36} is the PYY variant with the greatest biological relevance for the satiety effect [3]. However, the anorectic potential of PYY_{3-36} is still a matter of debate [7]. PYY_{3-36} mediates its effects through the G-protein coupled receptors of the Y family. It specifically shows high affinity for the Y2 receptors in the hypothalamus [3]. After binding to the Y2 receptor, PYY_{3-36} inhibits food intake by activation of the auto-inhibiting presynaptic NPY receptor present on the NPY-expressing neurons of the arcuate nucleus, thus suppressing NPY synthesis and release [3]. The balance between the circulating long form of PYY (PYY_{1-36}) and PYY_{3-36} might also be important for the strength of possible anorectic effects.

One key question is whether the high fasting PYY_{3-36} level observed in the present patients with decompensated LC could theoretically contribute to the high prevalence of malnutrition seen in this group. This is difficult to answer from the present study, which aimed to gather only preliminary data on the question of whether PYY_{3-36} is changed at all in this group because no group has previously investigated this question. There are, however, other disease conditions associated with high PYY_{3-36} levels and lower food intake from which it cannot be completely excluded that high PYY_{3-36} is associated to malnutrition in decompensated LC. PYY_{3-36} is also high in patients with anorexia nervosa [16] and those with a critical illness, especially in patients with enteral feed intolerance [17], in whom an altered gastrointestinal motility can further aggravate the situation [18]. Naslund et al. [19] reported that fasted and meal-stimulated PYY levels are markedly increased in bariatric surgical patients after jejunoileal bypass. Meguid et al. [20]

investigated putative etiologic factors producing unwanted weight regain after an initial fast weight loss after Roux-en-Y gastric bypass surgery in an animal model. Overall, 80% of animals developed elevated $PYY_{3–36}$ levels after Roux-en-Y gastric bypass surgery, and interestingly, exactly those animals were protected from unwanted weight gain, whereas the remaining animals regained weight [20]. Graded intravenous infusions of synthetic human $PYY_{3–36}$ cause dose-dependent nausea, abdominal discomfort, fullness, and sweating during food intake in healthy humans [21], which might also add to the anorectic effect.

$PYY_{3–36}$ response in decompensated LC

The $PYY_{3–36}$ response to oral nutrition was delayed in the decompensated LC group, reaching the peak concentration 2 h after the nutritional stimulus compared with 30 min in controls. Such a delayed and more persistent increase in circulating PYY levels was also observed in another high-risk group for malnutrition, namely community-dwelling elderly persons [22]. In this study postprandial satiety lasted significantly longer compared with younger individuals, and hunger was suppressed throughout the postprandial period. Satiety was directly and hunger inversely correlated with delayed gastric-emptying time, a feature often observed in patients with LC [9]. Delayed gastric emptying has also been observed after PYY infusion [23].

$PYY_{3–36}$ response in patients with TIPS

In the patients with TIPS, baseline $PYY_{3–36}$ concentrations were normal but the physiologic postprandial increase could not be observed. We cannot explain the latter finding with our model.

Insertion of TIPS in cirrhotic patients normalizes appetite and increases voluntary nutritional intake by 30%, leading to a persistent gain in body weight [12], sometimes beyond predisease values. The missing postprandial response might support an increased appetite but drawing any conclusion would be premature.

$PYY_{3–36}$ during parenteral nutrition

During parenteral nutrition we observed trends for decreasing $PYY_{3–36}$ levels in all three study groups. This is interesting because patients receiving parenteral nutrition often report feeling hungry despite adequate provision of energy intravenously. Murray et al. [24] reported decreased total PYY concentrations during parenteral infusion of lipids but not during infusions of amino acids and glucose. Our parenteral nutrition contained lipids, which might explain this effect.

Peptide $YY_{1–36}$ and $PYY_{3–36}$ are also potent vasoconstrictors and affect gastrointestinal blood flow [5] and the elevated levels in decompensated LC with portal hypertension may be a compensatory reaction to the altered hemodynamic situation. Therefore, it was of special interest to investigate the relation between portal hypertension (hepatic venous portosystemic pressure gradient) and $PYY_{3–36}$. Due to ethical reasons we were able to measure only the portal pressure in the subgroup of patients with TIPS who were scheduled for a clinically indicated mesenteric catheter. In the patients with TIPS, portal pressure was normal but showed a variation within the normal range from 1 to 13 Torr, which might have already elucidated a compensatory PYY response. However, we found no correlation between $PYY_{3–36}$ levels and hepatic venous portosystemic pressure gradient in this patient group, which does not exclude an existing relation in our patients with decompensated LC who had portal hypertension as shown by significant amounts of ascites.

The patients with decompensated LC had lower energy expenditure than the TIPS group. Guo et al. [8] found a negative correlation between fasting PYY levels and 24-h REE, a correlation we also observed in the entire group of subjects ($r = -0.433$, $P = 0.030$). In previous studies, other circulating hormones and adipokines (e.g., leptin) have been found to be altered in patients with LC and these may contribute to the inadequate energy expenditure and malnutrition associated with a negative prognosis [25]. In our patients the correlation between $PYY_{3–36}$ and RQ was positive ($r = 0.767$, $P = 0.001$), which is not in line with previous results showing $PYY_{3–36}$–mediated increases in fat oxidation and thus a decrease in RQ [26].

Our study was limited by the small number of patients and a lack of measurements of food intake and satiety. We did not measure $PYY_{1–36}$, so we do not know if just the relation or the absolute amount of PYY was changed in decompensated LC. Thus we cannot extrapolate our results to effects known to be mediated by total PYY ($PYY_{1–36}$ and $PYY_{3–36}$), such as delayed gastric emptying [27] and hemodynamic changes.

In conclusion, we evaluated $PYY_{3–36}$ and found increased baseline values in patients with decompensated LC. This may be associated to some symptoms often seen in this group, such as anorexia and aberrations in energy expenditure. The neuroendocrine regulation of satiety and hunger is, however, complex and involves a number of anorectic hormones, e.g., leptin, GLP-1, and oxyntomodulin [2,28]. Further studies are warranted to elucidate the exact interplays and mechanisms underlying our observation.

References

[1] Tatemoto K, Mutt V. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature 1980;285:417–8.

[2] Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. Nature 2006;444:854–9.

[3] Karra E, Batterham RL. The role of gut hormones in the regulation of body weight and energy homeostasis. Mol Cell Endocrinol 2010;316:120–8.

[4] Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE, et al. Two molecular forms of peptide YY (PYY) are abundant in human blood: characterization of a radioimmunoassay recognizing PYY 1–36 and PYY 3–36. Regul Pept 1994;51:151–9.

[5] Ballantyne GH. Peptide YY(1–36) and peptide YY(3–36): part I. Distribution, release and actions. Obes Surg 2006;16:651–8.

[6] Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, et al. Gut hormone PYY(3–36) physiologically inhibits food intake. Nature 2002;418:650–4.

[7] Boggiano MM, Chandler PC, Oswald KD, Rodgers RJ, Blundell JE, Ishii Y, et al. PYY3–36 as an anti-obesity drug target. Obes Rev 2005;6:307–22.

[8] Guo Y, Ma L, Enriori PJ, Koska J, Franks PW, Brookshire T, et al. Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. Obesity (Silver Spring) 2006;14:1562–70.

[9] Kalaitzakis E, Sadik R, Holst JJ, Ohman L, Bjornsson E. Gut transit is associated with gastrointestinal symptoms and gut hormone profile in patients with cirrhosis. Clin Gastroenterol Hepatol 2009;7:346–52.

[10] Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. Clin Nutr 2006;25:285–94.

[11] Allard JP, Chau J, Sandokji K, Blendis LM, Wong F. Effects of ascites resolution after successful TIPS on nutrition in cirrhotic patients with refractory ascites. Am J Gastroenterol 2001;96:2442–7.

[12] Plauth M, Schutz T, Buckendahl DP, Kreymann G, Pirlich M, Grungreiff S, et al. Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism. J Hepatol 2004;40:228–33.

[13] Muller MJ, Lautz HU, Plogmann B, Burger M, Korber J, Schmidt FW. Energy expenditure and substrate oxidation in patients with cirrhosis: the impact of cause, clinical staging and nutritional state. Hepatology 1992;15:782–94.

[14] Ockenga J, Kroencke TJ, Schuetz T, Plauth M, Kasim E, Petersein J, et al. Covered transjugular intrahepatic portosystemic stents maintain lower portal pressure and require fewer reinterventions than uncovered stents. Scand J Gastroenterol 2004;39:994–9.

[15] Holland-Fischer P, Vilstrup H, Frystyk J, Nielsen DT, Flyvbjerg A, Gronbaek H. The IGF system after insertion of a transjugular intrahepatic porto-systemic shunt in patients with liver cirrhosis. Eur J Endocrinol 2009;160:957–63.

[16] Scheid JL, Williams NI, West SL, VanHeest JL, De Souza MJ. Elevated PYY is associated with energy deficiency and indices of subclinical disordered eating in exercising women with hypothalamic amenorrhea. Appetite 2009;52:184–92.

[17] Nguyen NQ, Fraser RJ, Chapman M, Bryant LK, Wishart J, Holloway RH, et al. Fasting and nutrient-stimulated plasma peptide-YY levels are elevated in critical illness and associated with feed intolerance: an observational, controlled study. Crit Care 2006;10:R175.

[18] Vizzini A, Aranda-Michel J. Nutritional support in head injury. Nutrition 2011;27:129–32.

[19] Naslund E, Gryback P, Hellstrom PM, Jacobsson H, Holst JJ, Theodorsson E, et al. Gastrointestinal hormones and gastric emptying 20 years after jeju-noileal bypass for massive obesity. Int J Obes Relat Metab Disord 1997;21:387–92.

[20] Meguid MM, Glade MJ, Middleton FA. Weight regain after Roux-en-Y: a significant 20% complication related to PYY. Nutrition 2008;24:832–42.

[21] Degen L, Oesch S, Casanova M, Graf S, Ketterer S, Drewe J, et al. Effect of peptide YY3–36 on food intake in humans. Gastroenterology 2005;129:1430–6.

[22] Di FV, Zamboni M, Dioli A, Zoico E, Mazzali G, Omizzolo F, et al. Delayed postprandial gastric emptying and impaired gallbladder contraction together with elevated cholecystokinin and peptide YY serum levels sustain satiety and inhibit hunger in healthy elderly persons. J Gerontol A Biol Sci Med Sci 2005;60:1581–5.

[23] Allen JM, Fitzpatrick ML, Yeats JC, Darcy K, Adrian TE, Bloom SR. Effects of peptide YY and neuropeptide Y on gastric emptying in man. Digestion 1984;30:255–62.

[24] Murray CD, Le Roux CW, Gouveia C, Bassett P, Ghatei MA, Bloom SR, et al. The effect of different macronutrient infusions on appetite, ghrelin and peptide YY in parenterally fed patients. Clin Nutr 2006;25: 626–33.

[25] Ockenga J, Bischoff SC, Tillmann HL, Rifai K, Widjaja A, Boker KH, et al. Elevated bound leptin correlates with energy expenditure in cirrhotics. Gastroenterology 2000;119:1656–62.

[26] Van den Hoek AM, Heijboer AC, Voshol PJ, Havekes LM, Romijn JA, Corssmit EP, et al. Chronic PYY3–36 treatment promotes fat oxidation and ameliorates insulin resistance in C57BL6 mice. Am J Physiol Endocrinol Metab 2007;292:E238–45.

[27] Chelikani PK, Haver AC, Reidelberger RD. Comparison of the inhibitory effects of PYY(3–36) and PYY(1–36) on gastric emptying in rats. Am J Physiol Regul Integr Comp Physiol 2004;287:R1064–70.

[28] Milanski M, Souza KL, Reis SR, Feres NH, de Souza LM, Arantes VC, et al. Soybean diet modulates acetyl-coenzyme A carboxylase expression in livers of rats recovering from early-life malnutrition. Nutrition 2009;25:774–81.