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# Ceramides as a hypothetical molecular link between high-fat diet and immune dysregulation in rheumatic diseases: a narrative review

**Author:**

Mateusz Michał Pysiewicz

Norbert Barlicki Memorial Teaching Hospital No. 1

Dr. Stefana Kopcińskiego 22 St.

90-153 Łódź, Poland

dreo@outlook.com

https://orcid.org/0009-0007-0094-2857

**Abstract:**

One of the components of the Western diet is saturated fatty acids (SFA). Their excessive consumption is associated with obesity and atherosclerosis, but they also appear to be related to immunity and rheumatic diseases. Ceramides are bioactive sphingolipids that have recently attracted growing scientific interest, as their role as a potential link between high-fat diet and rheumatic diseases is investigated. Ceramides are predominantly precursors of sphingolipids, which are basic components of cell membranes. They have also immunomodulatory functions, but their biological functions are context-dependent and are determined by pathway of their biosynthesis, the type of cell, and presence of cytokines. Experimental studies suggest that ceramides synthesized in response to excessive amounts of SFA in the diet may promote pro-inflammatory responses, including M1 macrophage polarisation, activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, Th17 polarisation of naïve CD4+ T cells, and production of pro-inflammatory cytokines. However, human data remain limited and heterogeneous, and it is unclear if ceramides function as drivers or biomarkers of immune activation. This review critically evaluates data from animal models and in vitro studies and summarizes data from human studies. It discusses pathways of ceramide biosynthesis, their immunological role, attempts to determine their role in rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis and evaluates their potential as biomarkers and potential therapeutic targets in these diseases.

**Materials and methods:** A literature search was conducted in PubMed using the term "ceramides" alone and combined with the following keywords: "high-fat diet", "immunity", rheumatic diseases", "rheumatoid arthritis", "systemic lupus erythematosus", "psoriasis".

**Keywords:** ceramides, high-fat diet, autoimmune diseases, rheumatic diseases

## 1. Introduction

The Western diet is characterised by excessive amounts of sugars, fats, and sodium and is frequently associated with obesity and metabolic disorders. One of their components, saturated fatty acids (SFA) has also been linked to the modulation of inflammatory pathways and

immune-mediated diseases, including rheumatic disorders. A potential molecular link between these seemingly unrelated conditions may constitute ceramides, which have recently attracted growing scientific interest [1]. Ceramides are sphingolipids containing a sphingosine and a fatty acid linked through an amide bond. They are precursors of sphingomyelin and glycosphingolipids – basic components of cell membranes [2]. To better understand their potential role in immune-mediated diseases, it is necessary to briefly outline the main pathways of ceramide biosynthesis.

**2. Biosynthesis of ceramides**

There are three main pathways of ceramide biosynthesis: de novo pathway, salvage pathway, and sphingomyelinase pathway. The relative contribution of each of them depends on cellular context and environmental conditions. Ceramides can be synthesized de novo from serine and palmitate under conditions of their accumulation from diet (serine is an endogenous amino acid derived mainly from milk, palmitic acid is the main SFA delivered from palm oil, cocoa butter, lard, and butter [3]), but also can be stimulated by oxidized LDL. The second way (salvage pathway) is the hydrolysis of other more complex sphingolipids such as sphingomyelin and glycoceramides, which is stimulated in response to oxidative stress/reactive oxygen species (ROS), tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and Fas ligand (FasL). The third route, the sphingomyelinase pathway, consists of the direct hydrolysis of sphingomyelin to ceramide by sphingomyelinases and has regulatory functions in cells. These pathways were presented in Figure 1.[4,5]. An important fact is that these stimulatory factors are cell-dependent. In macrophages, ceramide biosynthesis is promoted by lipopolysaccharide (LPS) activation (especially in conjunction with SFA) and by TNF-α, but blocked by interleukin-10 (IL-10); in dendritic cells (DCs), it is promoted by CD40 ligand (CD40L), TNF-α, and IL-1β; in neutrophils, it is promoted by IL-1β, TNF-α, and ROS; and in natural killer cells (NK cells), it is promoted by FasL and interleukin-2 (IL-2) deprivation [6].

**3. Role of ceramides in immunity**

Ceramides have immunomodulatory functions and alterations in their metabolism may directly influence immune cell function. They act via two mechanisms: 1) by changing membrane dynamics, forming ceramide-rich platforms and altering membrane fluidity and permeability; 2) by the activation or inhibition of ceramide-binding proteins (mainly protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A), ceramide-activated protein phosphatases (CAPPs), and protein kinase C zeta (PKC-ζ)) thereby modulating their functions [7]. Their action in innate immune cells is correlated with promoters of their synthesis. In macrophages, ceramides activate PKC-ζ and mitogen-activated protein kinase (MAPK) pathways (extracellular signal-

regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38), leading to nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation (especially in the presence of TNF-α), which increases IL-1β, interleukin-6 (IL-6), interleukin-8 (IL-8), and TNF-α production [8,9]. Wen et al. suggested that ceramide biosynthesis induced by palmitate accumulation activates the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and increases caspase-1 and IL-1β production, which disrupts the insulin receptor substrate-1 (IRS-1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway in adipocytes, leading to insulin resistance, as well as interleukin-18 (IL-18) secretion. They proposed that palmitate and ceramides alter cell membrane properties, rendering the AMP-activated protein kinase (AMPK)/unc-51 like autophagy activating kinase 1 (ULK1) pathway ineffective and promoting mitochondrial ROS accumulation, thereby triggering NLRP3 inflammasome activation. These effects has been shown in Figure 1. However, this mechanism appears to be highly context-dependent. A study by Desjardins et al. demonstrated that AMPK activation in response to elevated free fatty acids enhances autophagy and preserves mitochondrial homeostasis [10–12]. There is broader consensus that SFA, ceramides, and ROS contribute to inflammasome activation, but there is no agreement about the precise molecular mechanism [13]. Furthermore, SFA-induced ceramide synthesis is promoted by adipocyte fatty acid-binding protein (A-FABP), which increases apoptosis and pyroptosis, thereby contributing to chronic low-grade inflammation in obesity [6,11]. Ceramides promote M1 macrophage polarisation [14]. In DCs, ceramides promote maturation and inhibit antigen uptake and presentation to T cells [15,16]; in neutrophils, they decrease ROS production and oxidative burst, increase neutrophil extracellular trap (NET) formation, regulate migration, inhibit adhesion, and promote apoptosis [17]; in NK cells, ceramides also induce apoptosis [18]. Ceramides generally promote T helper 17 (Th17) differentiation and IL-17 production [19,20], although some data suggest they may enhance regulatory T cells (Treg) differentiation in the presence of transforming growth factor beta (TGF-β) [21]. These findings support a claim that their biological functions are highly context- and cell-dependent. However, mentioned studies were conducted mainly in vitro or in mouse models, which does not necessarily imply that their results can be directly translated to humans. There are also human studies that suggest ceramides seem to be associated with autoimmune rheumatic diseases, and potentially have clinical impact.

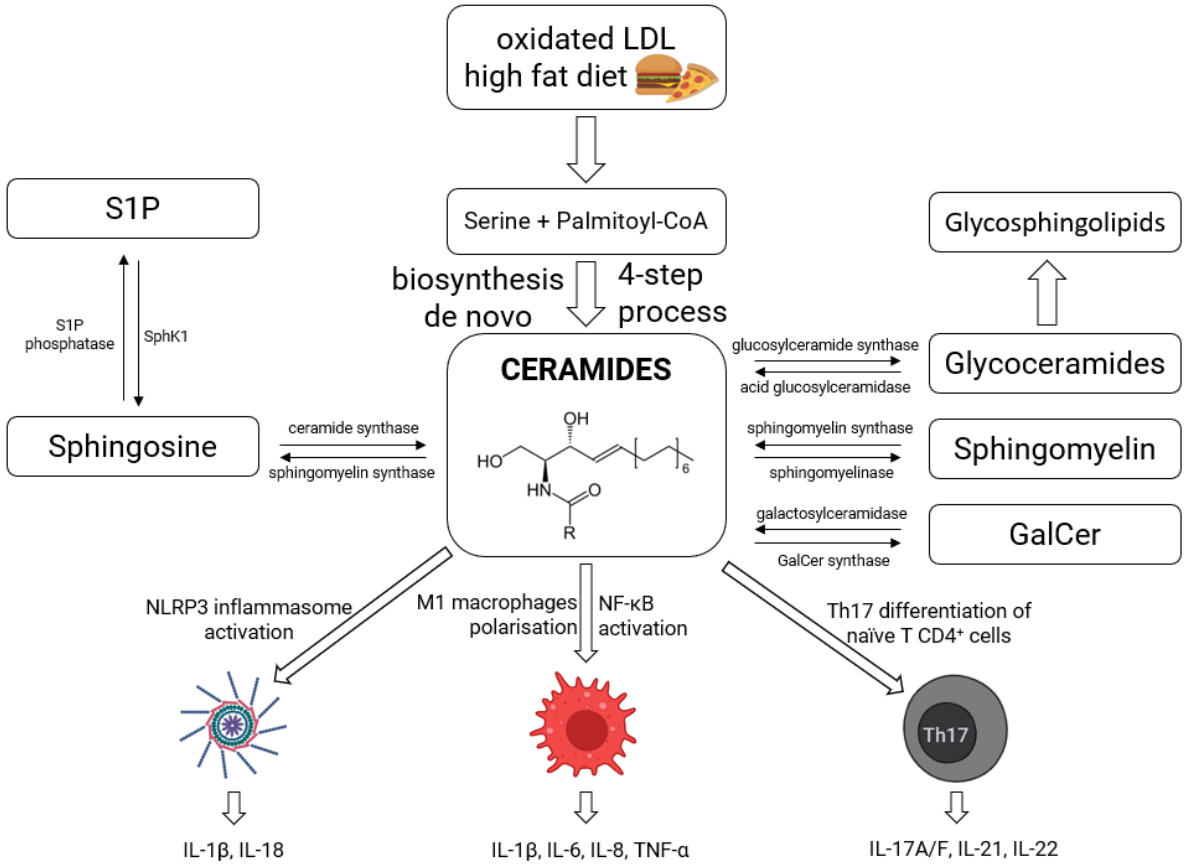


**Figure 1. Simplified biosynthesis of ceramides and their potential role as link between high-fat diet and inflammation (created with BioRender)**

Abbreviations: LDL – low-density lipoprotein, NLRP3 – NOD-like receptor protein 3, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells, S1P – sphingosine-1-phosphate, SphK1 – sphingosine kinase 1, GalCer – galactosylceramide

## 4. Ceramides and rheumatic diseases

### 4.1 Rheumatoid arthritis

Patients with rheumatoid arthritis (RA) exhibit elevated serum levels of secretory sphingomyelinase (an enzyme catalysing sphingomyelin hydrolysis to ceramides), although without a significant correlation with disease activity [22]. Compared with osteoarthritic patients and healthy controls, RA patients present increased concentrations of sphingosine-1-phosphate (S1P – a downstream metabolite of ceramides formed by sphingosine phosphorylation) and its receptor expression in synovial fluid (SF), as well as higher ceramide and sphingomyelin (SM) levels in SF and serum [23–25]. This profile may reflect the TNF-α-driven stimulation of ceramide synthesis, as TNF-α is typically elevated in RA. Notably, lactosylceramide (LacCer, CD17) has been identified as a biomolecule associated with

depression, anxiety, and fatigue in RA patients [26]. However, a study by Medcalf et al. demonstrated that 16 weeks of methotrexate treatment improved the plasma metabolome, including reductions in ceramide and SM concentrations [27]. The clinical relevance of these findings remains to be fully clarified.

Studies in animal models are more promising. Yang et al. administered glucocerebrosidase (an enzyme hydrolysing glycoceramides – precursors of glycosphingolipids – into ceramides and glucose) in mice with collagen-induced arthritis, which increased proteoglycan content, preserved the integral cartilage surface and tidemarks, and reduced IL-1β, IL-6, IL-18, and matrix metalloproteinase-1 (MMP-1) [28]. Moreover, intra-articular administration of C2-ceramide was found to induce apoptosis in rheumatoid synovial fibroblasts, thereby reducing synovial hyperplasia [29], and to block platelet-derived growth factor (PDGF)-induced cell cycle progression of rheumatoid synovial cells by inhibiting activation of Akt, mitogen-activated protein kinase (MEK), and ERK1/2 [30]. Another study by Beckmann et al. demonstrated that genetic ablation or pharmacological inhibition of acid sphingomyelinase reduced joint swelling and levels of IL-1β, IL-6, and IL-17 [31]. These findings indicate that the role of ceramides is contextual, depending on their formation pathway and cellular target. Both animal models and clinical studies implicate the sphingosine kinase 1 (SphK1, an enzyme converting sphingosine into S1P)/S1P/sphingosine-1-phosphate receptor (S1PR) axis in RA pathogenesis, promoting synoviocyte proliferation, migration, and T-cell recruitment; elevated serum S1P and sphingosine-1-phosphate receptor 1 (S1PR1) levels support their potential as biomarkers and suggest that targeting S1P signaling may represent a promising therapeutic approach, particularly in the context of sphingolipid metabolism disturbances observed in obesity [23,32]. Similar alterations in sphingolipid metabolism have been investigated in other autoimmune diseases.

### 4.2 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is characterized by both dyslipidemia and dyslipoproteinemia, which correlate with disease activity. Due to these conditions, SLE is considered an independent risk factor for atherosclerosis [33–35]. The total content of SM, S1P, and ceramides is not significantly different in patients with SLE compared with healthy controls. However, their relative proportions are altered and may correlate with disease activity as well as specific clinical manifestations, such as renal involvement or distinct autoantibody profiles [36–39]. An interesting finding is that rituximab treatment has been shown to normalize sphingolipid dysregulation in patients with SLE [37,40]. It may suggest that the relationship between ceramides and immunological disorders is potentially bidirectional. These findings

combined suggest that ceramide regulation may have potential as a therapeutic option for SLE. In murine models, ozanimod, a modulator of S1PR1/5, showed dose-dependent improvement in lupus nephritis. Treatment resulted in a significant decrease in proteinuria, mesangial expansion, endocapillary proliferation, glomerular deposits, interstitial infiltrates, tubular atrophy, and interstitial fibrosis compared to placebo [41]. Despite these promising results, there are no ongoing clinical trials in humans with ozanimod in SLE. However, another S1PR1 modulator, cenerimod, is being investigated. In a phase 2 randomized trial in adults with moderate-to-severe SLE, in the highest tested dose (4 mg) it reduced disease activity assessed by modified SLE Disease Activity Index 2000 (mSLEDAI-2K). The drug was generally well-tolerated, but higher doses were correlated with lymphopenia. The drug has recently advanced to a phase 3 clinical trial [42]. However, these data do not suggest that it can become a breakthrough in the therapeutic strategy for patients with severe SLE.

4.3 Psoriasis

Psoriasis is widely considered as a Th17-driven disease, while ceramides are molecules that promote Th17 differentiation of naïve CD4+ T cells. These facts combined raise the question of what their mutual relationship is. Studies by H. Myśliwiec, D. Kozłowska et al. demonstrated that patients with psoriasis have increased serum S1P levels and decreased ceramide levels, whereas patients with psoriatic arthritis have significantly higher ceramide levels compared with patients with skin involvement only. No correlation with disease activity or inflammatory markers was observed. Moreover, lignoceric ceramide positively correlated with alanine aminotransferase (ALT) level ($r = 0.22$) in patients with psoriasis [43,44]. These studies may suggest that ceramide dysregulation in psoriasis is rather correlated with specific disease manifestations. An interesting question is whether they are only a biomarker, or represent a biological link between psoriasis and the often coexisting atherosclerosis and fatty liver disease. Due to their immunological functions, ceramide modulation has been considered a therapeutic strategy. Ponesimod is a selective modulator of S1PR1, which promotes its internalisation, rendering T and B cells insensitive to the concentration gradient of S1P and preventing their migration from secondary lymphoid tissues. This effect is dose-dependent and reversible. In a phase 2 clinical trial in patients with moderate-to-severe chronic plaque psoriasis, ponesimod achieved a $\geq 75\%$ reduction in the Psoriasis Area and Severity Index (PASI75) in approximately 47% of patients. Treatment was associated with dyspnoea, raised liver enzyme concentrations, and dizziness [45]. These data do not seem to show superiority of ponesimod over currently used anti-IL-17 and anti-IL-23 biologics [46], despite lack of direct comparisons; however, it

may become an interesting option as a secondary treatment. Currently, the drug is in a phase 3 trial.

4.4 Dietary interventions

It is worth emphasizing that most ceramides are synthesized via the de novo pathway, and dietary factors, particularly fatty acids, are the main determinants of their levels and composition. Because of this and the fact that ceramides are closely linked to lipid metabolism, potential dietary modulation has been explored [47–49]. A study conducted by H. Lindqvist et al. in patients with RA did not demonstrate a significant reduction in cardiovascular risk, as assessed by the ceramide-based ceramide risk score 2 (CERT2), following a dietary intervention. The cardiovascular benefits of a Mediterranean-style diet appear to be indirect or unrelated to ceramide modulation [50]. These results seem to be contradictory to in vitro and in vivo findings about ceramides, or may suggest that the role of ceramide dysregulation in RA is more complicated. Interestingly, a study by L. Chen et al. in overweight and obese African Americans showed that high-dose vitamin D (VitD) supplementation (4000 IU/day) may increase levels of C18-ceramide, a species implicated in metabolic dysfunction and insulin resistance [51]. There is a general lack of studies evaluating the role of dietary interventions in rheumatic diseases that treat ceramides as biomarkers. Despite solid theoretical foundations, this link has not been clinically confirmed.

## 5. Conclusion

Ceramides, in addition to being the precursors of sphingolipids, which are basic components of cell membranes, have also immunological functions. Their biological functions are highly context-dependent. The pathway of their biosynthesis, the type of cell, and presence of cytokines determines if they will play pro-inflammatory or anti-inflammatory role. Ceramides synthesized via de novo pathway as a result of their excessive dietary intake, through high consumption of SFA, especially palm oil, cocoa butter, lard, and butter may contribute to inflammation and autoimmunity. However, the precise mechanisms by which they exert these effects still need to be elucidated. Due to growing popularity in longevity concepts, ceramides' role in autophagy processes needs to be clarified. Studies in humans did not show that ceramides are directly correlated with the activity of rheumatic diseases. The current state of knowledge rather suggests that their relative proportions are altered and specific types of them may correlate with certain clinical phenotypes. There is a need for deeper research to establish their value as biomarkers. Agents targeting ceramide metabolism or S1P signalling have shown some efficacy, but there is currently no evidence that they are superior to existing biologics. At present, only ponesimod, which is a S1P1R modulator has recently entered planning for a Phase

3 clinical trial in patients with moderate-to-severe chronic plaque psoriasis. There is generally a lack of studies on the role of dietary interventions in ceramide regulation, and those published do not show efficacy of this approach, which makes it an interesting field for further research.

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ETHICAL APPROVAL

Not applicable

DISCLOSURE

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DECLARATION OF THE USE OF GENERATIVE AI AND AI-ASSISTEDTECHNOLOGIES IN THE WRITING PROCESS

While preparing this manuscript, the author used ChatGPT to perform linguistic editing, including correction of grammar, syntax, and spelling and to provide better readability. After using this tool, the author thoroughly reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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