Clinical Nutrition ESPEN 30 (2019) 131–137

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Identification of serological markers for pre- and postoperative fasting periods

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ARTICLE INFO

Article history:
Received 17 December 2018
Accepted 7 January 2019

Keywords:
Preoperative fasting
Fasting plasma markers
Metabolic markers

SUMMARY

Background & aims: Prolonged preoperative fasting periods lead to catabolic states and decelerate recovery after surgery. Valid plasma markers reflecting the patients' metabolic state may improve tailored nutrition support before surgery. Within this study, we sought to advance the knowledge on fasting time-sensitive plasma markers that allow the metabolic characterisation of surgical patients for an optimised preoperative metabolic preparation.

Methods: Patients scheduled for elective surgery of the upper (n = 23) or lower (n = 27) gastrointestinal tract participated in a prospective observational study. Patients' charateristics and nutritional status were recorded and blood samples were drawn on the day of admission. Further blood samples were collected before skin incision of the surgical procedure, on postoperative day 3 and on the day of discharge. Values of clinical chemistry, electrolytes, hemograms and plasma amino acids were determined and correlated with fasting times.

Results: Preoperative fasting times were positively correlated with plasma levels of valine, leucine, serine, α-amino butyric acid, free fatty acids, 3-hydroxy butyric acid and significantly negative correlated with chloride and glutamic acid. Postoperative fasting times were correlated with erythrocytes, leukocytes and plasma levels of albumin, CRP, HDL, asparagine and 3-methylhistidine. The multivariate regression analysis revealed glutamic acid and valine as significant independent predictors of preoperative fasting periods. The regression model showed best performance (sensitivity of 90.91% and specificity of 92.31%) to detect patients fasted for ≥20 h.

Conclusion: Valine and glutamic acid appear as independent metabolic markers for accurate prediction of prolonged fasting periods, independent of the overall nutritional status, age or BMI of patients.

1. Introduction

Practise Guidelines on perioperative fasting collectively refute prolonged fasting periods and instead recommend 2-h and 6-h fasting of clear fluids and solids, respectively, before and early oral feeding (start within 24 h after surgery) after surgery for the most beneficial effects on postoperative recovery [1,2].

Reduced fasting time and meeting patients' energy demands – at least to a certain extend - is vital for proper wound healing, immunity, early resumption of normal gut function after surgery, and proved its feasibility even after gastrectomy [3,4]. Optimal perioperative nutrition support can reduce postoperative

Abbreviations: AAS, amino acids; BCAA, branched-chain amino acid; CONUT, Controlling nutritional status; CRP, C-reactive protein; GI, gastrointestinal; HDL, High density lipoprotein; LDL, Low density lipoprotein; LoS, length of hospital stay; MCV, Mean corpuscular (erythrocyte) volume; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MNA, Mini Nutritional Assessment; MPV, Mean platelet volume; NRS, Nutritional Risk Screening; POD, postoperative day; RDWCV, Red blood cell distribution width.

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https://doi.org/10.1016/j.clnesp.2019.01.004

complications and the length of hospital stay (LoS) in patients undergoing elective surgery for GI tract malignancies, as reviewed before [5,6]. Prolonged fasting before surgery leads to depletion of liver glycogen and to increased mobilisation of muscle glycogen after surgery. Moreover, immune function is negatively affected by fasting, leading to an increased risk for infections [7].

In the short preoperative period (1–2 days) of admission to the surgical department, the time to treat and reverse malnutrition conditions is too short. Nevertheless, prolonged fasting times and catabolism can be avoided before surgery. Structured multidisciplinary programs to support patients' recovery after surgery, like "Enhanced Recovery After Surgery" (ERAS) include "diet" as one important integral pillar [8]. ERAS recommendations about the patients diet include 1) patients are allowed to drink clear liquid until 2 h and eat solid food up until 6 h prior to induction of anesthesia, 2) carbohydrate-rich drinks are provided the night and the morning of surgery (up to 2 h prior to the induction of anaesthesia), and 3) re-establish oral food intake early after surgery [8]. Several studies concluded that patients undergoing surgical resection for upper or lower GI tract malignancies profit from the ERAS protocol by a reduced postoperative systemic inflammatory response, accelerated postoperative gastrointestinal and overall functional recovery [9–11].

Optimal preoperative metabolic preparation of patients is challenging and often limited to a relatively short timeframe, as admission to the clinic before surgery does not exceed one or two days prior to surgery. General malnutrition conditions are unlikely to be normalised within this short time period but prolonged fasting times are preventable, although preoperative diagnostic procedures often require further fasting periods during the hospital stay. To avoid prolonged fasting periods and to counteract catabolic metabolism before surgery, targeted nutrition support and nutrient timing is required.

Cachectic cancer patients show distinct profiles of biochemical plasma markers compared to non-cachectic patients [12], but so far, no study has addressed time-sensitive metabolic makers in patients undergoing GI tract surgery for curative cancer treatment. Such markers could be helpful to identify patients at increased risk for catabolic states already at the time of admission to the clinic prior to surgery. By targeted intervention, the metabolic pre-stressed condition could be normalised before surgery. Possible serum markers that respond time-sensitive to fasting duration are amino acids, as one study already found in healthy human subjects (mean age 27.8 years), [13].

We herein describe, for the first time, fasting time-sensitive metabolic markers measured in plasma of patients undergoing surgery for GI tract malignancies. By applying these measurements at the time point of clinical admission, prolonged fasting periods can be detected and appropriately treated to ensure that patients are optimally prepared for surgery.

2. Methods

2.1. Study protocol

Patients undergoing major elective surgery for malignancies of the upper or lower GI tract at the Department of Surgery, Campus Charité Mitte | Campus Virchow-Klinikum at Charité – Universitätsmedizin Berlin were eligible for inclusion in this study. Exclusion criteria were age below 18 or above 85 years and the inability of patients to cooperate during the study. The study protocol was approved by the local ethic committee at Charité - Universitätsmedizin Berlin and conducted in accordance with the Declaration of Helsinki. The study is registered in clinicaltrials.gov (NCT01838109) and written informed consent was obtained from each patient before enrolment.

At the day of admission, clinical history and anthropometric measurements (body weight, forearm and calve circumferences) were obtained and blood samples taken to determine electrolytes, haematology, amino acids, clinical chemistry, 3-hydroxy butyric acid and free fatty acids (non-esterified fatty acids) (Supplemental Table 1 shows a detailed list of all measured blood parameters). Blood levels of metabolic markers (except haematology) were also assessed immediately before surgical skin incision, on post-operative day (POD) three and on the day of discharge. The nutritional status was assessed by the Mini Nutritional Assessment (MNA), Nutritional Risk Screening (NRS) and Controlling nutritional status (CONUT) scores. Furthermore, pre- and postoperative fasting periods (solid and liquid food) were recorded.

2.2. Malnutrition screening

The nutritional status of each patient was classified with the MNA, NRS and CONUT. The CONUT score was calculated from serum albumin, total cholesterol and lymphocyte count, as described by Tokunaga et al. [14] and assessed on the day of admission, POD3 and the day of discharge. The NRS [15] and MNA [16] scores were assessed solely on the day of admission [16].

2.3. Patients

In total 53 patients were enrolled between May 2017 and February 2018, of which three patients were dropouts due to no operation ($n = 2$) or appendectomy ($n = 1$). Patients who received neoadjuvant chemotherapy prior to surgery had a chemotherapy-free interval of at least four weeks. Mean age of the patients was 58.36 years and 72% were males; further detailed patients' characteristics are summarised in Table 1.

2.4. Blood sample analyses

All blood samples were collected in EDTA, heparin or fluoride containing VACUETTE® tubes (Greiner Bio-One International GmbH, Kremsmünster, Austria) and immediately sent to our in-house laboratory (Labour Berlin, Charité Vivantes Services GmbH, Berlin, Germany) for analyses of all blood and plasma values. Plasma amino acids were determined following ninhydrin derivatisation by the B30 cation exchange chromatography system (Biochrom, Berlin, Germany). Keton bodies and non-esterified fatty acids were measured using the 3-HB or NEFA kit (Wako Chemicals GmbH, Neuss, Germany) on a Konelab 30i analyser (Thermo Fisher Scientific, Dreieich, Germany).

2.5. Statistical analysis

Pearson correlation coefficient was used to assess the relation between fasting time and plasma markers. The T-test was used to compare values between two groups, as the examined variables followed a normal distribution. A multivariate linear regression analysis was carried out to determine independent predictors, amongst the analysed blood metabolites (assessed preoperatively, before induction of anesthesia), for preoperative fasting times. The analysis included all plasma markers that correlated with preoperative fasting times, but not correlated with BMI or being different between "normal" patients and patients at "risk for malnutrition". Stepwise multiple regression through backward elimination was performed for the best model fit, followed by receiver operating characteristic (ROC) analysis to describe and compare the performance of the model and to identify the best predictive value on preoperative fasting times. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version

Table 1
Baseline characteristics of study subjects including nutritional status and information about the performed surgical procedures.

		Total (n = 50)	Upper GI tract (n = 23)	Lower GI tract (n = 27)
Sex, n male (% male)		36 (72)	17 (73.9)	19 (70.4)
Age [years]		58.36 ± 13.46	60.43 ± 9.39	56.59 ± 16.12
Body weight [kg]		77.37 ± 13.88	77.88 ± 13.59	76.93 ± 14.36
BMI		25.47 ± 4.69	26.11 ± 4.81	24.94 ± 4.62
LoS [days] (median, range)		11 (5–33)	14 (5–27)	8 (5–33)
POD of discharge (median, range)		8 (3–32)	11 (3–20)	7 (4–32)
Time of surgery (begin till end of surgical procedure) [min]		376 ± 133	446 ± 114	316 ± 119
Preoperative fasting time [h]		23.17 ± 13.99	22.54 ± 18.24	23.70 ± 9.38
Postoperative fasting time [h]		50.15 ± 35.48	79.69 ± 31.63	27.42 ± 16.43
MNA (n = 48)	normal (n)	26	9	17
	risk (n)	19	12	7
	malnourished (n)	3	1	2
NRS (n = 49)	normal (n)	20	8	11
	risk (n)	29	14	16
CONUT (n = 24)	normal	12	8	4
	light	10	2	8

Results are given as mean ± SD, if not otherwise indicated. CONUT, Controlling nutritional status; LoS, length of hospital stay; MNA, Mini Nutritional Assessment; NRS, Nutritional Risk Screening; POD, postoperative day.

25.0, IBM, USA) or GraphPad Prism 5.0 (Graphpad Software Inc., San Diego, CA, USA). Results are expressed as the mean ± standard deviation (SD) if not otherwise indicated and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Correlation between nutritional status and serological markers

Within our patient cohort, the prevalence of "risk for malnutrition" was 61.2% or 38% when assessed with the NRS or MNA score, respectively. The MNA also graded 6.3% (three patients) to be manifest malnourished at the time of admission. The NRS assigns one extra point to each subject older than 69 years, increasing the likelihood of these patients to be graded as at "risk for malnutrition". Not surprisingly, the patients with a nutritional risk (NRS≥3) were significantly older (P < 0.01) compared to those graded "normal" nourished, but no BMI differences were detectable between the patient groups with "normal" or "risk for malnutrition" status when grouped by the NRS score. In contrast, when grouped by the MNA score, a significant reduced BMI in "risk for malnutrition" or manifest malnourished patients compared to patients with no risk (24.4 ± 4.5 vs. 26.9 ± 4.5, P = 0.020) were observed. Therefore, we used the nutritional risk classification of the MNA for further analyses. Regarding the site of surgery, 9 of 27 (33.3%) with lower GI malignancies and 13 of 22 (59.1%) with upper GI malignancies were at risk for malnutrition or manifest malnourished. Patients at risk for malnutrition (MNA<24) had significantly different plasma levels (p < 0.05) of aspargine, citrulline, ornithine, lysine and erythrocytes compared to normal nourished patients (Supplemental Table 2). The CONUT score was assessed in 24 patients at the day of admission, on POD3, and at clinical discharge. On the day of admission 61.9% of the patients were graded as normal nourished and 38.1% as "light undernourished". On POD3, all patients had aggravated CONUT scores, which improved to the day of clinical discharge (Fig. 1).

3.2. Correlation between age, BMI and sex with serological markers

Fasting plasma levels of albumin, total cholesterol, serine, asparagine, α-amino butyric acid, valine, leucine, and 1-methylhistidine were all significantly negative correlated with patients' age. The BMI correlated significantly positive with plasma levels of triglycerides, glucose, isoleucine, and phenylalanine and

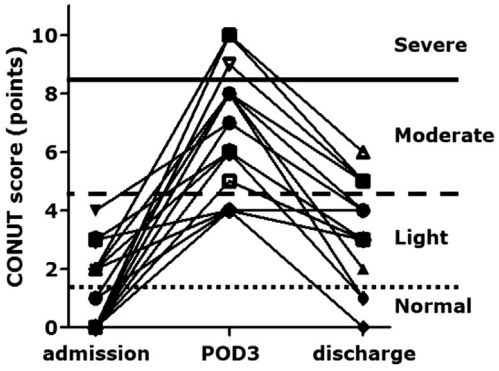

Fig. 1. CONUT score values of the single patients during hospital stay. Depicted are the CONUT values from the day of admission, POD3 and the day of discharge. Horizontal lines mark the cutoff values for malnutrition status "normal", "light", "moderate" and "severe".

negatively correlated with HDL. Gender-specific differences were found for fasting plasma levels of potassium, calcium, HDL, glycine, and isoleucine (Supplemental Table 3).

3.3. Correlation between pre and postoperative fasting periods with serological markers

Preoperative fasting time correlated significantly positive with valine, leucine, serine, α-amino butyric acid, free fatty acids, 3-hydroxy butyric acid and significantly negative with chloride, glutamic acid, and the alanine/lysine ratio (Table 2). Postoperative fasting times were correlated with erythrocytes, leukocytes and plasma levels of albumin, CRP, HDL cholesterol, asparagine, and 3-methylhistidine (Supplemental Table 4). Fasting times of 16 h or longer, already at clinical admission on the day before surgery, were negatively correlated with postoperative (POD3) values of total cholesterol (r = −0.550, p = 0.042) and asparagine (r = −0.550, p = 0.041), while preoperative fasting times did not correlate *per se* with any blood values on POD3.

3.4. Prediction of preoperative fasting time by serological markers

A multivariate stepwise regression analysis was conducted to identify plasma markers, which are independently associated with

Table 2
Correlations between preoperative fasting time and preoperative plasma metabolite levels.

Parameter	Pearson's r	P-value	Parameter	Pearson's r	P-value
Sodium	−0.072	0.695	Alanine	0.076	0.722
Potassium	−0.221	0.216	Citrulline	−0.101	0.638
Chloride	−0.401	0.023	α-Amino butyric acid	0.548	0.006
Calcium	0.115	0.536	Valine	0.463	0.023
C-reactive protein	−0.032	0.856	Cystine	−0.002	0.992
Albumin	−0.043	0.809	Cystathionine	0.318	0.130
Bilirubin total	0.063	0.733	Methionine	0.116	0.590
Bilirubin direct	−0.012	0.952	Isoleucine	0.255	0.228
Creatinine	0.314	0.320	alloIsoleucine	0.061	0.779
Triglycerides	−0.042	0.817	Leucine	0.459	0.024
Cholesterol	0.033	0.854	Phenylalanine	0.304	0.149
HDL	0.020	0.914	Tyrosine	0.173	0.419
LDL	0.045	0.803	Tryptophane	0.307	0.145
Glucose	−0.046	0.864	Histidine	0.313	0.136
Lactate	0.072	0.798	1-Methylhistidine	0.074	0.733
Taurine	−0.041	0.849	3-Methylhistidine	0.034	0.873
Aspartic acid	−0.172	0.422	Ornithine	0.143	0.505
Glutamic acid	−0.450	0.031	Lysine	0.343	0.100
α-Aminodipic acid	0.102	0.634	Arginine	−0.081	0.707
Hydroxyproline	−0.269	0.203	Alanine/Lysine ratio	−0.306	0.146
Threonine	0.201	0.347	free fatty acids	0.389	0.060
Serine	0.473	0.020	3-Hydroxy butyric acid	0.36	0.084
Asparagine	0.181	0.409	Sum of BCAAs	0.443	0.030
Glutamine	0.124	0.565	Sum of essential AAS	0.412	0.045
Proline	0.259	0.223	Sum plasma AAS	0.358	0.102
Glycine	0.273	0.198			

fasting time. The included plasma markers were chloride, glutamic acid, valine, serine, the alanin/lysine ratio, 3-hydroxy butyric acid, and free fatty acids. The resulting regression model contains two predictors, glutamic acid and valine (Fig. 2).

Area under the ROC curve analysis was performed to test the predictive ability of the regression model. AUC values increased with increasing fasting durations and best model predictions were observed for fasting times ≥20 h (Table 3).

4. Discussion

To identify patients in catabolic states due to prolonged fasting before clinical admission, we herein present the first data on reliable plasma markers of fasting times in patients scheduled for elective surgery of the upper or lower GI tract. Following multiple regression analysis, valine and glutamic acid remained as most significant predictors for preoperative fasting duration (see Fig. 3).

Our results of increasing valine levels in correlation with increasing fasting time are in accordance with several previous studies [13,17]. Valine oxidation is increased in times of inadequate amino acid supply [18]. The increased plasma concentration might be explained by an increase of muscle protein breakdown to provide substrates for hepatic gluconeogenesis [19,20]. Alanine, one of the principal nitrogenous glucose precursor utilised in gluconeogenesis, has also been described to be released from muscle during starvation [21]. However, alanine plasma levels remained unchanged during fasting in our study. This might be due to too short starvation periods (<48 h) and the parallel increased uptake and utilisation of alanine for gluconeogenesis in the liver [22]. Plasma levels of glutamic acid decreased with increasing fasting duration. One possible mechanism causing this decline is the hepatic glutamic acid catabolism, which is enhanced during fasting by an increase in glutamate dehydrogenase activity [23]. Furthermore, glutamic acid as an amino group donor supports the synthesis of tricarboxylic acid cycle intermediates, what requires an increased uptake in the cells or glutamic acid production from glutamine [24]. Glutamine levels were not altered due to fasting in our study cohort.

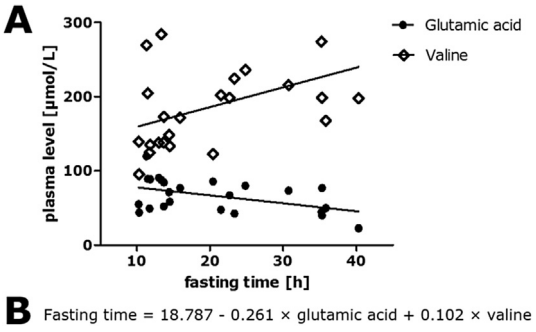

Fig. 2. Correlations between preoperative fasting time and plasma levels of glutamic acid and valine. (A) Glutamic acid (filled circles) correlated negatively ($r = -0.45$, $p = 0.031$) and valine positively ($r = 0.463$, $p = 0.023$) with fasting time. (B) The final regression model for predictive calculation of fasting times, including plasma levels of glutamic acid and valine (concentration in µmol/L).

Plasma amino acid levels depend on multiple factors besides fasting time. It has been reported before by Sarwar et al., that plasma levels of lysine, leucine, methionine, valine, and total essential amino acids were significantly lower in older than in younger subjects [25]. In a recent study of 920 subjects, Ottosson et al. found that plasma levels of glutamate and all three BCAAs were correlated with the individuals' BMI [26]. These findings are only partially comparable to our study results with fasting plasma levels of triglycerides, glucose, isoleucine, phenylalanine, and HDL being correlated with patients' BMI. Metabolomic profiles are known to vary additionally depending on the gender [27]. In our study cohort, gender-specific differences of fasting plasma levels of potassium, calcium, HDL, glycine, and isoleucine were found. Lower fasting HDL cholesterol levels in men were also reported by Gruchot et al., however the observed higher triglyceride levels in men compared to woman after >8 h fasting were not detectable in our study cohort [28]. Gender-specific differences had also been described for total serum bilirubin levels, which were reported to increased with fasting times only in men but not in woman [29,30].

Table 3
Performance of the regression model to predict fasting durations.

Fasting duration	AUC	Sensitivity	Specificity	95% CI	P value	Positive predictive value	Negative predictive value
≥12 h	0.750	88.89%	16.67%	0.560–0.941	0.072	76.19%	33.33%
≥16 h	0.750	88.89%	16.67%	0.560–0.941	0.072	55.56%	83.33%
≥20 h	0.881	90.91%	92.31%	0.706–1.057	0.002	90.91%	92.31%
≥24 h	0.908	100%	82.35%	0.789–1.026	0.002	57.14%	82.35%

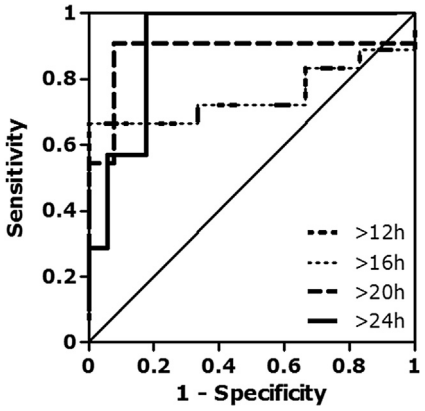

Fig. 3. AUROC curves for the final model predictions of several fasting time durations (≥12 h, ≥16 h, ≥20 h, ≥24 h). The AUROC analyses for discrimination between patients fasted for different periods showed for >12 h (AUC: 0.750, sensitivity 88.89%, specificity 16.67%, P = 0.072, 95% CI 0.560–0.941), >16 h (AUC: 0.750, sensitivity 88.89%, specificity 16.67%, P = 0.072, 95% CI 0.560–0.941), >20 h (AUC: 0.881, sensitivity 90.91%, specificity 92.31%, P = 0.002, 95% CI 0.706–1.057) and >24 h (AUC: 0.908, sensitivity 100%, specificity 82.35%, P = 0.002, 95% CI 0.789–1.026).

In our study cohort, total bilirubin was not correlated with fasting time, but a correlation was found between conjugated "direct" bilirubin and fasting times of more than 12 h. Beside bilirubin, plasma levels of total cholesterol, HDL and LDL were also – in line with previous studies - negatively correlated with fasting times longer than 8 h [28]. Similar results were observed in our study, when total cholesterol, HDL or LDL levels at admission were compared to the immediately preoperative levels of the single patients in a paired analysis (Supplemental Fig. 1).

No differences were found for triglyceride levels between admission and immediately preoperatively. Also, no statistically significant fasting time-dependency between free fatty acid levels and fasting time was observed in our study – although a trend could be observed (p = 0.06). Fasting metabolism is characterised by an increase in fat oxidation and increased free fatty acid (non-esterified fatty acids) plasma levels [31]. Free fatty acids react sensitive to nutrient intake, like a preoperative oral glucose load, which was shown in patients undergoing lower GI tract surgery. Consuming 400 ml of a carbohydrate-rich drink containing 12.5 g maltodextrin/100 mL on the evening before surgery and another 400 mL in the morning (till 3 h before induction of anesthesia) before surgery led to lower free fatty acids levels [32].

The duration of the postoperative fasting period was associated with a range of altered plasma markers. Amongst those, CRP and 3-methylhistidine levels correlated significantly with the length of fasting time. Increased postoperative CRP levels have been described before and consuming a 300 kcal supplement, in addition to a soft diet, does not change CRP levels in the postoperative period [33]. In the study by Imamura et al., it was not demanded to ingest drinks or soft food at a certain time point after surgery. This indicates that not the amount of ingested energy but the actual timing might influence postoperative CRP levels. As shown by Lidder et al., early postoperative nutrition led to a trend towards lower CRP levels on POD3 in patients undergoing CRC surgery [34]. Whether CRP can be used as valid biomarker for postoperative wound healing and recovery remains to be investigated by future studies. An already well known factor influencing postoperative recovery is malnutrition of the patients. It is associated with an·aggravated clinical outcome of surgical patients, because of impaired immune function and wound healing, that leads to increased complication rates, prolonged length of hospital stay and increased costs [35,36]. Furthermore, the risk for anastomotic leakage in colorectal surgery is increased in malnourished patients [37]. Adequate nutrition is vital to establish an optimal anabolic environment and so to reduce the incidence of general surgical complications [38,39].

In patients undergoing abdominal surgery, protein demand is postoperatively increased and protein hypercatabolism is an unavoidable consequence of tissue injury, while energy expenditure and utilisation of nutrients remains unchanged [40–42]. Our results further showed the prototypic marker of skeletal muscle degradation, 3-methylhistidine to increase with increasing postoperative fasting time. This correlation has been shown for the first time, but muscle function (measured by grip strength) is already well known to correlate with nutritional status and can be improved postoperatively by nutrition support, even in malnourished patients [43]. However, as some studies did not find differences in hand grip strength between improved nutritional treatment as part of the ERAS protocol [44], or individual nutritional counselling [45], or prehabilitation with whey protein supplementation [46], 3-methylhistidine might be a more sensitive marker of muscle protein catabolism than grip strength measurements.

It still remains elusive, how the optimal pre- and postoperative diet might look like and what the most adequate nutrient supply might be. Patients with wounds seem to generally require more protein (appr. 1.85 g/kg body weight/day) [47]. Whether this amount is also optimal for patients undergoing GI tract surgery is to date unknown. Therefore, future studies should aim to exactly define the optimal perioperative nutritional therapies for surgical patients. An overall malnourished condition before surgery is not favourable for surgical patients. Especially for patients with gastrointestinal cancer, a significant cumulated energy deficit is an independent risk factor for postoperative morbidity and mortality [48].

Our study offers the first description of fasting time-sensitive plasma markers that can be used for preoperative screening of surgical patients and identify patients requiring nutrition support to effectively prevent prolonged preoperative fasting periods and associated complications. Plasma values of the identified markers allow an objective evaluation of the actual metabolic state of a patient, even in cases of nutrient intake overreporting. Technically, measuring plasma amaino acid profiles would be possible within 2 h after blood sampling, which allows timely nutrition support for prolong fasted patients before surgery. In conclusion, fasting time-sensitive metabolic markers will be helpful diagnostic tools for optimal preoperative metabolic priming of surgical patients.

Statement of authorship

TW, FA, MB developed the study design and strategy of the research project. FA was the lead study physician and contributed together with TW, JQ, VM, AM, JW, and BK to the data acquisition and analysis. TW, MK, MS, MB were involved in interpretation of the data. TW drafted the manuskript and JP, FA, JQ, and JW critically revised it.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2019.01.004.

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