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REVIEW ARTICLE

The role of glucose homeostasis on immune function in response to exercise: The impact of low or higher energetic conditions

Ana E. Von Ah Morano[1*] | Gilson P. Dorneles[2*] | Alessandra Peres[2] | Fábio S. Lira[1]

[1]Exercise and Immunometabolism Research Group, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente, Brazil

[2]Department of Basic Health Sciences, Laboratory of Cellular and Molecular Immunology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil

Correspondence
Fabio S. Lira, Exercise and Immunometabolism Research Group, Department of Physical Education, Universidade Estadual Paulista (UNESP), Rua Roberto Simonsen, 305, Presidente Prudente, São Paulo 19060-900, Brazil.
Email: fabio.lira@unesp.br

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Abstract

Immune cells are bioenergetically expensive during activation, which requires tightly regulated control of metabolic pathways. Both low and high glycemic conditions can modulate immune function. States of undernourishment depress the immune system, and in the same way, excessive intake of nutrients, such as an obesity state, compromise its functioning. Multicellular organisms depend on two mechanisms to survive: the regulation and ability to store energy to prevent starvation and the ability to fight against infection. Synergic interactions between metabolism and immunity affect many systems underpinning human health. In a chronic way, the breakdown of glycemic homeostasis in the body can influence cells of the immune system and consequently contribute to the onset of diseases such as type II diabetes, obesity, Alzheimer's, and fat and lean mass loss. On the contrary, exercise, recognized as a primary strategy to control hyperglycemic disorders, also induces a coordinated immune-neuro-endocrine response that acutely modulates cardiovascular, respiratory, and muscle functions and the immune response to exercise is widely dependent on the intensity and volume that may affect an immunodepressive state. These altered immune responses induced by exercise are modulated through the "stress hormones" adrenaline and cortisol, which are a threat to leukocyte metabolism. In this context, carbohydrates appear to have a positive acute response as a strategy to prevent depression of the immune system by maintaining plasma glucose concentrations to meet the energy demand from all systems involved during strenuous exercises. Therefore, herein, we discuss the mechanisms through which exercise may promotes changes on glycemic homeostasis in the metabolism and how it affects immune cell functions under higher or lower glucose conditions.

KEYWORDS

exercise training, glycemic homeostasis, immune cell functions

1 | INTRODUCTION

Cellular homeostasis is a physiological condition inherent to the health of the human body (Kanungo, Wells, Tribett, & El-gharbawy, 2018). The level of blood glucose, in the absence of disease, is maintained under precise and constant regulation, indispensable to

*Ana E. Von Ah Morano and Gilson P. Dorneles contributed equally.

maintain the energy homeostasis of individuals (Thorens & Mueckler, 2010). Excess or deficiency in glucose can cause effects that are harmful to health status. Acutely, hyperglycemia or hypoglycemia can lead to immediate disorders, such as a loss of consciousness and fainting (Kovatchev, 2019). In a chronic way, the breakdown of glycemic homeostasis in the body can influence cells of the immune system and consequently contribute to the onset of diseases such as type II diabetes, obesity, Alzheimer's, and cancer (Hotamisligil, 2017). Multicellular organisms basically depend on two mechanisms to survive: the regulation and ability to store energy to prevent starvation and the ability to fight against infection. In fact, the synergic interactions between metabolism and immunity impact on many systems underpinning human health. Although the term immunometabolism has only recently been defined (Mathis & Shoelson, 2011), physicians at the end of 19th century already had the notion that patients with meningitis exhibit an acute and strong metabolic phenotype (i.e., hyperglycemia and polyuria) related to diabetic syndrome (Fox, Kuzma, & Washam, 1947). Moreover, Raymond et al. (1981) showed that the infusion of lipopolysaccharide (LPS), a constituent molecule found in the outer membrane of Gram-negative bacteria, caused insulin resistance through the induction of abrogating insulin action to induce glucose uptake in skeletal muscle tissue. Moreover, acute pathogenic infection in human subjects induces lower insulin binding to insulin receptors (IRs) in a variety of metabolic active cells (hepatocytes, myocytes, endothelial cells; Drobny, Abramson, & Baumann, 1984).

The blood glucose level can be affected by nutrient intake (mainly carbohydrates) and regulated by insulin (Sylow, Kleinert, Richter, & Jensen, 2017). Insulin is the hormone that regulates the uptake of peripheral glucose and the production of glucose in the liver (Boucher, Kleinridders, & Kahn, 2014). Glucose is transported via diffusion, facilitated through the plasma membrane of the cell by one of the five membrane proteins, known as glucose transporters (GLUT), which differ in tissue kinetics and distribution (Huang & Czech, 2007). The main regulatory mechanism by which glucose uptake occurs is through the transport of insulin-stimulated glucose to skeletal muscle and adipose tissue, mediated primarily by type 4 glucose transporter protein (GLUT-4). GLUT-4 is extremely important in glucose homeostasis and the removal of glucose from the circulation (Bryant et al., 2002).

The immune system monitors and responds to specific metabolic signals and is very sensitive to environmental changes to maintain systemic homeostasis (Mathis & Shoelson, 2011). Eating behavior is one of the main environmental factors and exerts several effects on the function and development of the immune system (López-Otín, Galluzzi, Freije, Madeo, & Kroemer, 2016). An excess or deficiency in nutrients alters the responses of the immune system.

Undernourishment states depress the immune system (Cunha, Friedler, Vaisberg, Egami, & Costa, 2003), while, in the same way, excessive food intake, such as the obesity state, compromise its functioning (Asghar & Sheikh, 2017). Moreover, there is an advantage to the coordinated regulation of metabolic and immune response in acute conditions, as the organism needs to coordinate its energy resources during the induction of accurate inflammatory responses (Figure 1).

Chawla et al. (2011) proposed a model explaining the immune-metabolic link in visceral adipose tissue (VAT) and other metabolically active tissues (i.e., hepatic, brain, and skeletal muscle): the "energy-on-demand model" hypothesized that immune cell subpopulations in VAT are involved in a cross-link with adipocytes to fulfill the correct energetic demands for an effective immune response against a variety of pathogens, from bacterial species to parasitic worms. According to this model, in the case of bacterial infection and systemic and hypertrophic adipose tissue inflammation, insulin resistance is stimulated to raise circulating nutrient levels and allow a fast and strong bactericidal response. In the case of parasitic infections, immune cells work to sequester nutrients to slow down parasite growth and development. Thus, this model indicates that

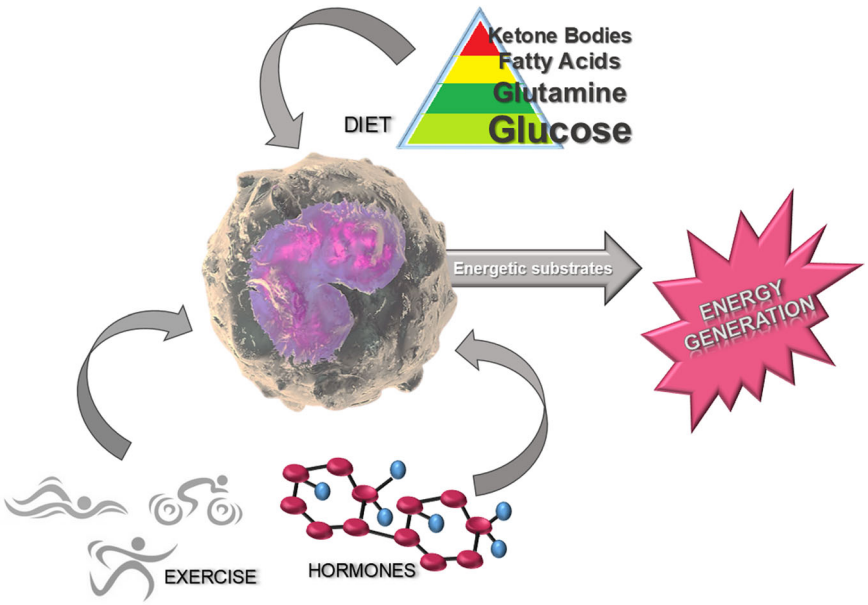

FIGURE 1 Immune cells are bioenergetically expensive during activation and besides protecting the body against pathogens, are mostly affected by diet, exercise volume, and hormonal activities

obesity and cardiometabolic diseases are characterized as bacterial infection, which leads to an inflammatory response of immune cells (Odegaard & Chawla, 2014).

Exercise is recognized as a subset of physical stress, like thermal and traumatic injury, that impacts several physiological systems (Walsh et al., 2011). Each single bout of physical exercise induces a coordinated immune-neuro-endocrine response that acutely modulates the cardiovascular, respiratory, and muscle functions. In this way, exercise is a good model for understanding the relationship between metabolism and inflammation in the pathogenesis of noninfectious diseases. The transient immune response to exercise is widely dependent on the intensity, volume, and mode of exercise, and characterized by changes in immune cells (mainly monocytes and T cells) distribution, phenotype, and cytokine response (Simpson, Kunz, Agha, & Graff, 2015). These altered immune responses induced by exercise are modulated through the "stress hormones" adrenaline and cortisol that impact on leukocyte metabolism. On the contrary, carbohydrate supplementation during acute bouts of exercise impacts on the cytokine and myokine profile by muscle tissue (Bermon et al., 2017). Longitudinal randomized controlled studies have highlighted the synergic adaptations in glucose metabolism and inflammatory mediators in a range of conditions, such as obesity, type 2 diabetes, and elderly subjects (Pedersen, 2017). Thus, the purpose of this review was to discuss the mechanisms through which higher or lower glucose levels promote alterations in immune cell functions.

1.1 | Control of glycemic homeostasis: Skeletal muscle and liver

The maintenance of metabolic homeostasis during eating or fasting depends on the synergy between the organs and fuel available (Sylow et al., 2017). During the postprandial period of a high-carbohydrate meal, pancreatic β-cells respond to nutrient augmentation, releasing insulin into the bloodstream, andincreasing the insulin-glucagon ratio (hormones with oordinated antagonistic responses that work to maintain glycemic homeostasis; Boucher et al., 2014).

Stimulated by insulin, the uptake glucose in hepatocytes is actived from the circulation (glycogenesis) and cut off (this time by glucagon action). Glycogenolysis and gluconeogenesis are metabolic processes to obtain glucose and generate energy, from other substrates that are not carbohydrates, such as by the degradation of glycogen in the liver and muscles or synthesis of lactate, glycerol, and amino acids, (Yang et al., 2018).

Skeletal muscle accounts for 60–80% of increased glucose metabolism in response to insulin (Ng et al., 2019). The regulation of insulin-dependent glucose uptake by muscle cells occurs from the activation of intracellular proteins (Thorens & Mueckler, 2010). Binding of insulin to the α subunit of its receptor (IR) leads to an increase in β-subunit tyrosine kinase activity, leading to autophosphorylation of this receptor and phosphorylation of insulin receptor substrate-1 (IRS1). Thus, signaling of two distinct pathways occurs, the end of which occurs through the translocation of GLUT-4 to the sarcoplasmic membrane and to the T-tubules, allowing the entry of glucose into the cell (Richter & Hargreaves, 2019).

The transport of glucose to muscle cells is stimulated by insulin independent mechanisms such as muscle contractions, which activate the adenosine monophosphate-activated protein kinase (AMPK) pathway. AMPK is an enzyme activated by the decrease in the cellular energy storage, which increases GLUT-4 translocation to the surface of the plasma membrane. One of the mechanisms responsible for the greater activation of AMPK is the increase in contractile activity that alters the energy status of skeletal muscle cells.

During high-intensity exercise, skeletal muscle may exhibit decreases in phosphocreatine and adenosine triphosphate (ATP) concentrations, which require increased activation of AMPK (Jørgensen, Richter, & Wojtaszewski, 2006; Kahn, Alquier, Carling, & Hardie, 2005).

By the way, the activation of AMPK in cells of the immune system would promote the shift from a proinflammatory to an anti-inflammatory phenotype. Such a context suggests a shift from glucose uptake and glycolysis to mitochondrial oxidative metabolism, which also includes fatty acid oxidation (Hardie, 2013). In an attempt to restore energy homeostasis by activating the catabolic pathways that are more efficient in generating ATP (Hardie, Ross, & Hawley, 2012), there is a disruption of other processes that are more expensive in energy expenditure as biosynthesis and cell-cycle (Imamura, Ogura, Kishimoto, Kaminishi, & Esumi, 2001).

Therefore, the generation of ATP by alternatively activated macrophage ("M2") occurs mainly from the metabolism of mitochondria that can use multiple carbon sources and less production and release of reactive oxygen species (ROS) when compared to classical macrophages ("M1") (Haschemi et al., 2012). Thus, it is observed that when activated, the AMPK pathway promotes oxidative metabolism, typical of anti-inflammatory cells rather than the glycolytic metabolism characteristic of inflammatory cells (Jones et al., 2005).

As in muscle tissue cells, glucose uptake into adipose tissue also depends on the action of GLUT-4. In response to the action of insulin, adipose tissue decreases the rate of lipolysis and stimulates the synthesis of fatty acid and triacylglycerol from lipids, and, in unusual conditions, glucose can be converted into fatty acid. All this metabolic interaction ensures that tissue exposure to hyperglycemia is reduced and nutrients are stored in adipocytes for release and oxidation when there is a lack of nutrient supply (Goodpaster & Sparks, 2017).

The choice of cellular fuel depends on the type and amount of nutrients available. During fasting, when there are fewer carbohydrates and lipids circulating in plasma concentrations, in view of the need to maintain glycemic homeostasis, there is a change in the metabolic mechanism for the fast-track to fatty acid oxidation (Smith, Soeters, Wüst, & Houtkooper, 2018). Glucagon stimulates glycogenolysis and hepatic ketogenesis, whereas decreased insulin suppresses synthesis of malonyl-coenzyme A (CoA) from hepatocytes and lipogenesis, with concurrent activation of fatty acid oxidation (Heppner et al., 2010).

When blood glucose concentration is low, glucagon is secreted by the pancreas, and the lipolysis pathway is activated favoring fatty acid release to blood (Charron & Vuguin, 2015). Glycerol is converted into cetonic body, a glucose-like molecule, of which part will also go into the bloodstream, contributing to the replacement of hepatic glycogen (Possik, Madiraju, & Prentki, 2017).

2 | CELLULAR AND MOLECULAR MECHANISMS INVOLVED IN THE UPTAKE, MOBILIZATION, AND OXIDATION OF GLUCOSE IN IMMUNE CELLS: IMMUNOSUPPRESSION. EXERCISE (TYPE, DURATION, VOLUME)

The role of the body's immune system against pathogens is intrinsically associated with energy metabolism and is essential in maintaining homeostasis and preventing uncontrolled chronic inflammatory responses and metabolic diseases (Calder, Dimitriadis, & Newsholme, 2007). When physical and chemical natural barriers fail to contain pathogenic invasion, a highly coordinated cellular system composed of innate cells from the myeloid progenitor (monocytes/macrophages, dendritic cells, neutrophils, eosinophils, basophils, and mast cells) and adaptive cells from the lymphoid progenitor (natural killers [NK cells]; B and T cells) are responsible for recognizing the nonself antigens and secreting a variety of cytokines and immunoglobulins to eliminate the nonself agent (Brodin & Davis, 2017). To be activated and operate effectively, the cells of the immune system require a large bioenergetic supply from the metabolic pathways (Al-khami, Rodriguez, & Ochoa, 2017). In this way, hormones, diet, and exercise are factors that can influence the metabolism of immune cells (Batatinha, Biondo, Lira, Castell, & D, 2019).

Glucose, glutamine, fatty acids, and ketone bodies are the main energetic substrates used by the metabolism of cells from the immune system (Newsholme, Curi, Gordon, & Newsholme, 1986). However, glucose is the primary substrate for the stimulation of immune cells, being the first to be recruited for energy generation

(Neill, Kishton, & Rathmell, 2016). Past studies discovered that monocytes/macrophages have a high appetite for glucose, and the suppression of glycolysis inhibits in vitro macrophage activation and suppresses inflammation (Alonso & Nungester, 1956; Newsholme et al., 1986). Although glycolysis is not the most effective way to generate ATP, it is well established that this glycolytic pathway could be rapidly activated via the induction of enzymes that are involved in this pathway, potentiating rapid ATP generation compared to oxidative phosphorylation (Curi et al., 2016).

Macrophages are plastic and versatile cells, adapting their function and phenotype to the microenvironment (Geissmann et al., 2010). In 2000, Mills proposed the terminology M1-M2 phenotype (Mills, Kincaid, Alt, Heilman, & Hill, 2000). Classically activated macrophages, known as M1, promote inflammation, extracellular matrix destruction, and apoptosis (Parisi, 2018). This phenotype presents a predominance of glycolytic metabolism, directly involving the cellular immune response, and microbicidal and tumoricidal activity through secretion of cytokines and proinflammatory mediators, in addition to presenting antigens to T lymphocytes (Bashir et al., 2016). Moreover, higher glycolytic flux in LPS-activated macrophages has been associated with increased expression of pattern recognition receptors, such as the well conservative toll-like receptors (TLR). Enhanced glycolysis enables the macrophages to generate ATP and biosynthetic intermediates to carry out phagocytosis, cytokine production, and antigen processing and presentation (Curi et al., 2016). Beyond that, molecular insights into signaling pathways that involve glycolysis during immune cell activation have been revealed. In this sense, TLR4 binding LPS induces activation of hypoxia-inducible factor 1α (HIF-1a), a transcription factor that is crucial for the activation of several glycolytic enzymes (Tannahill et al., 2014). The nuclear factor κB (NF-κB) activation occurs through the regulation of ubiquitous isoform of phosphofructokinase-2, which is crucial for the regulation of glycolysis (Rodriguez-Prados et al., 2010).

Another glycolytic enzyme, hexokinase 1, is a crucial regulator of NLR family pyrin domain containing 3 (NLRP3) inflammasome, a regulator of caspase-1, which stimulates the production of interleukin 1β (IL-1β) and IL-18 and induces pyroptosis cell death. Hexokinase interacts with NLRP3 in the outer mitochondrial membrane, inducing the activation of this inflammatory pathway (Moon et al., 2015).

The alternatively activated M2 macrophages phenotype promotes the construction of extracellular matrix, cell proliferation, and angiogenesis and is related to tissue repair, and immuno-modulating action, being activated by IL-4 and IL-10. Concerning energy metabolism, M2 macrophages prefer the oxidation of fatty acids (Caputa, Flachsmann, & Cameron, 2019). Interestingly, the inhibition of pyruvate kinase isoenzyme M2 (PKM2), forcing the structure of this molecule to a tetrameric state (blocking entry to the nucleus and repressing their activity in glycolysis) reprogrammes macrophages to M2-like profile in their gene expression (Palsson-Mcdermott et al., 2015). As the proinflammatory role of PKM2 occurs during translocation to the nucleus and promotion in the expression of HIF-1a-dependent genes, including NF-κB activation and IL-1β expression; blocking of HIF-1a and nuclear PKM2 changes the phenotype of the macrophages from a proinflammatory phenotype to a regenerative M2 phenotype (Luo et al., 2011).

Although lymphocytes may have a preference for oxidative metabolism, through the immediate need for rapid and efficient energy generation in a state of activation and increased proliferation, the aerobic glycolysis pathway is used (Norata et al., 2015). In this context of lymphocyte proliferation, it is worth noting that in addition to glucose, glutamine, the nonessential amino acid most abundant in muscle tissue, is also a very important energy substrate for this type of cell, whereas ketone bodies and fatty acids might also be used to maintain the homeostasis of the immune system (Cruzat, Rogero, Keane, Curi, & Newsholme, 2018).

Glycolysis metabolism has also been observed in effector T cells and activated B cells (Michalek et al., 2012). Notably, increased

glycolysis in effector T cells enables higher production of interferon-γ (IFN-γ) by CD4+ T helper cells with type 1 inflammation (Th1) phenotype; regulates the function of Th1, Th2, and Th17 phenotypes and activated CD8+ T cytotoxic cells; and increases the mammalian target of rapamycin (mTOR) pathway, which is associated with the initial generation of peripheral regulatory T (Treg) cells (Chang et al., 2014; Gubser et al., 2013; Shi et al., 2011). Interestingly, the hyperactivation of mTOR and HIF-1 pathways in T cells leads to reprogramming of T cells to a Th17 pathway and a more proinflammatory profile (Shi et al., 2011). On the contrary, fatty acid oxidation and oxidative phosphorylation are both associated with Treg phenotype and M2 macrophage gene expression, suggesting an anti-inflammatory and suppressed immune response role (Fessler, 2016; Nomura et al., 2016).

Leukocyte cells, such as neutrophils, have glucose as the main energetic source, and the oxidation of this substrate is greatly increased in phagocytic events (Schuster et al., 2007). When there is glucose restriction, glutamine plays a key role in the proper functioning of these immune cells (Cruzat et al., 2018).

However, the performance of immune cells that generally utilize nutrients in a similar way to other cells, may also have their energy metabolism influenced by other metabolic processes, as in the case of protein kinase B (AKT) pathway, AMPK, and the mTOR. Considered as nutrient sensors that work to maintain the energy homeostasis of immune cells, when activated, this protein determines cell responses through high or low levels of intracellular carbohydrates or amino acids (Batatinha et al., 2019). Although there is a lack of studies about the intracellular signaling of metabolic pathways in immune cells during exercise, some studies shed light on AMPK regulation in leukocytes. AMPK is a signaling molecule that is activated in cells by increased adenosine monophosphate (AMP):ATP ratio. Decreases in ATP levels indicate that the energy status of the cell is reduced, promoting AMPK activation that impacts on glycolysis and fatty acid oxidation (Hoffman et al., 2016; Jeon, 2016). Interestingly, AMPK can also be activated by pathways that are independent of AMP levels, such as increases in cellular redox state or by signaling agents such as Ca+ calmodulin-dependent protein kinase kinase β. Thus, AMPK orchestrates intracellular biochemical reactions that generate ATP within the cell, restoring the AMP:ATP ratio (Jeon, 2016).

Interestingly, monocytes induce inflammatory response activated anaerobic respiration via AMPK-mediated phosphorylation of the glycolytic enzyme inducible 6-phosphofructo-2-kinase (Marsin, Bouzin, Bertrand, & Hue, 2002). In this way, the anti-inflammatory phenotype observed in mononuclear cells (lymphocytes and monocytes) after moderate-high intensity exercise may be impacted by AMPK expression. A preliminary study conducted by Moir et al. (2008) showed lower AMPK activation immediately after a single bout of exercise (45 min; 70–75% VO_2max) which coincided with transient decreases in salivary immunoglobulin A, systemic cytokine levels, and CD36 monocyte expression.

Another study conducted by the same group found that AMPK inactivation in PBMCs correlated with lower ROS and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) gene expression after exercise (Moir et al., 2010). Moreover, the purinergic system seems to be altered during acute exercise in both ATP/ADP/AMP concentrations and cell surface ectonucleotidases and purinergic receptor expression, suggesting that the AMPK is no longer activated during exercise due to higher purinergic activity (Dorneles, Romão, & Silva, 2019; Harkness et al., 1983).

In the 1980s, when the literature contained few studies about exercise and the immune system, it was much speculated that marathon runners had a higher susceptibility to upper respiratory tract infections after a run. Therefore, a group of researchers randomly selected 150 runners who participated in the Two Oceans Marathon in 1982 in Cape Town. The athletes were compared to a control group that did not participate in the race. The runners were consulted the day before and 2 weeks after the race. Symptoms of upper respiratory tract infections occurred in 33.3% of runners, compared to 15.3% of controls, and were more common in those who achieved faster run times. The incidence in slow runners was not higher than in controls. This study raised a possible relationship between acute stress and susceptibility to upper respiratory tract infections, speculating on possible impairment of the immune system being responsible for this effect (Peters & Bateman, 1983). Intensive or higher volume training is related to lower immunity symptoms. In this context, it may be common for athletes to have a history of recurrent infections after intense training or strenuous competitions (Nieman, 1994; Venkatraman & Pendergast, 2002).

Nowadays, it is well documented in the literature that exhaustive and high-intensity exercises decrease resistance to pathogens and consequently increase the risk of infection (Pedersen & Bruunsgaard, 1995; Peters & Bateman, 1983; Schwellnus et al., 2016), especially diseases of the upper respiratory tract, generating an immunodepression state induced by exercise (Gleeson, 2006; Gleeson, Bishop, Oliveira, & Tauler, 2013). The immunomodulatory actions of exercise are very dependent on the intensity and duration of the exercise. Endurance athletes such as marathon runners and triathletes, for example, are more vulnerable within 72 hr after completing the race. Pedersen and Brunnsgaard in 1995, referring to the time in which the number and function of immunological cells are at risk, called this hypothesis the “open window” period (Figure 2).

After intense and high-volume workouts (in which practically all of the glycogen reserve is used as an energy source during physical exertion) glycemia and cardiac glycogen need to be re-established (Jensen & Richter, 2012). If glucose does not come from carbohydrates to provide supplemented at the right time (Jeukendrup, 2011), the body will begin to produce glucose through other sources such as glycerol, lactate, or protein degradation, in this case, amino acids are the source for glucose generation (Hawley & Leckey, 2015).

That is, often, the body begins to degrade proteins to generate glucose. In this process, there may sometimes be a lack of substrate for the production of other important molecules, such as immunoglobulins, proteins that also act in the body’s defense system and fight against viruses and bacteria (Simpson et al., 2015). If the immune system has higher demand after strenuous effort, when the raw material for power supply is lacking, the problem becomes even more serious (Hargreaves et al, 2004).

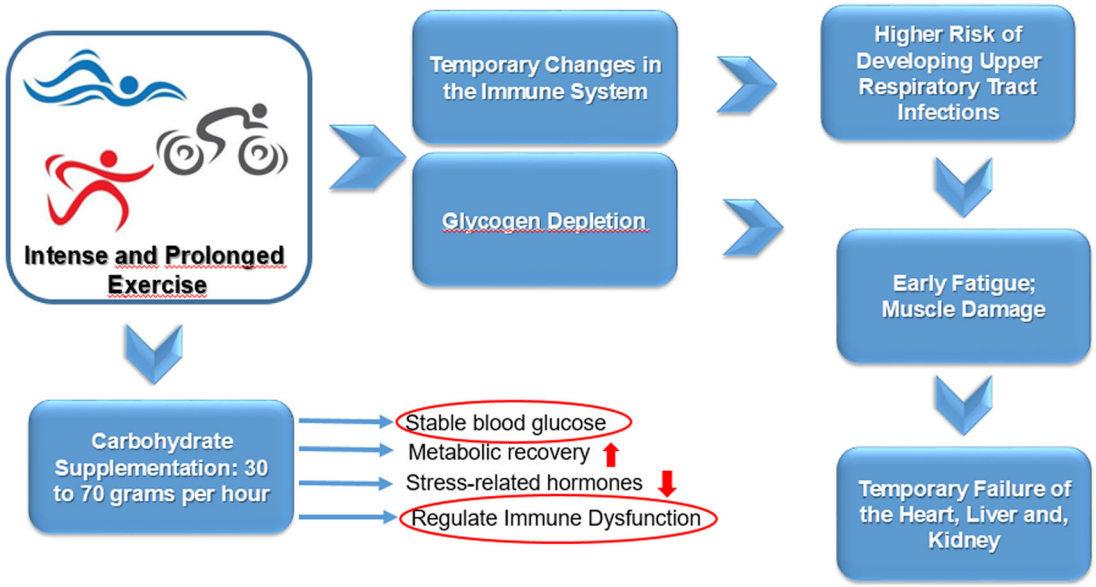

FIGURE 2 Low energy available after strenuous exercise can affect the immune system and lead to many health issues. Maintaining glucose homeostasis appears as an important strategy to maintain energy and prevent health risks in the body

Exercise alters the distribution and trafficking of peripheral mononuclear cells, while suppressing cellular immunity, leading to increased susceptibility to infections (Barros et al., 2017). High-intensity and long-duration exercise can generate acute leukocytosis induced by the effort (McCarthy and Dale, 1988). This is due to increased neutrophil, monocyte, and lymphocyte concentrations and alterations in the balance between the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-10 (e.g., Nielsen et al., 2010).

With this, the growth, differentiation, and functional activation of all the cells of the immune system are compromised after intense exercise when performed in a chronic way, without the immune system having the ability or time to recover, which may lead to immunodepression or the "open window" (Pedersen & Bruunsgaard, 1995). During this time, the organism may be more susceptible to microorganisms that pass through the first line of defense of the immune system (Nickel & Sisic, 2012).

During exercise, NK cells and T cells are recruited into the blood (Brahmi et al., 1985; Zimmer et al., 2015). NK cells are the first line of defense against viral infections, and acute and chronic diseases. After intense exercise, the activity of NK cells is suppressed (Shephard, Rhind, & Shek, 1994). The composition of the T cell subpopulation is altered. After intense exercise, the CD4+/CD8+ ratio decreases because the number of CD8+ T cells increases more than the number of CD4+ cells (Gabriel & Kindermann, 1997). Thus, the level of lymphocytes decreases below pre-exercise values and the duration of suppression depends on the intensity and duration of the exercise (Gabriel et al., 1992; Luk et al., 2016; Simpson et al., 2006).

Exercise also affects the phenotype and functional activity of NK cells and T cells in an intensity-dependent way. There are three main events that determine the preferential mobilization of some leukocyte subtypes during exercise. First, exercise mobilizes cells that have an effector function with increased cytotoxic activity, and a mature/differentiated phenotype. In this sense, exercise mobilizes cytotoxic cells as activated NK cells, CD8+ memory cells and γδ T cells, and CD16+ monocytes (Minuzzi et al., 2018; Shantsila et al., 2012; Simpson, Bigley, Agha, Hanley, & Bollard, 2017). On the contrary, cell subtypes with a lower effector profile or in previous stages of maturation, such as CD4+ cells, B cells, and classical monocytes (CD16−) are less mobilized.

Indeed, both CD8+ and CD4+ T cells show a pattern of redistribution phenotype with higher effector/cytotoxicity activity, KLRG1+/CD28−/CCR7− (Gustafson et al., 2017). Moreover, exercise mobilizes immune cells with a migratory phenotype that express higher levels of integrins, adhesion molecules, and receptors of chemokines (Okutsu et al., 2014). All of these previously cited events are regulated by the catecholamine discharge on β-adrenergic receptors found in the cell surface of immune cells (Graff et al., 2018). After exercise, effector T cells migrate from the blood to the peripheral tissues where a series of proapoptotic stimuli induce apoptosis in these cells (Kruger et al., 2009). The reduced repertoire of memory T cells in the peripheral blood, generated by their migration and apoptosis, expands the immune space and stimulates the thymopoiesis of newly naïve T cells (Simpson, 2011).

Although these modifications in T cell phenotypes in peripheral blood reduce the immunosurveillance hours after the exercise bout, the generation of immune space and naïve T cells contributes to the rejuvenation of the immune system observed in athletes and individuals with high aerobic fitness.

In addition, catecholamine exerts immunomodulatory effects in lymphocytes through the elevation of maximal activity of hexokinase, GluTase, and citrate synthase activities and glucose consumption (Rosa, 1997). Activated CD4+ and CD8+ T cells present higher expression of GLUT-1 and GLUT-4, glucose uptake and glycolysis,

and higher lactate production (Macintyre et al., 2015). In this way, a recent study demonstrated that exercise increases GLUT-4 in mononuclear cells, which are composed mainly by lymphocytes (Sticka et al., 2018). However, excessive adrenaline discharge induced by high-intensity exercise has immunosuppressive effects, such as lower TNF-α expression in monocytes and lower CD4+ IFN-γ T cells (Dimitrov, Hulteng, & Hong, 2017; Yano, Uchida, & Nakai, 2010; Zalli et al., 2015). High-intensity exercise favors the anti-inflammatory Th2 phenotype and GATA3 expression, higher systemic levels of IL-4, IL-1ra, and IL-10, and low lymphoproliferative response of T cells to a variety of mitogens (Kakanis et al., 2014; Siedlik et al., 2016; Zhao, Zhou, Davie, & Su, 2012). Furthermore, single bouts of exercise performed at high intensities seem to be more potent to mobilize Treg cells to the peripheral blood of healthy individuals (Krüger et al., 2016; Wilson, Zaldivar, Schwindt & Cooper, 2009). Interestingly, continuous or interval exercise sessions performed at high intensities (>80% of maximal capacity) seem to induce several anti-inflammatory responses (i.e., Treg mobilization, apoptosis of proinflammatory terminally differentiated memory T cells, higher IL-10, and IL-1ra production) that coincide with glycolysis metabolism predominance during the bout. In this way, exercise performed at a severe domain leads to changes in systemic glucose and lactate concentrations and increased IL-10 production by LPS-stimulated whole blood (Antunes et al., 2019). Also, high-intensity interval exercise mobilized more Treg cells and induced higher rates of apoptosis in highly and low differentiated T cells than continuous exercise, which was associated with low plasma free fatty acid concentrations and higher systemic lactate levels (Krüger et al., 2016).

Elite and endurance athletes who engage in severe exercise, frequently without allowing the immune system to recover from one session to another, need to be alert to illness and disease caused by viral and bacterial infections at this stage of training (Walsh & Oliver, 2016).

In addition to the volume of exercise, another fundamental point to guarantee the preservation and functioning of the immune cells is the nutritional state of the athletes (Gleeson, 2006). There is a reduction in substrate concentrations, such as glucose and amino acids, due to the energy demand induced by strenuous and long-duration exercise (during muscle contraction a lot of glucose is used, reducing the availability in the bloodstream). Therefore, there is a reduction in the functions of the immune system, whose metabolic pathways are dependent on the same substrates (Castell, Nieman, Bermon, & Peeling, 2018).

A study review (Gunzer, Konrad, & Pail, 2012), to evaluate the immunomodulatory potential of some macronutrients, among carbohydrates, during strenuous exercises that may induce immunosuppression, showed that, in general, the impairment postexercise is greater when the effort is continuous, prolonged (>1.5 hr), moderate to high intensity (50–77% of maximal O_2 uptake (VO_2max)), and performed without food intake.

This same study review suggests that carbohydrate supplementation during high-intensity exercise in addition to improving athlete's performance also positively impacts on the immune function. Of the 29 studies selected by the researchers for their study review, all of which included a control (placebo and/or crossover), all results pointed to a significantly higher postexercise blood glucose level in the carbohydrate-supplemented groups than in the placebo-controlled groups. Due to the level of glucose maintained in the blood at the postexercise moment, even after exercise of long duration and high intensity, some researchers reported a decrease in the total count of leukocytes induced by exercise, as well as lower lymphocytosis and a tendency to attenuate lymphocytopenia during recovery.

In relation to NK cells, which are part of the innate immune system and mainly use glucose to maintain functionality, Nieman et al. (1997) (subjects performed 2.5 hr of high-intensity running, 76.7 ± 0.4% (VO_2max) and 0.25 L carbohydrate intake every 15 min), reported a significantly lower number of NK cells. Timmons et al. (2006), confirmed a similar result for NK cells, (the subjects cycled for 60 min to 70% of the VO_2max, with 6% carbohydrate intake every 15 min).

In 2002, Bacurau et al., evaluated the effect of carbohydrate supplementation on some aspects of immune function in athletes, showed a reduction in the proliferation of blood mononuclear cells, and reduced production of IL-1, IL-2, TNF-α, IFN-γ by cultured cells in order of 37%, 35%, 26%, and 16%, respectively, induced by exercise. In this study, the exercise protocol was performed by males who cycled for 20 min at a velocity corresponding to 90% of that obtained at the anaerobic threshold and rested for 20 min. This protocol was repeated six times. The athletes received, during the trial, water or a solution of carbohydrate (95% glucose polymers and 5% fructose) every 20 min.

In a randomized, double-blind study of 30 experienced marathon runners who underwent a 2.5 hr high-intensity run (76.7 ± 0.4 VO_2max), the results show that carbohydrate intake attenuated cytokine levels in the inflammatory cascade in response to intense exertion (reduction in IL-6, IL-1ra, and cortisol concentration). The subjects drank a liquid containing 6% carbohydrate or placebo (Nehlsen-Cannarella et al., 1997). Another study (12 subjects, 2 hr of exercise on the bicycle, 64% Watts max, 6% carbohydrate drink intake or placebo every 15 min) evaluated the influence of carbohydrate supplementation compared with placebo intake on changes in cell count and functions of the immune system.

The authors demonstrated that the carbohydrate ingestion group presented attenuated plasma cortisol concentration induced by exercise, as well as which the neutrophil and monocyte blood counts were lower. However, total lymphocyte counts in the blood, T cells, and NK cells, and lymphocyte proliferation did not change (Nieman et al., 2006).

To examine whether glucose ingestion during exercise may affect the release of specific limb IL-6 during muscle contraction, one study evaluated seven men who underwent 120 min of cycling and ingested a beverage with 6.4% carbohydrate or placebo. The results demonstrated that glucose ingestion during exercise attenuated the release of IL-6 in the leg, but did not decrease the intramuscular expression of IL-6 messenger RNA (Febbraio et al., 2003).

Thus, carbohydrates appear to have a positive acute response as ingestion before, during, and after exercise can prevent depression of the immune system by maintaining plasma glucose concentrations to meet the energy demand from all systems involved during strenuous exercises.

3 | STATE OF LOW GLUCOSE AVAILABILITY (MALNUTRITION, MARATHONS, IRON MAN) IS ALWAYS A NUTRITIONALLY UNFAVORABLE CONDITION

In fasting conditions, blood glucose levels are held stable by the breakdown of glucose from liver glycogen (Cox et al., 2016). Because of the low concentration of glucose in the bloodstream, insulin levels are kept lower since there is increased lipolysis and higher plasma concentrations of fatty acids that become the main energy substrate for energy generation (Pinckaers, Churchward-Venne, Bailey, & van Loon, 2017).

In the absence of available carbohydrate for oxidation and energy generation, amino acids are converted to glucose via gluconeogenesis (Jensen & Richter, 2012). In normal conditions, amino acid participation is approximately 1–3%, in cases of chronic carbohydrate restriction; amino acid participation may be up to 15% for maintenance of energy homeostasis (Kim, Kim, Jeong, & Lee, 2013).

The daily recommendation for carbohydrate consumption for sedentary adults is currently 130 g (Murray & Rosenbloom, 2018). However, for athletes and people involved in exercise programs, this value should be increased, according to the training load, guaranteeing sufficient carbohydrate for the restoration of muscle and hepatic glycogen and thus maintenance of metabolic homeostasis (Cermak & Loon, 2013). Therefore, it is necessary for endurance athletes, such as marathoners and triathletes, to supplement with carbohydrates during long-term training and competitions to meet the energy demand imposed by exercise and to guarantee metabolic and cellular balance (Hawley & Leckey, 2015). The depletion of endogenous carbohydrate stocks contributes to fatigue during resistance exercise (Hargreaves, Hawley, & Jeukendrup, 2004).

Marathoners and endurance athletes generally present a higher risk of developing upper respiratory tract infections after races and periods of intense training, which are associated with temporary changes in the immune system J-shaped correlation curve (Nieman et al., 1997). Most of the reported changes are decreases in the function or concentration of certain immune cells (Nieman, 1998). Carbohydrate supplementation of from 30 to 70 g should be taken per hour, depending on the duration and intensity of exercise, in addition to maintaining stable blood glucose concentration during exercise. This strategy during extensive exercise, is also an effective strategy to improve metabolic recovery, decrease the secretion of stress-related hormones (decreasing hypothalamic-pituitary-adrenal activation), enhance postexercise inflammation, and regulate immune dysfunction in cells (Nieman & Mitmesse, 2017).

There is evidence in the literature that intense and prolonged exercise temporarily decreases NK cell function, creating a post-exercise window of immunosuppression that may increase the risk of infection (Nieman & Wentz, 2019). High-intensity exercise lasting more than 1.5 hr can induce a 35–60% reduction in NK cells and in cell cytotoxic activity for up to 6 hr after exercise (Rama et al., 2013; Timmons and Cieslak, 2008). When there is carbohydrate intake during this type of physical effort, there may be attenuation of the immune response at the postexercise moment with increases in plasma glucose and insulin concentrations, as well as a reduction in stress hormones such as cortisol and epinephrine (Nieman et al., 1997).

Cyclists performed a 75 km riding test on a bike. During the test, they ingested water, bananas, or a sugar beverage (6% carbohydrate). The two carbohydrate groups (banana or sugar) were associated with higher glucose levels and decreased cortisol, total leukocytes, neutrophils, and NK cell counts at the postexercise moment. An immediate postexercise increase in the NK cell count was observed for the group who drank water. When blood samples were analyzed 1.5 hr postexercise, there were no differences in NK cell counts between the groups that received carbohydrate or water supplementation. That is, carbohydrate supplementation prevented postexercise increases in leukocyte, neutrophil, and NK cell counts immediately after exercise (Wentz et al., 2018).

A recent study demonstrated how metabolites from glucose metabolism have a direct impact on immune function. An immortalized THP-1 monocyte lineage incubated for 6 hr with plasma obtained post cycling exercise presented a lower oxygen consumption rate (OCR) in response to LPS stimulation. On the other hand, higher OCR was found in LPS-stimulated THP-1 monocytes with plasma obtained from athletes who supplemented with carbohydrate (0.8 g/kg body weight per hour) post cycling exercise. Thus, carbohydrate ingestion attenuates proinflammatory events, such as COX2 expression in THP-1 and IL-6 systemic levels, through modifications in intracellular metabolic perturbations.

Mechanistically, the recognition of LPS by monocytes stimulates nonmitochondrial consumption of oxygen by NADPH oxidase-2, which is related to higher ROS and phagocytosis, inducing an event called as oxidative burst. Carbohydrate supplementation reduced the reliance on glycolysis for ATP generation, inducing metabolic power through mitochondrial respiratory capacity (Nieman, Gillitt, Sha, Esposito, & Ramamoorthy, 2018).

Moreover, carbohydrate supplementation during exhaustive exercise may prevent the decrease in several functions of T cells. In this sense, ingestion of a beverage containing 6% carbohydrate prevented a decrease in phytohemagglutinin (PHA) lymphoproliferative response, and T cell redeployment (Henson, Niemanl, Parker, Rainwater, & Butterworth, 1998). Moreover, 3.2 g carbohydrate/kg of body weight ingested during 2.5 hr of cycling at 85% of ventilatory threshold reduced both CD4 and CD8 T cell death in mitogen-stimulated cell culture, which suggests attenuation in exercise-induced lymphopenia events (Green et al., 2003). Bishop et al. (2005) showed that a carbohydrate solution may reduce the “open window”

opportunity for viral infections through modulations in T cell function, as demonstrated by higher T cell proliferative response to PHA, influenza, and tetanus toxoid in in vitro models after a trial composed of prolonged exercise plus carbohydrate intake. In a posterior study, Bishop et al. (2009) also demonstrated that a carbohydrate supplementation trial demonstrated higher CD4+ and CD8+ that express CD45RA+ (denoting naïve T cells) CD4+ CD45RO + (a marker of memory T cells) migration toward supernatants from a human rhinovirus infected bronchial epithelial cell line than the trial with placebo beverage intake. Modifications in the CD4+IFN-γ/CD4+IL-4 ratio, a marker of Th1:Th2 balance, was also attenuated in athletes who ingested 6.4% carbohydrate solution during 2.5 hr of cycling exercise at 65% of VO_2max (Lancaster et al., 2005). In fact, although cortisol secretion during prolonged exercise has a direct effect on the reduced frequency of proinflammatory T cells (IFN-γ+ cells), carbohydrate supplementation and maintenance of stable glucose levels during exercise bouts emerges as an effective strategy for the maintenance of a stable frequency of Th1 cell production and distribution (Lancaster et al., 2005). However, carbohydrate supplementation in the recovery phase, 1 hr after the trial, has little immunomodulatory effect (Sellar, Syrotuik, Field, & Bell, 2006).

A review article on Collapse Associated with Exercise published in 2011 by Asplund et al. suggests that states of hypoglycemia drive endurance athletes to become more susceptible to exercise-associated collapse. Since serum glucose levels are decreased (Adler et al., 2009), it is essential that glucose levels remain adequate in athletes who participate in these events. Exercise-associated collapse is a condition that can occur after the completion of endurance sporting events, such as ironman and ultra-marathons that require a lot of effort and endurance. Athletes affected by this problem remain conscious, and are unable to stand or walk unaided (Asplund, O'connor, & Noakes, 2011).

A study of 221 endurance athletes, who were assessed after participating in the Ironman, Half-Ironman, Marathon, and 100/150-km CYCLE races, showed that carbohydrate intake rates vary greatly between events and athletes. In addition, high carbohydrate consumption during exercise was related to the best performance during the Ironman races (Pfeiffer et al., 2012). When supplementation is inappropriate and the catabolic process is higher, the athlete may present early fatigue, muscle damage, and temporary failure of the heart, liver (increased liver enzymes), kidneys (temporary reduction in renal function), and immune and endocrine systems (Knechtle & Nikolaidis, 2018).

3.1 | Immune regulation of glucose homeostasis

A landmark in the field of metabolism was the discovery that inflammatory mediators, such as TNF-α, decrease the insulin-mediated glucose uptake (Mahoney et al., 1985; Pekala, 1983). In several metabolic tissues, mainly adipose tissue and liver, multiple close interactions between leukocytes and parenchymal cells contribute to the management of metabolic homeostasis in accordance with nutritional status of the subject (Osborn & Olefsky, 2012). Early observations from in vitro studies in the mid-1980s showed that conditioned medium from stimulated-LPS macrophages reduce the insulin action on glucose uptake of adipocytes (Mahoney et al., 1985). Moreover, Feingold et al. (1989) observed that administration of TNF-α led to higher systemic glucose concentrations, indicating that hyperglycemia may be induced by proinflammatory cytokine overproduction. Moreover, observations from the decade of 1990 pointed to elevated concentrations of TNF-α and IL-1β in adipose tissue as well as in the systemic circulation from obese individuals, and the neutralization of this cytokines ameliorated insulin resistance (Hotamisligil, Murray, Choy, & Spiegelman, 1994; Maedler et al., 2002).

From an evolutionary perspective, the immune response is dependent on energy sources and substrate availability, and the coordinated glucose fluctuations by leukocytes would be highly advantageous to the maintenance of immune surveillance (Hotamisligil, 2017). Furthermore, an intrinsic relationship between inflammatory mediators, such as cytokines, and metabolic hormones, mainly insulin, occurs during noninfectious and infectious conditions. In this sense, monocyte/macrophages play a key role in the crosstalk between immune and metabolic systems, suggesting that inflammation-mediating insulin resistance might be a physiological role under some circumstances (Osborn & Olefsky, 2012). During bacterial infection in mammals, innate immune cells adopt aerobic glycolysis to provide the phagocytosis and respiratory burst against the pathogen whereas lymphocytes use aerobic glycolysis for their clonal proliferation (Gleeson & Sheedy, 2016). In this circumstance, macrophages and resident T cells induce peripheral and tissue insulin resistance as an adaptive mechanism that allows the organism to mobilize fuel from metabolic sites. Therefore, infection-induced insulin resistance is a well conservative link between immune and metabolic systems that supports the bioenergetics demand of leukocytes to ensure survival of the organism.

In this sense, classical macrophages ("M1") accumulation in inflamed tissue has a crucial role in the induction of insulin resistance (Caputa et al., 2019). A mechanistic link between inflammation and insulin resistance was shown by the stimulation of signaling pathways leading to the activation of NF-κB, c-Jun N-terminal kinase or inflammasome that phosphorylate IR and the substrate of IRS proteins at inhibitory sites, thereby blocking propagation of downstream insulin signal transduction. Other insulin signaling pathway components, including glucose transporters and AKT, as well as metabolic genes expression are repressed by the NF-κB expression (Hotamisligil, 2017).

Moreover, inflammatory cytokines can increase the expression of suppressor of cytokine signaling proteins that bind to the IR, which reduces the phosphorylation of IRS1 and IRS2 (Zolotnik, Figueroa, & Yaspelkis, 2012). The signaling of intracellular inflammatory pathways also impacts insulin signaling through modulation of lipid metabolic signaling involved in insulin resistance. In this sense, both IL-6 and TNF-α stimulates adipocytes to undergo lipolysis, which leads to increased circulating free fatty acids concentrations and decreased insulin sensitivity (Holland et al., 2011). In fact, the

overexpression of genes involved in the synthesis of ceramide, a lipid that inhibits activation of AKT and IRS1 phosphorylation, is a hallmark of impaired lipid regulation in obesity and metabolic diseases (Fucho, Casals, Serra, & Herrero, 2017). Moreover, inflammatory signaling in the liver can stimulate de novo lipogenesis, a key role for steatosis and impaired glucose metabolism (Osborn & Olefsky, 2012).

On the other hand, alternatively activated macrophages ("M2") are less inflammatory than M1 macrophages and commonly related to tissue regeneration and the maintenance of physiological homeostasis (Mills et al., 2000). M2 macrophages have a crucial role in maintaining the insulin sensitivity of metabolic tissues via the secretion of anti-inflammatory cytokines that potentiates the anabolic action of insulin signaling (Zhang et al., 2017). Furthermore, type 2 immune response, related to extracellular immunity and parasitic infection, poses a metabolic challenge for the host, as the extracellular parasites chronically use host nutrients for their own growth (Gleeson & Sheedy, 2016). The type 2 inflammation, which involves the infiltration of tissues by eosinophils, M2 macrophages and T helper type 2 cells (CD4+ IL-4+) and regulatory T cells, have been demonstrated to enhance insulin action and promote glucose storage (Fabbiano et al., 2016; Lee & Lee, 2014). In fact, the polarization of immune response toward the type 2 inflammation axis induced by caloric restriction improves glucose tolerance and ameliorates insulin resistance (Fabbiano et al., 2016). Interestingly, infection with the migratory helminth *Nippostrongylus brasiliensis* confers long-term protection from obesity-induced glucose intolerance and insulin resistance, suggesting that immune response invoked by helminthes sequesters nutrients for long-term storage, a strategy that is probably advantageous to the host, as it prevents the growth of parasites (Wu et al., 2011).

4 | STATE OF HIGH AVAILABILITY OF GLUCOSE (DIABETES, OBESITY, AND CARBOHYDRATE-RICH DIETS); PROVIDED NUTRITIONALLY FAVORABLE CONDITIONS

According to data from the World Health Organization (WHO), noncommunicable diseases (diabetes, dyslipidemias, hypertension, cancer) are the leading causes of death in the world, accounting for 38 million (68%) of the 56 million of deaths in the world. More than 40% of these deaths were premature (individuals under 70 years of age).

The current low level of physical activity, added to the high caloric intake, are risk factors for obesity which is a common denominator for the majority of these diseases (Odegaard & Chawla, 2014). In this context, the WHO and other world authorities make recommendations for the general population, both adults and children, to reduce their intake of carbohydrates, specifically sugars and fast-digesting starches (Johnson et al., 2009; WHO, 2015). The justification for this warning is based on the fact that sugars, which make industrialized foods much tastier, contribute to the increase in the total energy density of diets and can lead to an excessive energy balance (which promotes the breakdown of energy homeostasis, critical for metabolic and cellular balance). In other words, it is indispensable to control caloric intake to maintain a healthy body weight and ensure optimal nutrient intake (Macdonald, 2016).

Excessive sugar intake, especially in the form of extremely sweetened drinks such as soft drinks, is alarming and, in addition to increasing total caloric intake, may contribute to the ingestion of foods with adequate nutritional balance being reduced by an unhealthy diet which contributes to the development of obesity and the emergence of diseases (Vartanian, Schwartz, & Brownell, 2007).

Carbohydrates are primarily responsible for insulin secretion (Little, Chilibeck, Ciona, Vandenberg, & Zello, 2009). In addition to being an anabolic hormone, insulin plays an important role in modulating adipose tissue (Bak et al., 2018). Excess glucose in the bloodstream triggers a state of hyperinsulinemia which inhibits the release of fatty acids from adipose tissue (Consitt, Bell, & Houmard, 2010).

In a high-carbohydrate diet, glucose stores in the liver and muscles are generally high (Bartlett, Hawley, & Morton, 2014). After a high-carbohydrate meal, blood glucose is elevated by the supply of glucose from the intestine, resulting in elevated levels of glucose and insulin and a temporary decrease in glucagon levels (Jeukendrup, 2014). This combination results in a marked decrease in glucose production from hepatic glycogen. At the same time, the release of fatty acids from adipose cells is inhibited and there is an increase in plasma concentrations of glucose and fatty acids, increasing glucose oxidation as an energy substrate in detriment of fatty acid oxidation to maintain energy homeostasis (Frank et al., 2013).

The insufficient practice of physical activity associated with high caloric diets directly affects the development of several chronic noncommunicable diseases widely discussed in the literature, such as obesity, type 2 diabetes mellitus, hypertension, dyslipidemias, and cardiovascular diseases (Chatzigeoegiou et al., 2013; Pedersen, 2009; Petersen & Pedersen, 2005; Hotamisligil, 2017; Wensveen, Valentić, Šestan, Turk Wensveen, & Polić, 2015).

Metabolic disturbances due to physical inactivity and an inadequate diet correlate directly with low-grade chronic inflammation (Asghar & Sheikh, 2017). This problem is characterized by plasma alterations in inflammatory mediators, with an increase in procytokine concentrations of inflammatory factors such as TNF-α, plasminogen activator inhibitor type 1, C-reactive protein, IL-6, and a reduction in anti-inflammatory cytokines, such as IL-10 and adiponectin. These inflammatory alterations contribute directly or indirectly to the pathophysiological regulatory process of these diseases (Ades et al., 2009; King, 2008).

A nutritional diet with excess calories and macronutrients, leads to the excessive percentage of body fat, mainly characterized by VAT accumulation. This fat, when remaining in a vicious cycle of hypertrophy of the adipocytes, culminates in greater infiltration of immune cells, favoring an increase in the secretion of adipokines with proinflammatory characteristics, targeting the installation, and

development of chronic low-grade inflammation that are recognized as the main link between obesity and insulin resistance (Hotamisligil, 2017; Ouchi, Parker, Lugus, & Walsh, 2011). Apoptosis and/or lipolysis of adipocytes, as well as inhibition of adipogenesis and lipogenesis, are events mediated by TNF-α and others adipokines (Cawthorn, 2007; Warne, 2003).

It is noteworthy that insulin and leptin, hormones secreted in the states that the body has overloading food, inhibit the AMPK pathway and in contrast, in the starvation state, the secretion of ghrelin and adiponectin activates the AMPK pathway (Yamauchi et al., 2002). This context allows us to infer that this metabolic profile induced by hormone secretion works synergistically with immune system cells (Ringseis, Eder, Mooren, & Krüger, 2015), which has its proinflammatory phenotype exacerbated in states of overfeeding, triggering chronic low-grade inflammation; or under food restriction and suitable nutrient balance anti-inflammatory states expressed (via AMPK) (Yamashita et al., 2018).

Besides the increased plasma concentrations of proinflammatory mediators such as TNF-α and IL-6, in low-grade chronic inflammation, there is a reduction in anti-inflammatory cytokines. The IL-10 anti-inflammatory cytokine is able to improve resistance and inhibit the production of inflammatory markers such as TNF-α and IL-6 (Dagdeviren et al., 2016). Adiponectin is able to reduce the expression of proinflammatory markers and increase the secretion of other anti-inflammatory mediators (Wedell-Neergaard et al., 2018).

The persistence of an elevated inflammatory process for a long period in the adipose tissue microenvironment is partly mediated by the presence of cells of the innate and adaptive immune system. A subset of the innate immune population in adipose tissue includes infiltrated macrophages that play an important role in local inflammation (Catrysse & van Loo, 2018). Macrophages exhibit a pleiotropic characteristic, which responses to diverse molecular signals in the microenvironment drive their identity and functional properties in response to differentiation to M1 or M2 phenotype.

Chronic low-grade inflammation correlates with other tissues that may culminate in other functional changes. These changes include alterations observed in muscle (insulin resistance), endothelial (endothelial dysfunction and atheromatous plaque formation), and hepatic tissue (glycogenolysis, gluconeogenesis, and accumulation of ectopic fat), as well as in the central nervous system (changes in eating behavior, decreased energy expenditure, and resistance to insulin action) (Prussick & Miele, 2017; Ruiz-Núñez, Pruimboom, Dijck-Brouwer, & Muskiet, 2013).

Thus, the excess food that culminates in adipocyte hypertrophy and imbalance in glycemic homeostasis with repeated events of hyperglycemia, leads to metabolic and cellular imbalances that cause chronic and acute impairments, promoting a loss of stability of the systems and consequently diseases, such as type II diabetes, dyslipidemias, hypertension, Alzheimer's, and cancer.

Metabolic disruption associated with insulin resistance and impaired glucose metabolism has a direct impact on innate and adaptive immune response. Patients with a hyperglycemic condition presented higher immune activation markers (i.e., HLA-DR and CD69+ expression) on the cell surface of leukocytes and higher expression of TLRs. In fact, insulin resistance and higher glucose levels are associated with higher frequencies of CD14+ CD16+ intermediate and CD14− CD16+ nonclassical monocytes, and elevated CD14+ monocyte TLR expression compared to age-matched normoglycemic individuals. In adaptive immunity, type 2 diabetes and metabolic syndrome patients present disturbed T cell subpopulations characterized by the accumulation of memory T effector cells, lower naïve T cells and Tregs, and a polarization to Th1/Th17 phenotype. These cellular immunity alterations result in higher proinflammatory cytokine (mainly TNF-α, IL-8, and MCP-1) secretion resulting in a proinflammatory environment. The chronic inflammatory condition in patients with impaired glucose metabolism results in reduced immunosurveillance, with obese and type 2 diabetes subjects representing some of the main risk groups for bacterial and viral infection and premature infectious diseases.

There is a synergic effect between chronic inflammation and metabolic disturbance. For example, crosstalk between macrophages and adipocytes leads to higher secretion of TNF-α by the former, which directly impairs insulin-mediated glucose uptake and lipogenesis through impaired phosphorylation of tyrosine kinase of the IR and lower Akt-GLUT-4 axis activation. Moreover, TNF-α infusion reduces whole-body insulin-mediated glucose uptake in healthy humans. The inflammasome-derived cytokine IL-1β mediates β-cell damage in diabetic patients, and depletion of resident pancreatic macrophages in high-fat-fed mice reduces IL-1β expression and improves β-cell insulin secretion. A number of cytokines and adipokines may impact on metabolism and negatively or positively alter key enzymatic processes in several peripheral metabolic tissues. The systemic increases in inflammatory mediators induce glucotoxicity and lipotoxicity in the brain, liver, adipose tissue, and muscle tissue, as viewed through the accumulation of intermediates of fatty acids (i.e. malonyl-CoA, which impairs mitochondrial oxidative process) and insulin resistance.

On the contrary, exercise is now recognized as a lower-cost effective therapy that improves metabolic profile and alleviates the inflammatory condition in a range of chronic diseases (Figure 3). Every single bout of moderate-high intensity exercise is able to induce a strong anti-inflammatory response characterized by the secretion of myokines (i.e., IL-6 and irisin) and anti-inflammatory cytokines IL-4, IL-1ra, and IL-1, which counteract the inflammatory cytokines for hours after the session. Moreover, emerging evidence denotes that acute exercise mobilizes immunoregulatory Treg cells and hematopoietic stem cells, and lowers TLR expression on monocytes and the peripheral frequency of proinflammatory terminally differentiated T cells. Although the immune response to exercise is widely dependent on the type, intensity, and volume of the bout, the general consensus indicates that moderate-to-high intensity exercise exerts a positive impact on inflammatory response.

Nonetheless, the anti-inflammatory effects of exercise coincide with improved glucose uptake by muscle tissue and improved insulin sensitivity. Longitudinal studies support the notion that changes in circulating cytokines are determinant for improvements in insulin

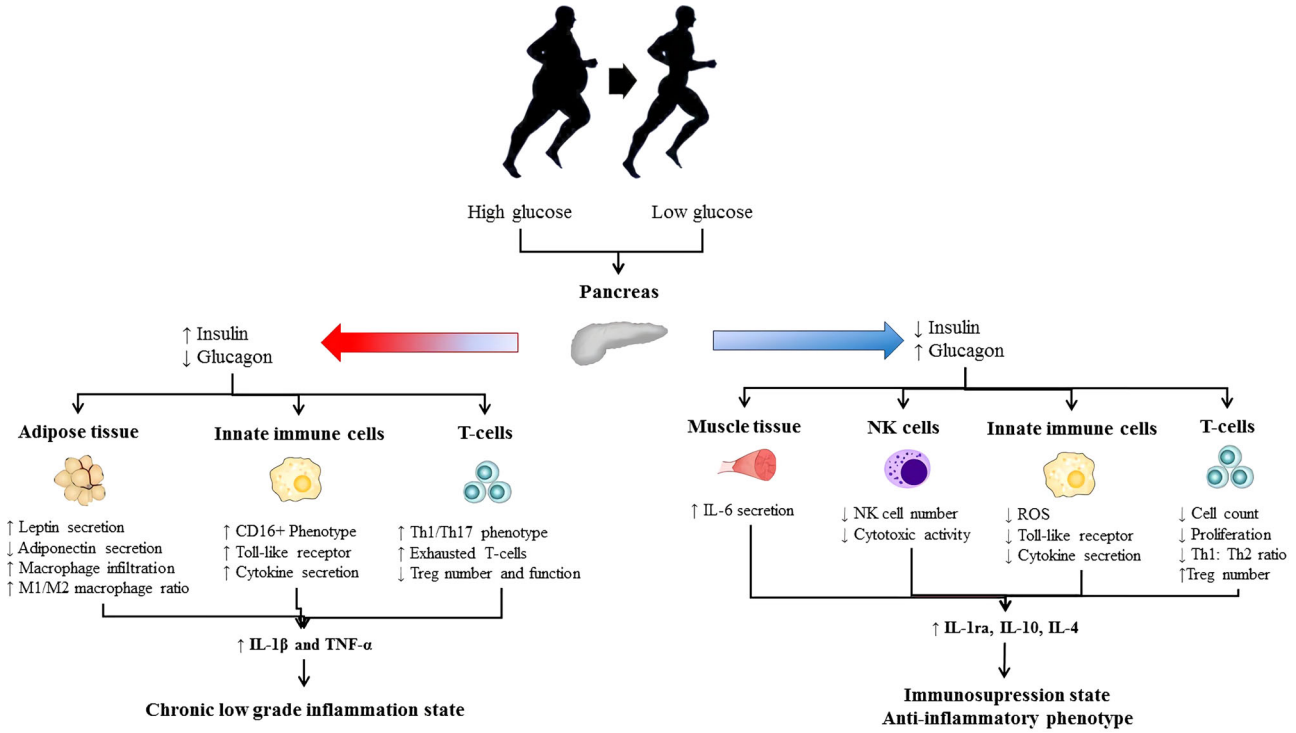

FIGURE 3 Potential impact of high glucose and low glucose conditions on immune-inflammatory response. High glucose condition increases systemic insulin levels which induce a proinflammatory condition through: (a) increased leptin secretion, higher macrophage infiltration, and M1 phenotype in adipose tissue; (b) higher CD16+ monocyte phenotype, increased toll-Like receptor expression, and TNF-α production; (c) an imbalance in T helper cells phenotype, inducing Th1/Th17 pattern, lower Treg number and function, and increased T cell senescence phenotype. On the contrary, low glucose condition is associated with increased glucagon levels and a state of immunosuppression/anti-inflammatory state through: (a) higher myokine, that is, IL-6, secretion by skeletal muscle tissue; (b) decreased NK cell number as well as their cytotoxic activity; (c) lower toll-like receptor expression, ROS generation and cytokine secretion by innate immune cells; (d) the T helper cells polarize to Th2 phenotype, higher Treg number and function, and lower proliferative response. IL, interleukin; NK, natural killer; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α

sensitivity in overweight sedentary patients. Mechanistically, the IL-6 secreted by contracting skeletal muscle cells activate AMPK in muscle and adipose tissue. The activation of AMPK increases glucose uptake through insulin signal transduction and GLUT-4 translocation, and stimulates glycolysis and fatty acid oxidation in muscle cells. Moreover, IL-6 production may be directly involved in the expansion of pancreatic β-cell mass, improved insulin secretion and glycogenolysis by the liver, and lipolysis in adipose tissue. In addition, the higher IL-1ra induced by exercise inhibits IL-1 activation, limiting pancreas damage.

Myokines, peptides released from muscle cells in response to contraction, are responsible for some immunometabolic improvements. Hundreds of myokines provide a basis for how muscle communicates with several organs, including adipose tissue, liver, brain, and bone, during and after exercise bouts (the readers are invited to read some of the excellent reviews about myokine regulation during exercise: Hoffmann & Weigert, 2019; Pedersen & Febbraio, 2012). In this way, the production of brain-derived neurotrophic factor and IL-6 are involved in AMPK- mediated fat oxidation and enhanced glycolysis. Moreover, IL-6 and IL-15 stimulate lipolysis of visceral fat in an intensity-dependent manner. During exercise, IL-6 maintains stable levels of systemic glucose through liver gluconeogenesis and glycogenolysis (Pal, Febbraio, & Whitham, 2014). Studies performed using isolated myotubes showed that myonectin and fibroblast growth factor-21 (FGF-21) stimulate mitochondrial biogenesis. IL-8 and CXCL1 induce angiogenesis in muscle tissue, enhancing metabolic improvements and oxygen supply. Finally, irisin plays a role in browning the white adipose tissue, which is related to better metabolic outcomes (Pedersen & Febbraio, 2012).

Muscle cells from diabetic patients presented inflamed muscle tissue, as evidenced by higher resting expression of NF-κB, which may induce insulin resistance and lower myokine expression (Tantiwong et al., 2010). Interestingly, metabolic benefits of myokines are not affected in response to exercise in patients with type 2 diabetes. Sabaratnam et al. (2018) showed that 60 min moderate-intensity cycling exercise increased muscle expression of IL-6, FGF-21, angiopoietin-like 4 (ANGPTL4), chitinase-3-like protein 1 (CHI3L1), connective tissue growth factor, and cysteine-rich angiogenic inducer 61, of which FGF-21, ANGPTL4, and CHI3L1 increased for a further 3 hr into recovery in both type 2 diabetes patients and matched-weight controls. Moreover, higher IL-6 signaling induced by exercise enhanced pancreatic β cell viability in a mouse model of type 1 diabetes (Paula et al., 2015). Collectively,

these data highlight the beneficial role of myokine expression in metabolic improvement independent of the metabolic condition of the patient. A recent randomized controlled trial confirmed that muscle-derived IL-6 plays a major role in the reduction of VAT in obese patients (Wedell-Neergaard et al., 2018).

Less is known regarding the adaptive immune response in acute and chronic exercise under hyperglycemic conditions. A recent study demonstrated that the blunted mobilization of highly differentiated CD8+ T cells in response to exercise was related to differences in blood glucose, catecholamine discharge, and sequestration of T cells in the pancreas of type 1 diabetic patients (Curran, Campbell, Drayson, Andrews, & Narendran, 2019). However, longitudinal studies revealed that ameliorations in blood glucose concentrations are related to changes in T cell subgroups (Wenning et al., 2013). In type 2 diabetic patients, regular tai chi chuan exercise increased T-bet transcription factor in CD4+ T cells and forkhead box P3 (FoxP3+) expression in Treg cells and decreased the CD8+ T cytotoxic population in parallel with decreases in glycated hemoglobin (Yeh et al., 2007, 2009). Increases in Treg frequency seem to play a key role in the improvement in insulin sensitivity, and the immunoregulatory cytokines IL-10 (the main cytokine secreted by Treg cells) and IL-33 revert adipose tissue insulin resistance induced by TNF-α (Han et al., 2015; Wang & Wu, 2018). Moreover, a closer relationship between tissue lymphocyte content and metabolism was identified in nonobese diabetic mice, since exercise training reduced lymphocyte infiltration into the pancreas and subsequently the insulitis index (Oharomari, de Moraes, & Navarro, 2017). However, to date, there is a lack of investigation regarding acute exercise mobilization of T cells in patients with metabolic disorders. Recently, Curran et al. (2019) demonstrated that type 1 diabetes blunts the mobilization of highly differentiated 874 CD8+ T cells during and after exercise.

Exercise also reduces the expression of TLR4 on the cell surface of monocytes, granulocytes, and lymphocytes in type 2 diabetic patients (Robinson et al., 2015). An endotoxemic condition, such as higher circulating LPS, enhances TLR4 expression in metabolic tissues, providing a link between a proinflammatory condition and dysregulated metabolism in metabolic diseases (Frisard et al., 2010). Mechanistic studies revealed a link between reduced expression of intracellular TLR pathways (JNK, IκB, andNF-κB) in adipose and hepatic tissue in conjunction with increased IR density and AKT phosphorylation (da Luz et al., 2011; Wang, Li, Wang, Zou, & Zhang, 2018). Moreover, exercise increases the expression of gene markers (AMAC1and IL-4) related to M2 through upregulation of transcription factors PGC-1α and PGC-1β (Yakeu et al., 2010). The activation of peroxisome proliferator-activated receptor via their coactivators (PGC-1α and PGC-1β) has beneficial effects through regulating inflammatory gene expression and glucose and fatty acid metabolism (Fernandez, 2008; Russel, 2005)

Finally, exercise alleviates adipose tissue migration and polarization of proinflammatory macrophages in high-fat obese mice and human obesity (Baturcam et al., 2014; Kawanishi, Mizokami, Yano, & Suzuki, 2013; Kawanishi, Yano, Yokogawa, & Suzuki, 2010). Again, immunometabolic improvements seem to be impacted by muscle secretion of IL-6, since exercised obese mice presented lower M1 macrophage content, higher IL-10 expression, and better insulin sensitivity in VAT than sedentary obese mice (Macpherson, Huber, Frendo-cumbo, Simpson, & Wright, 2015). Thus, the indirect anti-inflammatory effect of exercise in VAT, evidenced by lower TNF-α secretion in exercised mice, has strong effects on the attenuation of tissue insulin resistance.

5 | CONCLUSION

In our narrative review, it was not possible to make a direct comparison of the immunological changes between both glucose state availability conditions due to differences in methodology and immune markers analyzed. However, the hypoglycemia state induces a state of reduced immunosurveillance characterized mainly by lower NK and T cell function and increased anti-inflammatory cytokines. On the contrary, higher glucose availability state is related by the chronic low-grade inflammation, as visualized mainly by higher proinflammatory M1 macrophages and monocyte phenotype, Th1/Th17 polarization, lower Treg frequency and function, and higher proinflammatory cytokines and adipokines. The current evidence now argue that metabolism has a key role in immune cells to facilitate requirements for energy and biosynthesis that directly regulate immune cell functions. The modulation of immune cells function induced by acute and chronic exercise seems to be dependent, at least in part, of the glucose homeostasis condition from the subject. Although further studies are necessary, the emerging evidence suggest that the immunomodulatory effects of exercise are mediated by the ability of exercise to adjust the energetic and biosynthetic demands of lymphocytes in response to physiological and pathological conditions.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

A. E. V. A. M., G. P. D., A. P., and F. S. L. designed the study protocol. A. E. V. A. M. and G. P. D. conducted the main search for the review.

A. E. V. A. M., G. P. D., A. P., and F. S. L. contributed to the writing of the manuscript. All authors read the final version of the manuscript.

ORCID

Ana E. Von Ah Morano http://orcid.org/0000-0002-0733-5618
Gilson P. Dorneles http://orcid.org/0000-0001-6524-3204
Alessandra Peres http://orcid.org/0000-0002-3587-2832
Fábio S. Lira http://orcid.org/0000-0002-9645-1003

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