

Unraveling the Complex Nexus of Macrophage Metabolism, Periodontitis, and Associated Comorbidities

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Keywords

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Abstract

Background: Periodontitis is recognized as one of the most prevalent oral dysbiotic inflammatory diseases, ultimately leading to the irreversible destruction of periodontal tissues. Macrophages play a pivotal role in the development and progression of periodontitis, and the feasibility of targeting them therapeutically has been established. Since metabolic switching significantly contributes to macrophage regulation, conducting an in-depth review of macrophage metabolism in periodontitis may serve as the foundation for developing innovative treatments. **Summary:** This paper has been carefully reviewed to provide a comprehensive overview of the roles played by macrophages in periodontitis and associated comorbidities. Initially, detailed presentations on the metabolic reprogramming of macrophages, including glucose, lipid, and amino acid metabolism, were provided. Subsequently, dominating macrophage phenotype and metabolism under lipopolysaccharide (LPS) stimulation or during periodontitis were presented with emphasize on critical molecules involved. Furthermore,

in recognition of the close association between periodontitis and several comorbidities, the interaction among macrophage metabolism, periodontitis, and related metabolic diseases, was thoroughly discussed. **Key Messages:** Through the examination of current research on macrophage metabolic reprogramming induced by periodontitis, this review provides potential immunometabolic therapeutic targets for the future and raises many important, yet unstudied, subjects for follow-up.

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Introduction

Periodontitis is characterized by the formation of periodontal pockets and subsequent alveolar bone loss due to plaque biofilm dysbiosis [1, 2]. It is associated with various chronic systemic diseases, including diabetes, obesity, respiratory diseases, osteoporosis, cardiovascular disease, and Alzheimer's disease [3–7]. Understanding the mechanism of periodontitis is crucial for developing advanced treatment approaches, particularly as it remains

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a significant global health issue despite existing therapeutic options.

Macrophages are essential components of the innate immune response and serve as precursors to osteoclastic lineages. Excessive accumulation and activation of macrophages can lead to dysregulated inflammatory responses and tissue injury. Research indicates that periodontal tissue destruction in periodontitis is largely attributed to the host immune response to infection [8], with emerging evidence linking the enrichment of inflammatory macrophages, especially M1 macrophages, to overactive osteoclastogenesis during periodontitis. Therefore, targeting macrophage function in the periodontium may be promising for preventing and treating periodontitis and its complications.

Metabolic reprogramming regulates macrophage activation and function, and targeting macrophage metabolism has shown promise in treating orthopedic diseases. For instance, D-mannose stimulates macrophage lipid metabolism, mitigating calvarial osteolysis induced by lipopolysaccharide (LPS) [9]. Additionally, the inhibitor 2-deoxy-glucose (2-DG), which blocks glucose uptake and glycolysis, can alleviate arthritic symptoms in adjuvant arthritis rats through the restoration of M1/M2 polarization [10]. Therefore, an in-depth study of macrophage metabolic reprogramming in periodontitis may offer new insights into its treatment.

This review starts by examining the role of macrophages in periodontitis and their potential as therapeutic targets. Given the rapid growth of the field of immunometabolism, it explores how altered macrophage glucose, lipid, and amino acid metabolism contribute to periodontitis by regulating macrophage function and key regulators in the process. Lastly, given the strong association between periodontitis and systemic diseases, the bidirectional relationships between dysregulated macrophage metabolism and comorbidities such as obesity, diabetes, and atherosclerosis are discussed. These comorbidities may arise from perturbed macrophage functions due to periodontitis, and reciprocally, exacerbate periodontitis by promoting unfavorable macrophage metabolism. In conclusion, the current landscape of immunometabolism in periodontitis is discussed, presenting potential avenues for future research in this area.

Macrophage Functions in Periodontitis

Situated at the periodontal interface between the host and the external environment, macrophages collaborate with other innate immune cells to form the first line of

host defense against invading pathogens. However, their hyperactivation can lead to tissue destruction and exacerbate periodontitis.

Chemotaxis of Macrophages in Periodontitis

Macrophages are classified into two categories based on their locations: resident macrophages and circulating macrophages. Circulating macrophages, which originate from monocytes in the blood, are recruited to inflammatory sites, including those affected by periodontitis, in response to the release of cytokines and chemokines. As for the resident macrophages, invasion by periodontal microbes prompts them to produce monocyte chemoattractant protein-1, recruiting more macrophages to the periodontal tissue. Additionally, macrophages secrete chemotactic cytokines, such as interleukin 8 (IL-8), which drive polymorphonuclear neutrophil infiltration at inflammatory periodontal sites [11]. The chemotaxis of macrophages increases their presence in the inflammatory microenvironment, facilitating their subsequent functions.

Macrophage Polarizations in Periodontitis

Macrophages exhibit different polarizations in response to complex signals in the microenvironment, broadly classified as proinflammatory (M1) and anti-inflammatory (M2) [12–14] (shown in Fig. 1). Although various macrophage phenotypes have been identified through single-cell analysis, studies have yet to explore the relationship between these phenotypes and macrophage metabolism [15, 16]. Consequently, this review primarily focuses on the metabolic characteristics of M1 and M2 macrophages. M1 macrophages eliminate pathogens through phagocytosis and produce proinflammatory cytokines [17], while M2 macrophages primarily aim at resolving inflammation and tissue repair [18, 19]. M1 macrophages release prostaglandin E2, tumor necrosis factor- α (TNF- α), IL-1 β , IL-6, and IL-12 in the bone destruction site [20], promoting osteoclast activity [21]. In contrast, M2 macrophages counteract the response of M1 by producing IL-4, IL-10, IL-13, transforming growth factor- β , and chemokines like C-C motif chemokine ligand 17 (CCL17) and CCL22, as well as the enzyme arginase 1 (ARG1), functioning in reducing inflammation and tissue repair [22, 23].

During the development of inflammation, the existence of M1 and M2 is in a dynamic equilibrium. Periodontitis can be divided into active and static stages according to histopathological manifestations. The active stage is associated with the infiltration and activation of M1, leading to bone loss, while the static stage possesses a larger proportion of M2 and repair damaged tissue [24]. The phenotype of

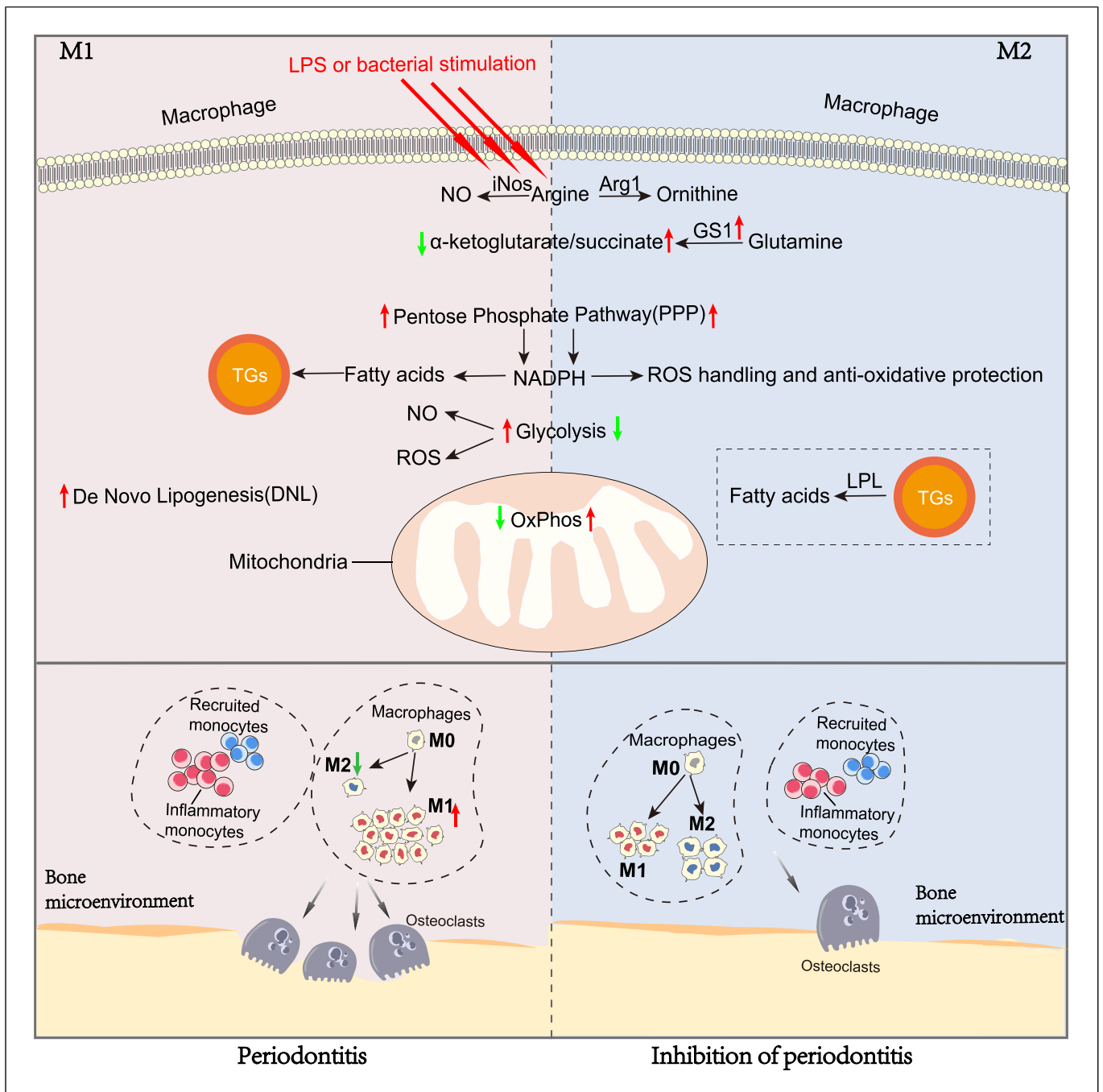


Fig. 1. Different metabolic reaction of M1 and M2 macrophages in periodontitis. The left half of the figure displays that after LPS or bacterial stimulation, macrophages polarize toward M1 due to metabolic pattern changes, thus inducing osteoclastogenesis and further aggravating bone loss. The right half of the figure illustrates the metabolism of M2 macrophages, exhibiting that M2 macrophages are inhibiting factors of periodontitis.

macrophages can be switched from M2 to M1 during some stages of periodontitis, thus aggravating periodontal tissue injury [24]. In periodontitis, M1 polarization can be induced by LPS, expressed on the outer membrane of *Porphy-*

omonas gingivalis, and binds to CD14 to activate Toll-like receptor 2 (TLR2) and TLR4 in macrophages [5]. Moreover, in diabetes mellitus (DM)-periodontitis, M1 polarization is enhanced compared to normal periodontitis, and elevated

IL-1 β and reactive oxygen species (ROS) production are the induction of M1 polarization [25, 26]. Both LPS and IL-1 β promote the activation and differentiation of osteoclasts, leading to periodontal bone resorption [27]. Therefore, the extent of M1 polarization differs according to the periodontal microenvironment and subsequently influences the severity of alveolar bone destruction. Similarly, M2 polarization can be increased during periodontitis under specific conditions. Inflammatory factors, like TNF- α , can uplift the expression of CD73 and WNT5A/RUNKL/OPG system through the exosome of gingival tissue-derived mesenchymal stem cells, thus inducing M2 polarization and inhibiting periodontal bone loss [28]. Moreover, exogenous IL-37, CCL2, and the hypoxia-inducible factor-1 α activator dimethylxalylglycine are capable to increase the number of M2 phenotype macrophages and downregulate TNF- α , IL-6, CD86, and monocyte chemoattractant protein-1 expression in vitro, relieving the bone loss in periodontitis [29–31]. These findings on promoting M2 polarization may provide an effective approach to periodontitis treatment.

Phagocytosis and Efferocytosis of Macrophages in Periodontitis

Macrophage phagocytosis refers to the process by which macrophages engulf and digest foreign particles, microorganisms, cellular debris, and apoptotic cells as part of the body's immune response. During periodontitis, the phagocytic ability, particularly of M1 macrophages, is enhanced [32]. Macrophages' phagocytosis relies on the expression of various pattern recognition receptors on the outer membrane, such as TLR2 or TLR4, to recognize LPS [33]. The efficiency of phagocytosis is regulated by molecules within macrophages. M2 macrophages secrete specialized pro-resolving mediators, a vital family of molecules involved in inflammation regression in periodontium [34], and some of specialized pro-resolving mediators, such as resolution E1 (RvE1), to enhance macrophage phagocytosis and promote periodontal regeneration [35, 36].

Efferocytosis is a multistep process that macrophages phagocytose apoptotic cells [37], and it helps maintain the homeostasis of tissues, since apoptotic cells release many harmful substances if not engulfed promptly [38]. In periodontal tissue, an increased number of apoptotic neutrophils, along with the release of neutrophil extracellular traps and reduced macrophage efferocytosis, resulted in prolonged inflammation [39]. Some molecules, like developmental endothelial locus-1 (Del-1), exert anti-inflammatory effects on periodontitis in mice via facilitating efferocytosis, presenting a potential therapeutic direction [37, 40, 41].

Immune Cross-Talk of Macrophages in Periodontitis

There are intricate communications and interactions among macrophages and other immune cells within the periodontal tissue during the inflammatory process. Macrophages closely interact with T helper cells (Th). On the one hand, M1 macrophages induce Th1 and Th17 responses through IL-12 and IL-23, respectively, leading to more severe bone resorption [8, 29]. In contrast, M2 macrophages produce IL-4 and transforming growth factor-beta, inducing Th2 and Treg cell responses, which attenuates gingival inflammation [42, 43]. On the other hand, Th1 lymphocytes secrete interferon-gamma and activate neutrophils and macrophages, intensifying the gingival inflammation [44, 45]. Th2 cells feature in producing IL-4, promoting M2 polarization [46]. For the receptor-ligand interaction, Agrafioti et al. [15] found that PVR-TIGIT, PVR-CD96, and PV-CD226 receptor/ligand pairs interact between M1 and T cells, while TNF-NOTCH1 and PVR-TNFSF9 receptor/ligand pairs interact between M1 and B cells, and many other cross-talks were enhanced in periodontitis-affected sites. Moreover, B cell also interacts with macrophages. Dendritic cells or macrophages produce B-cell activating factor, whose knockdown suppresses TNF- α expression and M1 polarization, reducing the bone loss in periodontitis [47, 48]. Coculturing B cells from mice infected with *Tannerella forsythia* with macrophage induces the formation of multinucleated osteoclasts via the RANKL-RANK interaction [49]. Therefore, the relationship between macrophages and other immune cells during periodontitis deserves attention.

To conclude, macrophages play a complex role during periodontitis, encompassing cell accumulation, polarization, phagocytosis and efferocytosis, cytokine production, and interaction with other immune cells. During the active stage of periodontitis, or under some systematic diseases like diabetes, M1 possesses a larger proportion in periodontal tissue and accelerates bone resorption, while M2 plays a vital role in the static stage, facilitating inflammation regression. Therefore, methods to inhibit M1 polarization, promote M2 polarization, and maintain periodontitis in a static stage are worth further exploration.

Metabolism of Macrophages in Periodontitis

In recent years, research on the dynamic modulation of cellular metabolism in macrophages in response to the microenvironment has flourished, highlighting its crucial role in regulating macrophage activation, function, and biology [50–52]. The focus has primarily centered

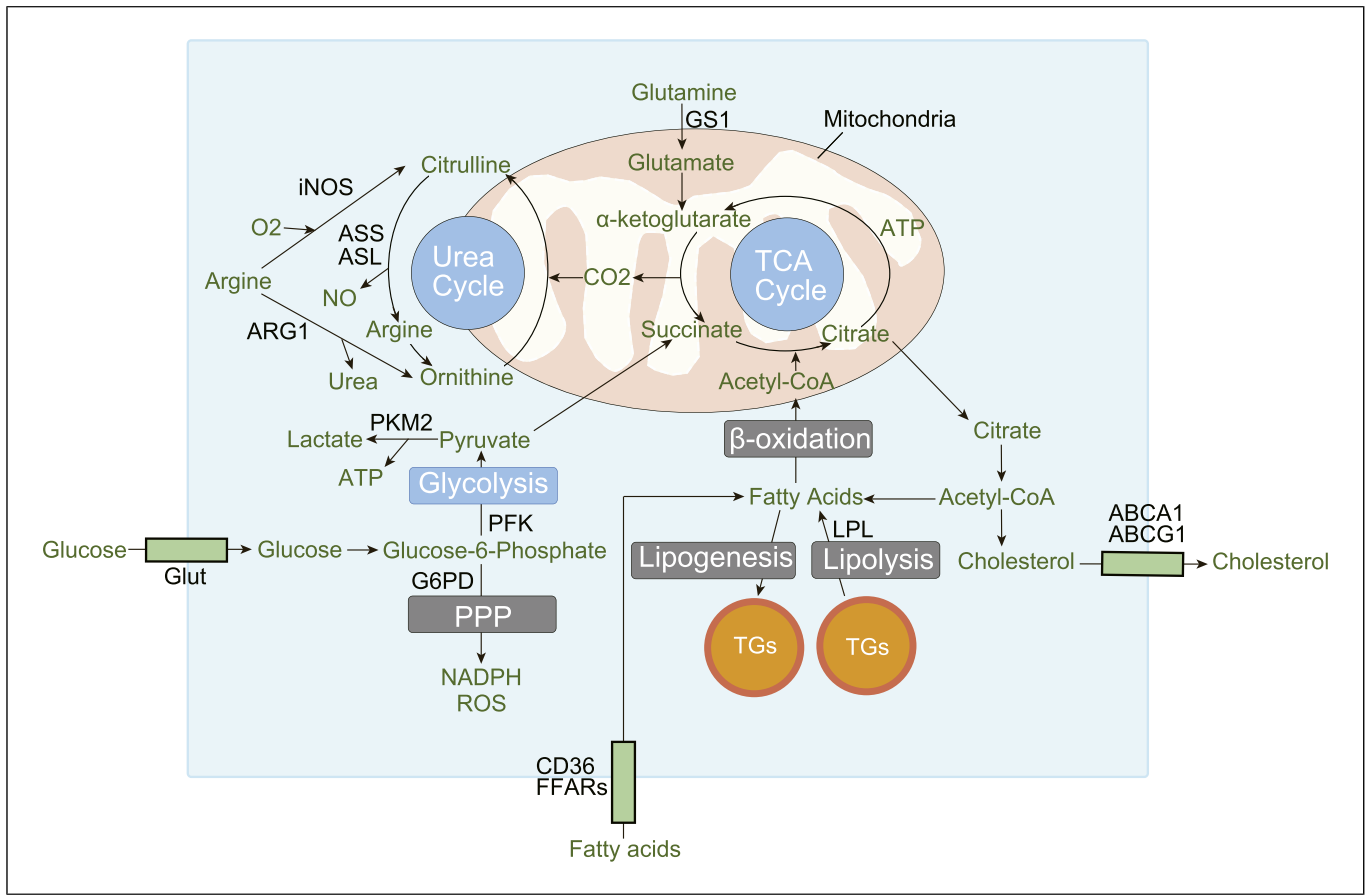


Fig. 2. Overview of glucose, lipid, and amino acid metabolism of macrophages. PPP, pentose phosphate pathway; TG, triglyceride; TCA, tricarboxylic acid cycle.

on the three major metabolic pathways in macrophages (shown in Fig. 2), which are valuable for determining phenotypes.

Glucose Metabolism of Macrophage

Glucose metabolism, the primary mechanism to generate adenosine triphosphate (ATP), has rapidly become a crucial subject due to its modulation on macrophage activation state and function [53]. The two distinct modes of the tricarboxylic acid (TCA) cycle, activated by different stimuli, significantly contribute to these processes. Upon stimulation with LPS/interferon- γ , macrophages undergo a metabolic shift characterized by suppressed oxidative phosphorylation (OXPHOS), heightened glycolysis, and the accumulation of succinate and itaconate, in stark contrast to IL-4-stimulated macrophages, which maintain full TCA cycle and OXPHOS functionality [54–57]. Despite the inefficiency of the glycolysis pathway in producing ATP, its

intermediates can be utilized as substrates in various other metabolic pathways [58]. Glucose utilization through the pentose phosphate pathway plays a dominant role in generating nicotinamide adenine dinucleotide phosphate hydrogen, providing the necessary redox power to produce reduced glutathione. This is crucial for maintaining macrophage functions, such as managing ROS and providing antioxidant protection [59].

Research has shown that polarized macrophage phenotypes, M1 and M2, are defined by unique glucose metabolic pathways: glycolysis for M1 and oxidative phosphorylation for M2 macrophages [60, 61]. These metabolic differences may be attributed to the distinct functionalities of M1 and M2 macrophages. M1 macrophages mainly function in innate immune response to infection. To meet the specific requirements of rapid bactericidal activity in a typical hypoxic inflammatory environment, anaerobic glycolysis suits the energy needs of macrophages. M2 macrophages, essential for tissue

remodeling and repair, rely on an intact TCA cycle and an enhanced mitochondrial OXPHOS for sustainable intracellular energy supply.

Reprogramming macrophage glucose metabolism not only initiates the inflammatory response but also represents a potential therapeutic target for inflammatory diseases. 2-DG, a competitive hexokinase inhibitor that blocks glucose uptake and glycolysis, has been found to suppress LPS-induced IL-1 β in M1 macrophages by downregulating the levels of the TCA cycle intermediate succinate [62].

Glucose Metabolism of Macrophage in Periodontitis

Studies concerning the periodontitis-related metabolic reprogramming in macrophages adopt both LPS and viable bacteria as the external stimuli [63, 64]. Multiple pathogenic bacteria, including *P. gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola*, and *T. forsythia*, participate in the development of periodontitis [65, 66]. In periodontitis, activated macrophages undergo metabolic switching from a resting to an active state to generate a large amount of ATP and macromolecules needed for their effector functions. It has been demonstrated in vitro that viable *P. gingivalis* leads to a metabolic shift toward glycolysis in macrophages, characterized by a reduction in OXPHOS, mitochondrial function, and the expression of regulatory genes in the TCA cycle [67]. The switch from OXPHOS to glycolysis activates proinflammatory macrophages [62, 68, 69], enhancing the clearance of intracellular pathogens, which are crucial factors in promoting periodontitis through immune invasion and tissue destruction [70, 71], by rapid ATP generation and production nitric oxide (NO) and ROS [72, 73]. Interestingly, once the switch to glycolysis occurs, these activated macrophages are unable to repolarize to the anti-inflammatory type, primarily due to mitochondrial dysfunction, particularly the inhibition of OXPHOS [73]. Therefore, metabolic reprogramming aimed at restoring mitochondrial function and OXPHOS could be a potential strategy for controlling periodontitis.

We also comprehensively discussed the function of two glycolytic enzymes, pyruvate kinase M2 (PKM2) and glucose transporter type 1 (GLUT1), which bridge metabolic and inflammatory dysfunction in periodontitis. In glycolysis, pyruvate kinase catalyzes the last step, converting glucose to pyruvate along with the production of ATP and nicotinamide adenine dinucleotide. PKM2 is expressed in proliferating cells, such as leukocytes, and is one of the four isoforms of pyruvate kinase [74]. PKM2 has been discovered in the gingival crevicular fluid (GCF) of healthy people and in the GCF and saliva of patients

with periodontitis and gingivitis [74]. It has been shown that PKM2 increases in the GCF from dogs with gingivitis progressing to the early-stage periodontitis [75]. Similarly, another study found a higher value of PKM2 in the saliva of periodontitis donors [76]. Upon LPS stimulation, PKM2 expression in macrophages is upregulated, and the translocation of PKM2 to the nucleus generates a complex formation with transcription factor “hypoxia-inducible factor-1 α ” to activate multiple gene transcriptions, such as IL-1 β [77], IL-6 [78], and high-mobility group box-1 protein (HMGB1) [79]. Inhibition or knockdown of PKM2 restricts the release of these mediators induced by LPS. The association between GLUT1-modulated glucose flux in macrophages and periodontitis is elucidated in the latter section on Macrophage dysfunction and metabolic syndrome related to periodontitis.

Lipid Metabolism of Macrophages

Recent findings have shown that lipid synthesis is of value in the modulation of macrophage functions. Acetyl-coenzyme A (acetyl-CoA) acts as a key building block for the synthesis of cholesterol, isoprenoids, and fatty acids (FAs), while FAs are utilized for the production of triglycerides and complex lipids [80]. In M1 macrophages, lipid biosynthesis is crucial for membrane remodeling and the synthesis of inflammatory mediators. To meet these requirements, glycolysis is upregulated to ensure ATP generation and fuels the TCA cycle, securing the supply of acetyl-CoA from citrate [81].

In contrast, OXPHOS in M2 macrophages is sustained by the uptake of FAs [82], which are subsequently oxidized through fatty acid oxidation (FAO). The process of FA uptake occurs through the lipolysis of circulating lipoproteins [83] and direct absorption of free FAs [55]. The acquisition of exogenous FAs in macrophages is mostly dependent on lipoprotein lipase, which hydrolyzes triglycerides into free FAs. Lipoprotein lipase activity is substantially higher in M2 macrophages in anti-infective treatment, resulting in increased FA uptake, whereas this pathway is inhibited in M1 macrophages [84, 85].

Lipid Metabolism of Macrophages in Periodontitis

Upon the stimulation of LPS, macrophages initiate the de novo lipogenesis process by oxidizing glucose to produce a cytosolic pool of citrate that later becomes acetyl-CoA, the essential component of FA [86]. Additionally, LPS stimulation also promotes FA synthesis through the facilitation of pentose phosphate pathway in glycolysis, where the essential reducing power, nicotinamide adenine dinucleotide phosphate hydrogen, is generated [87]. Furthermore,

FAs combined with glycerol 3-phosphate, another product out of glucose, can be esterified into triglycerides. In summary, upon microbial stimulation, macrophages convert the enhanced glucose metabolism to de novo lipogenesis and triglyceride synthesis.

The local inflammatory response in periodontal tissue can convert low-density lipoprotein into oxidized low-density lipoprotein (OxLDL) through free radical oxidation. Previous research has also verified the presence of OxLDL in the gingival crevicular fluid [88]. It has been shown that OxLDL can be taken up by macrophages via scavenger receptors [89]. However, the effects of OxLDL treatment on macrophage activation vary across studies. While some research indicates no significant changes, other studies have observed either proinflammatory or anti-inflammatory effects of OxLDL treatment [90]. The impact of OxLDL loading on macrophages in the context of periodontitis remains to be explored in future research.

Amino Acid Metabolism of Macrophages

Experimental evidence has shown that the modulation of macrophage activation is significantly influenced by amino acid metabolism, particularly through the utilization of arginine and glutamine.

Arginine Metabolism

Arginine is an essential basic amino acid that regulates macrophage activation through two enzymes: inducible nitric oxide synthase (iNOS) and ARG1. Highly expressed in M1 macrophages, iNOS recognizes arginine as a substrate to generate NO and citrulline using oxygen. Citrulline is catalyzed by argininosuccinate synthase and argininosuccinate lyase to generate arginine and release NO via the urea cycle, forming the citrulline-NO cycle. M2 macrophages produce ARG1, an enzyme that breaks down arginine into ornithine and urea, thereby suppressing the production of NO [91]. In general, ARG1 restrains the inflammatory response of macrophages, whereas iNOS promotes the inflammatory response.

Glutamine Metabolism

Through its involvement in the TCA cycle, glutamine plays a crucial role in polarizing macrophages into M1 and M2. The glutamine synthetase 1 converts imported glutamine into glutamate, which is then converted into α -ketoglutarate (α -KG). α -KG enters the TCA cycle to support OXPHOS and promote M2 macrophage polarization [54]. A low α -KG/succinic acid ratio enhances M1 macrophage activation and a high α -KG/succinic acid ratio promotes the polarization of M2-type macrophages [60]. Compared to M1 macrophages, glutamine meta-

bolism is significantly increased in M2 macrophages. Furthermore, previous studies have shown that α -KG can promote macrophage polarization to M2 type by regulating FAO and epigenetic pathways [54].

Amino Acid Metabolism of Macrophages in Periodontitis

Despite the lack of direct literature reports on the relationship between macrophage amino acid metabolism and periodontitis, a study found that the use of L-ornithine, a product of arginine metabolism, in conjunction with scaling and root planning treatment for periodontitis provides additional immunological benefits. This treatment was found to increase the CD163⁺ M2 macrophage subpopulation in the gingiva affected by periodontitis [92]. Besides, LPS increases the expression of argininosuccinate synthase and argininosuccinate lyase in mouse macrophages, leading to heightened arginine and NO synthesis [93], while LPS-stimulated M1-type macrophage polarization is less dependent on glutamine metabolism [54]. Given the importance of amino acid metabolism in macrophage polarization, it can be extrapolated that targeting this aspect holds great promise for treating periodontitis.

Macrophage Dysfunction and Metabolic Syndrome Related with Periodontitis

Impact of Metabolic Diseases on Periodontitis through Macrophage Metabolism

Extensive literature has explored the association between metabolic dysregulation and periodontitis. During infection, macrophages typically polarize to the M1 phenotype to initiate host immune response and later polarize to the M2 phenotype to dampen proinflammatory responses for the repair of damaged tissues. Disruption of phenotypic switch in macrophages, dysregulation of M1 activation, and prolonged restriction of M2 activation are associated with various diseases [94–96]. In general, periodontal treatment should alleviate the inflammatory response and restore lost tissue structure and function. Nevertheless, conventional treatments, such as mechanical plaque removal and guided tissue regeneration, have demonstrated limited effectiveness in patients with systemic diseases [97, 98]. Tissue-resident macrophages are key players in both periodontitis and these metabolic diseases; therefore, a better understanding of macrophage metabolism may provide new insights to the treatment of periodontitis with comorbidities.

Impact of Obesity on Periodontitis through Macrophage Metabolism

Obesity is a significant risk factor for periodontal inflammation, second only to smoking [99], with growing evidence confirming its potential to exacerbate the progression of periodontitis and associated inflammation [100–103]. This phenomenon may be explained by a blunted immune response in obese individuals to periodontal infections, referred to as immune tolerance [104]. A high-fat diet can cause gut flora imbalance, which facilitates the permeation of LPS through the gut mucosa and its entry into the bloodstream [105], leading to higher serum LPS levels in obese individuals [106]. Furthermore, in obese individuals, macrophages are frequently exposed to chronic, low-grade inflammatory signals such as free FAs. As a result, they develop immune tolerance, which diminishes their inflammatory response to subsequent infections caused by *P. gingivalis* or its components [104, 107, 108]. Interestingly, a blunted macrophage response is associated with increased arginase/iNOS ratios, which inhibits M1 polarization [109]. In the diet-induced obesity model, inhibition of arginase may allow macrophages to regain their active inflammatory functions when M1 macrophages were activated [19, 109]. Taken together, the detrimental effects of overweight/obesity on periodontal inflammation may be the consequence of disruption of M1 macrophage polarization due to biased arginine metabolism. However, another study has yielded incongruent results regarding the influence of high-fat diet on the immune response of macrophages in periodontitis, showing that high-fat diet increases the inflammatory response of macrophages to *P. gingivalis* infection [100].

Furthermore, various factors associated with obesity, including free FAs, cholesterol, and LPS, affect glucose-6-phosphate dehydrogenase in macrophages – an enzyme crucial for the pentose phosphate pathway [110]. Upregulation of glucose-6-phosphate dehydrogenase is also related to heightened glucose metabolism via the pentose phosphate pathway and redox regulation [111]. Its upregulation in obesity could potentially enhance glucose metabolism, making obese people more susceptible to hyperglycemia (HG). The adverse effects of HG on periodontitis will be discussed in the next section.

Impact of Diabetes on Periodontitis through Macrophage Metabolism

DM is an emerging and widely acknowledged systemic risk factor affecting periodontal health. HG induces chronic low-grade inflammation, which has recently been

identified as a contributor to diabetes-related tissue damage, including inflammatory bone loss in periodontitis. When macrophages are exposed to high-glucose conditions, their polarization shifts toward M1 phenotype [112]. As previously mentioned, M1 macrophages' glucose metabolism is characterized by glycolysis, which can activate the NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome in macrophages via ROS signaling [113], promoting the secretion of acute and long-term secretion of TNF- α and IL-1 β [112]. Elevated glucose levels, in combination with *P. gingivalis* – LPS, have been found to further enhance macrophage mitochondrial dehydrogenase activity, a crucial enzyme in glycolysis, and the secretion of proinflammatory cytokines IL-6, TNF- α , and prostaglandin E2 [114]. Compared to patients with chronic periodontitis alone, the GCF of patients with both DM and chronic periodontitis contains higher levels of proinflammatory cytokines [115]. Under hyperglycemic conditions, macrophages exhibit increased glucose metabolism through the upregulation of GLUT1 expression. GLUT1 is a membrane transporter that plays a critical role in the glucose uptake by macrophage. Though several GLUT-family members are expressed on macrophages, GLUT1 remains indispensable for glucose uptake. The selective GLUT1 ablation compromises glucose entry, resulting in decreased metabolite content for glycolysis and pentose phosphate pathway [116]. However, the release of inflammatory cytokines is not significantly affected by GLUT1 ablation [116], making its impact on periodontitis uncertain and in need of further validation. To sum up, HG in diabetes induces macrophage inflammation and accelerates periodontal damage through increased glycolysis, but the key regulatory factors remain unclear.

Impact of Periodontitis on Systemic Diseases through Macrophage Metabolism

Periodontitis has been associated with a number of systemic diseases [117–120]. The systemic inflammation caused by periodontitis can result from inflammatory substances overflowing from affected tissues or from periodontal pathogens entering the bloodstream, which is facilitated by the ulceration of periodontal pockets [7, 121, 122]. Though the correlation between periodontitis and systemic diseases has been shown to be significant, the underlying molecular mechanisms have not yet been sufficiently studied. As one of the most well-studied immune cells in periodontitis, macrophages may form part of the communication network bridging periodontitis and

systemic diseases. Pathogens related to periodontitis act directly upon local macrophages in periodontal tissue, while circulating periodontal pathogens can migrate to other tissues and affect their resident macrophages. Consequently, macrophage activation and the subsequent cellular responses to periodontal pathogen are topics of pivotal importance for uncovering the molecular mechanisms of systemic diseases induced by periodontitis.

Impact of Periodontitis on Atherosclerosis through Macrophage Metabolism

Ample evidence supports a causal relationship between periodontal infection and cardiovascular diseases. Multiple periodontal pathogens have been identified in atheromatous plaques surgically removed from patients with atherosclerosis, including *P. gingivalis*, *F. nucleatum*, *T. denticola*, and *T. forsythia* [123, 124].

Foam cells, derived from macrophages abundant in cholesteryl esters, are a typical feature of atherosclerotic plaques [125]. To prevent foam cell formation, it is vital to maintain macrophage cholesterol homeostasis, which depends on the balance among cholesterol synthesis, influx, and efflux. LPS appears to be a critical link bridging periodontitis and the development of atherosclerosis. The underlying mechanisms involve dysregulated cholesterol homeostasis, with excess cholesterol ester generation by acyl-coenzyme A acyltransferase 1 (ACAT1) and decreased cellular cholesterol efflux mediated by ATP-binding cassette transporter G1 (ABCG1) [126]. A notable feature of chronic periodontitis is multiple but transient episodes of bacteremia, which promote the spread of LPS from the periodontium to atherosclerotic plaques, ultimately contributing to foam cell formation [126]. Stimulation by viable bacteria has yielded the same results as LPS. In the presence of LDL, macrophages infected with *P. gingivalis* initiate foam cell formation in a dose-dependent manner, accompanied by the induction of LDL oxidation, likely a key step in atherosclerosis [127]. Besides, alterations in Ca^{2+} and ROS signaling induced by periodontal pathogens play a pivotal role in the dysregulation of lipid homeostasis, ultimately leading to the transformation of macrophages into foam cells [128].

In addition, *F. nucleatum* is closely associated with atherosclerosis. Studies have revealed that mice infected with *F. nucleatum* through oral gavage exhibit aortic tissue defects and more severe atherosclerotic lesions, characterized by subcutaneous macrophage infiltration, M1 polarization, and lipid deposition

[129]. Moreover, *F. nucleatum* regulates the expression of lipid metabolism-related genes (ACAT1, ABCA1, and ABCG1), thereby promoting OxLDL-induced cholesterol phagocytosis and accumulation [129]. Additionally, PI3K-AKT/MAPK/NF- κ B signaling pathways have been shown to be related to macrophage activated by *F. nucleatum*, resulting in facilitated gingival inflammation, reduced lipid intake, and increased lipid deposition [130].

Impact of Periodontitis on Diabetes through Macrophage Metabolism

A noteworthy point is the existence of a quantitative relationship between the surface area of inflamed periodontal tissue and the glycosylated hemoglobin level. Explicitly, every 333 mm² increase in the inflamed epithelial area of periodontal pocket is associated with a 1% increase in hemoglobin in patients with periodontitis and type 2 diabetes [131]. The theory that periodontitis exacerbates diabetes through macrophage metabolism is supported by the integration of several lines of evidence. Macrophages highly express FA binding protein 4 (FABP4), a member of the FABP family [132]. As a lipid-binding chaperone, FABP4 regulates the uptake, release, and storage of FA through reversible binding with high affinity to saturated and unsaturated long-chain FAs, thereby promoting the progression of multiple systemic diseases such as obesity and type 2 diabetes [133–135]. Consequently, FABP4 plays a central, critical role in connecting lipid metabolism to innate immunity functions and inflammation [133]. Infection with *P. gingivalis* or *F. nucleatum* can significantly elevate the expression of FABP4 on macrophages, resulting in enhanced lipid uptake [136]. Conversely, FABP4 blood level could be lowered in response to periodontitis treatment [137]. Available evidence shows the correlation between FABP4 and periodontitis and the potential contribution of periodontitis to the progression of diabetes through macrophage lipid metabolism.

Impact of Periodontitis on Obesity through Macrophage Metabolism

Several studies have explored the mechanisms behind the unfavorable impact of periodontitis on obesity, primarily focusing on the increase in systemic inflammatory biomarkers, as periodontal pathogens and their by-products may enter the circulation and affect systemic health. Compared to healthy individuals, patients with periodontitis exhibit higher blood levels of C-reactive protein, IL-1, and IL-6 [122, 138].

Adipose tissue macrophages (ATMs) are vital for adipose tissue function. However, their inflammatory polarization in obesity exacerbates tissue dysfunction, characterized by increased infiltration and activation of ATMs in white adipose tissue due to cytokine influence [139, 140]. Emerging evidence indicates that elevated glycolysis, cholesterol accumulation, and decreased FAO contribute to the M1 proinflammatory polarization of ATMs [141]. Nevertheless, no published data currently exist to confirm the hypothesized connection between elevated circulating cytokines due to periodontitis and ATM metabolism, posing an area of future work.

Impact of Periodontitis on Rheumatoid Arthritis through Macrophage Metabolism

Rheumatoid arthritis (RA) is one of the most common diseases characterized by chronic inflammation and bone destruction. The pathogenesis of RA includes the influx of macrophages, whose numbers is positively related with RA activity [142]. M1 macrophages are dominant in the RA synovium, exhibiting a metabolic profile characterized by high expression of the glycolytic enzyme glutathione, as well as COX-2 and elevated activity of iNOS2 [143, 144]. *P. gingivalis* from the periodontium can spread through the bloodstream, and its DNA has been detected in the synovial fluid of RA patients [145]. *P. gingivalis* also possesses a unique microbial enzyme, peptidylarginine deiminase (PAD), which mediates the onset of RA [146]. In periodontitis, apoptosis in macrophages can lead to the leakage of intracellular PAD into the extracellular environment, activating human PAD and exacerbating RA [147]. Moreover, LPS produced by *P. gingivalis* enhances the levels of glycolysis and accumulates intermediate metabolites of the TCA cycle, especially succinic acid in macrophages [148, 149]. Succinic acid has been found to be upregulated in the synovial fluid of RA patients and can induce the production of IL-1 β [143, 149]. All these studies demonstrate that macrophages, as the first responder to invading pathogens, are influenced by *P. gingivalis* and may be partially responsible for RA.

Conclusion

Current studies on macrophage metabolism and periodontitis primarily focus on macrophage polarization and cytokine/chemokine secretion. The potential link between macrophage metabolism and the regulation of

monocyte migration and local proliferation presents a significant area for further investigation, as the number of circulating leukocytes is closely related to periodontitis [150] and comorbidities such as atherosclerosis [59]. In summary, M1 macrophages rely on glycolysis, lipogenesis, and iNOS activity, whereas M2 macrophages depend on OXPHOS, FAO, ARG1 activity, and reduced iNOS activity. Identifying strategies to manipulate these metabolic pathways to reverse macrophage proinflammatory polarization could offer new treatments for periodontitis. Potential targets in macrophage glucose metabolism include 2-DG, PKM2, and GLUT1. However, further validation is needed for the roles of regulators in OXPHOS, lipid, and amino acid metabolism in periodontitis therapy.

Macrophages are pivotal in the interplay between periodontitis and metabolic conditions, driving inflammation and disease progression. Metabolic diseases such as obesity and diabetes alter macrophage metabolism, worsening inflammation and tissue damage in periodontitis. Furthermore, periodontitis can exacerbate systemic conditions like atherosclerosis, diabetes, obesity, and RA by disrupting macrophage function. Innovative metabolic treatments targeting these interactions could enhance the effectiveness of therapies in patients with refractory periodontitis and its related comorbidities.

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Author Contributions

Conception and design: Z.L. and Z.Z. Data collection: Z.Z. and Y.L. Drafting manuscript: Z.Z., Y.L., and T.Y. Revising manuscript content: Z.Z., Y.L., and Z.L. Approving final version of manuscript: Z.Z., Y.L., T.Y., and Z.L. Overall responsibility: Z.Z., Y.L., and Z.L.

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