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Metabolomics Unraveling the Biochemical Insight of High-Altitude Diseases and Sepsis–A Narrative Review

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ABSTRACT

High altitude diseases and sepsis may seem distinct at first glance, but there are underlying physiological similarities that lie in their responses to hypoxia, tissue dysfunction, inflammation, and multi-organ failure conditions. Understanding these commonalities can help medical professionals draw parallels between them and apply relevant knowledge to improve patient care and treatment.In this direction,a literature review of metabolomics-based studies has been done for high-altitude diseases and sepsis, and the panel of common disease-related metabolic markers and associated pathways areunraveled. Themetabolic pathways found dysregulated in both conditions are amino acid metabolism, lipid metabolism, energy metabolism, inflammatory response-related metabolism, bile acid metabolism, and purine and pyrimidine metabolism.

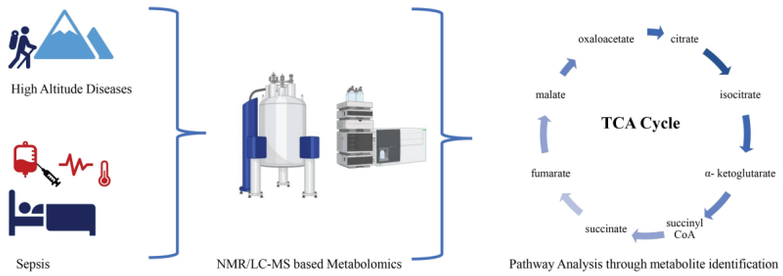

Image depicting pathway analysis as a major application of metablomics techniques

Keywords: AMS; HAPE; HACE; Sepsis; Metabolomics

NOMENCLATURE

AMS	Acute Mountain Sickness
HAPE	High-Altitude Pulmonary Edema
HACE	High-Altitude Cerebral Edema
TLR-4	Toll-Like Receptor-4
ARDS	Adult Respiratory Distress Syndrome
HIF-1	Hypoxia-Inducible Factor-1
ICU	Intensive Care Unit
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
GC-MS	Gas Chromatography-Mass Spectrometry
TCA	Tricarboxylic Acid Cycle
UPLC	Ultra-Performance Liquid Chromatography
Q-TOF	Quadrupole Time-Of-Flight
LC-MS	Liquid Chromatography-Mass Spectrometry
^{1}H-NMR	Proton Nuclear Magnetic Resonance

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1. INTRODUCTION

Human physiology efficiently integrates multiple signaling mechanisms to uphold tissue structure and function amidst external and internal stimuli. The body's resilience against adverse conditions highlights its sophisticated adaptability.[1] Extremes conditions like cold, heat, altitude, and space impact physiology[2], while internal factors like hormones, nutrition, stress, and infections (sepsis) also disrupt it. Adaptations occur with altered environments, involving increased respiratory and heart rates, blood pressure maintenance, metabolic rate elevation, and immune responses.[3] The body's homeostatic balance

combats deviations via regulatory mechanisms.[4] In extreme environments like high altitudes, inflammatory cells play a vital role in tissue repair, angiogenesis, and immune defense. High altitudes trigger increased red blood cell production to improve oxygen-carrying capacity.[5] Failure to adapt to high altitudes leads to health issues like high-altitude hypoxia (hypobaric hypoxia), acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE).[6] Imbalances can trigger an uncontrolled inflammatory cascade, leading to a systemic inflammatory response in both high-altitude diseases and sepsis.[7]Among different external and internal environmental factors that affect human physiology, high-altitude diseases, and sepsis are life-threatening conditions with significant global impact.[8,9]

Although sepsis and high-altitude diseases may appear to be completely different at first look, there are physiological commonalities between them that are caused by the way they respond to hypoxia, tissue dysfunction, inflammation, and multi-organ failure conditions. According to a new paradigm, pathophysiological responses seen in extreme conditions such as high-altitude diseases may be similar to the responses present in critical illnesses such as sepsis.[10–12] As altitude increases, blood pressure, partial oxygen pressure, and, ultimately, inspired oxygen pressure, all decrease.The cellular hypoxia seen at high altitudes is identical to that seen in critically ill sepsis patients when oxygen supply to the tissues is compromised.They share similarities in systemic inflammation mechanisms, involving toll-like receptor (TLR4) activation.[13,14]

It is well established that the inflammatory process is identical to that found in patients with adult respiratory distress syndrome (ARDS)/ sepsis patients in terms of both severity and features.Hypoxia-inducible factor-1 (HIF-1) plays a crucial function in maintaining the balance of oxygen in the bodyby promoting oxygen availability to the tissues under hypoxic settings or in the inflammatory molecular response that is common in sepsis. HIF-1 also regulates thenucleotide metabolism and glucose metabolism.[11] As some studies[10,12] have already proven the similarities in the body response in high altitude diseases and critical illness on different aspects, in this review article authors aim to decipher the commonalities by presentingthe metabolic window of these two disease states andproviding a close representation of the phenotype at the molecular level by doing extensive literature review.To the best of our knowledge, this is the first time that the similarities in the metabolic profiles of these two disease states are presented together along with the information on specific disease-related biomarkers.

By studying the profile of metabolites in high altitude diseases and sepsis, we can gain a deeper understanding of the pathophysiology of these diseases, and how the body responds in these situations like hypoxia (which is common in both groups), and mayultimately aid in devising effective treatment strategies, future diagnostic approaches and improving patient outcomes in intensive care unit (ICU) settings.

2. METABOLOMICS

Over the past decade scientific community has been working hard for the screening of markers and molecules associated with critical diseases. The omics cascade (Figure1) provides immense information used to gain insight into the various aspects of disease and helps in presenting a deeper understanding of the biological pathways involved in the disease.[15]As metabolites are the final products of gene expression, capture the end product of cellular processes, and consider as closest to the phenotype, consequently, metabolomics plays a crucial role in revealing information about the pathophysiology of illnesses.[16]

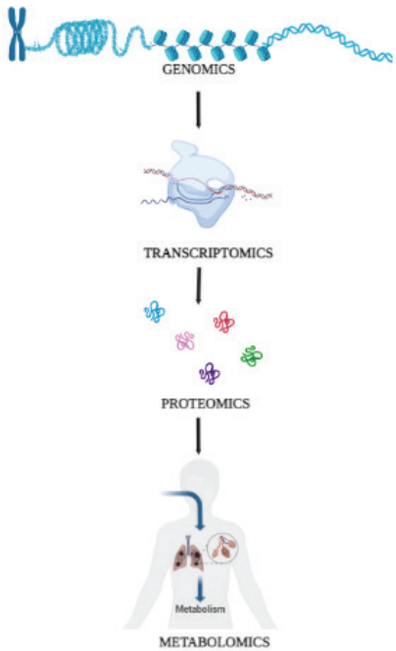

Figure 1. The omics cascade

Metabolomics is a field of study that focuses on the comprehensive analysis of small molecules (molecular weight < 1500 Da), known as metabolites, within biological systems.[17] The term metabonomics was coined by Nicholson[18], *et al.* and later, Oliver Fiehnn[19], *et al.* used the term metabolomics. The metabolomics workflow diagram is presented in Figure 2.Thedevelopment and advancements of techniques such as mass spectrometry (MS) and nuclearmagnetic resonance (NMR)spectroscopy empower the extensive analysis of metabolites,leading to the emergence of metabolomics as a distinct field. In disease states, perturbations occur in metabolites participating in various biochemicalpathways.By measuring the shifts in the metabolome of a diseased sample, it can be used to detect and quantify changes associated with a range of diseases, from cancer[20–22] and cardiovascular diseases[23] to neurological disorders[24] and critical illnesses such as ARDS.[25]

3. EXTREME EXTERNAL ENVIRONMENT

3.1 High-Altitude Diseases

Around 140 million people live in high altitudes

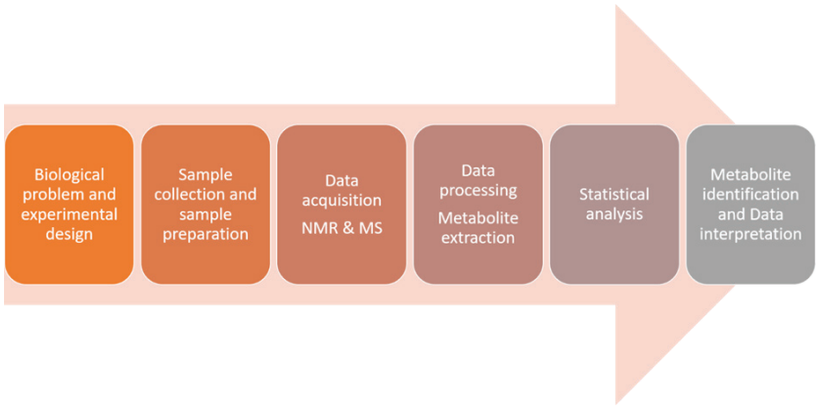

Figure 2. Metabolomics workflow diagram

globally, and many more travel to these areas for various activities including skiing, mountaineering, and others here on pilgrimages or as part of their duties.[26] The main physiological issue of high-altitude environments is hypoxia, which is caused by low oxygen and low-pressure levels and remains the most common cause of death related to high altitude.[27] Rapid ascent to high altitudes is a common cause of AMS and typically happens at elevations exceeding 2,500 meters (8,200 feet). In severe cases, AMS can progress to more dangerous conditions like high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema(HACE).HAPE occurs due to exposure to high-altitude conditions such as low air pressure and inadequate oxygen supplies, leading to a build-up of fluids in the lungs and breathing difficulties. The cause of pulmonary edema is a continuous imbalance between the forces that drive water into the lung's airways and the biological processes that remove it.[28] HACE is a condition that involves swelling of the brain. It can lead to confusion, altered mental state, loss of coordination, and eventually unconsciousness.Without immediate medical action, the severity of the HAPE and HACE condition rises, and the chances of associated mortality with it become high. Patients may experience low pulmonary artery occlusion pressure, low pulmonary hypertension, and decreased cardiac output as the condition worsens. If ignored, the death rate may increase to 50 %.[29]

The precise mechanism of AMS, HAPE, and HACE is not well understood; however, it is assumed that a marked elevation of the pulmonary artery and pulmonary capillary pressure combined with an imbalanced hypoxic pulmonary vasoconstriction are major contributors to its pathogenesis. The combination of physical examination, medical history, X-rays, and scansare frequently used to diagnose HAPE and HACE.[9] The identification of biomarkers specific to AMS, HAPE, and HACE is crucial and would be of great clinical value for the successful diagnosis and effective treatment of those affected.[30] The information on the physiological responses of high altitude diseases to hypoxia, tissue dysfunction, inflammation, and multi-organ involvement may be helpful in identifying the shared physiological features with critical illness like sepsis that will ultimately be beneficial for patient care, designing treatment regimes, and improving outcomes. Thus, this has become a significant area of focus and concern.

3.2 Metabolomics in High Altitude Diseases

In recent years, there has been significant research emphasis on identifying and studying biomarkers that can facilitate the early diagnosis and prognostic prediction of high-altitude diseases. In the review article by Chang[31],*et al*., the literature review was performed on the pathogenesis of altitude hypoxia and the clinical\preclinical metabonomics studies and thus presented the pathways altered during the disease state. Paul[32], *et al*. also presented cohesive information on omics studies in the very informative review article on HAPE.The sequential section includes a brief literature review of metabolomics-based studies on high-altitude diseases and data is also presented in Table 1.

In the GC-MSbased study on plasma samples of AMS patients conducted by Zhu[33],*et al*., the notable elevations in plasma concentrations of hypoxanthine, cysteinyl glycine, D-arabinol, L-threonine, 2-ketobutyric acid, and succinic semialdehyde was observed. Sibomana [34] also studied AMS severity by identifying urinary metabolites through untargeted NMR-based metabolomics. In pathway analysis, it was revealed that these differentially expressed metabolites serve a direct or indirect function in energy metabolism.

To characterize the urine metabolome under hypobaric hypoxic stress, Koundal[35], *et al*. used a preclinical rat model in a ^{1}H NMR-based metabolomics investigation. The metabolic pathway analysis of the study indicates that the TCA cycle and taurine metabolism were the two most affected pathways.Liao[36], *et al*. performed GC-MSbased plasma analysis of 60 subjects exposed to high altitude hypobaric hypoxia condition from plain region. The identified metabolites were found to be associated with a range of pathways related to energy metabolism, bile acid metabolism, inflammatory response-related metabolism, andheme metabolism.In a study by O'Brien[37] *et al*., ^{1}H NMR-based metabolomic analysis of plasma samples collected from 198 participants was done, both prior to and during an expedition to Everest

Table 1. Metabolomics-based studies on High altitude diseases

Authors / Year	Cases/controls	Sample type	Analytical platform	Upregulated metabolites at high altitude	Downregulated metabolites at high altitude
Lin[42], *et al.* / 2023	60 Rats Divided into HAPE andcontrol groups	Arterial–veinous blood	LC-MS	D-glucose-6-phosphate,D-fructose 6-phosphate, D-mannose-6-phosphate, acetoacetate, arginine and histidine	Arterial Blood:D-mannose, glutathione, glutathione disulfide, and dehydrocholic Acid Venous Blood:Leucine, cis-4-hydroxy- D-proline and thyroxine
Gao[41], *et al.* / 2023	25 Human volunteers at different altitudes	Plasma	UPLC-MS/MS analysis	Decanoylcarnitine and 2 arachidonoyl, glycerol,carn itine,acylcarnitines, 5-oxo-6,8,11,14-eicosatetraenoic acid, raffinose	Adenosine, guanosine, and inosine xanthurenic acid,biotin
Gandhi[38], *et al.*/2022	Sea level:70 individuals Siachen camp: 40 individuals	Urine	^{1}H NMR	Isoleucine and tyrosine	Cysteine
Siboma[34], *et al.*/2021	17 healthy males were transported to high altitudeAMS	Urine	^{1}H NMR	Creatine and acetylcarnitine	Hypoxanthine and taurine
O'Brien[37], *et al.* /2019	198 humans Samples: Everest Base Camp	Plasma	^{1}H NMR	Lactic Acid, palmitic acid, linoleic Acid, And oleic Acid	Isoleucine and glucose
Liao[36], *et al.* /2016	60 subjects Samples:(Hypobaric Hypoxia)	Plasma	GC-MS	Linoleic Acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, oleic acid, and palmitic acid. Hypoxanthine and uric acid	Lysophosphatidylcholines
Koundal[35], *et al.* /2015	Rat model /Hypobaric hypoxia	Urine	^{1}H NMR	Taurine, creatine, choline, α-ketoglutarate	Citrate, hippurate, N-acetylglutamate, andphenylacetylglycine.
Zhu[33], *et al.* /2015	12 AMS patients& 12 without AMS	Plasma	GC–MS	Cysteinylglycine, hypoxanthine, D-arabitol, 2-ketobutyric acid, L-allothreonine, and succinate semialdehyde	Galactose,monopalmitin, and 3-hydroxybutyric acid. L-homoserine, tryptophan,Maleamate, asparagine, glycine, caffeic acid, and 2-amino-2-norbornanecarboxylic Acid
Guo[40], *et al.* / 2015	57 HAPE patients & 57 controls	Plasma	UPLC-Q-TOFMS	C-8 ceramide and sphingosine	glutamine
Luo[39], *et al.*/ 2012	10 HAPE/10 controls	Plasma	^{1}H NMR	Glycine, valine, creatinine, citrate lysine, leucine, isoleucine, glycerol phosphorylcholine, glutamine, glutamic acid, and methyl histidine	**α- and β-glucose,** Trimethylamine and some lipids

Base Camp, the researchers revealed increased rates of glycolysis and mobilization of fat. Gandhi[38], *et al*. conducted a study in which metabolic alterations due to chronic environmental hypoxia were revealed by using a ^{1}H NMR-based metabolomics study of urine samples of 70 individuals from sea level and 40 individuals of Siachen camp. Metabolic pathways that were affected by prolonged exposure to high-altitude hypoxia included the TCA cycle, glutathione metabolism, glycine, serine, and threonine metabolisms, and alterations in cysteine pathways.

Luo[39], *et al*. utilized the application of NMR metabolomics in profiling the altered metabolic patterns of plasma of HAPE patients. According to this study, metabolic alterations in amino acid levels can result from dysregulation of gluconeogenesis, proteolysis, and oxidative catabolism. Guo[40], *et al*. performed the UPLC coupled with Q-TOF mass spectrometry-based study on the plasma samples of 57 HAPE individuals and 57 controls. They identified 14 discriminatory metabolites between the study and control group, furthermore, sphingosine, glutamine, and C8- ceramide were statistically selected as diagnostic markers for HAPE. This finding indicates an upregulation of sphingolipid metabolism in HAPE subjects. In a longitudinal cohort study conducted by Gao[41], *et al*., 25 healthy volunteers from a low-altitude area were transported to a high altitude for a week before being returned to the low-altitude area. They have highlighted the dysregulated pathways associated with the altered metabolites specifically purine metabolism, tryptophan metabolism, regulation of lipolysis in adipocytes, and neuroactive ligand-receptor interaction.Recently, Lin[42], *et al*. investigated the arterial–veinous blood of HAPE rats and control rats. They have adopted the samples using a quasi-targeted metabolomics approach by LC-MS/MS. They reported the effects on glucose metabolism, amino acids metabolism, bile acid metabolism, fatty acids metabolism, and oxidative stress in HAPE conditions.

4. INTERNAL ENVIRONMENT

4.1 Sepsis

The Third International Consensus (Sepsis-3), in 2016, defined sepsis as a severe condition characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection.[43] At present, blood cultures serve as the widely accepted gold standard for confirming the existence of infection within the body.[44] For several years, the quest for potential biomarkers has persisted, aiming to assist critical care physicians in differentiating the source and cause of sepsis while predicting the progression of the disease into septic shock. There are many potential sepsis biomarkers identified[45], but they lack specific sensitivity and specificity.

4.2 Metabolomics in Sepsis

Sepsis is a heterogeneous condition having complex pathogenesis. Metabolic phenotyping holds the potential to enhance diagnostic precision, enabling the early identification and intervention of sepsis for improved patient outcomes.[46,47]Numerous studies have focused on employing metabolomic techniques for sepsis (Table. 2). These studies also indicated the key metabolic pathways implicated in the pathogenesis of sepsis which are bile acid metabolism, amino acid metabolism, lipid metabolism, energy metabolism, inflammatory response-related metabolism, and purine and pyrimidine metabolism. Specifically, oxidative stress, mitochondrial dysfunction, lactic acidosis, organ malfunction, and tissue hypoxia are among the pathophysiological processes that are linked with the metabolic response in sepsis. A recently published review article also highlighted the metabolic perturbations in serum samples between survivors and non-survivors.[46] Another prospective feature of metabolomics is the identification of patient's responsiveness to therapies and some research groups are also working in this direction.[48] Such comprehension is a crucial step for identifying sepsis sub-phenotypes that can be treated more effectively and help in reducing heterogeneity. The clinical classification of patients could be improved with a better understanding of the metabolic implications of sepsis.

5. DISCUSSION AND CONCLUDING REMARK

Currently, the intricate pathophysiology of high-altitude diseases and sepsis remains poorly understood. Hypobaric hypoxia encountered at high altitudes is a form of cellular hypoxia similar to that suffered by critical sepsis patients.[12] High-altitude diseases could be

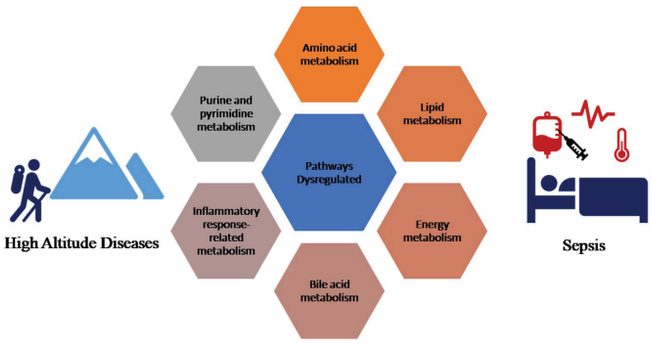

Figure 3. Representation of common dysregulated pathways in high altitude diseases and sepsis

Table 2. Metabolomics-based studies on sepsis

Authors / Year	Cases/ controls	Sample type	Analytical platform	Upregulated Metabolites in sepsis	Downregulated Metabolites in sepsis
Li[49], *et al.* /2023	22 sepsis patients / 10 healthy controls	Serum	LC-MS/MS	3-phenyllactate,N-phenylacetylglutamine, phenylethylamine	Methyl jasmonate, indole,L-tryptophan
Wang[50], *et al.* /2023	30 infants with sepsis / 30 non-infectious infants	Serum	LC-MS	Phosphatidic acid, phosphatidyl ethanolamine, and cytidine 5'-diphosphocholine	Sphingomyelin,prolylhydroxyproline, and phosphorylcholine.
Ding[51], *et al.* / 2022	96 sepsis patients / 66 healthy controls	Plasma	LC-MS	L-aspartic acid, 3-methoxytyramine, indoleacetic acid, 5-hydroxy-4-octanone, docosapentaenoic acid ,6-dimethyl-2-(1-methylpropyl)-4H-1,3,5-dithiazine, histidinyl-tryptophan, 3-methylene-indolenine, dihydro-4 alpha-linolenic acid,	Indole-3-carbinoland5-hydroxyomeprazole.
Li[52], *et al.* / 2021	84 Paediatric patients / 54 healthy controls	Serum	HPLC-MS	D-mannose, L-glutamate,glycocholic acid, and d-quinovose,	Phosphatidylcholine, phosphatidylinositol, phosphatidylglycerol,phosphatidylethanolamine
Pasierb[53], *et al.* / 2021	15 sepsis or septic shock / 15 healthy controls	Serum and urine	LC-MS	Serum: histidine, a-aminoisobutyric acid, sarcosine aminoadipic acid, tyrosine, phenylalanine, leucine, lysine, isoleucine, ornithine, threonine, asparagine,histidine, glutamine,arginine, glycine,4-hydroxyproline. Urine: arginine, glycine, thioproline,citrulline	Serum: dipeptide Gly-Pro Urine: histidine, aminoadipic acid, 3-methyl-histidine
Jaurila[54], *et al.* /2020	44 sepsis patients/14 healthy controls	Serum	^{1}H NMR	Glucose,3-hydroxybutyrate, glycine, creatinine, glycoprotein acetyls	Citrate and histidine
Lin[55], *et al.*/2020	31 sepsis patients/23 healthy controls	Plasma	GC–MS	6 Fatty acids,7 amino acids, 8 amino acids derivatives,27 organic acids, pyruvic acid and nicotinamide adenine dinucleotide phosphate, and dimethyl fumarate and 7 TCA cycle intermediates.	3-methyl-2-oxopentanoic acid, 4-methyl-2-oxopentanoic acid,10 saturated fatty acids,9 unsaturated fatty acids,tryptophan, glutamine, serine, proline,asparagine, 4 TCA cycle intermediates,2 amino acid derivatives

Grauslys[56], *et al.* /2020	55Paediatrics sepsis patients / 58 Systemic inflammatory response syndrome (SIRS)	Serum	^{1}H NMR	Lactate, phenylalanine,3-hydroxybutyrate, valine,urea,	Pyruvate,acetate,leucine, acetone, 2-hydroxyisobutyrate
Neugebauer[57], *et al.* / 2016	59 sepsis / 24SIRS	Serum	LC-MS/MS	Serine,kynurenine, spermine, aspartate, spermidine, phenylalanine, total dimethylarginine,	Glycerophospholipids sphingomyelins, phospholipids, acylcarnitine.
Kauppi[58], *et al.* /2016	65 bacteremic sepsis patients /49 SIRS	Whole blood	GC-TOF-MS	Pyruvic acid, myristic acid,	Phosphocholine,and isoleucine
Mickiewicz[59], *et al.* / 2015	37 Septic shock patients / 20 SIRS	Serum and plasma	^{1}H-NMR	Isobutyrate, myoinositol,phenylalanine, 3-hydroxybutyrate, 2-hydroxybutyrate, proline, O-acetylcarnitine	Arginine,valine, threonine, glucose, glutamate, methanol
Liang[60], *et al.* / 2015	1282 septic shock / 1346 healthy controls	Urine	UPLC-MS	Hippuric acid,acetylcysteine, 3-methyluridine,	Glycine,Kynurenic acid,
Su[61] *et al.* / 2015	35 sepsis patients / 18 healthy controls	Serum	LC-MS/MS	Arginine, aspartic acid, homocitrulline, ethanolamine, glutamine, glutamic acid, phenylalanine, taurine,	Asparagine, carnosine, citrulline, histidine, isoleucine, isoleucine, valine, lysine, ornithine, phosphoethanolamine, proline, sarcosine, threonine, tryptophan, tyrosine
Mickiewicz[62], *et al.* / 2014	39 Septic shock patients / 20 SIRS	Serum	^{1}H-NMR	Lactate, myoinositol, sucrose, proline, O-acetylcarnitine, isobutyrate, succinate, urea, creatinine, creatine, 2-hydroxyisovalerate, trimethylamine-N-oxide, 3-hydroxybutyrate, phenylalanine	Isoleucine, leucine, valine, lysine, glycine, serine, glutamine, alanine, threonine, glucose, mannose, glutamate, arginine, 2-aminobutyrate, methanol, 2-oxobutyrate, creatine.
Fanos[63], *et al.* / 2014	9 neonatal sepsis patients / 16 healthy controls	Urine	^{1}H-NMR and GC-MS	Lactate, glucose and maltose	2,3,4-trihydroxybutyric acid, rabitol 3,4-dihydroxybutanoic acid, ribonic acid, 3,4,5-trihydroxypentanoic acid, 2 ketogluconic acid, pseudouridine.
Stringer[64], *et al.* / 2011	13 sepsis patients / 6 healthy controls	Plasma	^{1}H-NMR	Adenosine, total glutathione, phosphatidylserine	Sphingomyelin

the result of hypoxia triggering inflammatory pathways, controlled by the toll-like receptor TLR4 and HIF-1. Interestingly, TLR4 and HIF-1 also play significant roles in sepsis. To put it in a nutshell, the metabolites that are found upregulated in both conditions i.e., high altitude diseases and sepsis are arginine, glycine, lysine, leucine, creatine, glucose, and lactate. This indicates that the main metabolic pathways that are dysregulated in both conditions are amino acid metabolism and energy metabolism. Overall analysis of studies of both the disease groups revealed that the lipid metabolism, inflammatory response-related metabolism, bile acid metabolism, and purine and pyrimidine metabolism are also altered to some extent (Figure 3).

Changes in amino acid levels indicate metabolic reconfiguration aimed at fulfilling energy needs. Variations in amino acid concentrations could potentially signify the usage of substances that contribute to glucose synthesis.[38] The branched-chain amino acidsare essential for energy metabolism, and an increase in them is a sign of oxidative stress and mitochondrial respiration impairment.Similar alterations in mitochondrial biogenesis in both high-altitude diseases and sepsis might indicate analogous adaptive reactions and propose therapeutic approaches centered around safeguarding or enhancing such mitochondrial biogenesis. In high-altitude conditions, there might be an increased reliance on carbohydrates (glucose) for energy due to reduced oxygen-dependent fat metabolism. In sepsis, increased gluconeogenesis can result in elevated blood glucose levels. Changes in lactate levels result from cellular ATP demand and supply pathways of both conditions. These metabolic alterations are aimed at maintaining cellular function.

For improving the diagnosis of high-altitude diseases and sepsis, metabolomics may provide a new perspective by providing in-depth biochemical insight into the pathophysiology of thesediseases. The identified potential markers and affected biochemical pathways of both disease groups discussed in this review article have the potential to enhance our understanding of physiological conditions and may serve as early warning signs for the timely detection of high-altitude diseases and sepsis. The information and in-depth knowledge related to high altitude disease physiology and adaptive mechanism of the individuals may help us in better understanding the way hypoxia affects critical sepsis patients and may aid in the development of effective treatment regimes. It is alsoto be kept in mind that metabolomics-based studies have limitations such as the choice of biofluids analyzed and the specific analytical platform used, which can result in variations in the generated metabolic profiles. Standardization of protocols in metabolomics is required to ensure consistency and comparability across studies.Multi-omics profiling is strongly encouraged as it provides a comprehensive understanding of molecular changes occurring in diseases and offers a holistic view of human health.So, it is suggested to perform standardized multi-omics studies on large sample sizes of both disease groups to establish some lab-to-bench protocol.

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