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Review Article

Metabolic Vulnerability and Immune Challenge: Interactions between Inherited Disorders, Metabolic Syndrome, and Infection Risk

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Abstract

Inherited Metabolic Diseases (IMDs) are rare genetic disorders with an enzyme and/or transport system dysfunction of a metabolic pathway. Infections frequently induce Acute Metabolic Decompensation (AMD) in patient with IMDs, and may also compromise the outcome of disorders not primarily recognized as crisis prone. On the other hand, immunocompromise resulting from metabolic defects can render the host more vulnerable to recurrent or severe infections. Metabolic syndrome (MetS) is a cluster of metabolic symptoms, including visceral obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension that are interlinked to cause increased population risk of chronic disease and impaired immune defences. The worldwide prevalence of obesity, a main contributor for MetS, nearly tripled between 1975 and 2018 and over half of all adults are predicted to be obese by 2050. In addition to NCDs, MetS modulates host-pathogen interactions, rendering the host more susceptible to severe viral infections including flu and coronaviruses. Here, we review recent findings that challenge this dogma and demonstrate a new concept in the regulation of host defense: early metabolic reprogramming of both immune and nonimmune cells powerfully determines infection outcome, severity of disease, and long term health. This review discusses the relationships between IMDs and infections in a bidirectional manner examining mechanisms, impact of diet, immune metabolic disturbances, and novel treatments.

Keywords: Inherited Metabolic Diseases; Metabolic Syndrome; Immune Metabolism; Host Pathogen Interactions; Acute Metabolic Decompensation.

INTRODUCTION

IMDs represent a heterogeneous group of more than 1,400 conditions classified by the International Classification of Inborn Metabolic Disorders [1]. Certain types of Inborn Metabolic Diseases (IMDs), including urea cycle disorders, amino acid disorders, organic acidemias, carbohydrate metabolism disorders, fatty acid oxidation disorders, and mitochondrial abnormalities, can be classified under the functional category of IMDs susceptible to Acute Metabolic Decompensation (AMD). The long-term organ problems in the severe crises are the part of the symptoms [2]. Patients are more prone to infections which is the common feature of many metabolic disorders. The body's metabolism can be overwhelmed when infectious occur as they raise energy needs, inflammation and the pressure of catabolic. Besides, the functionality of immune system cannot proceed properly when metabolic pathways and the production of energy are impaired. A vicious cycle is created when metabolism become weaker for infections which is the main cause for serious health problems or even death [3,4].

Lymphocytes refer to different sources of energy depending on their condition. For example, resting T cells largely use oxidative phosphorylation (OXPHOS), whereas effector T cells use aerobic glycolysis during anabolic metabolism [5,6]. B cells, unlike T cells, increase both aerobic glycolysis and mitochondrial oxygen consumption through OXPHOS upon stimulation [7]. When the pathways are collapsed like IMDs, the immune cells aren't work properly. As a result, the body can't fight against the infection [8,9].

HIV, SARS-CoV-2, and hepatitis C virus are examples of viruses that change glycolysis, The Tricarboxylic Acid (TCA) cycle, and mitochondrial activity to make the metabolites needed for viral replication while avoiding detection by the immune system. For people with IMDs, these changes in metabolism caused by pathogens put even more stress on already weak systems, making acute metabolic crises and severe disease more likely [10-13].

Also, acquired metabolic diseases have comparable weaknesses. Metabolic Syndrome (MetS) is a chronic proinflammatory state that makes the immune system work less well and makes infections worse [14]. Insulin resistance, hypertension, obesity, dyslipidemia, and glucose intolerance are the main consequence for MetS. The advantages of metabolic dysregulation in MetS is taken by viruses which much like they do in IMDs [15]. So, it shows a common theme that cellular metabolism can be changed inheritably or acquired which have a big effect on immune system. As a result, infection can occur easily due to vulnerable immune system. The recognition of intricate interplay emphasizes the necessity of proactive and early interventions. Besides, this strategy can be helpful to restore metabolic balance and offer a dual approve for improving metabolic health and host defense.

Infections Facilitate Metabolic Decompensation

Ammonia is more difficult for the body to excrete when UCDs are present. Hyperammonemia which is caused by a viral or bacterial infection that is the result of a protein-based breakdown cycle and it is difficult to manage [16,17]. Standard host immune responses can trigger crises in UCD patients as seen in experimental models such as influenza-infected OTC deficient mice which show infection-induced decreases in carbamoyl phosphate synthetase and ornithine transcarboxylase activity [18]. When the body is under physiological stress or fasting, fatty acid oxidation disorders make it less efficient at using fats as a source of energy. Immune

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cell types that rely on fatty acid oxidation, such as CD8+ memory T cells, show impaired activity during infections. This might weaken the host immune response and make the disease worse [18,19]. The most severe types are caused by problems with the breakdown of long-chain acylCoA dehydrogenase (LCAD), Long-Chain Hydroxyacylcoa Dehydrogenase (LCHAD), and Tri-Functional Protein (TFP). Decompensation episodes are marked by hypoglycemia, metabolic acidosis, rhabdomyolysis, and severe liver and heart disease [20].

Experimental studies in long-chain acyl-CoA dehydrogenase deficient mice have demonstrated that viral infections exacerbate hypoglycemia and induce substantial modifications in acylcarnitine patterns [21]. Even when compensatory mechanisms are triggered through different metabolic pathways, these changes are often not enough to supply the energy needs of important tissues. As a result, important organs, such as the liver and skeletal muscles, are under more metabolic stress. These results show how viral triggers can make the metabolic weakness that is already present in FAOD patients worse, making them more likely to have serious consequences in several organs.

Nutrition and Immune System Management

Dieting is very important, for many inherited metabolic disorders [22]. Less protein lowers the level of zinc, iron, and vital amino acids that are important for T and B cell functions. As a result, patients have low levels of immunoglobulins and altered patterns of cytokine activities. Branched-chain amino acid disorders, organic acidemias, and urea cycle abnormalities are all examples of conditions that necessitate low-protein diets and have similar dangers [23]. Phenylketonuria (PKU) is the most prevalent hereditary amino acid condition, resulting from a lack of Phenylalanine Hydroxylase (PAH), which catalyzes the conversion of Phenylalanine (Phe) to Tyrosine (Tyr). To regulate blood Phe levels, the afflicted individual must adhere to a low-protein regimen diet from birth [24]. Lack of micronutrients like zinc, iron, and selenium makes innate immune cells less able to survive, grow, and work, which makes infections more likely illustrate in Figure 1. So, therapeutic diets need to find a balance between keeping the immune system healthy and controlling metabolism [23-25].

Immunometabolism in Inherited Disorders

Mitochondria provide energy for immune cell activation and operate as centers for innate antiviral signaling. Lymphocyte activation, phagocyte function, and cytokine signaling are all hurt by faulty oxidative phosphorylation (OXPHOS) [26-28]. Patients with this condition often have respiratory and systemic infections that come back, low white blood cell counts, low levels of immunoglobulin G, and, in certain circumstances, opportunistic infections. Sepsis and pneumonia are primary causes of mortality in pediatric muscular dystrophy cohorts [29]. These conditions are caused by the buildup of harmful organic acids. Patients also include metabolic instability, neutropenia, lymphocyte malfunction, and low levels of immunoglobulin. There have been reports of severe bacterial and viral illnesses with strange symptoms, such as molluscum contagiosum and Pseudomonas ecthyma gangrenosum [30,31]. In GSD (Glycogen storage diseases) type Ib, a lack of glucose-6-phosphate transporter makes neutrophil metabolism less effective, which causes apoptosis, a weak respiratory burst, and persistent neutropenia [32]. This is what causes repeated infections and inflammatory bowel illness [33]. Recently, empagliflozin has showed potential in enhancing neutrophil function by decreasing harmful glucose analogs [34]. Congenital Disorders of Glycosylation (CDGs) are a good example of how problems with metabolism can lead to problems with the immune system [35]. Linked to low levels of immunoglobulin G and frequent respiratory infections makes the immune system weaker, but strangely makes it harder for glycosylated viruses to infect cells [36-38]. Due to faulty fucosylation, it makes it harder for leukocytes to stick together, which causes repeated sepsis and serious infections. Causes mixed immunodeficiency, which leads to repeated bacterial and fungal infections, high IgE levels, and bone problems. Targeted therapies are only available for a few cases, such as fucose supplementation in SLC35C1-CDG and stem cell transplantation in Phosphoglucomutase 3 (PGM3)-CDG [39,40].

Emerging Role of the Gut Microbiome

The gut microbiota interacts with both host metabolism and immunological function. Changed microbial profiles have been seen in PKU and GSD, and this is due to both the diet and the genetic abnormality [41]. Microbiome-based therapies, such as probiotics, dietary manipulation, and fecal microbiota transplantation, hold promise as future strategies for alleviating infection burden and modifying immunity in Immune-Mediated Diseases (IMDs) [42].

Obesity and Viral Illness

Obesity induces chronic low-grade inflammation and metabolic impairment, compromising both innate and adaptive immunity [15]. Experimental and clinical experimental data suggests that obese individuals experience prolonged virus shedding, worse wound healing, and longer immunological recovery after influenza infection [43].

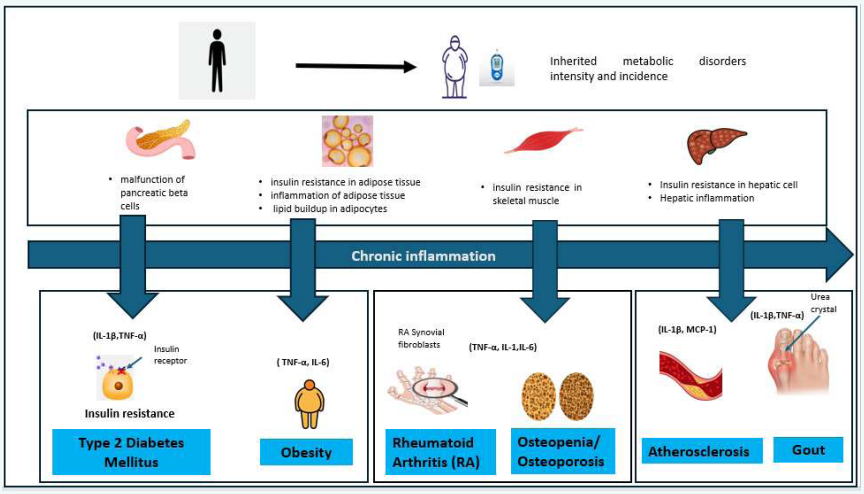

Figure 1: Cross Talk between Inflammation and Metabolic Disorders.

Table 1: The relationship between infectious illnesses and metabolic conditions

Type of Infections	Association with Metabolic Disorder(s)	Key findings	Reference
Hepatitis C Virus (HCV)	Insulin resistance, Type 2 Diabetes, Hepatic steatosis, Atherosclerosis,	HCV facilitates insulin resistance through disrupted insulin signaling pathways (e.g., PP2A, SOCS-3, IRS), produces both viral and metabolic steatosis, and increases the risk of fibrosis. Atherosclerosis and type 2 diabetes mellitus; meta-analysis indicates a substantially elevated prevalence of type 2 diabetes mellitus in individuals with chronic hepatitis C virus.	[50,51]
Hepatitis B virus (HBV)	Non-alcoholic fatty liver disease (NAFLD), Insulin resistance	Hepatitis B virus infection modifies hepatic lipid metabolism; metabolic syndrome exacerbates fibrosis and increases the risk of hepatocellular cancer.	[52,53]
Human Immunodeficiency Virus (HIV)	Dyslipidemia, Lipodystrophy, Insulin resistance	Antiretroviral medications produce mitochondrial breakdown and fat redistribution; prolonged immunological activation leads to insulin resistance.	[54,55]
Helicobacter pylori (*H. pylori)*	Diabetes, Obesity, Metabolic Syndrome (MetS)	*H. pylori* infection is significantly associated with components of MetS, including hypertension, insulin resistance and obesity. Chronic inflammation caused by *H. pylori* may facilitate the onset and advancement of MetS.	[56]
Cytomegalovirus (CMV)	Metabolic Dysfunction	Chronic CMV infection may help the immune system age and cause metabolic problems, which might make metabolic illnesses more likely to happen.	[57-59]
SARS-CoV-2 (COVID-19)	Dyslipidemia, Type 2 Diabetes	The overall risk of acquiring newly diagnosed diabetes is elevated by a factor of 1.46 in individuals infected with COVID-19. The infection may aggravate metabolic impairment via inflammatory mechanisms.	[60,61]
Mycobacterium tuberculosis (TB)	Type 2 Diabetes	Tuberculosis produces chronic inflammation and cortisol secretion, exacerbating insulin resistance and glycemic dysregulation.	[62,63]
Salmonella spp.	Diabetes	Infection with *Salmonella* species, such as *S. typhi* and *S. paratyphi*, has been associated with modifications in immunological responses and may affect the onset of diabetes.	[64,65]
Dengue Virus	Insulin resistance, Lipid dysregulation	Viral replication relies on the creation of host lipids; infection increases triglycerides and decreases HDL levels.	[66,67]
Influenza Virus	Obesity-linked immune dysfunction, Hyperglycemia	Obese hosts have diminished antiviral immunity, extended viral shedding, and increased production of inflammatory cytokines.	[15,68]
Helminth Infections	Metabolic Syndrome, Type 2 Diabetes	Some helminth infections, like *Schistosoma mansoni*, are linked to better metabolic outcomes, such as lower fasting blood glucose levels and a decreased incidence of MetS.	[69,70]

Moreover, when influenza viruses replicate in obese hosts, the weaker interferon response can allow the virus to develop more harmful mutations, increasing its severity [44]. Importantly, vaccine efficacy diminishes in individuals with obesity: although they produce antibody titers, obese individuals demonstrate an elevated risk of influenza infection following vaccination [45,46].

Obesity has become a prominent risk factor for severe illness outcomes in the setting of COVID-19. Almost half of the hospitalized patients with SARS-CoV-2 infection who needed mechanical ventilation were overweight [47]. Obesity is linked to changes in the expression of ACE2, the cellular receptor for SARS-CoV-2, in adipose tissue. This increases the number of places where the virus could enter [48,49]. Furthermore, obesity-induced dysregulated lipid metabolism exacerbates viral replication and the release of inflammatory cytokines, leading to cytokine storm syndromes and acute respiratory failure (Table 1) [49].

TYPE 2 DIABETES MELLITUS (T2DM) AND VIRAL INFECTION

T2DM, which commonly comes after being overweight, makes people much more likely to get viral infections. In previous study, people with diabetes were far more likely to be hospitalized, go to the ICU, and die from the flu during the 2009 H1N1 pandemic [71]. Experimental models indicate that elevated blood glucose levels inhibit the function of protective surfactant protein D, facilitating viral entry and replication in the lungs [72]. Glycemic variability intensify influenza by increasing oxidative stress and causing serious lung damage [73].

Diabetes is another important risk factor for severe coronavirus infections. Models of MERS-CoV and SARS-CoV illustrate that diabetes restricts the migration of immune cells to the infection site and extends the duration of the illness [74]. Recent studies indicate that individuals with diabetes are at an high risk for severe pneumonia, cytokine storm, and adverse outcomes related to COVID-19 [75,76]. The interconnection between T2DM, endothelial dysfunction, and ACE2 expression may increase the risk of vascular and cardiac complications after SARS-CoV-2 infection [77,78].

Models for Experiments

Several models have been applied in order to find the major impact of metabolic disorders on viral infections and disease intensity by the researchers in recent time. These include obese mice given a high-fat diet to replicate the metabolic alterations linked to obesity, transgenic mice designed to express human viral receptors, primarily human epithelial cell cultures for a thorough examinations of virus-host interaction at the cellular level [74-79]. Each model has various benefits whereas the learning process of immune system and cell function from basic human cells as well as the impact of metabolic disorders on infection outcomes from mouse models become faster. To illustrate the point, basic human cells teach us about cellular processes and the immune system's inner workings, while models including mice provide light on the impact of metabolic disorders on infection outcomes.

The striking similarity between ferrets and humans makes them an ideal model for studying respiratory viruses like influenza and SARS-CoV-2. Viruses that infect humans can infect ferrets similarly to how they infect mice: with a high temperature, viral replication in the upper respiratory tract, and the ability to spread the infection via the air [78]. This makes them ideal for research into the effects of variables like body mass index on viral dissemination and severity.

Various models have been developed in the recent era to represent human metabolic failure. For the long-time issues, it is challenging to create such as models that accurately represent that. It is too much tough to duplicate these effects in a controlled laboratory context as there is a complicated interaction among exercise, nutrition, chronic inflammation, and hormone regulation. Another challenge for direct translation to humans is that various species have various receptors, metabolic rates, and immunological responses. These research gaps highlight the necessity of developing the precise models that can easily identify the complexities of metabolic diseases in people and their effects on viral infections which will help researchers to create more effective therapies and preventive actions.

The Body's Antiviral Defense Relies Heavily on Metabolism.

An "innate metabolic response" works in tandem with the immune system to combat viral infections; this is the crucial point. While viruses may employ metabolic pathways to replicate themselves, hosts can also use these processes to ward against other viruses. The resolution or progression of an infection to chronic illness and metabolic implications is determined by the balance between these competing processes, which are influenced by pre-existing metabolic issues [80]. Before adaptive immunity takes effect, cells rapidly alter their energy metabolism in response to an infection. As metabolic sensors, mTOR, AMPK, and HIF-1α react to changes in energy and nutrition. Metabolism is linked to antiviral signaling via this sensors [81,82]. Additionally, viral sensors like cGAS-STING and NLRP3 inflammasomes regulate mitochondrial activity, reactive oxygen species production, and glycolysis to aid in the immune system's battle against infections [83,84].

This coordination is very important which relies heavily on mitochondria. The release of mitochondrial DNA initiates the pathway of cGAS-STING which mainly causes type I interferon response when they are under stress. On the contrary, prolonged activation may damage inflammation and oxidative phosphorylation, showing the need of keeping metabolic control in check [11]. There some energy molecules such as NAD+/NADH, ATP, and TCA cycle intermediates which are cofactors in antiviral signaling. When the glycolysis increases, the activity of ATP and JAK-STAT1 also increase that in turn maintains interferon-induced gene expression. To function precisely, there has to be a sufficient amount of NAD for the PARP enzyme. The compromising of the body's defenses against viruses happens when NAD level decreases as a result of metabolic diseases or age [85,86].

The success of an infection is largely dependent on the overall metabolic status of the host. Dyslipidemia, insulin resistance, excision inflammation and obesity hinder the virus clearance. Autophagy, mTOR and AMPK is inhibited for the consumption of an excision amount of nutrients which allowing the viruses to persist in the body and reasons for metabolic harm. The immune system is also affected by the metabolites of the TCA cycle. Itaconate and related compounds reduce ROS levels, halt NLRP3 activation, and prevent viral replication, while succinate stabilizes HIF-1α and enhances inflammation. These findings demonstrate that metabolism is the best source of energy for the body as well as body's defender against virus.

Important Metabolic Reprogramming Mechanisms

The strong relationship between metabolism and infection has been elucidated by several studies: Viral entrance is facilitated by metabolic receptors. Some proteins on cells serve as both metabolic facilitators and entrance points for viruses; examples of this include the glucose transporter GLUT1 and the fatty acid transporter CD36 [87,88]. By opening a channel for viral entry and initiating intercellular communication, these receptors facilitate viral replication by altering the host cell's metabolic rate. Physiological alterations in immune cells: The metabolic shift that occurs in activated immune cells is known as the Warburg effect. Aerobic glycolysis is the next step after oxidative phosphorylation (OXPHOS). This fast production of ATP and building blocks for biosynthesis is particularly crucial for immune effector functions like making cytokines and growing clones. mTOR and HIF-1α are two transcription factors that play a big role

in this change. Interferon-Stimulated Genes (ISGs) that affect metabolism. The type I interferon system not only produces conventional antiviral ISGs, but it also controls metabolic enzymes. For instance, it may stop Fatty Acid Synthase (FASN), which limits the lipids that viruses can use to build themselves, or it can make certain metabolites like itaconate, which has anti-inflammatory and antiviral effects [81,89]. Metabolites as antiviral Effectors: Some metabolites may stop viruses from replicating directly. Viperin (RSAD2) is a major example of an ISG that makes the nucleotide analogue ddhCTP, which stops the RNA-dependent RNA polymerase of various viruses from making more RNA [90,91].

Pathogen-Specific Metabolic Hijacking and Its Effects

Researcher uses HIV and SARS-CoV-2 as specific examples to show how various viruses take advantage of the metabolism of their hosts. HIV prefers to infect CD4+ T cells that are metabolically active and have high levels of GLUT1 and oxidative metabolism. The virus uses both glycolysis and OXPHOS to make the lipids and nucleotides it needs to copy itself. This metabolic stimulation also helps the virus stay in the body and causes long-term inflammation, which may lead to long-term health problems including heart disease [11]. There is an increase in glycolysis as a result of SARS-CoV-2 infecting cells because it disrupts the equilibrium of the mitochondria. Because of the virus's affinity for metabolic tissues such as the pancreas, liver, and fat, it has the potential to disrupt the general control of glycometabolism in the body. This may lead to diabetes and other metabolic disorders that occur during acute COVID-19 and Long COVID periods [12-93].

Implications for Translation and Future Directions

The review shows that concentrating on immunometabolism has a lot of promise for translation. Using Metabolic Pharmaceuticals for Different Purposes: FDA-approved medications including rapamycin (an mTOR inhibitor), [94,95]. Metabolites as Medicines: Itaconate, a metabolite from the TCA cycle, has derivatives including 4-octyl-itaconate and dimethyl fumarate (DMF) that could stop SARS-CoV-2 from replicating and lessen harmful inflammatory reactions [96]. Metabolomic studies of blood plasma have revealed specific metabolic patterns, including higher levels of succinate and lower concentrations of NAD+, that seem to relate to the severity of COVID-19 and the period before HIV returns. These findings suggest new possibilities for identifying biomarkers that could help predict how a disease might progress or respond to treatment [97,98].

CONCLUSIONS AND FUTURE DIRECTIONS

The disease development and overall mortality can be influenced by the interconnection of two factors such as infections and immune-related disorders. The infections arise from the microorganisms and virus can increase the existing metabolic problems more serious. The immune system may be more vulnerable to overreaction because of the metabolic conditions. In the recent years, this relationship has held the most attention for the researchers as depth knowledge of biological processes is not comprehended. More researches should be needed in future to find the best connections following up the patients with immune-mediated diseases. It can be monitored the history of infections as well as the immune changed in their profiles.

The necessity of the formulation of clinical research as well as exploration of the interference in infections with normal metabolism is needed which can evaluate the immune metabolic therapy aiming at the gut microbiota. The importance of maintaining adequate metabolic health in the context of infectious illness prevention and therapy is highlighted by the increasing incidence of the persistent development of novel viral infections and metabolic syndrome (MetS). Diabetes and obesity are associated with a weakened immune system increasing inflammation and replication. As a result, COVID-19 and Influenza become more severe when these effects are present. The vaccines which are developed for the treatment of those affected patients are not responsive and it becomes reducing the more later. There are several areas that needed to be further investigation in the future such as the immune response to infections in metabolically compromised people, the development of personalized treatments, and metabolic alterations on immunological responses. According to Palmer's findings, metabolic alterations constitute an integral aspect of the immune system's antiviral defense mechanism, rather than only a byproduct of immunological action. Researching viral infections from an immunometabolism standpoint helps in decreasing illness processes which in turn can lead to the development of novel diagnostic therapies, tools and knowledge of the consequences of viral infections on human health.

DECLARATIONS

Author contributions

MSI: Writing-original draft, Writing-review & editing, Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision. Authors read and approved the final manuscript.

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