REVIEW ARTICLE

What is the role of brown adipose tissue in metabolic health: lessons learned and future perspectives in the long COVID?

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Abstract

Metabolic physiology plays a key role in maintaining our health and resilience. Metabolic disorders can lead to serious illnesses, including obesity. The pathogenesis of the new long COVID syndrome in individuals with long-term recovery after SARS-Co-2 infection is still incomplete. Thus there is growing attention in the study of adipose tissue activities, especially brown adipose tissue (BAT) and associated resilience which plays a crucial role in different types of obesity as potential targets for pharmacologic and nutritional interventions in the context of obesity and long COVID. The number of studies examining mechanisms underlying BAT has grown rapidly in the last 10 years despite of role of BAT in individuals with COVID-19 and long COVID is modest. Therefore, this review aims to sum up data examining BAT activities, its resilience in health, obesity, and the possible link to long COVID. The search was conducted on studies published in English mostly between 2004 and 2022 in adult humans and animal models. Database searches were conducted using PubMed, Scopus, and Google Scholar for key terms including adipose tissue, BAT, adipokines, obesity, VPF/VEGF, and pathogenesis. From the initial search through the database were identified relevant articles that met inclusion and exclusion criteria and our data regarding adipose tissues were presented in this review. It will discuss adiposity tissue activities. Current literature suggests that there are BAT integral effects to whitening and browning fat phenomena which reflect the homeostatic metabolic adaptive ability for environmental demand or survival/adaptive mechanisms. We also review neural and vascular impacts in BAT that play a role in resilience and obesity. Finally, we discuss the role of BAT in the context of long COVID in basic research and clinical research.

Keywords Adipose tissue · Adipokine · Brown adipocyte tissue · Obesity · VPF/VEGF · Long COVID · Semicarbazide-sensitive amine oxidase inhibitors

Introduction

Plenty of recent evidence-based data supports the prominent role of metabolic physiology processing and essential survival/adaptive mechanisms in health. Metabolic health and its disorders, including diabetes mellitus, insulin resistance, and obesity, corresponding to the World Health Organization (WHO) consider being major risk factors for serious illnesses (WHO 2022). Despite all global public health and medical care efforts, the number of patients with metabolic disorders during the last 2 decades increased markedly in countries of all income levels. Moreover, researchers have repeatedly found during the coronavirus disease-2019 (COVID-19) pandemic patients with metabolic diseases were in risk groups for the onset of severe forms of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) infection and predisposition of long COVID (synonym of post-acute sequelae of CoV-2), a new and separate chronic syndrome that has different manifestations in people, later (Finucane and Davenport 2020; Callard and Perego 2021; Loosen et al. 2022). Patients with obesity and who have often a deficiency of lymphocyte proliferation-improving micronutrients are referred to as one of the risk groups

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for long COVID significant reason for abnormal defense system functioning related to the delayed and ineffective immune response (Krams et al. 2020; Sattar et al. 2020; Karkhut et al. 2021). In other words, nowadays is still an incomplete end-all understanding relationship between metabolic health and SARS-CoV-2 infection and how to provide effective prevention for negative consequences of the onset long COVID. Despite of plenty publications about long COVID, there is a lack of knowledge in understanding of long COVID pathogenesis in the context of metabolic health induced by SARS-CoV-2 infection associated with brown adipose tissue (BAT) dysfunction. The current review is a supplementary contribution to a series of publications about BAT, long COVID, and metabolic health focusing on our previous study and the crucial importance of brown adipocytes-related metabolic health and resilience. We screened the latest scientific literature in three separate databases including PubMed, Scopus, and Google Scholar platforms (search date until December 24, 2022), to identify relevant studies, using Medical Subject Headings vocabulary produced by the National Library of Medicine, USA, MeSH, terms for COVID-19, metabolic health, and brown tissue by keywords: "long COVID", "long-term effects of COVID-19", "post-acute sequelae of CoV-2", "metabolic health", "fat tissue", "brown adipose tissue" (BAT), "adipocyte" and "adipokine". Studies were included in research when they met the following conditions: (1) recognition of long COVID in patients after SARS-CoV-2 infection; (2) for metabolic health associated with fat tissue functioning conducted on humans, mammals, or in vitro; (3) published in English. The following studies were excluded: (1) studies related to children; (2) studies about novel therapeutic approaches targeting BAT; (3) studies about novel operating technics for obesity treatment. Figure 1 presents a flowchart illustrating the number of reviewed studies associated with adipose tissue activities, long COVID-19, and metabolic health screened with included and excluded criteria.

The publication dates of most of the selected articles for review are from 2004 to 2023.

Adipose tissue: what is the link to obesity?

Accumulating evidence has suggested the importance of fat tissue in the body for health and resilience (individual physiological multisystemic mechanism linked with capability to recovery after extreme factors actions). Recently it was recognized different types of adipose tissues and their various morphological properties, physiological and metabolic functions, plasticity, and adaptive potential as well as regulation. All types of adipose tissues, composed of white adipocytes, brown adipocytes, beige adipocytes, and pink adipocytes, as well as adipocyte-like cells which are in the lungs and
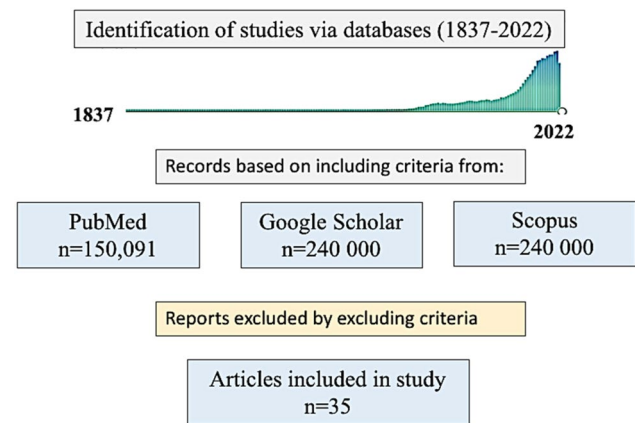

Fig. 1 The flowchart of the study

liver, have secretory activities (Cannon and Nedergaard 2004; Harms and Seale 2013; Giordano et al. 2014; Frigolet and Gutiérrez-Aguilar 2020). Considering recent advances, adipose tissues are highly dynamic endocrine organs that secrete adipokines, and several key transcriptional regulators in auto-, para- and endocrine manners might be remodeling white adipose tissue (WAT), BAT, pink adipose tissue (adipocyte-derived milk-producing cells), as well as adipocyte-like cells, lipofibroblasts in the lung and liver, as well as change their metabolic and physiological effects. Table 1 illustrates a summary of their different functional and metabolic roles and resilience mechanisms. Their physiological and metabolic effects realized by myriad signaling pathways under influence of exogenous and endogenous stimuli might lead to sequential changes in the inter- and intracellular communications which have diverse outcomes also. They involve changes not only in food intake behavior, accelerating aging as well as the development of obesity with serious and highly prevalent clinical disorders with increased risk of all-risk mortality, including severe forms of COVID-19 (Basolo et al. 2022). A well-known fact is that adipose tissue supports the replication of various adeno-associated viral vectors, including cytomegalovirus, influenza A, HIV, and SARC-CO-2 (Bates et al. 2020). Infected by the COVID-19 virus adipocyte tissue may be the cause of long COVID (de Lucena et al. 2020; Farve et al. 2021).

Nearly 50 years ago, the determination of obesity which was defined as a disorder with increased fat mass was first, transformed into a new term related to the "metabolic obese" condition (Ruderman et al. 1981) which might be present in a person with normal body mass index (BMI). It was the first mention of a wider understanding of the role of adipose tissue in obesity than just hyperplasia of white fat tissue (WAT) and increased weight of the body. This is significant for better observation of metabolic health which might be compromised in individuals who are "metabolic obese

Table 1 Types of cells in adipocyte tissue and their different functional and metabolic roles and impact in resilience mechanisms

Type of adipose cell	Location	Additional place	Adipokine	Metabolic effects	Physiological effects	Adaptive potential
White adipocytes	S Subcutaneous, V visceral organs	Adipocytes in the stomach and intestinal epithelium, placenta, muscle, mammary gland, and brain	Leptin	Lipid oxidation, thermogenesis, insulin sensitivity	Anorexigenic, Satiety	Long-term energy storage and insulation, feeding behavior, cytoprotection, accelerated proliferation under a hypercaloric diet
		Adipocytes	Adiponectin	Lipid oxidation, hepatic gluconeogenesis suppression, inhibition of monocytes adhesion	Anorexigenic, (anti-inflammatory and antiatherogenic)	
		Vascular stromal cells of visceral adipose tissue and intestinal cells	Omentin	Increased insulin-stimulated glucose uptake and release of orexigenic peptides in the hypothalamus	Orexigenic	
		Adipocytes	Resistin	Insulin resistance and fatty acid synthesis in liver	Anorexigenic	
		Adipocytes	Retinol-4 binding protein	Retinol transport and insulin resistance due to reduced expression of GLUT4		
		Adipocytes, hepatocytes, and lung cells	Quemerin	Adipogenesis, angiogenesis, pro-inflammatory	Orexigenic	
		Adipocytes in visceral adipose tissue	Visfatin	Possible influence on the development of obesity, pro-inflammatory and proatherogenic	Visceral lipotoxicity	
		Adipocytes	Palmitoleic acid	Insulin sensitivity, lower lipogenesis	Control lipid metabolism	
		Subcutaneous and perigonadal adipose tissue in fasting	APHAE (palmitic-hydroxyl-stearic acid)	Insulin sensitivity due to increased glucose capture, increased insulin secretion and glucagon-like peptide-1, anti-inflammatory	Control glucose and lipid metabolism	
			IL-6	Inflammatory	Visceral lipotoxicity, low-grade inflammation	
			angiotensin II	Vasospasm, entry receptors for SARS-CoV-2	Vascular control, involvement n immune response, the onset of long COVID (?)	
			IGF-1 (in response to GH)	Anabolic stimulating effect	Growth and proliferation-promoting effects	

Table 1 (continued)

Type of adipose cell	Location	Additional place	Adipokine	Metabolic effects	Physiological effects	Adaptive potential
Brown adipocytes	Neck area, the upper part of the back	Superficially: Interscapular, Cervical, Supraclavicular, Subclavian, Thoracic spine Axillary areas Near visceral organs: Perirenal, Periaortic, Pericardial areas Near reproductive organs: Parametrial genuine brown-like fat cells Epididymal fat depots	Uncoupling proteins (UCPs)	Thermogenesis, ROS regulation, adaptation of cellular metabolism to an excessive supply of substrates to regulate the ATP level, the NAD(+)/NADH ratio, and various metabolic pathways	Control in whole-body temperature, energy expenditure, control of ATP level, NADH/NAD+Proton translocation ratio, ROS level, metabolic adaptation to fatty acid cycling and glucose fluxes response to oxidative stress, lipid peroxidation, inflammatory processes, fever, and regulation of body temperature	Defense against hypothermia, cold exposure, involvement in adaptive reaction during acute stress, sympathetic nervous influence, thyroid hormones thyroxine and tri-iodothyronine, bone morphogenetic protein 7 (BMP7) activates, control lipoproteins balance and glucose uptake
			Brain mitochondrial carrier protein 1 (BMCP1, also known as UCP5)	Mitochondrial oxidative phosphorylation, ATP synthesis	Heat production	Adaptation to extreme/survival factors
			PR domain zinc finger protein 16 (PRDM16)	Transcription coregulator in the development of brown adipocytes	Formation of both classical brown and beige adipocytes	Adipogenesis, browning white adipose tissue
			Peroxisome proliferator-activated receptor γ coactivator 1 (PGC1α)	Transcriptional coactivator that is a central inducer of mitochondrial biogenesis in cells	Oxidative metabolism, aging	Oxidative stress control, adaptation to metabolic demand
			Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF)	Growth factor induced by hypoxia (HIF activation), and different cytokines and growth factor	Microvascular remodeling (trans-endothelial cell pores, fenestrated endothelium) in SVF, trigger for the extrinsic clotting pathway, generating serum, and depositing fibrin after SARS-CoV-2 entry by endothelial ACE2 receptors (?)	Stimulation the endothelial cells in SVF to proliferate, to migrate, prevention microvascular hyperpermeability, extravasation of fibrinogen and other plasma proteins as the result of formation of vascular connective tissue, angiogenesis

Table 1 (continued)

Type of adipose cell	Location	Additional place	Adipokine	Metabolic effects	Physiological effects	Adaptive potential
Beige/brite (brown in white), UCP1-containing multilocular adipocytes	In WAT (direct and reversible transdifferentiation of into brown adipocytes)	Within WAT depots alongside brown cells in BAT	UCPs	Energy expenditure	Control in whole-body energy expenditure, lipid balance	Adaptation related to cold exposure and sympathetic influence, survival adaptation, excess of fat
Pink (adipocyte-derived milk-producing cells)	Mammary gland during pregnancy and lactation	During neoplastic processes	Perilipin B	Control of metabolism of neutral lipids stored in lipid droplets	Production and secretion milk, control lipolysis	Survival adaptation
Adipocyte-like cells: lipofibroblasts in the lung, lipocyte stellate cells (Ito cells) in the liver	Near type 2 alveolar epithelial cells, liver		Fibroblast growth factor 10 (FGF10)	Mitogenic activity, cell survival activities, control of proliferation and differentiation of preadipocytes to mature cells	WAT development, remodeling, metabolism, angiogenesis, pro-inflammatory, the reservoir for SARS-CoV-2 (?)	Adipogenesis, fibrogenesis

ATP adenosine triphosphate; *ACE2* angiotensin-converting enzyme 2; *HIF* hypoxia inducible factor; *NAD(+)/NADH* nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydride; *ROS* regulation of reactive oxygen species; *SARS-CoV-2* severe acute respiratory syndrome with coronavirus 2 infection; *SVF* stromal vascular fraction; *UCPs* uncoupling proteins

normal weight" (normal BMI). In the last decades, among obese metabolic phenotypes the additional term of this type of obesity was introduced, as "TOFI", from "thin outside and fat inside" Goossens 2017; Zdrojewicz et al. 2017). TOFI refers to the condition when a person with BMI above 18.5–25 kg/m^2 and normal waist circumference has signs of ectopic fat lipotoxicity or visceral lipotoxicity. It could be the valid risk factor for the onset of metaflammation, the tissue-specific alterations based on chronic low-grade inflammation linked with abnormal metabolism related to cellular damage and oxidative stress, as well as accelerated cellular senescence and oncogenes activation (Tchkonia et al 2010). Our animal model data about mesenteric adipose tissue has shown a role of visceral lipotoxicity in age-related endothelial dysfunction, redox disbalance, and the positive effect of hydrogen sulfide influence on decreased metaflammation (Revenko et al. 2018, 2021). It could be a potential therapeutic approach for obesity-related several serious illnesses, especially mesenteric chronic inflammation of the gastrointestinal tract, cardiovascular diseases, diabetes mellites 2 type (T2D) related disorders, infertility, and cancer.

Brown adipose tissue: focus on its impact on metabolic health and resilience

It has been almost 470 years since the understanding of BAT role began by Conrad Gessner (1516–1565), a Swiss physician and scientist who first found in the interscapular area "tissue as neither fat nor flesh but something in between". Figure 2 represents the chronological outline of milestones in understanding the physiological role of BAT in metabolic disorders based on its remodeling, biochemical and physiological effects, adaptive potential, and secretory activity (Marlatt and Ravussin 2017).

Transformation of 17th-century initial understanding of BAT as a part of the thymus and eighteenth century—the organ involved in blood formation or/and fat storage, to organ involved in metabolic health was begun by Andrew Theodore Rasmussen (1883–1955). He was the pioneer who suggested that BAT is the ductless gland that functions regulated by temperature influence like during hibernation. It was the first description of the role of brown adipocytes, which represent a relatively little amount (1–2% in adults) in comparison to total white adipose tissue, in thermogenesis, indirectly indicates on their involvement in metabolic physiology. The introduction of positron emission tomography (PET) and computed tomography (CT) imaging 20 years ago changed the paradigm of BAT activity could be only in newborns and children, confirming its active functioning and ability have a prominent role in metabolic health, survival, and other essential adaptive mechanisms in adulthood.

About two decades after the pioneering discovery of BAT as a gland Hans Selye (1907–1982) describes the participation of BAT during induction acute stress illustrating its morphological changes, involving stromal vascular fraction (SVF)—local vascular functioning (Selye and Timiras 1949). He was the first who explained BAT changes in general adaptation during the alarm reaction stage of stress emphasizing that BAT appears to be a lipid-storing endocrine gland with intensive blood supply and sympathetic innervation. Selye recognized that BAT activities are similar to another important gland, involved in stress response as the adrenal cortex, as well as glandular cells related to reproduction: the corpus luteum or the Leydig cells of the testis. It was the first mention of brown adipocytes' ability during stress-related metabolic demand to release energy from the form of lipid droplets by lipolysis using exporting free fatty acids from lipids, which are nowadays recognized as thermogenic substrates. This ability of brown adipocytes makes perfect sense from a physiological standpoint about BAT additional role in controlling lipoproteins balance and glucose uptake which are crucial for systemic metabolism and the development of metabolic disorders. It's very similar to WAT response during metabolic demand, e.g. stress, intensive physical load, or nutritional deprivation (Morigny
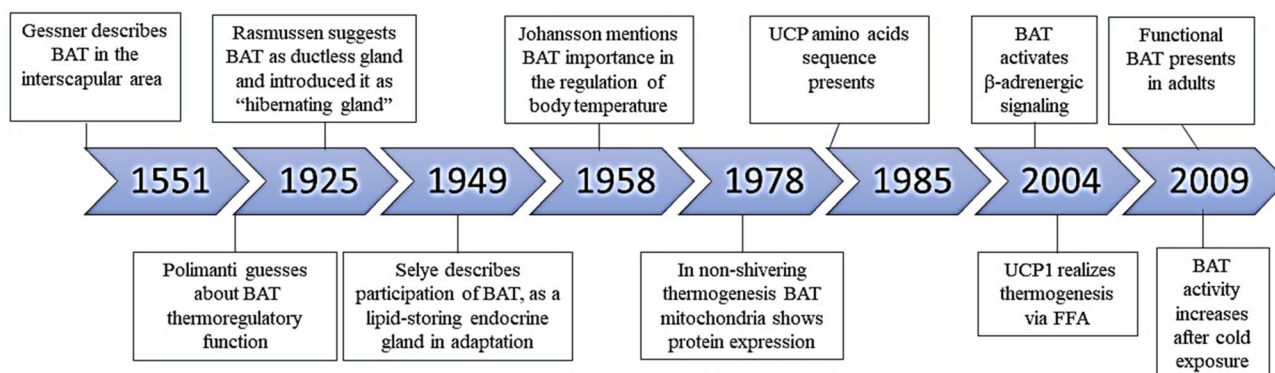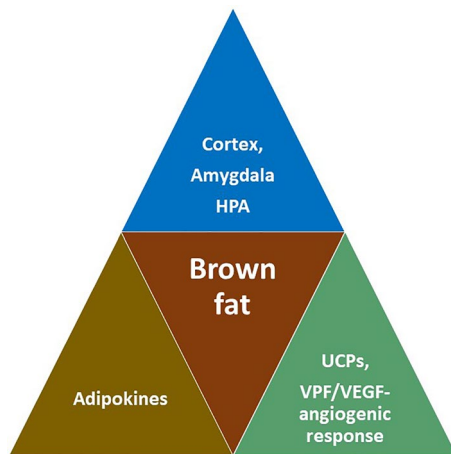

Fig. 2 Chronological outline of the brown fat tissue study

Fig. 3 Schematic diagram showing the integration of neural, endocrine, and vascular regulatory interactions in brown fat tissue functioning during health and resilience. *HPA* hypothalamic–pituitary–adrenal axis

et al. 2016). Our data of ultracellular changes of mesenteric white adipocytes during experimental obesogenic diet and stress has shown defragmentation of the intracellular big fat drop to smaller droplets of fat into the cytoplasm of white adipocytes or outside of the cell, lipid-laden phagolysosomes and detective ring-like mitochondria (Revenko et al. 2021). Thus, Selye's pioneered observational study was a great step in understanding the homeostatic role of BAT in systemic energy balance and survival/adaptative mechanisms in the whole organism. His prediction of the role of the vascular supply of BAT its SVF is vital in maintaining adaptive thermogenesis, as well as for survival mechanisms during hypoxia conditions which increased the release of vascular permeability factor/vascular endothelial growth factor (VPF/VEGF). Moreover, Selye's provisional view on the connection between BAT and sympathetic innervation was supported by a recent investigation of the cortex, amygdala, the hypothalamic–pituitary–adrenal axis with sympathetic influence via β-adrenergic receptors (β-AR) expression: β1-, β2-, and β3-Ars. The key role of them in metabolic health and resilience belongs to both β1-AR which is important for the proliferation of classical brown adipocyte precursors after norepinephrine influence, and β3-AR—for mature brown adipocytes accumulation of fat drops in the bounds of adaptive thermogenesis, inducing whitening of BAT, accumulating chemical energy in the form of lipid droplets. It helps build resilience during acute stress and other extreme situations associated with different metabolic demands, as well as create possible therapeutic attempts to affect BAT (Fig. 3).

A recent investigational study considered that hypoxia-based vascular rarefaction and insufficiency might cause the whitening of BAT, and additional obesity-linked BAT

dysfunction (Shimizu and Walsh 2015). This phenomenon correlates with our animal data of prenatal in utero programming BAT in the model of obesogenic environment based on the maternal diet (combination high-fat and high-sugar diet) and chronic stress exposure (Bezpalko et al. 2015). It had shown whitening of BAT and SVF changes in off-springs during an obesogenic diet and browning of WAT during resilience (Fig. 4). In addition, the marked increase of key pro-inflammatory interleukins (IL)-1 β and IL-8 levels, leptin/adiponectin ratio, the main markers of pro-inflammatory condition confirmed metaflammation, resulting in systemic tissue damage and inflammation.

Our results showed that BAT changes induced furthermore liver damage that represents histologically by hepatocellular ballooning, accommodation lipid drops, decomplexation of hepatic cords, and lobular inflammation. Both morphological changes of BAT and liver are key components of visceral lipotoxicity, developing onset of steatosis associated with metabolic disorders, including subcellular and biochemical changes with signs of endoplasmic reticulum and oxidative stress, lipoapoptosis, and impaired autophagy (Rada et al. 2020). It might transform into nonalcoholic steatohepatitis, the disease, which can remain asymptomatic for years in TOFI humans, and/or progress to cirrhosis and hepatocellular carcinoma.

Since the 50–80 s the most important discoveries about BAT were associated with its secretory activities of uncoupling proteins (UCPs) and their key role in general energy expenditure and adaptive thermogenesis (Heaton et al. 1978; Aquila et al. 1985). In the regulation of body temperature and energy homeostasis, the unique mitochondrial UCP1 (i.e., thermogenin) is the most important player, and its deficiency results in decreased heat production (Ricquier and Bouillaud 2000). Preadipocytes differentiate in maturated cells in BAT in a cold environment. Compensatory browning WAT related to the involvement of silent beige/ brite adipocytes has been described recently as an additional phenomenon of demonstration important link of BAT role in metabolic homeostasis which results directly in resilience (Harms and Seale 2013). These fluctuations in BAT activity have an impact on the development of obesity (Morigny et al. 2016).

Brown adipose tissue and long COVID: potential avenues for SSAO inhibitors

During acute COVID-19 infection, all adipocytes as well as adipose-like cells represent the reservoir of SARS-CoV/ CoV-2 which is involved in systemic inflammatory reactions (Kruglikov and Scherer 2020). Figure 5 represents the preliminary concept of the involvement of BAT in the pathogenesis of long COVID which present diverse forms
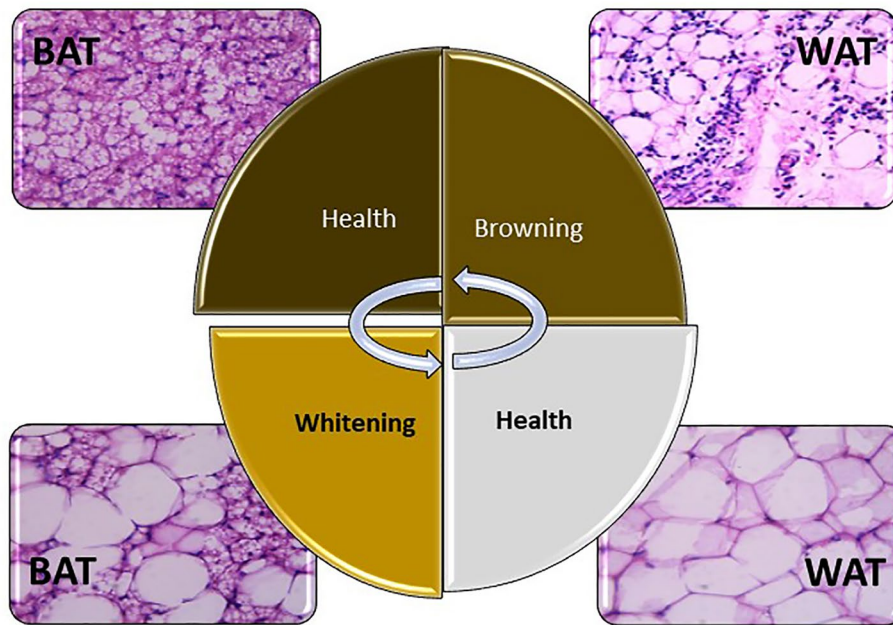
Fig. 4 Histopathology adipose tissue of rats, H&E staining, magnification 400: (1) brown adipose tissue (BAT) in health (from a control case); (2) stress-related browning of white adipose tissue (WAT) with severe polymorphism of adipocytes, leucocyte infiltrating and hemorrhage; (3) whitening of BAT with large lipid droplets, multifocal leucocyte infiltration, and capillary rarefaction during obesogenic diet; (4) mild polymorphism of adipocytes in white adipose tissue (WAT) in health (from a control case) (Bezpalko and Zayachkivska 2003–2005). Arrows show bidirectional influences between BAT and WAT, damage of one part leads to adjustment changes of another and reflects the adaptive process during resilience

Fig. 5 Schematic diagram of the preliminary conceptual model of brown fat tissue role in long COVID
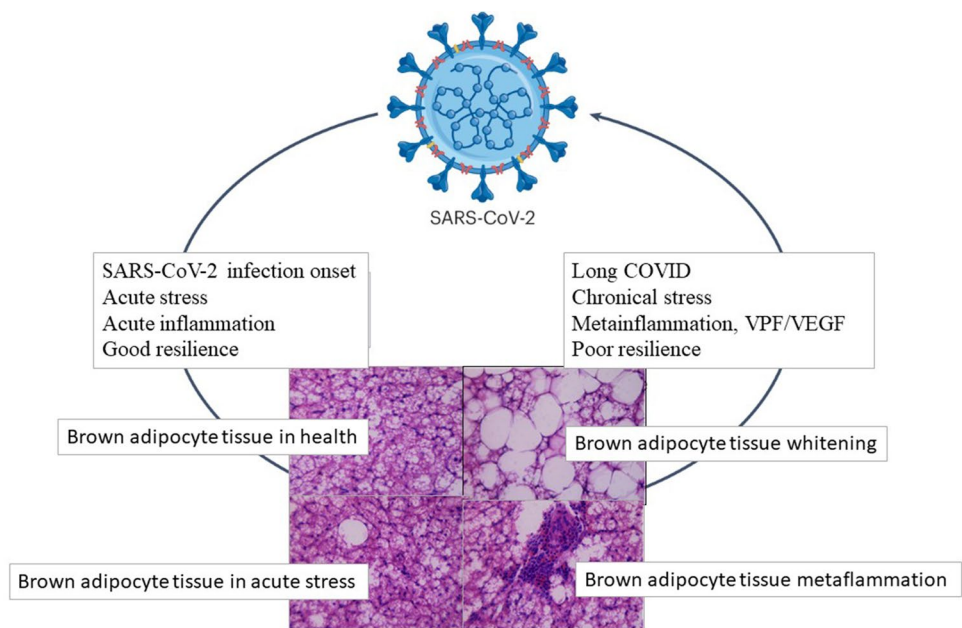
(Reese et al 2023). Since the browning of white adipose tissue (WAT) (Jing et al. 2022) and adipocytes of WAT could express the entry point of the SARC-CO-2 infection (Stefan 2023), changes in BAT functioning could be a missing link in understanding the pathogenesis of onset long COVID in individuals who did not have pre-existing metabolic disorders but could be TOFI individuals. Taking into account that the entry receptors for SARS-CoV-2 are angiotensin-converting enzyme 2 (ACE2) receptors that are widely expressed on endotheliocytes of SVT, an essential

part of BAT, and adipocytes in WAT, mostly located in the visceral tissue than in the subcutaneous tissue, dysregulated production of VPF, VEGF, lipids, cytokines, and other pro-inflammatory chemokines, could be additional factors for vasculature–adipocyte induced systemic inflammation during COVID-19 (Favre et al 2021) and prolong recovery after acute infection. The pathogenetic relevance of their impact on redox balance, oxidative stress, cell homeostasis, and death, synthesis of pro-inflammatory molecules, and fat droplets release into interstitial fluid and in the systemic circulation, could have the potential for pathogenic therapy (Jeremic et al. 2017). Furthermore, vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) is a potent factor for vasculature–adipocyte induced metaflammation and associated mechanisms related to NO and H_2S interaction which are responsible for endothelial dysfunction, accelerated coagulation, and long-term changes in hemostasis, as well as chronic inflammation, could increase the severe risk of the onset of long COVID.

Since vascular adhesion protein-1 (VAP-1), a semicarbazide-sensitive amine oxidase (SSAO), has very similar activities as VPF/VEGF during metaflammation (Wang et al. 2018; Pannecoeck et al. 2015), thus the introduction of SSAO inhibitors will have pharmacological potential long COVID since they provide vascular integrity in BAT, decrease proinflammatory adipokines levels and oxidative stress (Magyar and Mészáros 2003; Landecho et al. 2021; Li et al. 2021).

Summary and future perspectives

The ascending global obesity rate and COVID-19 pandemic have shown urgent efforts of fundamental and clinical researchers, as well as public health and society to decrease metabolic disorders prevalence. The modern view on metabolic health reflects the essential role of BAT, its functioning requests better recognition, including an understanding of cellular and physiological BAT mechanisms for their impact on resilience. Considering the present data there is still a strong opening question about the association between long COVID and BAT-related metabolic health and resilience which would help to optimize the syndrome-based treatment approach in the treatment of these massive health problems. Further studies are required to determine whether the BAT might be potential for SSAO inhibitors. Living in the new era of long COVID research, multidisciplinary investigation of BAT will help in finding a potential target for pharmacologic and rehabilitation interventions in the context of vasculature–adipocyte-induced metaflammation that could be the new avenue for long COVID treatment.

Despite big progress in understanding long COVID pathogenesis which reflects symptoms exacerbations of long COVID in individuals with metabolic disorders, including TOFI type of obesity, there is still an incomplete understanding of the impact of BAT on its onset. To get the full picture important to clarify what is the relationship in the pathogenesis of long COVID between the severeness of hypoxia during acute infection of COVID-19 and BAT-associated VPF/VEGF receptors overexpression. What the diagnostic criteria related to BAT functioning, resilience, and metabolic health should be used to diagnose long COVID? Are there patients with pre-existing "subclinical" abnormal BAT functioning among long COVID? To answer all these questions additional specific imaging studies with diagnostic instruments for BAT, need use for patients with long COVID.

Declarations

Conflict of interest Yes, all authors state that there is no conflict of interest.

Ethical approval No requirement for ethical approval.

Informed consent Not required.

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