



Branched-chain amino acids are linked with iron metabolism

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Background: The branched-chain amino acids (BCAAs) valine, leucine and isoleucine are reported to influence erythropoiesis and the human iron status. Large study cohorts encompassing biomarkers of iron metabolism and BCAAs are still lacking.

Methods: We investigated potential interactions between blood concentrations of all three BCAAs valine, leucine and isoleucine and biomarkers of iron metabolism [i.e., hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), iron, transferrin, ferritin, transferrin saturation, soluble transferrin receptor (sTfR)] in 430 outpatients referred for a medical health check-up. Linear regression models were performed to assess possible associations between variables.

Results: All three BCAAs were positively correlated with Hb, ferritin and the sTfR (r-values: 0.145–0.382; P values: <0.001–0.003). The strongest correlation was observed between valine and Hb (r=0.382; P value <0.001). Linear regression models showed a statistically significant influence of all three BCAAs on Hb and ferritin (β -coefficients: 0.173–0.351; all P values: <0.001). Seventeen patients with anemia (4%) were found with significantly lower serum BCAA concentrations compared to 413 non-anemic individuals (P<0.05).

Conclusions: These data indicate a pathophysiological link between the three BCAAs valine, leucine and isoleucine and the human iron indicators Hb and ferritin. Further studies are needed to clarify the exact causal mechanisms of these findings.

Keywords: Anemia; branched-chain amino acids (BCAAs); iron metabolism

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Introduction

The proteinogenic branched-chain amino acids (BCAAs) valine, leucine and isoleucine belong to the nine essential amino acids for humans. Dietary BCAAs are usually derived from meat, fish, dairy products and eggs. Unlike the other amino acids, only a minor BCAA fraction is metabolized by the liver after absorption in the gut.

The largest part of dietary BCAAs appears in the blood circulation and can be utilized for new protein synthesis (1). Leucine has the most anabolic effect of BCAAs, which is mediated by activation of the mechanistic target of rapamycin complex 1 (mTORC1) (1,2).

The mTORC1 is a multi-protein complex, which regulates protein synthesis and cell growth through various downstream effectors (3). Recent evidence suggests, that

BCAAs play multiple roles via this mTORC1 pathway and that a metabolic imbalance of these nutrients is associated with diabetes, cardiovascular diseases, obesity, cancer or mood disorders (4-7). High concentrations of BCAAs were shown to promote oxidative stress, inflammation and the migration of peripheral mononuclear blood cells through mTORC1 activation (8).

Certain studies suggested a possible link between BCAAs, mTORC1 and hematological parameters (9-11). Significant increases in hemoglobin (Hb), serum iron, red blood cell count and hematocrit were observed in a small cohort of 23 athletes after a 90-day administration of a BCAA-mixture (9). These data implicate, that BCAAs might also promote erythropoiesis and iron status improvement (9). Since the BCAAs are a limiting factor for protein synthesis and cell growth, a nutritional deficiency of them may also lead to lowered protein biosynthesis of haemoglobin and other indicators of iron metabolism. This could represent one possible pathophysiological link between BCAAs and human iron indicators. Many of these effects are mediated by the mTORC1 pathway (6), which may represent a possible link between BCAAs and human iron metabolism.

Currently, serum ferritin and transferrin saturation remain the widespread biomarkers of the human iron status in clinical practice. Both parameters are known to be affected by acute-phase reactions (12), whereas the soluble transferrin receptor (sTfR), which is inversely correlated with the human body's iron stores, is not influenced by acute or chronic inflammatory illness (12-14). Despite the established associations between elevated serum BCAA levels and various diseases, little is known about possible interactions between BCAAs and iron metabolism. There is still a lack of study designs comprising biomarkers of human iron status and BCAAs in large study cohorts. Considering the central role of BCAAs in metabolic pathways, the hypothesis of this study was, that BCAAs may also interact with the human iron metabolism, which also represents an important part of strong health.

The aim of this study was to investigate potential associations between peripheral blood levels of valine, leucine and isoleucine and indicators of iron metabolism [i.e., Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), iron, transferrin, ferritin, transferrin saturation, sTfR] in a large cohort of outpatients referred for a medical health check-up.

We present the following article in accordance with the Materials Design Analysis reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-624a>).

Methods

Patients

In total, 430 ambulatory individuals, who were referred to the outpatient clinic for iron status assessment, were included in this study. They underwent investigation of iron biomarkers (i.e., Hb, MCV, MCH, iron, transferrin, ferritin, transferrin saturation, sTfR) and also the BCAAs (i.e., valine, leucine, isoleucine).

The inclusion criteria were a minimum age of 15 years and an obligatory overnight fasting state of >12 h. Individuals with the unavailability of all study parameters and iron supplementation within the last 12 months were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Johannes Kepler University Linz (Linz, Austria) (No. 1027/2019) and informed consent was taken from all patients.

Laboratory procedures

Fasting blood samples were collected between 8.00 and 10.00 a.m. Hb (anemia: males, <13 g/dL; females, <12 g/dL) and erythrocyte indices (MCV and MCH) were determined on the ADVIA[®] 2120i Hematology Analyzer (Siemens Healthineers, Erlangen, Germany). Ferritin was assessed by chemiluminescent technology, serum iron by photometric method, and transferrin and the sTfR by nephelometric technology on a Dimension Vista[®] 1500 System (Siemens Healthineers, Erlangen, Germany). The percentage of transferrin saturation was calculated based on the formula: transferrin saturation (%) = serum iron (µg/dL) × 70.9 / transferrin (mg/dL). The reference ranges of the study parameters are listed in *Table 1*. Iron deficiency was defined as a serum ferritin level <30 µg/L and/or a transferrin saturation <20% (12,14,15).

Serum concentrations of the BCAAs valine, leucine and isoleucine were measured by previously described chromatographic methods (5,16). Briefly, after precipitation of serum with perchloric acid following neutralization of the supernatant with sodium carbonate, the extracted amino acids were derivatized with o-phthalaldehyde and separated on a reversed phase column with gradient elution. Quantification was performed with ratios of fluorescence signals of the interesting amino acids to the internal standard norvaline in comparison to the appropriated calibration curves. Intra- and inter-assay correlation coefficients were all <10%. The reference ranges of BCAAs

Table 1 Baseline characteristics of the study population

Characteristic	N=430	Reference ranges
Age (years)	40.6±15.5	–
Sex, male (%)	32.6	–
Body mass index (kg/m ²)	24.2 (21.5–27.7)	18.5–25.0
Iron biomarkers		
Hb (g/dL)	13.9 (13.3–14.7)	Males: 13.0–18.0; Females: 12.0–16.0
MCV (fL)	86.2 (83.3–88.5)	88–99
MCH (pg)	29.8 (28.7–30.6)	27–36
Iron (µg/dL)	101 (76–128)	65–175
Transferrin (g/L)	2.6 (2.4–2.9)	2.0–3.6
Ferritin (µg/L)	58.0 (27.0–105.1)	≥30
Transferrin saturation (%)	27 (20–35)	≥20
sTfR (mg/L)	1.1 (1.0–1.3)	0.76–1.76
BCAAs		
Valine (µmol/L)	198.8 (179.3–224.3)	143–287
Leucine (µmol/L)	118.5 (101.2–137.1)	76.7–159.5
Isoleucine (µmol/L)	56.4 (48.8–66.3)	36.4–85.0

Data are presented as means ± standard deviation, or medians (Q1–Q3), or percentage. Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; sTfR, soluble transferrin receptor; BCAAs, branched-chain amino acids.

were calculated according to the literature (17).

Statistical analysis

Sample size estimation was performed according to the literature (18). A sample size of approximately 400 individuals was assessed to obtain insights about potential associations between BCAAs and indicators of iron metabolism.

The distribution of the data was calculated with the Kolmogorov-Smirnov test. Not normally distributed continuous variables were presented as medians with interquartile ranges (Q1–Q3). Categorical variables were expressed as percentages. To evaluate potential correlation between two continuous variables the Spearman's rank correlation coefficient (r) was used. Furthermore, linear regression models were performed to assess the association between variables. The Mann-Whitney U test was calculated for the comparison between two groups for not normally distributed continuous variables. A P value <0.05 was considered statistically significant. For statistical analysis, the Analyse-it[®] software version 4.92 (Analyse-it Software, Ltd., Leeds, United Kingdom) was used.

Results

Study population characteristics

The baseline characteristics of the study population are shown in *Table 1*. The average age was 40.6 ± 15.5 years, and 32.6% of participants were men. Based on a serum Hb-level <13 g/dL for men and <12 g/dL for women, 17 (2 men and 15 women) out of 430 individuals (4.0%) were found with anemia. Based on a ferritin of <30 µg/L and/or a transferrin saturation of <20%, 159 (20 men and 139 women) patients (37.0%) were identified with iron deficiency.

Correlations between BCAAs and parameters of iron metabolism

As illustrated in *Table 2*, the BCAAs valine, leucine and isoleucine were significantly correlated with Hb, ferritin and the sTfR. The strongest positive correlations were observed between BCAAs and Hb (r -values: 0.244–0.382; all P values <0.001), followed by BCAAs and ferritin (r -values: 0.182–0.312; all P values <0.001), and BCAAs and sTfR (r -values: 0.145–0.157; P values: 0.001–0.003), respectively.

Table 2 Spearman's rank correlation coefficients (r) between BCAAs, Hb, ferritin, and sTfR

N=430	Hb (g/dL)		Ferritin (µg/L)		sTfR (mg/L)	
	r	P value	r	P value	r	P value
Valine (µmol/L)	0.382	<0.001	0.312	<0.001	0.151	0.002
Leucine (µmol/L)	0.349	<0.001	0.260	<0.001	0.145	0.003
Isoleucine (µmol/L)	0.244	<0.001	0.182	<0.001	0.157	0.001

BCAAs, branched-chain amino acids; Hb, hemoglobin; sTfR, soluble transferrin receptor.

Table 3 Univariate linear regression models for Hb, ferritin and sTfR

N=430	Hb (g/dL)		Ferritin (µg/L)		sTfR (mg/L)	
	β-coefficient	P value	β-coefficient	P value	β-coefficient	P value
Valine (µmol/L)	0.351	<0.001	0.307	<0.001	0.084	0.083
Leucine (µmol/L)	0.331	<0.001	0.254	<0.001	0.077	0.112
Isoleucine (µmol/L)	0.195	<0.001	0.173	<0.001	0.093	0.055

Hb hemoglobin, sTfR soluble transferrin receptor.

Associations of Hb, ferritin and sTfR with BCAAs

The univariate linear regression models for Hb, ferritin and sTfR are presented in *Table 3*. The BCAAs valine, leucine and isoleucine showed a statistically significant influence on Hb and ferritin (β-coefficients: 0.173–0.351; all P values <0.001). Valine and isoleucine were in tendency (β-coefficients: 0.084 and 0.093; P values: 0.055 and 0.083) associated with sTfR. *Figure 1* demonstrates linear regression models between Hb, ferritin, sTfR and all three BCAAs (valine + leucine + isoleucine) taken together.

As shown in *Figure 2*, patients with anemia had significantly lower median serum BCAA (valine + leucine + isoleucine) levels [329.1 (292.0–393.0) vs. 373.6 (335.6–427.9) µmol/L, P<0.05] compared to individuals without anemia.

Discussion

In the current study, the three BCAAs valine, leucine and isoleucine were significantly correlated with Hb, ferritin and the sTfR. The linear regression models showed strongest associations between BCAAs and Hb. Lowered BCAA levels were found with lowered Hb values.

These findings are consistent with the results of a previous study by Chung *et al.*, who demonstrated, that

the uptake of the essential BCAAs is a very important component of Hb synthesis in hematopoietic stem cells (19). In this context, the mTORC1 was shown to be a key regulator in hematopoietic stem cell function (20). This multi-protein complex acts as an intracellular sensor of BCAA availability, which coordinates the Hb production (19,21).

Here, the strongest correlation was found between the BCAA valine and Hb (r=0.382; P<0.001). These data corroborate a recently published experimental study, which reported, that hematopoietic stem cells are highly sensitive to valine availability (22). Moreover, protein-energy malnutrition in fasting surgical patients showed, that low valine blood levels were highly correlated with low Hb concentrations (r=0.52; P<0.05) (23). This fact suggests that insufficient protein intake may be one possible reason for BCAA depletion and Hb reduction (23).

In the present study, patients with anemia were found with significantly lower serum BCAA concentrations compared to individuals without anemia. Several recent studies demonstrated that treatment with the BCAA leucine improves the anemia of the Diamond-Blackfan and of the 5q-myelodysplastic syndrome (24–27). Haploinsufficiency of ribosomal proteins in hematopoietic stem cells is the proposed cause of the anemia observed in these disorders (24,28). Leucine activates the mTORC1 pathway, which may overcome the ribosomal protein deficiencies and

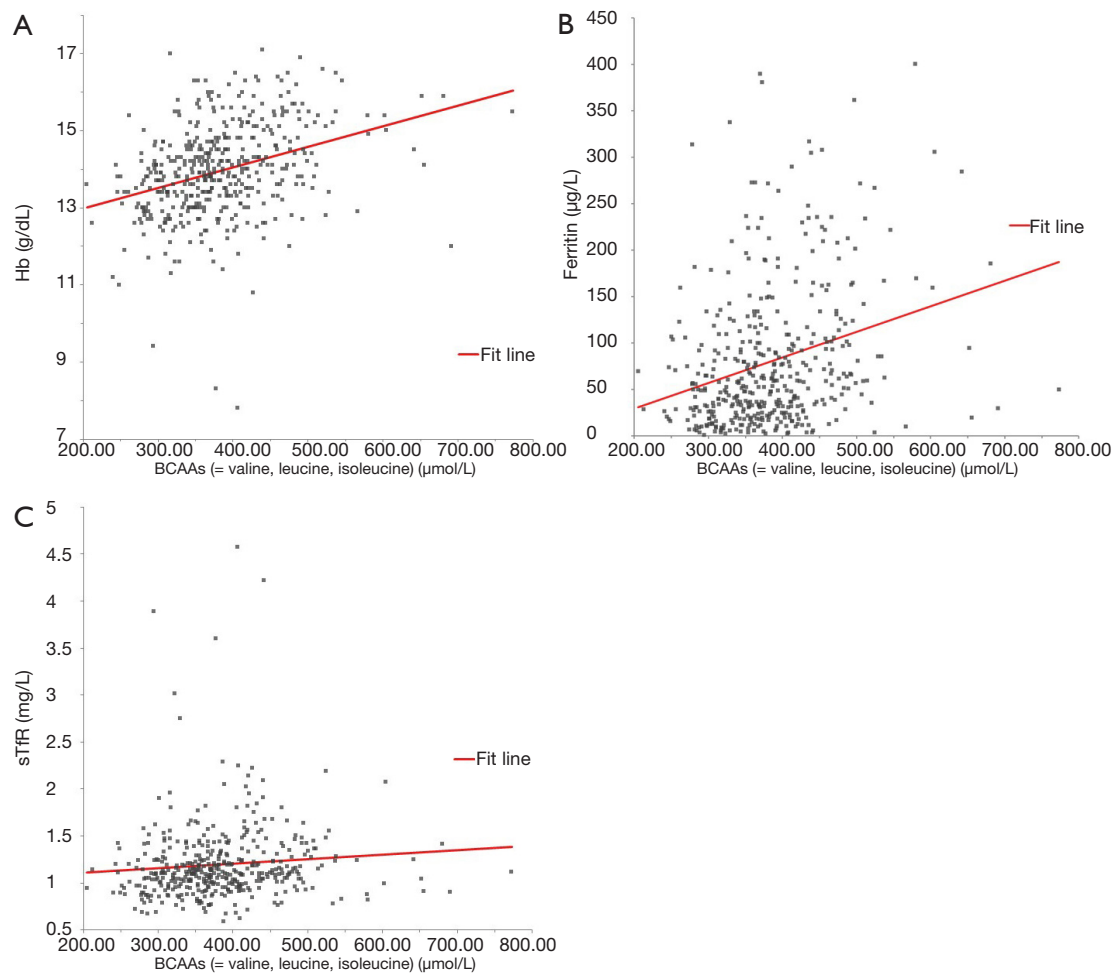


Figure 1 Univariate linear regression models between parameters of iron metabolism and BCAAs (valine, leucine, isoleucine). (A) Hb vs. BCAAs (β -coefficient =0.341, $P < 0.001$), (B) ferritin vs. BCAAs (β -coefficient =0.286, $P < 0.001$) and (C) sTfR vs. BCAAs (β -coefficient =0.091, $P = 0.061$). BCAAs, branched-chain amino acids; Hb, hemoglobin; sTfR, soluble transferrin receptor.

rescue the anemia (24,29). Recently, in elderly patients with myelodysplastic syndrome, oral leucine administration was shown to increase the absolute reticulocyte count, which is an indicator of hematopoietic functionality (30).

Present data show, that the valine, leucine and isoleucine blood levels significantly correlated with the iron storage protein ferritin. Lowered BCAA levels were found with lowered ferritin values. In a previous published study, it was shown that apoferritin, which is the hollow shell protein component of ferritin, contains amino acid residues of all three BCAAs (31). Little correlation was also observed between sTfR and BCAAs. Previous determination of the nucleotide sequence of human sTfR showed that the amino acid sequence of this iron biomarker comprises all three

BCAAs (32).

Valine, leucine and isoleucine are cellular nutrients, which are essential for the synthesis of human structural and functional proteins. A previous report demonstrated an increase of Hb, ferritin, red blood cell count and hematocrit in training athletes after daily consumption of an amino acid mixture, which encompassed all three BCAAs (33). Intermediaries of BCAA metabolism are also known to induce fetal Hb during definitive erythropoiesis (34).

The impact of BCAAs on erythropoiesis and iron metabolism should be investigated in further longitudinal studies, which are able to clarify the exact pathophysiological mechanisms of this observed link. The major advance of the present study is that the BCAAs and iron biomarkers were

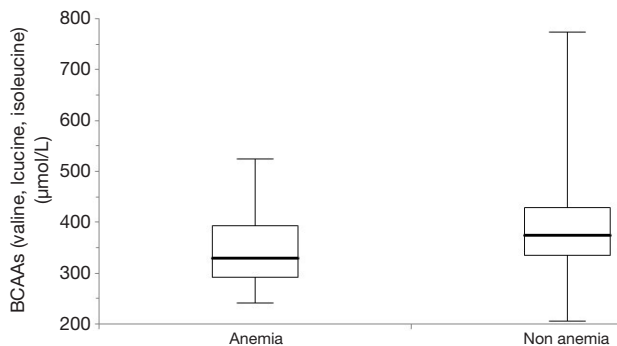


Figure 2 BCAAs (valine, leucine, isoleucine) and anemia. Box-and-whisker plot of BCAA serum level comparison between 17 anemic and 413 non-anemic individuals ($P=0.046$). The central boxes represent the 25th to 75th percentile range. The lines inside the boxes show the median value for each group. Minimum and maximum are indicated as whiskers with end caps. BCAAs, branched-chain amino acids.

measured in a well characterized large study cohort.

The major limitation of this cross-sectional study is that lifestyle factors and dietary habits were not considered.

Conclusions

Significant associations between the BCAAs valine, leucine, and isoleucine and the iron biomarkers Hb and ferritin were observed. Patients with anemia showed significantly lower serum BCAA levels compared to individuals without anemia. Lowered BCAA concentrations were found with lowered ferritin levels. These findings suggest a pathophysiological link between BCAA and iron metabolism.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-624a>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-624a>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at <http://dx.doi.org/10.21037/atm-20-624a>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Johannes Kepler University Linz (Linz, Austria) (No. 1027/2019) and informed consent was taken from all patients. This study can provide new insights in the pathophysiological link between BCAAs and iron metabolism.

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