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ORIGINAL ARTICLE

The Value of Metabolites and Vitamins for the Assessment of Nutritional Status in Hospitalized Patients

A Systematic Review

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This systematic review aims to summarize the currently available literature regarding the association of plasma metabolites and vitamins with the nutritional status in adult hospitalized patients. A systematic literature search was performed in PubMed and EMBASE, and all studies comparing metabolite or vitamin levels in malnourished versus well-nourished hospitalized patients were included. Twenty-three studies were eligible for inclusion, representing 3803 hospitalized patients. Several metabolites involved in the metabolism of methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan, as well as some vitamins, seem to be associated with malnutrition in hospitalized patients. These compounds can potentially be used to assess nutritional status.

Key words: biomarkers, malnutrition, metabolites, nutritional status, vitamins

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MALNUTRITION is the result of an imbalance between intake, uptake, and the required amount of macro- and micronutrients. This imbalance can lead to an altered body composition and body cell mass, which diminishes physical and mental function and impairs recovery from disease.¹ Together with stress-related catabolism caused by inflammation, malnutrition increases the risk for impaired wound healing, infections, and

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organ dysfunction.² These complications can cause an increase in the inflammatory response and therefore result in further exacerbation of malnutrition.^{2,3} To break this cycle, it is essential to adequately diagnose malnutrition and prevent adverse clinical outcomes.

Research has shown that up to 50% of hospitalized patients are malnourished, depending on the definition used and population included.² Several tools to assess nutritional status have been developed, including nutritional screening tools, such as the Subjective Global Assessment (SGA), Patient-Generated Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment (MNA), Nutritional Risk Screening (NRS-2002), and Malnutrition Universal Screening Tool (MUST), as well as visceral proteins and anthropometric measures (height, weight, and body composition). Some of these screening tools were developed for specific populations; for example, the MNA is designed to diagnose malnutrition in elderly patients, and the MUST and the PG-SGA are validated for oncology patients.^{4,5} However, there is still no criterion standard for measuring nutritional status in all hospitalized patients.⁶ The currently available nutritional screening tools include information on the history of a patient's weight and diet, which is not always available in clinical settings. The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition described a standardized approach to identify adult malnutrition in routine clinical practice.⁷ The criteria that a registered dietitian can obtain and document to support a diagnosis of malnutrition include energy intake, weight loss, and physical examination. Moreover, fluid resuscitation and edema influence weight, body circumferences, and other anthropometric measurements.⁸ In addition, visceral proteins (eg, albumin, and prealbumin) lack sensitivity as they are influenced by inflammation. During inflammatory states, the production of acute-phase proteins in the liver is increased and therefore the synthesis of visceral proteins is decreased regardless of nutritional status.⁹

A relatively new but promising method is the use of plasma metabolites and vitamins to assess nutritional status. Metabolites are intermediate- or end products of biochemical pathways, such as glycolysis and citric acid cycle. Examples include sugars, amino acids, and nucleotides. Metabolites are considered to be biomarkers of several phenotypic states, and research suggests that metabolites can even act as controllers of the phenotype.¹⁰ The metabolome is the global collection of all low-molecular-weight metabolites that are produced by cells during metabolism.¹¹ The human metabolome comprises more than 100 000 metabolites and new metabolites continue to be added to the human metabolome database.¹² Because the metabolite composition is influenced by many processes in the body, changes in plasma metabolite levels may occur much earlier than any clinical symptoms. Metabolites have been considered as biomarkers for many diseases, such as pancreatic cancer, non-insulin-dependent diabetes mellitus, and memory impairment.¹³⁻¹⁵ In addition, vitamins are related to a healthy diet and several vitamins are known to function as antioxidants. Since malnutrition is related to oxidative stress, the question arises whether vitamins might also be useful in identifying malnutrition.¹⁶ The purpose of this study is to systematically review the body of published scientific evidence and summarize the value of plasma metabolites and vitamins as potential biomarkers for monitoring nutritional status in hospitalized patients.

MATERIALS AND METHODS

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.¹⁷ A literature search was performed in PubMed and EMBASE in collaboration with an experienced medical librarian in December 2021. The search strategy included synonyms and related terms

for hospitalized patients, biomarkers, metabolites, vitamins, antioxidants, and nutritional status (see Supplemental Digital Content Appendix 1, available at: <http://links.lww.com/TIN/A54>).

Eligibility criteria and article selection

Article selection was performed independently by 2 researchers (E.A.H.V. and J.J.J.O.). The titles and abstracts of identified studies were screened, using the following selection criteria: (1) the study included adult hospitalized patients, (2) 1 or more plasma metabolites or vitamins were researched, (3) the nutritional status was assessed using a nutritional assessment/screening tool (eg, SGA, MUST, or MNA), the body mass index (BMI), or a combination of laboratory results and anthropometric measurements, and (4) the relationship between plasma metabolite/vitamin levels and nutritional status was evaluated. Articles that researched the nutritional status of patients after bariatric surgery were excluded. Publications between 1952 and 2021 in English, German, or Dutch were selected. The full text of potentially eligible articles was read and included when all the inclusion criteria were met. The reference lists of the included articles were screened for additional literature.

Data extraction and risk of bias assessment

Data extraction and risk of bias assessment were performed independently by the same 2 researchers (E.A.H.V. and J.J.J.O.). Data on study characteristics (study design, country, participants [number, mean age, sex], applied nutritional assessment tool, and researched biomarker(s)) and study results (percentage of malnourished patients, metabolite levels, and their association) were extracted from the articles.

The risk of bias in the selected studies was assessed according to the Methodological Index for Non-Randomized Studies (MINORS) criteria, which include 12 items for comparative studies and 8 items for noncomparative studies that are scored as 0 (not reported), 1

(reported but inadequate), or 2 (adequately reported). The maximum score is 16 for non-comparative studies and 24 for comparative studies.¹⁸

RESULTS

Selection of articles

The literature search identified 936 studies in PubMed and 126 studies in EMBASE; 1006 records were screened after duplicate removal. A total of 851 articles were excluded on the basis of title and abstract. Three articles were added after hand searching the reference lists. After reading the full-text articles of the remaining 158 studies, 135 studies were excluded for various reasons (Figure 1). Relevant data from the 23 included studies are summarized in Supplemental Digital Content Table 1, available at: <http://links.lww.com/TIN/A56>.

Risk of bias

Risk of bias of the included studies was assessed, using the MINORS-criteria, as low (total score of ≥ 20 out of 24) for the studies by Chou et al,¹⁹ Katić et al,²⁰ Tas Kilic et al,²¹ Ramel et al,²² and Vosoughi et al,²³ and moderate (total scores of 15–19 out of 24) for the other studies (Table 2). In all studies, the assessment of study end points was potentially biased, as no study evaluated the study end points blindly. In addition, only Chou et al¹⁹ and Vosoughi et al²³ performed a sample size calculation or noted why the sample size calculation could not be performed. In 2 studies,^{24,25} data were collected retrospectively and therefore did not score the maximum of 2 points for prospective collection of data.

Patient population

The selected studies included 3803 hospitalized patients, both intensive care unit (ICU) patients ($n = 365$) and non-ICU patients ($n = 3438$) (see Supplemental Digital Content Table 1, available at: <http://links.lww.com/TIN/A56>). Eight studies

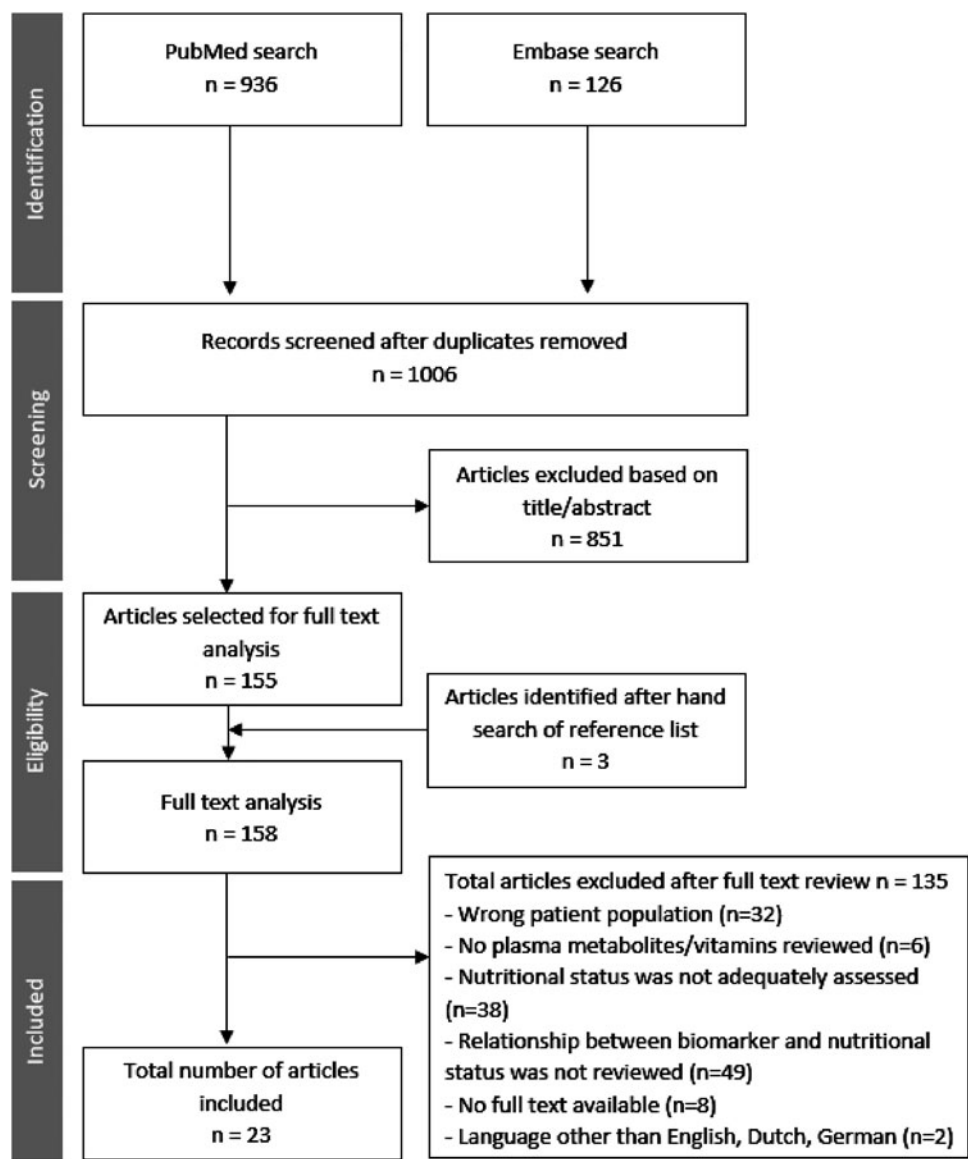


Figure 1. Studies resulting from literature search with reason for exclusion.

focused on elderly patients older than 60 or 65 years,^{22,25-31} and the other studies included all adult patients. Regarding the reason for hospital admission, 3 studies focused on patients with malignancies,^{24,32,33} 1 on patients with chronic graft versus host disease after allogeneic hematopoietic stem cell transplantation,²⁰ 2 studies included patients with systemic inflammatory

response syndrome or sepsis,^{19,34} and 2 studies included patients with fractures.^{30,35} Other studied patient groups included patients with pulmonary disease considered for lung transplantation,³⁶ chronic kidney disease,^{37,38} chronic heart failure,²⁷ and systemic sclerosis.²¹ The other articles included all patients admitted to the hospital ward or ICU.^{22,23,25,26,28,29,31,39-41}

Table 2. Risk of Bias in the Included Cohort Studies According to the Methodological Index for Non-Randomized Studies (MINORS) Criteria^a

	Avelino et al ³⁹	Christopher et al ³²	Chou et al ¹⁹	Cunha et al ²⁶	Djurasinović et al ³³	Førli et al ³⁶
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	1	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. End points appropriate to the aim of study	2	2	2	2	2	2
5. Unbiased assessment of study end points	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of study	2	2	2	2	2	2
7. <5% lost to follow up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	2	0	0	0
9. An adequate control group	2	2	2	1	2	1
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	2	1	1	1
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	19	22	17	19	18

	Holden et al ³⁷	Hosseini et al ²⁷	Jatoi et al ⁴⁰	Katić et al ²⁰	Li et al ³⁵	Mogensén et al ³⁴
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. End points appropriate to the aim of study	2	2	2	2	2	2
5. Unbiased assessment of study end points	0	0	0	0	0	0

(continues)

Table 2. Risk of Bias in the Included Cohort Studies According to the Methodological Index for Non-Randomized Studies (MINORS)
Criteria^a (*Continued*)

	Holden et al ³⁷	Hosseini et al ²⁷	Jatoi et al ⁴⁰	Katić et al ²⁰	Li et al ³⁵	Mogenssen et al ³⁴
6. Follow-up period appropriate to the aim of study	2	2	2	2	2	2
7. <5% lost to follow up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	0	0	0
9. An adequate control group	2	2	1	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	0	1	0	2	1	1
12. Adequate statistical analyses	2	2	1	2	2	2
Total	18	19	16	20	19	19

	Olivera-Soto et al ³⁸	Pourhassan et al ²⁵	Ramel et al ²⁸	Ramel et al ²²	Soysal et al ²⁹	Tas Kilic et al ²¹
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	0	2	2	2	2
4. End points appropriate to the aim of study	2	2	2	2	2	2
5. Unbiased assessment of study end points	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of study	2	2	2	2	2	2
7. <5% lost to follow up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	2	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	0	0	1	2
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	17	18	20	19	20

(*continues*)

Table 2. Risk of Bias in the Included Cohort Studies According to the Methodological Index for Non-Randomized Studies (MINORS) Criteria^a (*Continued*)

	Terlikowska et al ²⁴	Tsagari et al ³⁰	Venzin et al ⁴¹	Vischer et al ⁵¹	Vosoughi et al ²⁵
1. Clearly stated aim	2	2	1	2	2
2. Inclusion of consecutive patients	2	2	2	2	2
3. Prospective collection of data	0	2	2	2	2
4. End points appropriate to the aim of study	2	2	2	2	2
5. Unbiased assessment of study end points	0	0	0	0	0
6. Follow-up period appropriate to the aim of study	2	2	2	2	2
7. <5% lost to follow up	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	0	2
9. An adequate control group	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2
11. Baseline equivalence of groups	0	1	1	1	2
12. Adequate statistical analyses	2	2	2	2	2
Total	16	19	18	19	22

^aCriteria were scored 2 (reported and adequate), 1 (reported but inadequate), or 0 (not reported), with a maximum total score of 24.

Prevalence of malnutrition

In 5 studies including only elderly patients, 44% to 81% were at risk of malnutrition and 10% to 39% were diagnosed with malnutrition based on the MNA or MNA Short-Form (MNA-SF).^{25,27,29,31} In 3 other studies, 16.5% of the elderly patients had a BMI below 18.5 kg/m² and 58% were diagnosed with malnutrition based on a combination of anthropometric measurements and laboratory values.^{22,26,28} In 3 studies with patients with (hematologic) malignancies, 28% to 36% were diagnosed with mild malnutrition, and 6% to 24% had severe malnutrition based on the PG-SGA.^{20,24,32} Djurasinović et al³³ used the Nutritional Risk Screening (NRS-2002) and found that 45% of the patients with lymphoproliferative malignancies were malnourished. In the other patient groups, 20% to 26% of the patients were mildly malnourished and 0% to 24% were severely malnourished based on the SGA.³⁷⁻³⁹ In the study by Venzin et al,⁴¹ 20% were at risk of malnutrition and 10% were malnourished according to the MNA. Vosoughi et al²³ found that 29% of the patients admitted to the ICU were mildly malnourished and 10% were severely malnourished based on the mid-arm muscle circumference. Other nutritional assessment tools found a prevalence of malnutrition between 26% and 74%.^{19,21,34-36,40}

Metabolites and malnutrition

Many different plasma metabolites were studied in their relation with malnutrition. No association was found between creatinine levels and the SGA or MNA score,^{39,41} but creatinine levels were significantly higher in the patients with malnutrition diagnosed with the MNA-SF (1.7 ± 1.6 mg/dL vs 1.1 ± 0.8 mg/dL [$P < .001$]).²⁹ The NRS-2002 score was found to be significantly lower in the group with high trimethylamine N-oxide (TMAO) levels than in the groups with median or low TMAO levels (NRS-2002 score: 4.0 [3.0-4.0] vs 4.0 [4.0-5.8] vs 5.0 [5.0-6.0]; for groups with high vs median vs

low TMAO levels respectively $P < .001$).¹⁹ The percentage of osteocalcin that is not carboxylated (% ucOC) was not found to be related to the SGA score ($r = 0.02$; $P = .79$).³⁷ Osteocalcin levels were significantly higher in the well-nourished patients than in the patients with malnutrition based on the NRS-2002 score (3.7 ± 0.5 vs 1.3 ± 0.2 ng/mL; $P = .00$).³⁵ Hosseini et al²⁷ and Venzin et al⁴¹ did not find a relation between blood urea nitrogen levels and malnutrition diagnosed with the MNA score ($P = .9$ and $P > .05$, respectively), but Mogensen et al³⁴ found that high urea levels might be predictive for malnutrition when diagnosed through a combination of anthropometric measurements and laboratory results (variable importance of projection (VIP) = 2.05). The other metabolites that were the best predictors of malnutrition in a partial least squares discriminant analysis are described in Supplemental Digital Content Table 1, available at: <http://links.lww.com/TIN/A56>. Mogensen et al³⁴ also found that the levels of 5-methylthioadenosine, N-6-trimethyllysine, N-acetylmethionine, pyroglutamine, hypoxanthine, kynurenine, and phenyllactate were significantly higher, and the levels of 1-palmitoylglycerophosphoethanolamine and valerate were significantly lower in patients with malnutrition than in the well-nourished patients ($P < .05$). Ramel et al²⁸ concluded that cystatine C levels were significantly higher in the patients with malnutrition diagnosed through a combination of anthropometric measurements and laboratory results. Free T3 levels were significantly lower (2.9 ± 1.0 nmol/L vs 3.6 ± 0.9 nmol/L) and free T4 levels were significantly higher (15.4 ± 4.0 nmol/L vs 14.5 ± 3.6 nmol/L) in the patients with malnutrition based on the MNA-SF than in the patients with no malnutrition.^{29,31}

Vitamins and malnutrition

25(OH)D levels seemed to be lower in patients with malnutrition diagnosed with the PG-SGA score than in the well-nourished patients.^{20,24} However, when adjusted for

tumor type, BMI category, race, and gender, 25(OH)D levels were not related to the PG-SGA score.³² In addition, malnutrition diagnosed with the NRS-2002 was associated with a higher prevalence of severe 25(OH)D deficiency and with lower 25(OH)D levels.^{33,35} Malnutrition based on the MNA score was also found to be related with lower 25(OH)D levels ($P < .001$).³⁰ On the other hand, the MNA-SF, SGA, BMI, mid-arm muscle circumference, and a combination of anthropometric measurements and laboratory results were not related to 25(OH)D levels ($P > .05$).^{31,36-38} 1,25-dihydroxycholecalciferol (1,25di(OH)D) was not related to a BMI $< 20 \text{ kg/m}^2$.³⁶

Vitamin C levels were significantly lower in the severely and mildly malnourished group than in the well-nourished group based on the SGA score (0.3 [0.0-0.9] mg/dL vs 0.5 [0.2-1.3] mg/dL vs 0.7 [0.1-1.5] mg/dL; for groups who were considered severely vs mildly malnourished vs well-nourished respectively $P < .05$).³⁹ Vitamin C deficiency was also more common in the group with malnutrition based on the SGA score and a BMI $< 18.5 \text{ kg/m}^2$.^{26,39} A BMI $< 18.5 \text{ kg/m}^2$ was also related to a higher rate of carotenoid deficiency but not related to a vitamin A, vitamin E, or vitamin B₂ deficiency (diagnosed with the erythrocyte glutathione reductase activation coefficient).²⁶ Vitamin K1 and the related protein-induced vitamin K absence or antagonist-II (PIVKA-II) were not related to malnutrition diagnosed with the SGA or a combination of anthropometric measurements and laboratory results.^{37,40} The presence of vitamin B₁₂ deficiency was not significantly different in the malnourished group based on the MUST score and vitamin B₁₂ levels were not significantly different in the groups based on the MNA-SF or a combination of anthropometric measurements and laboratory results.^{21,28,29} Vitamin B₁ (thiamin) was not related to malnutrition measured using the MNA-SF, and vitamin B₉ (folic acid) was not related to a combination of anthropometric measurements and laboratory results or the

MNA-SF.^{25,28,29} Nicotinamide (vitamin B₃) levels were significantly lower in patients with malnutrition than in the well-nourished patients ($P < .05$).³⁴ Terlikowska et al²⁴ studied many carotenoids and tocopherols in relation with the PG-SGA score. Only all-trans-retinol levels were significantly lower in the severely malnourished group than in the mildly malnourished and the well-nourished group ($2.0 \pm 0.9 \text{ } \mu\text{mol/L}$ vs $3.2 \pm 1.0 \text{ } \mu\text{mol/L}$ vs $5.6 \pm 1.8 \text{ } \mu\text{mol/L}$; $P = .02$).

DISCUSSION

To our knowledge, this is the first systematic review that summarizes the evidence about the value of plasma metabolites and vitamins for assessing nutritional status of hospitalized patients. Our review demonstrates that several metabolites and vitamins are related to malnutrition and may offer a promising method for assessment of nutritional status in hospitalized patients.

Metabolites and related metabolic pathways

Most of the metabolites that showed significant difference between the malnourished and well-nourished hospitalized patients are shown in Figure 2.^{19,26,29,34,35,39,42-55} This figure depicts the relationship between these metabolites (striped and black boxes) and other metabolic pathways in the body. The essential amino acids lysine, methionine, phenylalanine, and tryptophan play an important role within the pathways in Figure 2. N-6-trimethyllysine, 5-methylthioadenosine, hypoxanthine, and N-acetylmethionine are all related to the methionine cycle,^{12,56-59} and the levels of these metabolites were all found to be increased in patients with malnutrition.³⁴ Phenyllactate, 4-hydroxyphenylacetate, 3-(4-hydroxyphenyl)lactate, N-acetylphenylalanine, and pyroglutamine are all related to the phenylalanine and/or glutamate metabolism.^{12,60-62} All 5 metabolite levels were increased in patients with

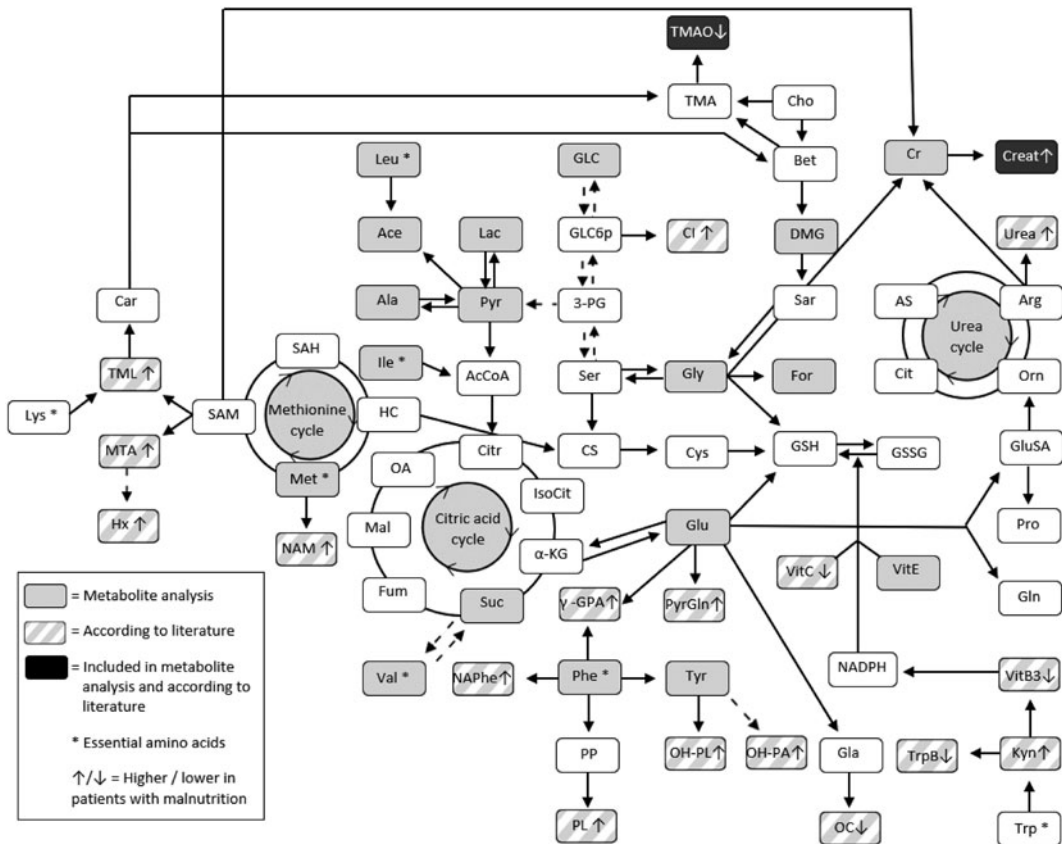


Figure 2. Metabolites analyzed in this study within their metabolic cycles and their association with malnutrition according to available literature. AcCoA indicates acetyl-CoA; Ace, acetic acid; Ala, alanine; α-KG, α-ketoglutarate; Arg, arginine; AS, argininosuccinate; Bet, betaine; Car, carnitine; Cho, choline; CI, chiro-inositol; Cit, citrulline; Citr, citrate; Cr, creatine; Creat, creatinine; CS, cystathionine; Cys, cysteine; DMG, N,N-Dimethylglycine; For, formic acid; Fum, fumarate; γ-GPA, γ-Glutamyl phenylalanine; Gla, γ-carboxyglutamic acid; GLC, glucose; GLC6p, glucose-6-phosphate; Gln, glutamine; Glu, glutamic acid; GluSA, glutamate-1-semialdehyde; Gly, glycine; GSH, reduced glutathione; GSSG, glutathione disulfide; HC, homocysteine; Hx, hypoxanthine; Ile, isoleucine; IsoCit, isocitrate; Kyn, kynurenine; Lac, lactic acid; Leu, leucine; Lys, lysine; Mal, malate; Met, methionine; MTA, 5-Methylthioadenosine; NADPH, nicotinamide-adenine-dinucleotidephosphate; NAM, N-acetylmethionine; NAPhe, N-acetylphenylalanine; OA, oxaloacetate; OC, osteocalcin; OH-PA, 4-hydroxyphenylacetate; OH-PL, 3-(4-hydroxyphenyl)lactate; Orn, ornithine; Phe, phenylalanine; PL, phenyllactate; PP, phenylpyruvate; Pro, proline; Pyr, pyruvic acid; PyrGln, pyroglutamine; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; Sar, sarcosine; Ser, serine; Suc, succinic acid; 3-PG, 3-phosphoglycerate; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; TML, N-6-trimethyllysine; Trp, tryptophan; TrpB, tryptophan betaine; Tyr, tyrosine; Val, valine; VitB3, vitamin B3 (nicotinamide); VitC, vitamin C; VitE, vitamin E.

malnutrition.³⁴ Andro steroid monosulfate 2, 1-palmitoylglycerophosphoethanolamine, and 1-stearoylglycerophosphoethanolamine are involved in the lipid metabolism, and these levels were all decreased in patients

with malnutrition. Chiro-inositol is also related to the lipid metabolism, but the level of this metabolite was increased in patients with malnutrition.^{12,34} Kynurenine is responsible for 95% of the catabolic route

of tryptophan and results in the production of tryptophan betaine and nicotinamide (vitamin B₃).⁶³⁻⁶⁵ Nicotinamide is the precursor of nicotinamide-adenine-dinucleotidephosphate (NADPH),⁶⁶ which is, together with vitamin E and vitamin C, responsible for the conversion of glutathione disulfide to reduced glutathione.⁶⁷⁻⁷⁰ According to Mogensen et al³⁴ kynurenine levels were higher in patients with malnutrition, and tryptophan betaine and nicotinamide levels were lower in patients with malnutrition. The percentage of vitamin C deficiency was significantly higher in the group with malnutrition according to Avelino et al³⁹ and Cunha et al.²⁶ Clinical studies have shown a correlation between elevated TMAO levels and an increased risk for cardiovascular events.⁷¹ Interestingly, Chou et al¹⁹ stated that decreased TMAO levels might be indicative of malnutrition.

Vitamins

Vitamins can be classified as fat-soluble or water-soluble. Vitamin A, D, E, and K are considered to be fat-soluble vitamins and are absorbed and transported similarly. Fat-soluble vitamins are packed into newly formed micelles in the small intestine and absorbed into the enterocytes. The vitamins are then repackaged into chylomicrons and secreted into the lymphatic system and the bloodstream.⁷² After release of the fat-soluble vitamins, retinol-binding proteins, vitamin D binding proteins, and α -tocopherol transporting proteins transport vitamin A, D, and E, respectively, through the body.^{73,74} Fat and protein are thus necessary for absorption of fat-soluble vitamins into the body and transport through the body. Several studies have found a relationship between low albumin levels and vitamin A, D, and E deficiencies in hospitalized patients.^{73,75-77} Malnourished patients might therefore not only have a lower vitamin intake but the absorption and transport of vitamins might also be diminished, which can cause a further decrease in vitamin levels. On the other hand, most of the vitamins D and E in the body are stored in fat tissue.^{78,79} When patients

become acutely malnourished, stored vitamins might be released into the bloodstream when fat is metabolized to produce adenosine triphosphate. Differentiating between chronic malnutrition (concerning patients who are already malnourished upon admission) and acute malnutrition (concerning patients who become malnourished during hospital admission) might therefore be important when using vitamins for nutritional assessment.

Other end points

Metabolites may also be used as prognostic biomarkers to assess the risk of developing complications during admission.⁸⁰ Mogensen et al³⁴ and Rogers et al⁸¹ studied the relationship between several metabolites and 28-day mortality. 3-(4-hydroxyphenyl)lactate, gamma-glutamylphenylalanine, and kynurenine were studied by both researchers and they found a significant relation between these metabolites and mortality in critically ill patients ($P < .05$). In total, Rogers et al⁸¹ found 57 metabolites to be related to the 28-day mortality.

LIMITATIONS

The most important limitation of this systematic review is that the researchers of the included studies used different nutritional assessment tools. This illustrates the fact that a criterion standard for the assessment of nutritional status is lacking, which poses a major challenge in nutritional research. Another limitation is that hospitalized patients with very diverse underlying conditions were included. Despite these limitations, our study is important because it points out the possibilities for future research.

RECOMMENDATIONS FOR FURTHER RESEARCH

Based upon the findings of this systematic review, metabolites and vitamins offer a

promising method for assessing the nutritional status in hospitalized patients. However, many challenges and questions need to be addressed. Further studies involving nutrition-related research in hospitalized patients should incorporate the following recommendations. First, the metabolite and vitamin levels should be assessed in large patient groups to obtain statistical power and identify clinically relevant metabolites. Second, standardized data collection, preferably by registered dietitians, on clinically relevant time points and universal assessment tools should be used to make international research comparable. Third, metabolite and vitamin levels should be measured at different time points during admission to analyze fluctuations over time. Our study group has initiated a multicenter prospective cohort study to gain greater insight in the value of lipoproteins and small metabolites for the assessment of nutritional status in severely injured patients.⁸² There is a need for an objective marker to assess nutritional status in this patient group, as nutritional assessment in these patients is even more difficult than

in the standard hospitalized patients. The goal of our study is to analyze the metabolite profiles of severely injured patients (Injury Severity Score ≥ 16) during their ICU stay, including several of the biomarker candidates described in this review.

CONCLUSION

The evidence for metabolites and vitamins as predictors of nutritional status is scarce; however, according to this literature review several metabolites partaking in the methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan pathways, as well as a number of vitamins seem to be associated with malnutrition in hospitalized patients. More research is needed to further evaluate the value of metabolites and vitamins to diagnose malnutrition and assess the risk of developing malnutrition in hospitalized patients. The clinical usability and effectiveness of the metabolite analysis should be investigated for use in clinical practice.

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