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Perspective

Investigating Ketone Bodies as Immunometabolic Countermeasures against Respiratory Viral Infections

Brianna J. Stubbs,[1] Andrew P. Koutnik,[2,3] Emily L. Goldberg,[4] Vaibhav Upadhyay,[5,6] Peter J. Turnbaugh,[6] Eric Verdin,[1] and John C. Newman[1,7,*]

Respiratory viral infections remain a scourge, with seasonal influenza infecting millions and killing many thousands annually and viral pandemics, such as COVID-19, recurring every decade. Age, cardiovascular disease, and diabetes mellitus are risk factors for severe disease and death from viral infection. Immunometabolic therapies for these populations hold promise to reduce the risks of death and disability. Such interventions have pleiotropic effects that might not only target the virus itself but also enhance supportive care to reduce cardiopulmonary complications, improve cognitive resilience, and facilitate functional recovery. Ketone bodies are endogenous metabolites that maintain cellular energy but also feature drug-like signaling activities that affect immune activity, metabolism, and epigenetics. Here, we provide an overview of ketone body biology relevant to respiratory viral infection, focusing on influenza A and severe acute respiratory syndrome (SARS)-CoV-2, and discuss the opportunities, risks, and research gaps in the study of exogenous ketone bodies as novel immunometabolic interventions in these diseases.

BACKGROUND

Respiratory viral infection represents an ever-present public health threat, which can readily overwhelm our existing tools to prevent spread and widespread fatalities. Not only must we deal with seasonal outbreaks, such as respiratory influenza A virus (influenza), but throughout human history, we have faced the regular emergence of novel viruses with global pandemic potential, such as 2003 severe acute respiratory syndrome (SARS)-CoV, 2004 N5N1 influenza, 2009 H1N1/09 influenza, 2012 Middle East respiratory syndrome (MERS)-CoV, and most recently 2019 SARS-CoV-2. Influenza causes more than 20,000 deaths annually in the United States, incurring an economic burden in excess of $87 billion each year.[1,2] Similarly, the 2019–2020 global pandemic of the novel coronavirus SARS-CoV-2, causative agent of COVID-19 respiratory disease, in only a few months infected millions of people, killed hundreds of thousands, and led to worldwide social and economic disruption. There is no efficacious universal vaccine for influenza or for SARS coronaviruses (SARS-CoV, SARS-CoV-2, and MERS); consequently, novel therapeutic approaches are vital for the treatment of these viral diseases.

Several population sub-groups appear to be at particularly high risk of complications with respiratory viral infections, such as influenza and SARS-CoV-2. First, older adults have increased risk of hospitalization and mortality.[3-8] Second, patients with diabetes (both type 1 and type 2) also appear to be particularly vulnerable[5,9-12];

[1]Buck Institute for Research on Aging, Novato, CA, USA

[2]Institute for Human and Machine Cognition, Pensacola, FL, USA

[3]Department of Molecular Pharmacology and Physiology, USF, Tampa, FL, USA

[4]Department of Physiology, UCSF, San Francisco, CA, USA

[5]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF, San Francisco, CA, USA

[6]Department of Microbiology and Immunology, UCSF, San Francisco, CA, USA

[7]Division of Geriatrics, UCSF, San Francisco, CA, USA

*Correspondence: jnewman@buckinstitiute.org

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hallmarks of diabetes include hyperglycemia, glycemic variability, and/or insulin dysregulation, all shown to worsen outcomes from infection.[13-19]

Respiratory viruses, including influenza and SARS-CoV-2, can lead to acute respiratory distress syndrome (ARDS)[20,21] and death from respiratory failure. ARDS is a complex syndrome that is characterized by lung vascular endothelial injury and alveolar epithelial injury and is associated histologically with alveolar filling with protein-rich fluid.[22] The pathophysiology of ARDS includes complex host-pathogen immune interactions along with cellular damage and death resulting from a delayed, pathological hyperactive inflammatory response, hyperoxia, hypoxia, and oxidative stress.[23] There is a critical need for mitigation strategies that attenuate these damage pathways, importantly without compromising the early, protective physiological immune response to viral infection. Even patients who recover from critical illness and ARDS can have long-term health consequences from prolonged critical illness, including cognitive impairment and physical disability, exacerbated with age,[24,25] reinforcing that clinical strategies should focus on not only mitigating the acute disease process but also on supporting recovery.[26]

Metabolic therapies represent novel strategies that could be used to target viral disease progression. In the last decade, the field of immunometabolism research has uncovered multiple points where metabolism influences host-pathogen interactions, not only in altering infection risk and viral replication but also affecting the response of specific immune cell types, thus profoundly controlling disease outcomes.[27-30] One metabolic therapy with promise in this area is the induction of a state of ketosis, where blood ketone body concentrations are elevated. Ketone bodies are endogenous molecules synthesized from free fatty acids. The primary ketone body, beta-hydroxybutyrate (BHB), directly acts as both a highly efficient oxidative fuel and signaling metabolite.[31] BHB has been shown to have diverse molecular effects, including metabolic regulation;[32] increased cellular resistance to oxidative stress;[33-35] inhibition of nuclear factor κB (NF-κB) signaling via HCAR2 receptor binding[36,37]; decreased activity of components of the innate immune system, such as the nonobese diabetic (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3) inflammasome;[38-40] decreased systemic inflammatory burden;[41] modifying gene expression;[33,42] and acting as a fuel in the context of energetic stress.[43,44] Ketogenic interventions have been used for decades in the treatment of intractable epilepsy[45] and are under clinical investigation for their possible roles in targeting mechanisms of aging and utility in managing diabetes, heart failure, neurodegeneration, and other diseases.[31,46] A recently registered clinical trial proposed use of ketogenic nutrition in intubated COVID-19 patients (NCT04358835). These multifaceted metabolites are not panaceas, but their pleotropic activities at the interface of aging, metabolism, and inflammation may be useful in mitigating aspects of respiratory viral infection, particularly among patients most susceptible to severe disease.

Blood ketone levels are normally only elevated during a period of fasting or when following a ketogenic diet (between 0.5 and 8 mM).[47] It is important to distinguish between "physiological" levels of ketosis,[48] which is an adaptive, regulated response to lowered carbohydrate availability and can be safely sustained over many months,[45,49] and the acute pathological condition of ketoacidosis. In ketoacidosis, a fundamental metabolic derangement (such as insulin resistance or substance abuse) leads to uncontrolled ketone production and to

ketone accumulation, which becomes a medical emergency.[50] Barriers to the implementation of novel dietary strategies to trigger controlled, physiological endogenous ketosis, such as fasting or ketogenic diet, include difficulty with adherence[51,52] and potential complications in disease states,[53] especially when there may be a higher risk of promoting dysregulated ketoacidosis. For example, undernutrition and prolonged fasting can be harmful when applied to the intensive care unit (ICU),[54,55] and infection (including COVID-19) may cause metabolic derangements that lead to development of ketoacidosis.[56,57] Notably, acidosis itself is associated with mortality in COVID-19 patients,[56] but it is unclear whether it plays a causative role versus being a marker of tissue hypoperfusion, renal failure, respiratory failure, or other pathologies.

Exogenous sources of ketones can directly raise circulating ketone levels equivalent to physiological levels (0.5–8 mM) within minutes, in a controlled manner without potentially burdensome dietary or pharmacologic interventions.[57] As ketones are normal, endogenous metabolites, bio-identical exogenous ketones have a strong safety profile and low risk of toxicity, and some examples are classified as "generally recognized as safe" for use as food ingredients (GRAS) by the US Food and Drug Administration, although none have yet undergone formal testing as part of an investigational drug program.

One family of exogenous ketone compounds are ketone salts. These are inexpensive to synthesize and are widely available to the public in consumer health products; however, they only modestly increase blood BHB levels (~1 mM BHB increase).[57] Medium-chain triglycerides provide a longer lasting modest ketosis (~0.5–1 mM BHB increase) without added salt load and have a body of clinical research supporting safety and efficacy for several metabolic outcomes in obese and diabetic patients and early-stage efficacy for improving metabolism in the aging brain and in Alzheimer's disease.[58–61] Medium-chain triglycerides are also widely commercially available, though acute dosing can be limited by gastrointestinal side effects.[62] Esters containing ketones and ketone precursors are also commercially available and result in higher blood BHB levels (~1–5 mM BHB increase).[57] The wide availability and extensive prior consumer use of most of these exogenous ketone compounds suggest that rapid clinical implementation would be feasible if and when clinical utility were to be demonstrated.

There may be immunological advantages of triggering a metabolic state that supports ketosis (i.e., lowered blood glucose and increased fatty acid oxidation), independent of increases in ketone bodies. For example, 4 h of fasting in mice, a time point that precedes detectable systemic elevations in ketone bodies, reduces circulating proinflammatory monocytes.[63] Also, ketogenic diet, but not the exogenous ketone precursor, 1,3-butanediol, protected mice against lethal influenza infection via activation of lung-resident gamma-delta T cells.[64] Given that different immune cell subsets express varying levels of ketogenic and ketolytic enzymes,[65] the role of ketone bodies in immune responsiveness will likely vary depending on infection, background inflammation, and underlying metabolic context.

Exogenous and endogenous ketone biology could be relevant to precisely the patient groups at greater risk of respiratory viral infection. First, with respect to aging, nutritional strategies that increase circulating ketone body concentrations increase healthspan and lifespan in laboratory rodents by mitigating multiple age-related

pathologies and improving overall health.[66–68] Second, patients with diabetes, with accompanying obesity, hyperglycemia, glycemic variability, and insulin resistance, have elevated NLRP3 activity, increased systemic inflammation, and high oxidative stress.[69] Endogenous and exogenous ketones have been demonstrated to reduce acute and/or chronic markers of glycemic load in healthy and diabetic populations.[41,49,70–73]

We hypothesize that consumption of exogenous ketones may improve specific clinical outcomes of respiratory viral infection through already-understood molecular mechanisms. Older patients and patients with diabetes, in whom these mechanisms are most relevant, may be the groups most likely to benefit from exogenous ketone body administration. In the following sections, we outline the rationale and highlight the mechanisms through which BHB alters cellular biology and integrated physiology, which may have direct or indirect impact on critical illness caused by respiratory viral infection, using SARS coronaviruses and influenza as key examples. Finally, we discuss outstanding questions that may be a "cause to pause" as investigations into this hypothesis move from bench to bedside.

MOLECULAR MECHANISMS AND CELLULAR BIOLOGY

Several known molecular mechanisms of the ketone body BHB have been implicated in respiratory virus life cycles and molecular pathogenesis (Figure 1). Most of these mechanisms are specifically implicated in viral replication. Here, we briefly summarize these BHB-regulated mechanisms and review the current state of knowledge of their roles in respiratory viruses.

BHB Protects against Oxidative Stress

Oxidative stress from a variety of sources can contribute to lung epithelial damage during infection with influenza[74] and subsequent ARDS.[75] Cytoplasmic nicotinamide adenine dinucleotide phosphate (NADPH) plays a dual role in the body's defense against oxidative stress. In immune cells, pentose-phosphate-pathway-derived NADPH serves as a cofactor for NADPH-oxidase-dependent reactive oxygen species (ROS) production, which plays a crucial role in the protective immune response but can also cause damage as part of pathological immune hyperactivation. In these cells, NADPH is also critical for reductive biosynthesis, activation-associated membrane expansion, and the production of lipid mediators, such as prostaglandins. However, in the cytoplasm of non-immune cells, NADPH reduces oxidized redox couples to sustain a protective antioxidant response (i.e., glutathione and thioredoxin systems). This is illustrated by data showing that maintenance of epithelial cell glutathione concentrations reduces viral replication following influenza infection,[76] although influenza-mediated decrease in NADPH oxidase activity in immune cells leads to increased susceptibility to further bacterial infection.[77]

Pentose phosphate pathway substrates are typically derived from glucose metabolism. However, in cells with the capacity to oxidize BHB, ketone metabolism can also result in an increase of cytoplasmic NADPH (via citrate).[78] Thus, in settings where glucose metabolism is unable to sufficiently maintain the cytoplasmic NADPH pool, BHB metabolism could provide an alternative route to reducing the cytosolic NADP/NADPH couple and protect against cell damage, although this effect still needs to be verified in the context of oxidative stress triggered by respiratory viral infection. Notably, the enzyme BHB

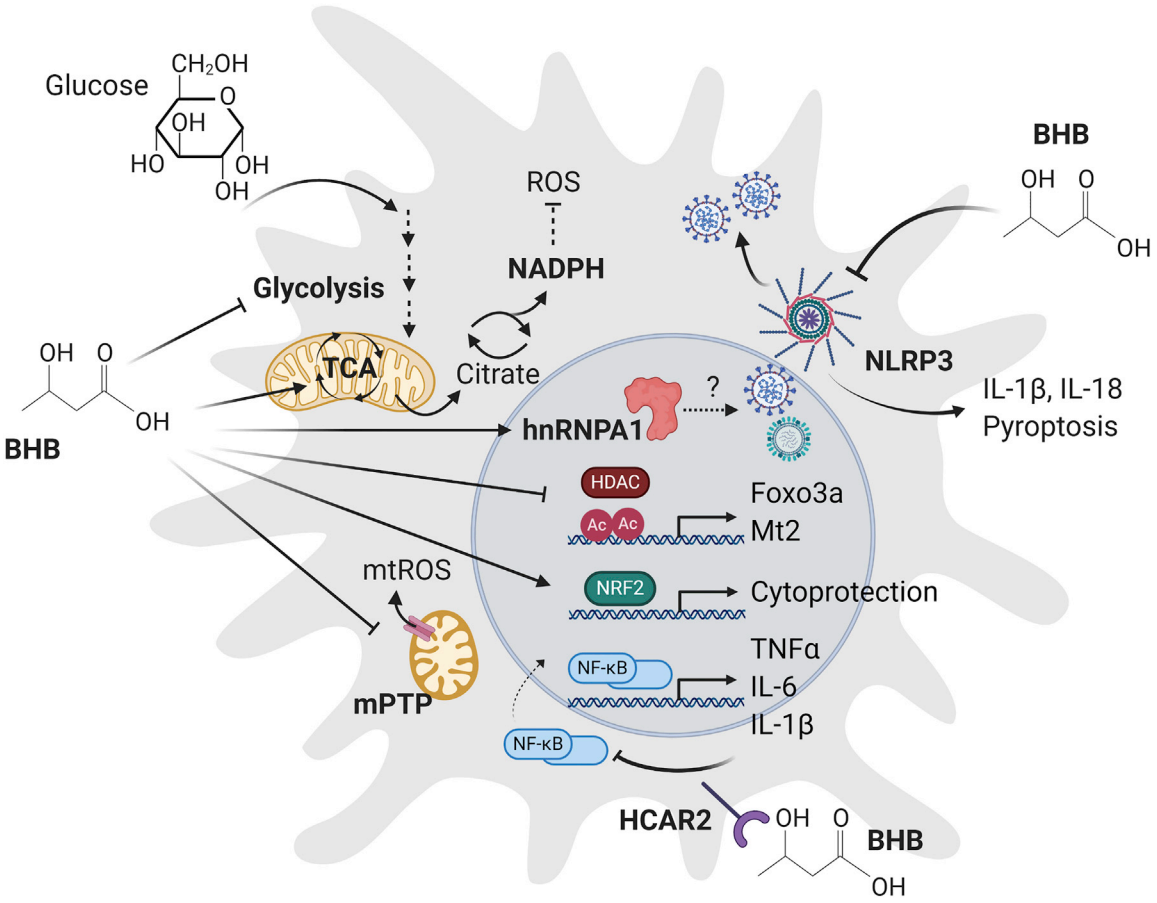

Figure 1. Molecular Mechanisms of Ketone Bodies Relevant to Viral Respiratory Infection

dehydrogenase, which catalyzes the initial step in BHB oxidation, is not expressed in neutrophils or monocytes,[79,80] and so elevated BHB would not be expected to affect cytosolic NADPH and have a stimulatory effect on either protective or pathological ROS production in these cells.

A second mechanism whereby exogenous ketones could mitigate oxidative stress is through upregulation of antioxidant genes. BHB activates the transcription factor Nrf2 to induce antioxidant response element (ARE) gene expression[81–83] and induces local histone acetylation at the promoter of oxidative stress resistance genes (*Foxo3a* and *Mt2*) by inhibiting activity of histone deacetylases histone deacetylase 1 (HDAC1) and HDAC2.[34,35,84] Both of these actions result in an increased expression of protective genes and cytoprotection, which was demonstrated in two independent studies using the kidney in a mouse model of chemically induced oxidative stress.[33,81] Similar effects have been further demonstrated in other tissues in multiple preclinical models.[34,35,82,83] Activation of Nrf2 is protective in multiple models of ARDS (reviewed in Liu et al.[85]). However, an inhibitory effect of BHB on HDAC activity may be counterproductive during viral infection. HDAC1 and 2 activity also play a protective role against influenza infection[86,87]; in fact, influenza actively dysregulates HDAC1 to allow effective replication.[86] The recently published SARS-CoV-2 interactome[88] indicates that this virus may also interact with HDAC2, although

the importance of this interaction in infection is unknown. Finally, in addition to BHB-induced upregulation of antioxidant defenses, ketone bodies may have a direct, protective antioxidant effect. Both BHB and acetoacetate can act as scavengers for diverse free radicals in both *in vitro* and *in vivo* models.[89] It should be noted that some evidence suggests that, under certain physiological conditions, such as hyperglycemia, acetoacetate (but not BHB) is associated with an increase in oxidative stress[90] (further reviewed in Jain et al.[91]), emphasizing that controlling glucose and ketone levels together may be important for optimal effect. Altogether, the multiple possible protective effects of ketone bodies on oxidative stress provide a compelling case for further examination in the specific context of viral infection and systemic inflammation.

BHB Directly Inhibits Proinflammatory NLRP3 Activation

Inflammasomes are essential components of innate immunity that sense pathogen- or damage-associated molecular patterns. They are highly regulated multimeric protein complexes that facilitate caspase-1 activation for the secretion of interleukin-1β (IL-1β) and IL-18. Although some degree of inflammasome activation is required for the protective immune response and the clearance of certain infections, excessive pathological activation can lead to tissue damage and systemic inflammation. As described in more detail below, both SARS-CoV and influenza are directly sensed by the NLRP3 inflammasome. NLRP3, which is expressed primarily in innate immune cells, is the best characterized inflammasome, in part due to its strong linkage to metabolic inflammation (i.e., obesity and diabetes) and driving age-related inflammation.[92,93] As obesity, diabetes, and age are also risk factors for respiratory viral infections, including influenza and SARS-CoV-2, collectively, these data strongly implicate inflammasome, and specifically NLRP3 activation, in their pathology.

Early clinical data from COVID-19 patients suggest a role for systemic inflammatory activation in the pathogenesis of severe disease, with higher levels of C-reactive protein (CRP), IL-6, IL-1β, and other proinflammatory cytokines and markers.[94–96] Some of this may be driven by excessive NLRP3 activation. A study of 47 patients with confirmed COVID-19 in Wuhan found that increased lactate dehydrogenase (LDH) levels most significantly correlated with disease severity.[97] LDH is released from cells undergoing an inflammatory form of cell death known as pyroptosis, which is induced by caspase-1 activation.[98] Systemic inflammasome-mediated inflammation could also instigate emergency granulopoiesis, which would explain the neutrophilia commonly observed in severe COVID-19 patients.

Preclinical data support a key role for the NLRP3 inflammasome in mediating the pathogenesis of both influenza[99] and SARS coronaviruses.[100] NLRP3 has several mechanisms for detecting viral infections, such as influenza or CoV. Cytosolic influenza RNA is directly sensed by the NLRP3 inflammasome, and this is required for protection.[101,102] Likewise, SARS-CoV proteins E, 3a, and 8b all activate NLRP3. E is a viroporin encoding a cation channel that increases intracellular sodium, calcium, and potassium flux, with the latter two being well-known inducers of NLRP3 activation and IL-1β production.[103] The ion channel activity of E protein is crucial for both viral fitness and severity of disease in mouse-adapted SARS-CoV. Abrogation of the ion channel activity results in improved survival, reduced ARDS pathology, and reduced airway inflammatory markers, including IL-1β.[104] Similarly, influenza virus encodes a proton channel, M2, that is required for virus fitness and stimulates NLRP3.[105] SARS-CoV

accessory protein 3a activates NLRP3 via TRAF3-mediated ubiquitination of apoptosis-associated speck-like protein containing a CARD (ASC), colocalizing with TRAF3 and ASC specks and increasing IL-1β production.[106] 3a is also a viroporin that encodes a potassium channel. Potassium efflux and mitochondrial ROS generation are required for activation of NLRP3 by 3a.[107] Finally, SARS-CoV accessory protein 8b interacts with the LRR domain of NLRP3 and also stimulates NLRP3 activation and IL-1β release along with forming insoluble intracellular aggregates to activate autophagy and ER stress pathways.[108] Altogether, studies of both influenza and SARS coronaviruses indicate a critical role for NLRP3 activation and IL-1β production in driving severe disease.

Although the possibility that additional inflammasome complexes contribute to COVID-19 morbidity has not been ruled out, it was recently reported that bats, the natural host of many zoonotic viruses and asymptomatically carry coronavirus, have reduced NLRP3 inflammasome activation in response to MERS and other stimuli.[103] Bat species show reduced *Nlrp3* transcriptional activation in response to inflammatory stimuli and reduced inflammasome activation and express an abundant splice variant with an exon 7 deletion that further reduces activation. These adaptations appear to all arise from positive selection within the LRR domain of NLRP3 and help bats avoid serious illness from RNA viruses, such as MERS and Ebola, without affecting viral load.[103]

Importantly, in multiple *in vitro* and animal studies that have utilized both dietary ketosis and exogenous ketone treatment, BHB inhibits NLRP3 activation in peripheral macrophages and neutrophils,38 in the retina,[109] and in the CNS[110] and reduced systemic inflammation in a rat model of gout, which is driven by NLRP3 activation.[40] However, experiments attempting to repeat these findings in human subjects challenged with lipopolysaccharide (LPS) have produced inconsistent results. A recent study of healthy young men given intravenous (i.v.) BHB and LPS found BHB was associated with a small increase in circulating IL-1β[111]; similarly, a study by Neudorf et al.[112] found a small increase in inflammatory markers in *ex vivo* LPS-stimulated peripheral blood mononuclear cells from healthy subjects given oral BHB compared with a calorie-free control. On the other hand, a follow-up study by the same group showed no additional effect of BHB on inflammatory markers in in *ex vivo* LPS-stimulated peripheral blood mononuclear from obese subjects following an oral glucose challenge,[113] which suggests a context dependency of BHB-NLRP3 on circulating glucose or insulin concentrations. This is further underscored by a recent study demonstrating that changes in insulin and glucose concentrations modulate the effect of BHB on NLRP3 on human monocytes from diabetic patients *in vitro*,[114] reinforcing the complexity of this interaction, which remains to be fully defined. In addition, it is not known whether BHB affects NLRP3 activation specifically in alveolar macrophages or lung epithelial cells as it does in blood macrophages. Given the strong preclinical evidence for BHB-mediated NLRP3 inhibition, and the key role of NLRP3 in both protective sensing of viral infection and the progression to pathological hyper-inflammation, it is vital to establish whether and how exogenous BHB may alter NLRP3 activity in the context of respiratory viral infection across a physiologically relevant range of BHB, glucose, and insulin concentrations. This would result in BHB dosing guidelines that account for timing of disease progression (i.e., possibly favoring late administration), background metabolic state (i.e., aging or diabetes), and a specific circulating level of BHB.

BHB Has Additional Anti-inflammatory Effects Mediated by HCAR2 and NF-κB

NF-κB is a potent proinflammatory transcription factor, induced by numerous signaling pathways, including the cell surface receptor HCAR2, and oxidative stress. Both NF-κB and HCAR2 are upregulated in diabetic patients,[37,115] and NF-κB is strongly activated during viral infection. Upon activation, NF-κB translocates into the nucleus to induce expression of tumor necrosis factor alpha (TNF-α), IL-6, and IL-1β with multiple downstream effects, including inflammasome activation, apoptosis, and, importantly, further stimulation of NF-κB activation, which creates an inflammatory positive feedback loop. Despite clear evidence that NF-κB plays an important protective role in the immune response to influenza infection[116] and that impaired production of downstream cytokines, such as IL-6, can increase influenza-related mortality,[117] other studies have shown NF-κB can be "hijacked" to promote influenza replication,[118,119] resulting in some debate over its overall role in disease progression.[119] Inhibition of NF-κB has been suggested to be a possible treatment strategy for influenza infection.[120,121] Although the role of NF-κB in SARS-CoV-2 has yet to be fully elucidated, the high levels of TNF-α and IL-6 in patients with severe COVID-19 infection are strongly suggestive of its activation.[96,122]

BHB strongly inhibits NF-κB-mediated inflammation by binding to HCAR2 on central-nervous-system-resident macrophages.[123,124] Chronic administration of various exogenous ketone bodies fed *ad libitum* in rodents mobilizes fatty acid substrates and lowers NF-κB-related circulating cytokines IL-1β and IL-6, among others.[125] The effect of BHB on HCAR2 and NF-κB in lung-resident macrophages has not yet been tested, although if an effect does occur, *in vivo* infection studies should consider timing of BHB administration to avoid interference with the protective effect of NF-κB, which could worsen overall disease outcomes.

BHB Reduces Apoptosis via Mitochondrial Permeability Transition Pore (mPTP) Closure

Prolonged opening of the mPTP is one of the mechanisms through which ROS can induce cellular injury and promote disease. Opening of the mPTP destroys the mitochondrial proton gradient that drives ATP production and allows entry of cations (Ca^{2+} and Mg^{2+}) into the negatively charged inner mitochondrial membrane space, both of which severely impair mitochondrial function. Many viruses directly take advantage of this pathway to trigger apoptosis; for example, influenza PB1-F2 protein acts via mPTP opening to sensitize cells to apoptosis stimuli.[126] Closure of the mPTP was suggested as a druggable target in a recent preprint describing a bioinformatics analysis of SARS-CoV-2 binding interactions.[127]

Oxidation of BHB closes the mPTP, providing cellular protection by maintaining the electrochemical potential gradient required for ATP generation through oxidative phosphorylation,[128] thereby providing the energy required to restore normal Ca^{2+} and Mg^{2+} homeostasis and cellular volume regulation. BHB-mediated closure of the mPTP in conjunction with protection against ROS has been directly demonstrated *in vitro*35 and *in vivo*.[129] A key question that must be addressed is whether physiological concentrations of BHB protect against virally triggered apoptosis via an mPTP-dependent mechanism.

BHB Interacts with RNA-Binding Ribonucleoprotein hnRNPA1

Several viruses are known to interact with host cells heterogeneous nuclear ribonucleoproteins (hnRNPs); a family of RNPs that regulate mRNA stability, splicing, and translation. The nucleocapsid proteins of the coronaviruses SARS-CoV,[130] mouse hepatitis virus (MHV),[131] and porcine epidemic diarrhea virus (PEDV)[132] all interact

in vitro and colocalize *in vivo* with human hnRNPA1, although influenza interacts with the related hnRNPA A2/B1.[133] The preprint interactome of SARS-CoV-2 reveals only weak interactions of hnRNPA1 that do not meet stringency criteria.[88] hnRNPs are thought to assist in viral replication.[134] Overexpression of human hnRNPA1 accelerates MHV genome replication,[132] and knockdown inhibits replication of both MHV and PEDV.[132] A similar pattern has been found whereby knockdown of hnRNPA2/B1 reduces influenza replication136 and overexpression increases replication.[135] Recently, BHB was reported to directly interact with hnRNPA1, in the first example of a BHB interaction target identified by a systematic binding screen.[136] The BHB-hnRNPA1 interaction enhances stabilization of Oct4 mRNA, leading to reduced senescence in mouse vascular endothelial cells. The implications of this BHB-hnRNP interaction for replication of viruses, such as SARS-CoV-2 or influenza, are currently not known but could imply enhancement of viral replication.

BHB Inhibits Glycolysis

Viruses can induce changes to host cell metabolism, or use host-derived metabolites, to facilitate their replication. Metabolic plasticity is key to a successful antiviral immune response: upregulation of glycolytic programming is essential for activation and effector function of many immune cell types, but transition back to oxidative metabolism is required for establishment of long-lived memory CD8 T cells.[137,138] Induction of non-immune cells by relatively common pathogens, such as influenza, rhinoviruses, and human respiratory syncytial virus, increases glycolytic rate and viral replication in infected cells.[139–141] Complete inhibition of glycolysis by 2-deoxy-D-glucose (2-DG), an inhibitor of hexokinase (i.e., the committed step of glycolysis), effectively defends against infection by several viruses in cell culture, suppressing influenza replication *in vitro*[141] and rhinovirus infection *in vivo*.[142] Although the primary mechanism for this is believed to be creation of energetic stress, secondary protective effects of 2-DG include activation of the unfolded protein response (UPR) to prevent the assembly of viral proteins[143] and modulation of viral release through changes in glycosylation.[144] Recent work demonstrated that non-toxic concentrations of 2-DG prevented SARS-CoV-2 replication in Caco-2 cells,[145] and a 2-DG analog (WP1122) is under accelerated development for use in a COVID-19 clinical trial.

BHB directly inhibits glycolysis in multiple tissues, such as heart, brain, skeletal muscle, and in tumors.32,[146–148] This occurs via an increase in cytoplasmic citrate, which decreases the activity of phosphofructokinase as well as a direct inhibitory effect on pyruvate dehydrogenase that is mediated by an increase in ketone-derived acetyl coenzyme A (CoA). Inhibition of glycolysis by ketones may not create the same energetic stress as 2-DG and analogs (given the availability of ketones) and may not have the same effects on the UPR or glycosylation. The current gap is to demonstrate that inhibition of glycolysis specifically reduces viral replication, and that this can be driven by exogenous application of BHB to infected epithelial cells. It would be important to expand this testing in an *in vivo* model to ensure that glycolysis required for immune cell function was not suppressed by BHB.

INTEGRATED PHYSIOLOGY

Clinical outcomes in severe respiratory virus infection are driven not only by replication of the virus itself but by also the complex host-pathogen immune interactions that give rise to ARDS, by other organ-specific dysfunctions driven by the virus or by hypoxemia, and by complications of critical illness, such as loss of muscle function and the acute confusional state delirium. These disproportionately affect both

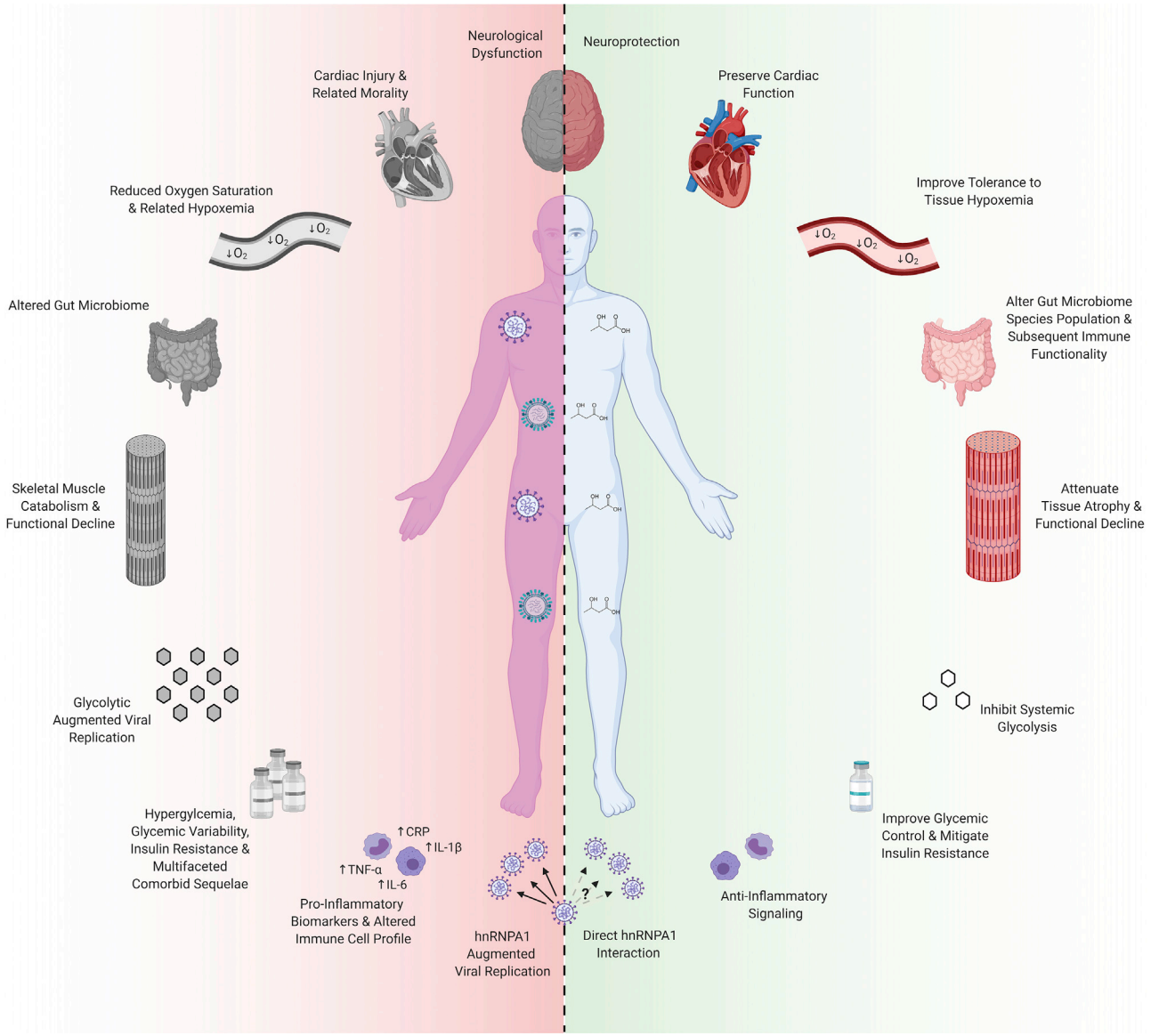

Figure 2. Physiological Mechanisms of Ketone Bodies Relevant to Severe Respiratory Viral Infection and the Syndromes of Critical Illness

mortality and long-term outcomes in survivors, such as cognitive and functional decline. Here, we review how the molecular mechanisms of ketone bodies described above may impact these crucial, complex manifestations of severe respiratory viral infection (Figure 2), including drawing analogies from existing literature of ketone bodies effects in, e.g., cardiac function and hypoxemia in other clinical contexts.

Immunometabolic Modulation in ARDS

ARDS develops if the protective, early immune response is insufficient to contain viral infection. The pathophysiology of ARDS includes aberrant immune and inflammatory responses in the lung driven by innate immune activation that results in endothelial injury, interstitial and intra-alveolar edema, filling of alveoli with protein-rich cellular exudates, and interstitial fibrosis.[23] Inflammatory markers, including IL-1β, IL-6, and TNF-α, are elevated in blood and alveolar fluid. Inflammation and mitochondrial dysfunction result in cell death and damage of epithelial cells.[149]

Iatrogenic injury from ventilation, including overpressure and hyperoxia, can cause further inflammatory and mechanical damage.[150] Current therapy centers on supportive care that maintains adequate gas exchange while minimizing further injury.[22]

Modulation of innate immune cells activation by ketone bodies may be relevant to patients who have progressed to ARDS. As described above, BHB inhibits NLRP3 in peripheral macrophages to affect inflammation-mediated disease[38,40] and inhibits NF-κB-mediated inflammation by binding to HCAR2 on central-nervous-system-resident macrophages.[123,124] Oxidation of the ketone body acetoacetate by liver-resident macrophage-like Kupffer cells reduces fibrosis in mouse models of high-fat liver injury.[79] Whether this modulation of innate immune responses extends to alveolar macrophages and the lung, and whether ketone bodies would thereby slow the inflammation and fibrosis of ARDS, is an area for investigation. Similarly, other effects of ketone bodies, including increasing mitochondrial energy production, reducing oxidative stress, and promoting resistance to ischemia and hypoxia (discussed further below), may be relevant to reducing alveolar injury in ARDS.

BHB Preserves Cardiac Function

Viral infection with influenza increases the risk of both acute and chronic cardiac injury and related mortality[151–154]; early reports so far suggest that cardiac injury may be even more important in COVID-19.[155] In early reports, cardiac complications and markers of cardiomyocyte injury are among the most important predictors of mortality in COVID-19.[156,157] Mechanisms for cardiac injury in COVID-19 may include viral or inflammatory myocarditis, arrhythmias, cardiac stress from hypotension and hypoxemia, and acute coronary syndrome associated with the hypercoagulable state.[155] Pre-existing heart failure is common in patients hospitalized with COVID-19 and associated with worse outcomes, but these manifestations also occur in patients without underlying cardiac disease. The link between heart failure and respiratory virus mortality is starkly illustrated by the 18% reduction in all-cause and cardiovascular death achieved with yearly influenza vaccination in patients with heart failure.[158]

Ketones are readily oxidized as a fuel for the heart, particularly under conditions of energetic stress, such as heart failure (reviewed in Puchalska and Crawford46). Data from both humans with heart failure and mouse models identify a metabolic switch to favor ketone body metabolism in cardiomyocytes,[159,160] which is adaptive: genetic deletion of the enzymes required to metabolize BHB accelerates dysfunction and pathological remodeling.[44,161] *Ex vivo* models have shown an ~24% improvement in cardiac efficiency when ketones are metabolized compared with glucose alone.[128] More recently, both *in vivo* and human clinical studies have shown significant improvements in cardiac function with intravenous ketone body infusion, including dose-dependent increases in ejection fraction and cardiac output.[44,162,163] In preclinical models of acute cardiac ischemia, BHB protects against myocardial injury,[164] likely through similar mechanisms as described below for hypoxemic injury. Ketone infusion is not part of any clinical care guideline for heart failure or cardiac ischemia but is under active clinical investigation.46 As mechanisms of cardiac injury in respiratory viral infection are clarified, investigation might be extended into this context as well.

BHB Improves Tolerance to Tissue Hypoxemia

Respiratory viral infections, such as influenza and COVID-19, commonly cause severe hypoxemia, which is also a defining feature of ARDS.22 Lung-protective ventilation strategies require tolerating moderate hypoxemia, and refractory hypoxemia

eventually causes multiorgan failure and death. Hypoxia elevates systemic and tissue-specific (i.e., lung) inflammatory and oxidative stress biomarkers.[165–168] Activation of several key common pathways is conserved during hypoxia, infections, and lung injury, including hypoxia-inducible factor-a (HIF-1α) and inflammatory and oxidative pathways, such as NF-κB and NLRP3 (discussed above).[169–171] HIF-1α appears to mediate its effect in these environments via adenosine receptor activation.[169,170]

Elevation of blood ketones has been shown to be broadly protective against hypoxia-related tissue damage, particularly in the brain. In a variety of models of hypoxic and ischemic cerebral injury, treatment with exogenous BHB maintained brain ATP levels, increased neuron survival, decreased cerebral infarct volume, decreased cerebral edema, and improved cognitive performance.[172–174] Additionally, exogenous ketones mitigate inflammation and neuropathology in various model systems via adenosine 1a receptor activation,[175–177] suggesting ketones may attenuate HIF-1α-induced inflammation and oxidative stress in hypoxia. Furthermore, exogenous sources of ketones protect cognitive function during hypoglycemia in mice (A.P.K., unpublished data) and humans,[178] hypoxia in mice177 and humans (B.J.S. and A.P.K., unpublished data), and strenuous exercise.[179] The effect of ketones on non-neuronal metabolism during hypoxia and in the specific context of respiratory viral infection is an open area for investigation.

BHB Improves Systemic Glycemic Control and Mitigates Insulin Resistance

Type 1 and 2 diabetes are distinct diseases that share the common hallmark of glycemic dysregulation with elevated circulating glucose levels, glycemic variability, elevated HbA1c, and sequelae of overlapping comorbidities. Both forms of diabetes impact several stages of viral respiratory disease.[13-17] First, as discussed above, glucose availability and glycolytic metabolism has been directly implicated in increased viral replication.[141,180] Second, glycemic dysregulation linked to diabetes increases systemic inflammation and oxidative stress,72,[181] both processes that are also heavily implicated in disease progression of influenza77 and SARS-CoV-2.[182] Avoiding both hypo- and severe hyperglycemia by insulin therapy is associated with improved outcomes in hospitalized and ICU patients[183] and would be the standard of care applied to most patients with severe cases of influenza or COVID-19. A recent retrospective case study of COVID-19 patients with type 2 diabetes supports this, demonstrating that blood glucose between 3.9 and 10 mM (70 and 180 mg/dL) was associated with lower mortality.[19] Taken together, this suggests that strategies that target inflammation and oxidative stress, improve insulin sensitivity, or improve glycemic control without adverse effects of hypoglycemia could potentially alter respiratory viral infection risk and/or progression to severe disease.

Acute exogenous ketone administration improves metrics of insulin sensitivity in both healthy and obese patients.[41,70,71] Fasting-adapted ketosis prevents symptoms from even severe insulin-induced hypoglycemia.[184] Furthermore, both acute and chronic administration of exogenous ketones lowers glucose levels, mitigates hypoglycemic injury, and improves disease outcomes in multiple animal models of multifactorial inflammatory disease.[178,185] BHB-mediated lowering of blood glucose might have the further benefit of facilitating optimal ketone body action on inflammatory and oxidative stress pathways, which may be attenuated in the presence of high glucose[91,114] (discussed above). Together, these data suggest that exogenous ketone bodies might attenuate glycemic dysregulation and its associated adverse outcomes in patients at high mortality risk from viral infection.

BHB Alters Gut Microbiome to Modulate Inflammation

Ketogenic diets alter the human and mouse gut microbiota.[186] Separately, multiple groups have also observed a reduction in T_H17 cells in human and mice exposed to ketogenic diet.[187,188] Recent studies suggest a casual pathway wherein the ketone body BHB suppresses the growth of specific immunomodulatory members of the human gut microbiota (*Bifidobacterium sp*), leading to a decrease in small intestinal lamina propria T_H17 cells.[189] More work is needed to explore the mechanisms through which BHB impacts gut bacterial growth, host-microbiome interactions within the intestinal mucosa, and the broader consequences of these observations for systemic inflammation.

The impact of this specific pathway in COVID-19 is unknown, but there is evidence that the microbiome influences host inflammation and antiviral immunity in influenza.[190] In antibiotic-treated mice, primary challenge with influenza results in higher viral titers within the lung and lower antigen-specific immune responses.[190] In germ-free mice, the antibody-specific responses to influenza are diminished, and the innate signaling molecule TLR5 has been invoked as a specific mediator of the adjuvant effects of the gut microbiome.[191] The effect of gut microbiota in human response to respiratory viral infections is still emerging. Although broad-spectrum antibiotics provided prior to influenza immunization did not affect initial responses to influenza vaccination, human subjects receiving broad spectrum antibiotics with low initial titer to vaccination had significantly lower immunoglobulin G1 (IgG1) and IgA1 on re-challenge.[192] Though conceptual, the role of ketone bodies in augmenting human inflammatory responses and protective immunity to respiratory viruses through modulation of the microbiome could be relevant to individuals with COVID-19.

Ketone Bodies Attenuate Muscle Catabolism and Functional Decline

Muscle function and mass are strong predictors of morbidity and mortality in many clinical settings.[193–195] Surviving critical illness and ARDS often does not mean a return to "normal life"—disability and loss of prior independent functioning are common, especially in older adults.[196] More than half of survivors have significant post-recovery weakness[197] and new disabilities in instrumental activities of daily living.[198] Consequently, early mobilization aimed at preventing weakness and disability is a core element of new critical care practice guidelines.[199,200] Even non-critical illness in hospitalized older adults commonly results in functional decline and loss of independence.[201,202] Muscle atrophy, damage, and dysfunction, driven by immobility, inflammation, and catabolism, are major drivers of these phenomena.

Influenza can disrupt patient mobility and directly induce catabolism in a dose-dependent manner via augmented proinflammatory cytokines (TNF-α and IL-6) and myostatin and repressed anabolic signaling (insulin growth factor 1 [IGF-1]), which is exacerbated and/or prolonged with aging.[203,204] In fact, proinflammatory cytokines (TNF-α, IL-6, and IL-1β),[182,203–206] increased markers of muscle catabolism, occurrence of excessive muscle breakdown, myalgia, myositis, and functional decrements have all been observed in patients with COVID-19[207–210] and influenza.[211] Patients requiring ventilation also experience ubiquitin-associated diaphragmatic atrophy that predicts morbidity and mortality even 1 year following hospitalization.[197,212–214]

Exogenous ketone bodies can directly regulate muscle protein metabolism and prevent catabolism[111,215–220]; a muscle-sparing effect is consistent with the evolutionary role of ketones to prolong survival during starvation. BHB infusion lowers blood urea

nitrogen and urinary excretion[215,219] similar to diet-induced ketosis.[221–224] Anti-catabolic effects of exogenous ketones occur in multifaceted inflammatory settings and ubiquitin-driven atrophy.[111,185,225] For example, a single dose of exogenous ketones attenuated infection-induced tissue catabolism by 46% while improving time to recovery from inflammation-induced catabolism.[185] Furthermore, exogenous ketones mitigated muscle function decrements induced by depletive exercise training.[226] A driver of this effect is believed to be a reduction in pro-catabolic inflammation mediated by BHB interaction with HCAR2 and NF-κB as discussed above.[125] However, anti-catabolic effects of ketones can occur independently of NF-κB signaling.[111,185] We demonstrated that ketone bodies can attenuate atrophy in multifactorial catabolic environments where alterations in proinflammatory cytokines, IGF-1/insulin, FOXO3a, and ubiquitin proteasome degradation pathway are observed,[185] pathways mechanistically implicated in respiratory viral infection and aging.[203,204] Altogether, mechanistic evidence suggests that ketones could mitigate muscle catabolism and functional impairment in patients with severe infection, although the specific catabolic pathways in the skeletal muscle of influenza or COVID-19 patients and the functional impact of ketones on ICU recovery have not yet been directly determined.

Immunometabolic Modulation in Delirium

Delirium is an acute confusional state that occurs in the majority of patients with critical illness and is most common in older adults.[227] It is independently associated with mortality, prolonged ICU and hospital stays, and post-recovery cognitive decline.[228,229] Delirium is not inevitable, as half of cases or more are preventable through systematic multicomponent clinical interventions,[230] including in the ICU.[231] The impact of delirium on both acute resource utilization and long-term outcomes makes it a crucial clinical target in viral pandemics.[232] The pathophysiology of delirium is not well understood but features both systemic and central nervous system inflammatory activation as well as metabolic disturbances, leading to neuronal dysfunction.[233] Unsurprisingly, delirium appears to be common in early descriptions of COVID-19.[234] Whether delirium is specifically affected by SARS-CoV-2 is unknown, but it may be suggestive that inflammatory biomarkers similar to those elevated in COVID-19 are among the most common biomarkers associated with delirium (e.g., IL-1β, IL-6, IL-8, and CRP).[235]

Several of the ketone body mechanisms described above may be relevant to preventing or resolving delirium in severe respiratory illness. Inhibition of NLRP3 and NF-κB may reduce systemic or brain inflammatory activation. Protection from hypoxic stress responses or hypoglycemic energy deficits may protect neuronal function. Provision of ketone as energetic substrates, particularly in older adults with impaired cognitive function,[234] may improve resilience to delirium or restore neuronal function. The utility of exogenous ketones in delirium is unknown, but elucidating their impact on molecular mechanisms and outcomes in preclinical models and clinical studies are important subjects for investigation.

CAUSE TO PAUSE?

It is important to re-emphasize that the characteristics of ketone metabolism and biological effects in the specific context of viral infection are as yet largely unknown. Most work has been undertaken in model systems that do not always translate directly to humans, whether due to inter-species differences in ketone metabolism or the targeted cellular pathways. Furthermore, based on existing data, some effects of exogenous ketones could be considered either ineffective or detrimental in the context of severe illness. As we have highlighted throughout this review, some

effects of BHB on cellular immune processes could be harmful if they interfered with the early immune response rather than dampened the late, pathological immune hyperactivation.

First, although *in vitro* and animal work consistently reinforce an inhibitory effect of BHB on NLRP3 activity, recent human studies have been equivocal and suggest that exogenous ketones might have no effect or even increase cytokine release under some conditions.[111–113] It is also unclear whether inhibition of NLRP3 (should this occur) is helpful to control the excessive immune response in ARDS or in fact harmful by inhibiting the response that is vital to infection control. Therefore, the timing of exogenous ketone treatment may be an essential consideration. Second, some of the proposed mechanisms above might increase viral replication, for example, if the BHB-hnRNAPA1 interaction stabilizes or promotes the activity of that host RNP in RNA virus replication, or if BHB-mediated inhibition of HDAC1 and 2 increases viral replication. Third, several observed physiological effects of exogenous ketones may complicate severe illness and require careful monitoring. Acute cardiovascular changes, such as increasing resting heart rate[162,163] and increasing blood flow to the brain and heart via vasodilation,[162,163,236] are perceived as potentially therapeutic but would need to be monitored in severely ill patient groups. Studies have demonstrated a transient, mild metabolic acidosis following ketone ester administration, a mildly alkalizing effect of ketone salts,[57,237] and a transient fall in plasma potassium with both esters and salts.[57,162] Exogenous ketosis in healthy individuals decreases endogenous ketone production via inhibition of lipolysis and therefore should reduce the risk of uncontrolled ketoacidosis.[72,238] However, any proposed exogenous ketone studies should proceed with caution and carefully monitor and control ketone and glucose levels, titrating administration as needed, which may be complicated given the increased incidence of ketoacidosis during infection.[239,240]

Mechanistic work using ketone bodies in relevant models is vital to support any move into clinical investigations, and any clinical testing should be appropriately staged and managed. As the relevant mechanisms of ketone action are defined, it would be important to monitor for mechanism-specific adverse effects; this could be informed by known pharmacological agents that target the same mechanism. Finally, it will be essential to investigate the ideal timing, dose, ketone compound (ester versus salt), and delivered ketone moiety (BHB versus acetoacetate) in order to effectively utilize exogenous ketones as an immunometabolic countermeasure.

OUTSTANDING RESEARCH QUESTIONS

Despite a robust body of supporting basic science data underpinning these mechanisms of ketone bodies potentially relevant to severe respiratory viral illness, there is a clear need to directly demonstrate the role of these mechanisms in viral infection. A coordinated approach could simultaneously pursue clinical and preclinical studies in order to rapidly appraise the utility of exogenous ketones in viral infection, such as influenza and SARS-CoV-2 (Table 1). We provide to the community a detailed outline of proposed investigations at https://www.impactmetabolism.org/, including key mechanistic questions to be resolved in animal and *in vitro* models, and guidance on designing clinical studies of exogenous ketones targeting respiratory viruses or the complex syndromes of critical illness.

Table 1. Key Outstanding Research Questions

Key Questions
Preclinical
How do ketone bodies affect replication of influenza A or SARS-CoV-2?
What is the fate of ketone bodies in the lung?
How does treatment with ketones affect cellular metabolism, redox state, and mitochondrial energetics in lung immune and non-immune cells in health and during viral infection?
How do ketone bodies affect innate immunity in the lung following influenza or SARS-CoV-2 challenge? What is the role of NLRP3, HCAR2, and adenosine A1 receptor?
What are the mechanisms by which ketone bodies affect cardiomyocyte, skeletal muscle, and/or cognitive dysfunction caused by influenza or SARS-CoV-2?
Clinical
How might exogenous ketones affect viral replication and progression to disease in ambulatory influenza- or SARS-CoV-2-positive patients?
Do exogenous ketones affect systemic and local lung inflammation, innate immune activation, and progression to ARDS following viral infection?
In severely ill patients, can exogenous ketones support cardiac, skeletal muscle, and cognitive function through reduced oxidative stress and increased tolerance of hypoxemia?
How will exogenous ketones affect glycemia and hemodynamics in critically ill patients?
In older adults, can exogenous ketones help preserve muscle function in acute illness and/or affect the incidence or severity of delirium associated with inflammatory activation and metabolic dysfunction?

SUMMARY

There are multiple cellular and systemic mechanisms whereby ketone bodies might impact severe viral infections, such as influenza or SARS-CoV-2. Evidence across various model systems and/or clinical contexts support potentially relevant molecular mechanisms of ketone bodies, including provision of energetic support, attenuation of inflammation and oxidative stress, apoptosis resistance, maintenance of metabolic homeostasis, and others. These mechanisms have yet to be tested in the specific context of severe respiratory viral infection but could be hypothesized to prevent and mitigate disease as well as support recovery. Further investigation of ketone bodies in respiratory viral illness is warranted, informed by preclinical mechanistic work and with appropriate caution used in clinical studies. In considering the translatability of potential interventions, the natural history of ketone biology in humans provides strong evidence of safety, and the existence of multiple sources of exogenous ketones could facilitate translation. Consequently, exogenous ketone bodies represent a readily deployable tool that could impact multiple mechanisms directly linked to disease outcomes, making these compounds a priority for rapid investigation.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.J.S., A.P.K., and J.C.N.; Writing – Original Draft, B.J.S., A.P.K., E.L.G., V.U., and J.C.N.; Figures, A.P.K. and E.L.G.; Writing – Review and Editing, all authors.

DECLARATION OF INTERESTS

J.C.N. and E.V. are co-founders of and shareholders in BHB Therapeutics, Ltd., which is developing products relating to ketone bodies. B.J.S. is a shareholder of HVMN, Inc., which markets products relating to ketone bodies and of BHB Therapeutics, Ltd. J.C.N., E.V., B.J.S., and A.P.K. are inventors on patents related to the use of ketone bodies. J.C.N. is on the scientific advisory board of Virta Health, Inc. E.V. is an advisor to Keto Fuel, Inc. P.J.T. is on the scientific advisory boards for Kaleido, Pendulum, Seres, and SNIPRbiome. All other authors declare no competing interests.

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