Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism

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Background/Aims: To search for changes in body composition and energy metabolism associated with the repeatedly observed weight gain of cirrhotic patients after portosystemic shunting.

Methods: Twenty-one patients were studied prospectively before and 6 and 12 months after transjugular intrahepatic portosystemic shunt (TIPS) to assess body cell mass by two independent methods (total body potassium counting: body cell mass determined by TBP, BCM_TBP, bioelectric impedance analysis: body cell mass determined by BIA, BCM_BIA), muscle mass (anthropometry), resting energy expenditure (REE_CALO) by indirect calorimetry, and nutritional intake by dietary recall analysis.

Results: Prior to TIPS patients were hypermetabolic in terms of measured vs. predicted REE (REE_CALO median 1423 (range 1164–1838) vs. REE_PRED 1279 (1067–1687) kcal; P < 0.05) and their body cell mass was lower (19.1 (10.9–33.4) vs. 31.7 (16.8–47.1) kg; P < 0.001). After TIPS body cell mass (BCM_BIA) increased to 23.5 (12.7–44.3) (P < 0.025) and 25.7 (14.2–39.7) kg (P = 0.05) at 6 and 12 months after TIPS and this was confirmed by total potassium counting (BCM_TBP before TIPS: 18.8 (10.6–26.7) vs. 22.4 (12.9–28.5) kg at 6 months; P < 0.01). Hypermetabolism persisted throughout the study period. Energy and protein intake increased significantly by 26 and 33%.

Conclusions: An increase of prognostically relevant variables body cell and muscle mass contributes to the weight gain after TIPS in malnourished patients with cirrhosis and hypermetabolism.

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1. Introduction

Protein energy malnutrition is a frequent consequence of hepatic cirrhosis which puts patients at a higher risk of complications [1], death [2–4], and a complicated course after liver transplantation including death [5,6]. After successful treatment of portal hypertension by surgical or interventional shunt procedures weight gain and improvement in the nutritional status have been reported repeatedly [7–10]. In cirrhosis, however, the precise assessment of nutritional state is complicated by water retention [11]. Recently, Selberg and coworkers [6] found that the reduction in preoperative body cell mass was a relevant
predictor of a less favourable outcome of liver transplantation.

In a prospective study we therefore assessed the evolution of body composition, energy expenditure, nutrient intake, as well as mental state over periods of 6 and 12 months after a transjugular intrahepatic portosystemic stent-shunt (TIPS) had been inserted [12]. As a reference body cell mass estimated by bioelectrical impedance analysis and resting energy expenditure were determined in healthy controls, too. Specifically, we were interested to see: (1) whether the weight gain following TIPS was associated with an increase in the metabolically relevant compartments muscle mass or body cell mass as assessed by two independent methods; and (2) whether patients with TIPS do tolerate a diet according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [1] without adverse effects on mental state.

2. Patients and methods

2.1. Patients

Twenty-one patients (13 men, eight women; age: 60.0 (38.7–71.6) years) with liver cirrhosis of alcoholic (n = 19) or non-alcoholic (one autoimmune hepatitis, one primary biliary cirrhosis) origin were studied prospectively before and 6.0 (5.0–7.4) months as well as 12.5 (11.8–14.9) months after TIPS insertion. The indications for TIPS insertion were recurrent esophageal variceal bleeding in 14 patients (nine without ascites and five with ascites) and refractory ascites in seven patients. The Child–Pugh Score [13] was calculated to classify severity of cirrhosis. Of the 21 patients included in the study five dropped out after month 6 due to transplantation (n = 1), death (n = 1), TIPS occlusion (n = 2) and loss to follow-up (n = 1).

During the initial and follow-up hospitalizations all patients received dietary counselling according to the ESPEN guidelines [1]. Nutritional and mental state were assessed on the occasion of the scheduled visits at months 6 and 12 as part of routine admissions (months 1, 3, 6 and 12 after TIPS insertion) to check for TIPS patency. All patients gave written informed consent for the metabolic study after the indication for the TIPS procedure had been established independently and the patients’ consent for the TIPS procedure had been obtained. The study protocol conformed to the 1975 Helsinki declaration and was approved by the local ethics committee.

A cohort of 310 healthy volunteers consented to have indirect calorimetry and body composition analysis done by means of bioelectrical impedance analysis (BIA). From this cohort gender specific regression equations were derived to calculate expected resting energy expenditure (REE) values for each patient. For the comparison of body cell mass determined by BIA (BCM), one healthy individual was matched to each patient according to gender and age within ± 2 years.

2.2. Methods

2.2.1. TIPS procedure

TIPS insertion was performed according to the method described by Rösle et al. [14] using Memotherm (Angiomed, Karlsruhe, Germany) devices. There were no intervention associated complications during the first 4 weeks. In all patients the TIPS angiography was done 6 months after TIPS insertion as scheduled, while in seven patients additional angiographic interventions were necessary prior to the scheduled one at 6 months. In the whole group reinterventions with dilatation (n = 5) or dilatation and insertion of additional stents (n = 10) were required to maintain TIPS patency until 6 months and eight reinterventions were required at 12 months.

2.2.2. Body composition

Body weight was measured to the nearest 0.1 kg on a hospital scale and body mass index (BMI) was calculated. Anthropometric measurements were made at the non-dominant arm using a skinfold caliper (Holterm, Crompton, UK) and a flexible tape measure to calculate mid-arm muscle area (MAMA), mid-arm fat area (MAFA) and muscle mass [15,16].

Bioelectrical impedance analysis was performed as described elsewhere [17] using a BIA 2000-M analyzer (Data Input, Frankfurt/Main, Germany) at 50 kHz to measure resistance (R), reactance (Xc) and phase angle (φ). The coefficients of variation for R and Xc were 1.1 and 2.7% in patients without ascites and 2.1 and 3.9% in patients with ascites. BCM was calculated as BCM = FFM × 0.29 × ln (α) [18] using the formulae for fat-free mass (FFM) as TBW/0.732 and total body water (TBW) = 0.69 × height2/75 + 0.048 [19].

Total body potassium content (TBP) is being considered a valid measure of BCM [20] and due to limited access was determined only prior to TIPS and after 6 months by measuring the amount of the naturally occurring radioisotope 40K using a shielded-room whole-body counter (Nuclear Enterprises Ltd., Edinburgh, UK) working with four NaI(T1) detectors (Berthold, Wildbad, Germany), as described elsewhere [21].

The coefficient of variation for repeated measurements was < 2%. BCM was calculated from TBP as BCM = TBP × 0.092 according to Cohn [22]. TBP measurement was not available for the cohort of 310 healthy individuals. Therefore, measured TBP (TBP) in cirrhotic patients was compared with predicted normal values (TBP) calculated from the equations given by McMillan [23] for males as TBP = (35.76 × height2) – (4.51 × age) – 2483 and for females as TBP = (35.76 × height2) – (4.51 × age) – 3211.

2.2.3. Resting energy expenditure

Respiratory gas exchange was measured by indirect calorimetry (Deltatrac II, Datex, Bremen, Germany). The intradividual coefficient of variation of repeated measurements was 3.4% for oxygen consumption and 5.1% for carbon dioxide production. Resting energy expenditure (REE) was calculated according to Consolazio [24]. To search for hypermetabolism in each patient the REE was compared to REE calculated as a function of measured BCM. REE was calculated from the equations given by our cohort of healthy controls as REE = 28.765 × BCM + 727.074 (males) and REE = 25.822 × BCM + 784.956 (females).

2.2.4. Nutritional intake

Energy and protein intake of the preceding 2 weeks were assessed prior to TIPS and after 6 months by a standardized diet history (EBIS, Forschungszeit für Ernährung, Stuttgart, Germany) [25].

2.2.5. Mental state

A battery of six validated psychometric tests (number connection tests A and B, digit symbol test, pointing test, line tracing test time and line tracing test mistakes) were performed prior to TIPS insertion as well as 6 and 12 months thereafter. In addition to the time needed to execute or the number of mistakes the results of each test were classified on a five mark scale: (+1) better than mean ± 1 SD, (0) between mean and mean ± 1 SD, (−1) between mean − 1 SD and mean − 2 SD, (−2) between mean − 2 SD and mean − 3 SD, and (−3) less than mean − 3 SD using age matched reference values [26]. The global performance of each patient at one test session was expressed as the average of marks scored in each of the six tests. For follow-up visits four different test arrangements were available to minimize learning effects.

2.2.6. Statistical analysis

Results are given as median and range. Statistical analysis was performed using the computer software program SPSS (Version 9.0). The Wilcoxon signed rank-sum test was used to compare the values before and after TIPS insertion as well as between patients before TIPS and controls. Predicted and measured values were analysed by Mann–Whitney U-test.
Linear regression analysis based on the control group was used to calculate predicted values for REE in the study population. Frequencies were evaluated by the \( \chi^2 \)-test. Correction for multiple comparisons (6 and 12 months after TIPS vs. before TIPS) was performed according to Bonferroni with a probability level of less than 0.025 accepted as statistically significant. Otherwise \( P < 0.05 \) was considered statistically significant.

3. Results

TIPS was well tolerated by all patients. Among the 14 patients in whom TIPS was performed for treatment of variceal hemorrhage, there was one episode of variceal bleeding within the first 6 months and one at month 9 due to TIPS occlusion which required a surgical shunt procedure as compared to 4 (0–10) episodes in the year prior to TIPS (\( P < 0.001 \)) and ascites was absent (\( n = 4 \)) or moderate (\( n = 1 \)) in the five patients who also had ascites prior to TIPS. Ascites improved significantly in all seven patients in whom TIPS was performed for treatment of refractory ascites so that ascites grade decreased from a median grade of 2 (moderate ascites) to a median grade of 1 (no ascites).

In fact, none of the patients required further paracenteses. TIPS insertion resulted in a persistent reduction of portocaval pressure gradient from 23.0 (12–29) mmHg prior to TIPS to 15.5 (8–21) mmHg at 6 months (\( P = 0.002 \)) and 11.5 [6–21] mmHg at 12 months (\( P = 0.001 \)) determined on control angiography prior to any TIPS reintervention. Endogenous creatinine clearance increased from 94.9 (34.4–184.3) ml/min prior to TIPS to 98.1 (33.4–205.7) ml/min at 6 months and 126.7 (51.1–286.6) ml/min at 12 months (n.s.). Prior to TIPS insertion 67% (14/21) of patients were on diuretics with a median daily dose of oral spironolactone (141.4 [85.7–200.0] mg, \( n = 11 \), and furosemide (62.9 [5.7–80.0] mg, \( n = 10 \)). At 6 and 12 months, 67 and 44% of patients were on diuretics, but at a significantly lower daily dose (spironolactone 6 months: 100.0 [42.9–142.9] mg, \( n = 13 \), \( P < 0.01 \); 12 months: 75.0 [50.0–100.0] mg, \( n = 6 \), \( P < 0.01 \); furosemide 6 months: 40.0 [2.9–80.0] mg, \( n = 11 \), \( P < 0.025 \); 12 months: 30.0 [20.0–80.0] mg, \( n = 6 \), \( P < 0.01 \)).

3.1. Body composition

Weight 69.5 (52.0–115.0) kg, height 170 (158–185) cm and body mass index 22.3 (18.0–35.1) kg/m\(^2\) were different between patients and controls. However, patients with cirrhosis showed a significant reduction in metabolically relevant lean tissue, both in terms of body cell mass (BCM\(_{\text{BIA}}\) 19.1 (10.9–33.4) vs. 31.7 (16.8–47.1) kg; \( P = 0.001 \), Fig. 1) calculated from impedance measurements and in terms of the directly measured variable phase angle \( \alpha \) (4.5 (2.9–6.2)\(^\circ\) vs. 6.5 (5.8–7.5)\(^\circ\); \( P < 0.001 \)) when compared to age and gender matched controls.

Six months after TIPS insertion the patients as a group had gained body weight (77.0 (49.0–138.5) vs. 69.5 (52.0–115.0) kg; \( P = 0.001 \); weight change 8.0 (–3.7–23.5); increase \( n = 16 \), stable \( n = 3 \), loss \( n = 2 \)) reflected by a significant increase in BMI by 11% from 22.3 (18.0–35.1) to 26.2 (18.3–40.0) kg/m\(^2\) (\( P < 0.001 \)). This increase was due to a gain in muscle mass by 18% in terms of MAMA (48.0 (27.6–95.9) vs. 42.6 (21.7–88.3) cm\(^2\); \( P = 0.001 \)) or muscle mass as determined by the Heymsfield method (23.3 (14.2–45.7) vs. 20.6 (11.4–42.7) kg; \( P = 0.002 \)), while fat mass remained unaltered (MAFA 21.3 (6.7–64.9) vs. 23.3 (6.1–51.3) cm\(^2\)). Accordingly, a gain in the metabolically active compartment body cell mass could be demonstrated by two independent methods: bioelectrical impedance analysis (BCM\(_{\text{BIA}}\); 23.5 (12.7–44.3) vs. 19.1 (10.9–33.4) kg; +15%; \( P < 0.025 \)) and total body potassium counting (BCM\(_{\text{TBP}}\) 22.2 (12.9–28.5) vs. 18.8 (10.6–26.7) kg; +15%; \( P < 0.01 \); Fig. 2). BCM\(_{\text{TBP}}\) even increased to the level of predicted normal values (87 ± 5%; ns) at 6 months, as opposed to 77 ± 5% prior to TIPS (\( P < 0.01 \)), again showing a significant improvement (\( P < 0.01 \)) after TIPS insertion (Fig. 2).

In the subgroup of 16 patients also studied 12 months after TIPS insertion, a persistent gain in weight of 0.9 (–0.6–3.1) kg, height 171 (152–185) cm, and body mass index 22.3 (18.0–35.1) vs. 25.6 (16.9–37.4) kg/m\(^2\) were not different between patients and controls. However, patients with cirrhosis showed a significant reduction in metabolically relevant lean tissue, both in terms of body cell mass (BCM\(_{\text{BIA}}\) 19.1 (10.9–33.4) vs. 31.7 (16.8–47.1) kg; \( P = 0.001 \), Fig. 1) calculated from impedance measurements and in terms of the directly measured variable phase angle \( \alpha \) (4.5 (2.9–6.2)\(^\circ\) vs. 6.5 (5.8–7.5)\(^\circ\); \( P < 0.001 \)) when compared to age and gender matched controls.
3.2. Resting energy expenditure

Before TIPS patients had a measured total body REE \(_\text{CALO}\) of 1449 (1164–1838) kcal/d which was lower than in matched controls (1644 (1117–2181) kcal/d; \(P < 0.05\)). However, when the patients’ energy expenditure was calculated using the regression equations, their predicted metabolic rate REE \(_\text{PRED}\) (1279 (1067–1687) kcal/d was significantly lower than the measured REE \(_\text{CALO}\) 1423 (1164–1837) kcal/d; \(P < 0.05\); Fig. 3) indicating hypermetabolism.

Within 6 months after TIPS measured REE \(_\text{CALO}\) increased by 9.5% to 1516 (1205–2232) kcal/d (\(P < 0.025\)). Measured REE \(_\text{CALO}\) remained higher than predicted values REE \(_\text{PRED}\) at 6 months (1550 (1203–2364) vs. 1402 (1112–2000) kcal/d; \(P = 0.001\)) and 12 months (1532 (1208–2232) vs. 1465 (1152–1868) kcal/d; \(P < 0.05\)) after TIPS, but the initial difference decreased during follow-up.

3.3. Nutritional intake

Total energy intake before TIPS was 1842 (1334–3687) kcal/d and increased by 6 months after TIPS by 26% to 2533 (1014–4062) kcal/d (\(P < 0.05\)). This was due to an increase in protein (1.2 (0.7–1.7) g kg\(^{-1}\) d\(^{-1}\) vs. 0.9 (0.5–1.2) g kg\(^{-1}\) d\(^{-1}\); \(P = 0.05\)) and carbohydrate intake (3.7 (2.0–5.4) g kg\(^{-1}\) d\(^{-1}\) vs. 2.9 (1.7–4.9) g kg\(^{-1}\) d\(^{-1}\); \(P = 0.05\)), while fat intake remained unchanged (1.4 (0.6–2.0) g kg\(^{-1}\) d\(^{-1}\) vs. 1.2 (0.6–2.0) g kg\(^{-1}\) d\(^{-1}\)).

3.4. Mental state

The majority of patients (63–95% before TIPS and 47–95% after TIPS) performed below the limit (age adjusted mean minus two standard deviations) in individual psychometric tests with the exception of line tracing errors, but not time. After TIPS, there were significant improvements in the number connection test \(B\) (\(P = 0.001\)) at month 6 and the pointing test at months 6 and 12 (\(P < 0.01\) and \(P < 0.025\)) (Table 1). In terms of global performance, however, there was no improvement after TIPS (n.s.).

4. Discussion

4.1. Body composition

In this prospective study we demonstrated that body cell mass in patients with liver cirrhosis is severely reduced and this condition does not inevitably run a downhill course but can be ameliorated as demonstrated in a patient cohort treated with TIPS. Using three independent methods (anthropometry, bioelectrical impedance analysis, total body potassium counting) to analyse body composition we could not only confirm the repeatedly claimed improvement in nutritional state after successful portosystemic shunting but also show that this improvement is associated with a gain in the metabolically relevant compartments muscle mass (anthropometry) and body cell mass (bioelectric impedance analysis and total body potassium counting). As would be expected, this gain in lean body mass was not correlated with weight change since improvement of ascites was observed after TIPS as well. BCM is the sub-compartment of lean body mass, in which 99% of the body’s metabolic processes take place [27], and significant losses of which are tightly linked to mortality [28–30]. The fact that the improvement in nutritional state was more readily observed in our patient population but only less so in
another study [31] may be related to the degree of malnutrition prior to TIPS insertion as reflected by the severe reduction in BCM in our patients. As shown recently [17], there is reasonable agreement between BIA and TBP counting regarding the determination of BCM even in cirrhotic patients with massive ascites. Body cell mass calculation from TBP or BIA data is based on assumptions which may not be fully adequate in cirrhosis and, therefore, it is important to see the major result of the study confirmed by independent methodology, such as an increase in muscle mass and the recent findings of increased total body nitrogen [31].

4.2. Energy metabolism

Searching for changes in energy metabolism as a potential cause for the improvement of nutritional status, we observed an increase in total resting energy expenditure $REE_{CALO}$ following TIPS and this occurred irrespective of the presence of ascites prior to TIPS [32]. To correct for the effects of changes in BCM [33], we related $REE_{CALO}$ to $REE_{PRED}$ predicted from the measured BCM of each patient using regression equations derived in the group of 310 healthy controls. We chose this approach to allow for the curvilinear relationship between $REE$ and BCM [34] instead of expressing this relationship as the ratio of $REE$/BCM which may erroneously overestimate $REE$ in individuals with low BCM. This analysis revealed hypermetabolism in patients prior to TIPS which persisted throughout the observation period of 12 months but showed a tendency to decrease. This observation may reflect the ongoing chronic liver disease and the TIPS associated augmentation of portosystemic shunting on the one hand and the improved nutrient balance on the other hand which requires long-term rather than short-term follow-up to detect an improvement of body composition.

4.3. Malnutrition and nutritional intake

Before TIPS, our patients were malnourished despite a numerically adequate nutrient intake. Many patients with cirrhosis cannot reach a stable anabolic state despite dietary counselling, unless supplemental artificial feeding provides additional energy and protein [35,36]. We were pleased to see that, after TIPS insertion patients managed to increase total energy (+26%) and protein intake (+33%) and reached a stable anabolic state without any nutritional intervention apart from dietary counselling. This observation shows that in a group of patients with predominantly repeated variceal hemorrhage receiving TIPS as salvage therapy the loss of BCM does not inevitably progress but can actually be stopped and reverted to increase. Whether this favourable change was causally related to TIPS cannot be answered from the present data. One may speculate, however, that the treatment of portal hypertension may have improved intestinal nutrient absorption, food intake due to relief from abdominal fullness, or protein anabolism after a prolonged period without catabolic insults from hemorrhage or paracenteses. It is conceivable that the absence of a worsening in mental state in our cohort of patients with psychometrically diagnosed subclinical encephalopathy is a result of pro-encephalopathic interventions like TIPS on the one hand and anti-encephalopathic interventions like adequate nutrition with a 33% percent increase in protein consumption on the other hand. This would not be surprising since controlled trials feeding high protein diets to patients with liver cirrhosis [35–38] have generated sound data to dismiss protein intolerance as a dangerous myth rather than a clinically relevant pathogenic principle of hepatic encephalopathy [39].

We conclude that even malnourished patients with liver cirrhosis and hypermetabolism are capable to improve their lean body mass and this increase of prognostically relevant variables body cell and muscle mass contributes to the weight gain after TIPS.

References


