



## Narrative Review

# Modulation of ceramides through nutrition: A new target in obesity and insulin resistance (Narrative Review)



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## SUMMARY

**Background:** Ceramides (Cer) are signaling sphingolipids that participate in insulin signaling, mitochondrial integrity, and inflammation. In obesity and insulin resistance (IR), Cer biosynthesis is exacerbated, leading to metabolic dysfunction and chronic diseases.

**Objective:** This narrative review synthesizes current evidence on how Cer metabolism can be modulated through dietary components and dietary patterns, with emphasis on lipidomic analyses.

**Key findings:** The synthesis and accumulation of Cer are influenced by dietary abundance and quality, such as carbohydrates, fat and phenolic compounds. High-fructose corn syrup and saturated fatty acids promote Cer accumulation and IR, while monounsaturated and polyunsaturated fatty acids—abundant in the Mediterranean and Nordic diets—attenuate these effects. Polyphenol-rich foods and caloric restriction may also reduce Cer concentrations and improve metabolic markers. The emerging evidence from lipidomic analyses is expanding our knowledge on the role of diet in Cer modulation.

**Conclusion:** Nutritional strategies targeting ceramide metabolism represent a promising approach to improve metabolic health. Beyond their therapeutic potential, ceramides also emerge as dynamic lipidomic biomarkers capable of reflecting early metabolic changes and monitoring the efficacy of nutritional interventions.

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## 1. Introduction

Obesity and insulin resistance (IR) are risk factors for metabolic diseases and represent a growing public health concern. In 2022, 890 million adults were living with obesity, while an estimated

537 million adults globally were diagnosed with type 2 diabetes (T2D), a number projected to rise by 2045 [1–3]. Lipidomics has identified ceramides (Cer), the primary signaling sphingolipids (SLs) involved in metabolic regulation, as key lipid molecules implicated in metabolic dysregulation, including IR and T2D [4,5].

**Abbreviations:** ALT, alanine aminotransferase; NT, Adenine Nucleotide Translocase; CerS1–6, Ceramide Synthases 1 to 6; CerS6, Ceramide Synthase 6; Cer, Ceramides; C1P, Ceramide-1-Phosphate; CERK, Ceramide Kinase; CPT1, Carnitine Palmitoyltransferase 1; CR, Caloric Restriction; DNL, de novo lipogenesis; ETC, Electron transport chain; ER, Endoplasmic Reticulum; FAO, Fatty Acid Oxidation; FFA, free fatty acids; GLUT4, Glucose Transporter Type 4; GSL, Glycosphingolipids; HFCS, High-Fructose Corn Syrup; IR, Insulin Resistance; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; mTOR, Mechanistic target of rapamycin; mPTP, Mitochondrial Permeability Transition Pore; nSMase, Neutral Sphingomyelinase; PC, Phosphatidylcholine; PKC $\zeta$ , Protein kinase zeta; PP2A, Protein Phosphatase 2A; PUFAs, Polyunsaturated Fatty Acids; RCT, Randomized Controlled Trial; S6K1, S6 kinase beta-1; S1P, Sphingosine-1-Phosphate; SLs, Sphingolipids; SM, Sphingomyelins; SPT, Serine Palmitoyl Transferase; T2D, Type 2 Diabetes; TOM20, Translocase of Outer Mitochondrial Membrane 20; TXNIP, Thioredoxin-Interacting Protein.

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Mechanistic studies indicate that excessive ceramide accumulation impairs insulin signaling by promoting mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation [6,7]. Specifically, increased abundance of long-chain ceramides (C16:0 and C18:0) in adipose tissue and the liver, shows strong correlations with IR and lipid accumulation [8]. This is in line with recent evidence that observed elevated Cer and other complex sphingolipid species in obesity and type 2 diabetes (T2D) [9]. Furthermore, hepatic levels of dihydroceramides and Cer are markedly increased in subjects with IR [9,10]. Conversely, circulating total Cer have been inversely correlated with insulin sensitivity in individuals with IR and obesity [10]. This evidence is positioning Cer as potential metabolic drivers of adipose tissue dysfunction and hepatic injury.

These observations also support the growing interest in Cer and SLs as potential therapeutic targets for metabolic diseases, so different therapeutic strategies are being explored, including anti-diabetic therapies (e.g., thiazolidinediones, metformin, GLP-1 receptor agonists) – which may reduce the synthesis of reactive SLs species in non-adipose tissues [9] – and emerging nutritional strategies. Given the growing burden of obesity and type 2 diabetes (T2D), understanding the link between Cer metabolism and metabolic disorders can help in the design of novel therapeutic targets and dietary strategies to prevent excessive Cer accumulation in metabolic tissues [8].

Considering the critical role of Cer and SLs in metabolic diseases, a targeted, data-driven approach to dietary therapies is essential for optimizing nutrient quantity and quality in order to finely tune Cer biosynthesis for the maintenance of metabolic health and addressing diverse metabolic conditions. From this perspective, research has revealed that nutritional treatments or specific nutritional patterns can impact the biochemical pathways governing lipids and Cer synthesis and degradation [11]. However, despite their biological importance, the wide variety of SLs species in the human body makes their identification and elucidation of specific roles difficult to assess. Lipidomics has emerged as a critical and robust tool to address these difficulties. However, the role of SLs in different health conditions are still poorly understood, primarily due to the limited number of lipidomics studies conducted to date [12].

This study is a narrative review that aims to synthesize the current evidence on how nutritional patterns modulate ceramide metabolism in the context of obesity and IR. Specifically, it explores the metabolism and physiological role of Cer, their involvement in metabolic disorders, the impact of specific nutrients on Cer regulation and the influence of dietary patterns, to provide perspectives for future research and clinical implications.

## 2. Methods

### 2.1. Scope of the review

This narrative review aims to link findings of current evidence on how ceramides (Cer) can be modified through nutrient-mediated modulation and dietary patterns, with a specific focus on obesity and insulin resistance (IR). By integrating evidence from molecular, physiological, and clinical studies, this approach allows the interpretation and synthesis of data to support a conceptual framework of the nutritional modulation of ceramides.

This work was conducted as a Structured Narrative Review [13], as our goal is to explore and contextualize the influence of diet on ceramide metabolism. This strategy allows for a comprehensive approach to integrate diverse forms of evidence, determining the mechanistic, physiological, and clinical perspectives on how

dietary factors impact ceramide metabolism, thus enhancing the understanding of their role in human health.

### 2.2. Search strategy

A literature search was conducted in PubMed and Scopus databases. The literature search was performed using Medical Subject Headings (MeSH) and Boolean operators. The search terms used are as follows: (Obesity [MeSH] OR “Insulin Resistance”[-MeSH]) AND (Ceramides [MeSH] OR “lipidomics”[TIAB]) AND (“Diet Therapy”[MeSH]) AND (y\_10[Filter]). Inclusion criteria comprised original human studies (interventional and observational) that quantified ceramides or sphingolipids (preferably using lipidomic or targeted analyses) and evaluated their association with nutritional factors such as caloric restriction, dietary fat quality, polyphenols, or established diet patterns. Eligible studies included adults with overweight, obesity, insulin resistance, metabolic syndrome, or type 2 diabetes. Mechanistic and pre-clinical studies were selectively included to illustrate biochemical pathways underlying ceramide metabolism. Exclusion criteria included reviews, meta-analyses, conference abstracts, and studies lacking quantitative ceramide data or a nutritional component. Studies exclusively involving pharmacological interventions, non-metabolic conditions, or special populations (pregnant women, children) were excluded. This structured yet flexible approach emphasizes conceptual synthesis and translational interpretation.

The extracted information was organized thematically according to the biological and clinical hierarchy of evidence. Mechanistic findings describing ceramide biosynthesis pathways and their metabolic effects were grouped in Sections one and two to provide the molecular framework. Nutritional evidence was then stratified by the level of dietary complexity from single nutrients to dietary patterns in Sections 3 and four. Methodological aspects such as study design and consistency of findings were considered to interpret the evidence. A summary of key nutritional intervention studies assessing Cer modulation for clinical interpretation is provided in [Supplementary Table 1](#).

## 3. Results and discussion

The database search retrieved 68 papers. Following title, abstract, and full text screening, 52 studies were excluded as they report results of pharmacological treatments or non-metabolic pathologies. A total of 16 studies met the eligibility criteria and were included in the present review. As expected, the low number of eligible studies was limited as the integration of lipidomic profiling into nutritional intervention research is still developing.

### 3.1. Sphingolipid and ceramide metabolism and physiological functions

Lipids are a diverse class of biomolecules essential for cellular structure, extracellular signaling, and energy storage. Among them, SLs represent approximately 10 %–20 % of total cellular lipids, of which Cer are the central molecule of sphingolipid metabolism [14]. Cer act as precursor molecules for more complex SLs, and are primarily synthesized via the *de novo* pathway [15,16].

SLs are a complex class of lipids derived from sphingosine, an aliphatic amino alcohol O-linked to ethanolamine, serine, or choline. Sphingosine is also amide-linked to fatty acids. SLs are classified into three major types: Cer, sphingomyelins, and glycosphingolipids, which are fundamental components of eukaryotic cell membranes, playing critical roles in both physiological and pathological processes [10,12,14]. They contribute to membrane

structure and integrity, regulate cellular signaling pathways, and are involved in key metabolic and stress-related responses, including lipid and carbohydrate metabolism, inflammation, apoptosis and autophagy [14,17]. Moreover, several SLs bind to proteins to regulate their activity, acting as first or second messengers of several signal transduction pathways. For example, Sphingosine-1-phosphate (S1P) regulates cell migration, embryonic development of the heart, and lymphocyte trafficking as a first messenger [18].

Cer are composed of a sphingosine linked to a fatty acid varying in length from C14 to C32 (Fig. 1). Sphingomyelin (SM) consists of a sphingosine base with an 18-carbon chain and a double bond at position 4, attached to a phosphorylcholine fatty acid [18]. Glycosphingolipids (GSL) consist of a carbohydrate attached to the 1-hydroxyl of ceramides through a glycosidic bond in the β configuration, which are subdivided into different groups: cerebroside (which has a single glucose or galactose at the 1-hydroxy position); gangliosides (which are sialic acid-containing glycosphingolipids) [19]; and globosides (which contain two or more sugar residues and an N-acetylgalactosamine group linked to Cer) [20].

Cers are predominantly found in the liver, adipose tissue, and neural tissue, where they modulate several signaling pathways. Three major metabolic pathways are involved in ceramide biosynthesis: the de novo, the salvage pathway, and the sphingomyelinase pathway [15,16,21] as represented in Fig. 2.

In the de novo pathway occurs on the cytoplasmic surface of the endoplasmic reticulum (ER) and comprises the most important source of Cer in the body. This pathway begins with the condensation of L-serine and a fatty-acyl CoA such as palmitoyl-CoA, myristoyl-CoA, or stearoyl-CoA at the ER membrane, catalyzed by the enzyme serine palmitoyltransferase (SPT) to form 3-ketosphinganine, which is then reduced to dihydrosphingosine by the NADH-dependent 3-ketosphinganine reductase (KDSR). Ceramide synthases (CerS) catalyze the acylation of dihydrosphingosine to dihydroceramide (Fig. 3). The genes encoding CerS enzymes differ in their spatial and temporal expression patterns, as well as in their ability to produce ceramides with varying chain lengths. Although all identified CerS enzymes exhibit similar Km values (affinity for substrates), they vary in their selectivity for acyl-CoAs depending on the length of the acyl chain [15,22]. According to their carbon chain lengths, six CerS isoforms have been reported in mammals displaying selective specificity for acyl CoAs. CerS1 attaches the C18 fatty acyl CoA (long chain); CerS2 exhibits activity toward the very long acyl CoAs such as C22–C24; CerS3 attaches the ultra-long fatty acyl CoA as C26, CerS4 is specific for the C18–C20 CoA; whereas CerS5 and CerS6 have specificity for the C14–C16 CoA [13–15,21]. The abundance of the different Cer

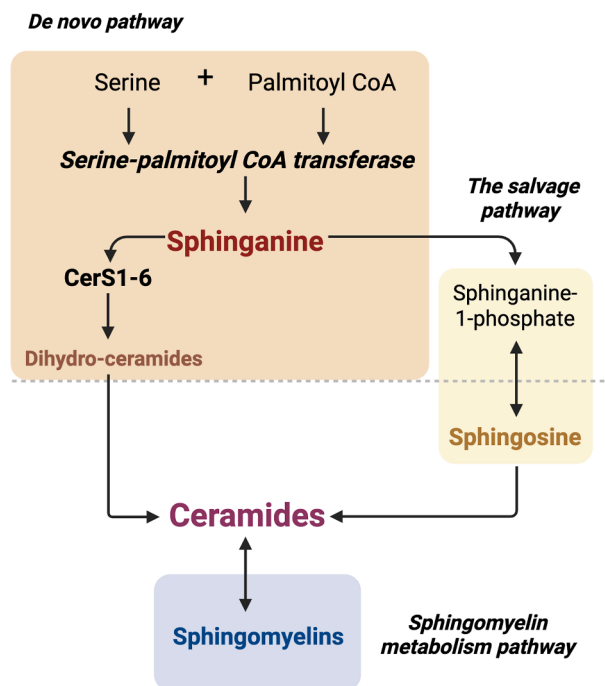


Fig. 2. Three major metabolic pathways for ceramide biosynthesis. Ceramides are synthesized via three interconnected routes: the de novo pathway, starting with serine and palmitoyl-CoA; the sphingomyelinase pathway, which hydrolyzes sphingomyelins; and the salvage pathway, which recycles sphingosine from sphingolipid catabolism.

species is dependent on the tissue-specific distribution of the different CerS. For instance, CerS1 is mainly expressed in the brain, CerS2 is highly abundant in the liver and kidney, CerS3 is highly expressed in the testis and skin, CerS4 mRNA is found in the skin, heart, liver, and leukocytes, CerS5 is mainly expressed in lung epithelia and brain, whereas CerS6 show high expression in the intestine [22–25]. The final step in Cer biosynthesis is mediated by a desaturation reaction by the dihydroceramide desaturase (DDase) which expression is ubiquitous [22,26]. This evidence suggests that the distribution of the different Cer species in the body is dependent on the tissue-specific distribution of individual CerS. However, the transcriptional and post-transcriptional regulation of CerS in the different metabolic organs is not yet fully understood [15].

As illustrated in Fig. 3, in the salvage pathway, Cer is generated from partial degradation of membrane glycolipids by glucosylceramidase (GCCase). Also, in the sphingomyelin pathway, complex sphingolipids are hydrolyzed by sphingomyelinases (SMase) in lysosomes. Next, Cer is transported to the Golgi complex through vesicular and nonvesicular protein ATP-dependent coupling, allowing the production of complex SLs. Once synthesized, Cer is used as substrate for four major pathways, in whose Cer is either: 1) phosphorylated by the ceramide kinase (CEK) to form ceramide-1-phosphate (C1P); 2) incorporated into sphingomyelin-by-sphingomyelin synthase (SMS); 3) converted into glucosylceramide-by-glucosylceramide synthases (GCS), leading to the generation of complex SLs such as cerebroside, gangliosides, sulfatides and globosides; and; 4) deacylated by the ceramidases (CDase) to produce sphingosine. Sphingosine kinases (SKs) phosphorylate sphingosine to produce S1P, which is degraded by sphingosine phosphate phosphatase (SPP) or S1P lyase, synthesizing sphingosine. These molecules are crucial for membrane stability and cellular signaling and can be broken down

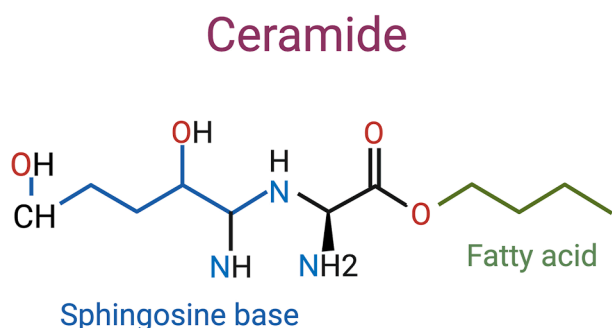
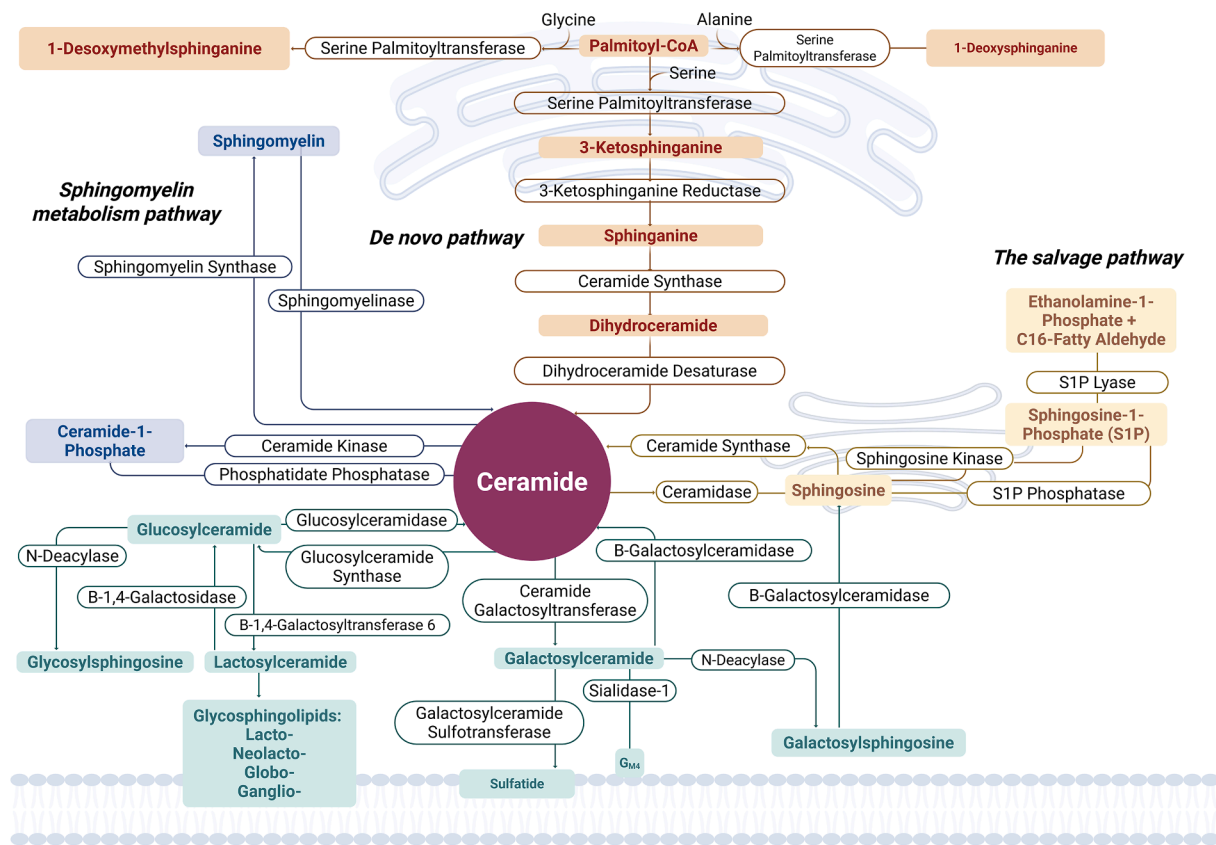


Fig. 1. Structure of a ceramide molecule: sphingosine and fatty acid linked by an amide bond.



**Fig. 3.** Ceramide biosynthesis pathways. The de novo pathway produces dihydroceramides that are desaturated to ceramides; the sphingomyelin metabolism pathway generates ceramides from sphingomyelin hydrolysis; and the salvage pathway reconverts sphingosine into ceramides. These pathways regulate ceramide abundance and provide substrates for the synthesis of sphingolipids such as glycosphingolipids.

in lysosomes to regenerate Cer. This process further produces sphingosine and S1P, both important for metabolic regulation [15].

Interestingly, Cer can be synthesized by the mitochondria itself. For instance, initial reports in murine models identified three CerS subtypes CerS1/2/6 in the mitochondria of mouse brain [27,28]. In fact, CerS2 colocalizes with the translocase of outer mitochondrial membrane 20 (TOM20) on the outer mitochondrial membrane, and the CerS6 associates with the adenine nucleotide translocase (ANT) on the inner mitochondrial membrane [28,29]. In addition, mitochondria has been shown to recruit additional enzymes related to Cer metabolism, including neutral sphingomyelinase (nSMase) [27,28] and neutral ceramidase, potentially by its interaction to ER [28,30]. This suggests that mitochondria by itself possess the enzymatic machinery to properly regulate Cer abundance and thus, its Cer-dependent biological activities.

Cer synthesis and abundance are also responsive to metabolic cues. Under states of obesity and lipid overload, Cer synthesis is increased, leading to their accumulation, favoring metabolic dysregulation [16,21]. Also, given their role as bioactive lipids in mitochondria, Cers have been implicated in several metabolic disorders mediated by mitochondrial dysfunction [14].

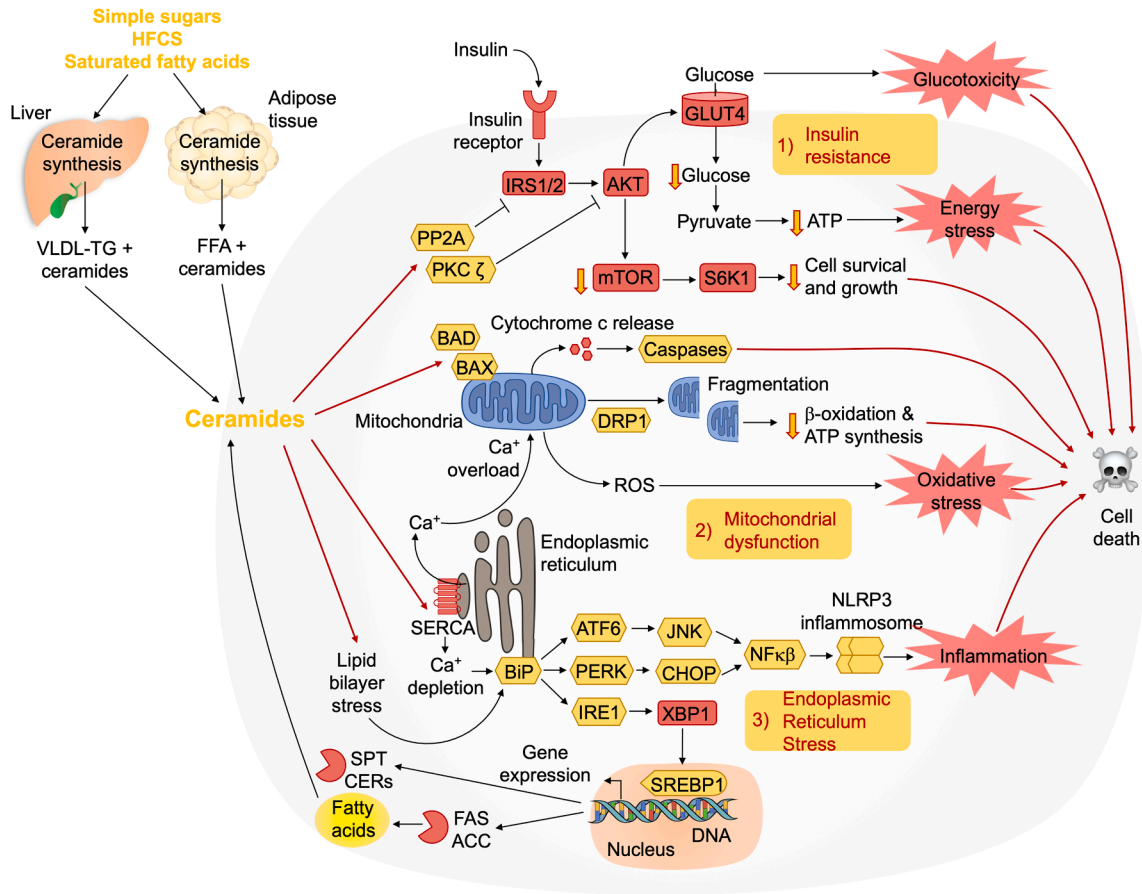
Based upon the previous information, CerS6 and CerS5 (to a lesser extent) are particularly relevant in the context of IR and obesity. These isoforms synthesize C16:0 and C18:0 ceramides which are consistently associated with impaired insulin signaling, mitochondrial dysfunction, and adipose tissue inflammation. In contrast, very-long-chain ceramides such as C22:0–C24:0, mainly generated by CerS2 are associated to a better metabolic health.

### 3.2. Ceramides and their implication in metabolic disorders: the underlying cause

Accumulating evidence has positioned Cer as a critical mediator in the pathogenesis of metabolic disorders such as obesity, IR, hepatic steatosis and dyslipidemia, which in turn progress to chronic diseases such as metabolic dysfunction-associated steatohepatitis, cardiovascular diseases, atherosclerosis, chronic kidney disease, and T2D. Excess Cer accumulation induces metabolic derangements in metabolic tissues -as the liver, skeletal muscle, and adipose tissue-by at least three well-defined mechanisms: **1)** impairing insulin signaling, leading to reduced glucose uptake and ATP synthesis **2)** altering mitochondrial electron transport chain and inducing mitochondrial fragmentation, leading to mitochondrial dysfunction, impaired respiration and augmented release of radical oxygen species (ROS) [16]. **3)** Induction of endoplasmic reticulum (ER) stress, increasing lipid synthesis and pro-inflammatory signaling [7,21]. The combination of energetic stress, oxidative stress, lipotoxicity, and inflammation disrupts vital cellular functions, leading to necrotic cell death (Fig. 4).

#### 3.2.1. Ceramides impair the insulin signaling pathways

The first mechanism of Cer-mediated metabolic alterations is the impairment of insulin signaling: in skeletal muscle, liver, and adipose tissue, Cer inhibits insulin receptor-IRS-Akt signaling pathway, a crucial regulator of glucose uptake and metabolism. This occurs through the activation of protein phosphatase 2A (PP2A), which dephosphorylates the activatory tyrosine residues



**Fig. 4.** Mechanisms of cellular damage induced by ceramides. Excess ceramide accumulation disrupts insulin signaling, mitochondrial function, and endoplasmic reticulum homeostasis, promoting oxidative stress, inflammation, and lipotoxicity. These processes lead to metabolic dysfunction and cell death.

of insulin receptor substrates (IRS) and Akt, and atypical protein kinase zeta (PKC $\zeta$ ), which phosphorylates both IRS and Akt on inhibitory serine residues, rendering them inactive. Reduction of Akt activity in skeletal muscle and adipose tissue prevents insulin-induced glucose transporter type 4 (GLUT4) translocation to the cell membrane and thereby reduces glucose uptake [16], whereas in the liver, Akt inhibition disrupts the insulin-induced suppression of hepatic gluconeogenesis, leading to uncontrolled glucose release. Thus, Cer accumulation impairs glucometabolic activities in metabolic tissues, resulting in hyperglycemia [18].

Elevated Cer content in adipose tissue also impairs insulin-mediated inhibition of lipolysis, increasing free fatty acids (FFA) release to circulation. Unrestrained lipolysis increases lipid uptake in tissues as the liver, kidney, heart and skeletal muscle, leading to lipid overaccumulation and lipotoxicity. Accordingly, increased Cer content in adipose tissue is strongly associated with metabolic alterations, such as IR, hepatosteatosis and myosteatosis, as observed in obesity [31].

Insulin signaling also favors cell growth and survival. The anabolic activities of insulin are mediated by the Ras/Raf/MEK/extracellular signal-regulated kinase (ERK) signaling pathway and the activation of the mechanistic target of rapamycin (mTOR) and S6 kinase beta-1 (S6K1) pathway. Cer accumulation inhibits both the ERK and mTOR signaling pathways, leading to impaired cell growth and survival [32].

The mechanisms involving Cer inhibition of insulin signaling involves the formation of highly structured lipid microdomains in the plasma membrane by Cer. Within these caveolin-enriched

domains, ceramide specifically reduces the association of PKC $\zeta$  with 14-3-3, a scaffold protein typically localized to less structured membrane regions. This dissociation leads to PKC $\zeta$  activation and subsequent phosphorylation of Akt3 at Ser34. Hence, structured membrane microdomains are necessary for ceramide-induced PKC $\zeta$  activation, which leads to the suppression of Akt activity and impairs the insulin signaling pathway [33].

Notably, specific acyl chain length and intracellular localization of Cers are important determinants of their metabolic effects [7]. For instance, long-chain ceramides, such as C16:0 and C18:0, have been closely associated with IR and hepatic steatosis. These ceramides are primarily produced by ceramide synthase 6 (CerS6) in adipose and liver tissue, and CerS1 in skeletal muscle [7,8,34], where they might also alter mitochondrial function.

**3.2.2. Ceramides induce mitochondrial dysfunction**

The second mechanism of Cer-mediated metabolic alterations is the induction of mitochondrial dysfunction. Ceramides accumulate in the mitochondrial membranes, leading to mitochondrial dysfunction by several pathways. Initially, C16:0 and C2:0-ceramides can self-assemble into large, barrel-like channels in the mitochondrial outer membrane [35]. These membrane channels are formed from columns of ceramides that arrange in an anti-parallel fashion, making a cylindrical shape spanning the hydrophobic interior of the mitochondrial outer membrane. Each column is composed of six Cer molecules associated to the MOMP and mitochondria permeabilization [14]. The formation of ceramide-induced pores has been associated with interactions between

ceramides and proteins such as Bax or the voltage-dependent anion channel (VDAC), which facilitate cytochrome *c* release and initiate apoptosis [36,37].

Researchers have identified that mitochondrial permeability transition pore (mPTP) is particularly sensitive to C2 ceramide, favoring the escape of ROS from the mitochondrial matrix [38]. Conversely, the accumulation of C16:0 ceramide has been shown to alter the balance between sphingolipids, phospholipids, and other membrane constituents, leading to increased membrane rigidity and permeability [21]. Additionally, in isolated liver mitochondria, C16:0 ceramides induce a significantly higher number of membrane channels compared to C22:0 ceramide [39].

Cer also modulates mitochondrial permeability by influencing external stimuli such as calcium concentration, cellular pH, redox balance, and conformational changes in the adenine nucleotide translocase (ANT). These alterations contribute to the opening of the mPTP, thereby affecting mitochondrial integrity and cell fate. Globally, changes in the lipidomic profile of mitochondrial membranes by particular ceramide species compromise their permeabilization, favoring metabolic dysfunction.

Mitochondrial permeability also disrupts the mitochondrial membrane potential, resulting in mitochondrial depolarization. Reduced membrane potential impairs the respiratory chain activity, leading to a loss of oxidative phosphorylation, blocking ATP synthesis. Ceramide accumulation has been reported to reduce mitochondrial membrane potential by 30–50 % in specific cell types [40]. Studies in mice have shown that genetic overexpression of CerS2 reduces mitochondrial membrane potential compared to a control group [41]. Accordingly, the accumulation of ceramides in the mitochondria of skeletal muscle cells showed loss of the mitochondrial respiratory chain components, resulting in mitochondrial dysfunction and IR [42].

The alteration in the electron transport chain (ETC) induced by Cer accumulation also increases ROS production, leading to oxidative stress and further promoting cell death [38]. A recent study shown that the C2:0 ceramide species blocks the activity of Complex II, favoring ROS production, tentatively by electron transfer to molecular oxygen at or near the same site where antimycin A acts within the Q-cycle of Complex III [43,44]. The C16:0 ceramide was also reported to inhibit the Complex IV activity in isolated liver mitochondria and induce ROS production [45]. In pancreatic  $\beta$ -cells, the accumulation of ROS induced by Cer buildup impairs insulin secretion and ultimately triggers  $\beta$ -cell death [31].

Crivelli and colleagues (2024) reported that elevated levels of 18:0, 22:0, and 24:1 ceramide also reduces the ETC and increase ROS production in brain cells [46,47]. Mechanistically, C16:0 ceramide potentially disrupts mitochondrial  $\beta$ -oxidation by inhibiting carnitine palmitoyltransferase 1 (CPT1), a key enzyme regulating the entry of long-chain fatty acids into mitochondria for oxidation [45]. Based on this scenario, it is expected that inhibition of mitochondrial oxidation results in a lipid overload state, where non-oxidized fatty acids are diverted into SLs biosynthetic pathways. The effect is the increased production of ceramides, thereby perpetuating a self-reinforcing cycle of metabolic stress and dysfunction, which worsens IR and cellular damage [7,21,48].

A study in rat cardiomyocytes found that the decrease in mitochondrial membrane potential induced by C2-ceramide was accompanied by fragmentation of the mitochondrial network [49]. This finding indicates that Cer accumulation also alters mitochondrial dynamics. Mitochondrial networks are in continuous remodeling, to match mitochondrial activity with energy demands. In this respect, mitochondrial fusion increases mitochondrial size for greater energy production during conditions of high metabolic activity, whereas fission reduces oxidative capacity and

ATP synthesis when energy demands are met. Mitochondrial fission also facilitates the removal of damaged mitochondria via mitophagy [50]. In fact, recent exciting evidence has documented that mitochondria split into two separate types, one of which is concentrated on energy production, whereas the other on anaplerosis, to produce essential cellular building blocks [51].

Cellular Cer accumulation alters the delicate balance between fission and fusion, leading to mitochondrial dysfunction and contributing to the pathogenesis of metabolic disorders, neurodegeneration, and organ injury. Ceramide promotes mitochondrial fission by increasing the activity and recruitment of proteins such as Drp1 and Fis1, resulting in mitochondrial fragmentation. At the same time, it suppresses fusion by downregulating key proteins like mitofusin 2 (MFN2) and OPA1, further driving mitochondrial stress. These effects are observed across various cell types such as cardiomyocytes, skeletal myocytes, neurons, hepatocytes, pancreatic beta cells, and glomerular cells [52].

For instance, C18:0 ceramide, synthesized CerS1 has been shown to mediate mitophagy in the brain by targeting damaged mitochondria [51,53]. This selective targeting is facilitated by the mitochondrial transport protein p17/PERMIT, which translocates CerS1 to the outer mitochondrial membrane to initiate C18:0 ceramide-dependent mitophagy [53]. In carcinoma cells, CerS1 and its metabolic product, C18-ceramide [54], induce non-apoptotic Bax/Bak and caspase-independent lethal mitophagy [55]. Recent findings highlight the importance of ceramide-LC3-II interactions as a key mechanism linking ceramide signaling to mitophagy [55]. Overall, ceramide metabolism emerges as a critical regulator of mitochondrial dynamics and a promising therapeutic target in diseases driven by mitochondrial dysfunction.

### 3.2.3. Ceramides activate the unfolded protein response by inducing endoplasmic reticulum stress

The third mechanism of Cer-mediated metabolic alterations is the activation of the UPR by inducing ER stress. The UPR is a critical cellular mechanism activated in response to alterations in ER homeostasis, which includes accumulation of unfolded or misfolded proteins, calcium depletion and changes in the ER membrane lipid composition. The ER stress activates three protein sensors, named IRE1, PERK, and ATF6, which initiate the UPR signaling pathways to restore homeostasis. However, if these adaptive responses fail, prolonged UPR activation disrupts cellular homeostasis, impairing insulin signaling as occurs in skeletal muscle, liver, and adipose tissue [56]. Additionally, ER stress promotes lipogenesis and lipid accumulation, leading to lipotoxicity. It also activates the NF $\kappa$ B-inflammatory pathway, ultimately leading to cell death.

Ceramide induces ER stress by two main mechanisms; 1) disrupting calcium homeostasis through inhibition of the SERCA pump, leading to depletion of ER calcium stores and 2) generating lipid bilayer stress, which is sensed by the IRE1 through a specialized intermembrane amphipathic helix [57]. Both cer-induced alterations in ER homeostasis activate the protein chaperone BiP/GRP78m, which binds and activates the three UPR sensors. In response to Cer accumulation, ATF6 activation induces SREBP1 transcription and activity, which then induces lipogenic gene expression, leading to lipid biosynthesis. PERK activates the elongation initiation factor 1a (eIF2a), which increases translation of specific proteins, such as the transcription factor CHOP, which in turn increases the expression of the NLRP3 inflammasome. Cer-induced IRE1a activity activates the pro-inflammatory intermediates JNK and NF $\kappa$ B, along with the activation of the transcription factor XBP1, which in turn increases the transcription of pro-inflammatory genes [58]. The combined activity of the three UPR sensors in response to Cer overload induces inflammation,

mitochondrial dysfunction, and ROS generation, leading to necrotic cell death [59].

Together, dysbalance in Cer synthesis and metabolism lead to Cer overload in different tissues, impairing insulin signaling, altering mitochondria dynamics and bioenergetics and inducing ER stress. These cellular alterations lead to activation of pro-inflammatory and pro-apoptotic signals, causing metabolic dysfunction in critical organs such as the liver, skeletal muscle, adipose tissue and kidney. These metabolic alterations progress to chronic diseases such as obesity, T2D, cardiovascular diseases, atherosclerosis, MASLD, chronic kidney disease, and neurodegeneration. The primary cause of Cer accumulation in tissues is overnutrition [21]. Long-term consumption of calorie-rich foods containing simple sugars or high-fructose corn syrup (HFCS) [60] and saturated fatty acids (SFAs) [61] increases lipid synthesis and ceramide production. This evidence highlights the significance of dietary choices on Cer accumulation and cellular dysfunction.

Based on the provided information, we next discuss the effect of specific nutrients and dietary patterns in human intervention studies.

### 3.3. Nutrient-mediated modulation of ceramide metabolism

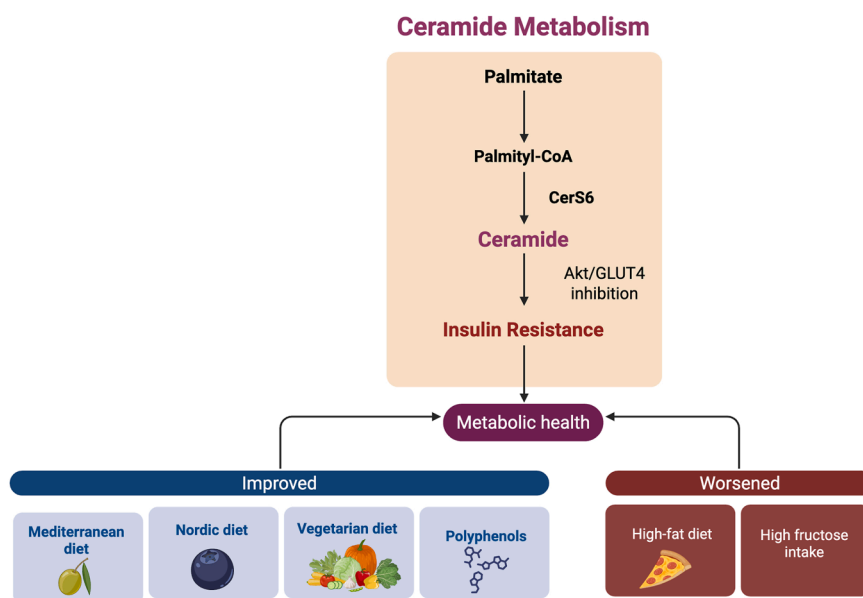
#### 3.3.1. Dietary fatty acids

Ceramides are increasingly recognized as key lipid signaling molecules that link nutrient intake to metabolic dysfunctions. Among the dietary components, the quality of dietary fat stands out as a major determinant of alteration in Cer profiles in humans. Diets rich in simple sugars and SFAs consistently promote Cer accumulation and adverse metabolic effects. In contrast, unsaturated fatty acids have been shown to attenuate ceramide levels and support beneficial lipidomic remodeling (Fig. 5). Mechanistically, SFA excess increases a substrate flux through SPT and CerS6, leading to the accumulation of C16:0-Cer that inhibits Akt/PKB signaling [62]. At the same time, MUFA and PUFA fats have been reported to favor CerS2-derived very long chain Cers (C22–C24) and activate ceramidase, promoting sphingosine and S1P formation that support insulin signaling [63].

In a controlled crossover trial, Kien et al. [64] evaluated how dietary fatty acid composition affects lipid metabolism and insulin sensitivity in 26 healthy adults. Both diets provided 40 % of total energy from fat: one high in palmitic acid (~16 % SFA, 16 % MUFA) and the other high in oleic acid (~2.4 % SFA, 28.8 % MUFA). The high oleic diet significantly reduced total and muscle ceramide concentrations and improved insulin sensitivity, particularly in women. These findings reflect a shift in acyl-CoA utilization whereby oleate competes with palmitate, decreasing CerS6 activity and enhancing SCD1-mediated desaturation, ultimately limiting C16:0 ceramide formation and improving insulin signaling.

Consistent with these results, Rosqvist et al. [65] compared overfeeding with SFA-and PUFA rich diets for seven weeks in 39 overweight adults. The SFA group (butter-based, ~19 % of energy as SFA) exhibited increases in Cer(d18:1&16:0), Cer(18:1/18:0) and Cer(d18:1/24:1), along with higher hepatic fat and alanine aminotransferase (ALT), whereas the PUFA group (sunflower-oil-based, 12 % of energy as PUFA) prevented hepatic lipid accumulation and maintained lower ceramide concentrations despite equivalent weight gain. These findings demonstrate that the quality rather than the quantity of dietary fat determines ceramide remodeling and metabolic impact.

Supporting evidence comes from interventions using MUFA and PUFA rich foods. A short-term study with extra virgin oil significantly decreased Cer (d18:1/16:0) and improved insulin-resistant markers compared with a palm-oil-rich diet, which increased the same ceramide species as sphingomyelin C18:0 [66]. Replacing palmitate with oleate-rich sources thus limits ceramide accumulation, mitigating cellular stress. Furthermore, the study by Lankinen et al. [67] showed that consuming fatty fish (150–300g per week for 12 weeks) decreased Cer species d18:1/23:0 and d18:1/24:1 along with diacylglycerols and lysophosphatidylcholines, lipids association with inflammation and IR. In contrast, Ottestad et al. [68] found that supplementing 36 healthy adults with 1.6 g/day EPA + DHA for seven weeks within a controlled diet (24.4 % fat) did not change ceramide levels but enriched plasma phospholipids and triglycerides with long-



**Fig. 5.** Nutritional modulation of ceramide metabolism. High intake of saturated fatty acids and simple sugars promotes ceramide synthesis and insulin resistance. Dietary patterns rich in unsaturated fatty acids and polyphenols (such as the Mediterranean, Nordic, and vegetarian diets) attenuate ceramide accumulation and improved metabolic health.

chain n-3PUFAs. This lipidomic remodeling, in the absence of ceramide reduction, suggests that fish-oil benefits arise from changes in membrane composition and anti-inflammatory signaling rather than direct suppression of ceramide synthesis [69].

On the other hand, plant-based PUFAs exert comparable effects. Tuccinardi et al. [70] demonstrated that short term walnut consumption (48 g/day) for five days significantly reduced plasma ceramides, hexacylceramides and sphingomyelins while increasing sphingosine levels, consistent with enhanced ceramide degradation. These changes were accompanied by lower small dense LDL, higher large HDL, and improved insulin resistance indices. The effect likely involves activation of ceramidase and production of sphingosine 1 phosphate, a metabolite that supports insulin sensitivity and endothelial protection.

Additional information highlights the broader physiological effects of PUFAs. Supplementation with n-3 omega fatty acids modifies ceramide profiles and improves cognitive and metabolic function, particularly through modulation of phospholipase A2 and membrane fatty acid composition [71–73]. Experimental studies also show that omega-3 fatty acids protect against sphingolipid turnover induced by ethanol [74], and that DHA prevents oxidative stress-induced apoptosis by reducing neuronal ceramide levels [75,76]. Collectively, these findings suggest that omega-3 fatty acids favor sphingolipid remodeling toward neuroprotective and anti-inflammatory pathways, consistent with their metabolic effects.

Furthermore, Eichelmann et al. (2024) applied lipid network analysis and identified a distinct ceramide-enriched cluster—including Cer(d18:0/24:0) and Cer(d18:1/16:0)—that was particularly responsive to changes in fatty acid composition [77]. These Cer, known for their pro-inflammatory and IR-promoting properties, were elevated following high saturated fat intake and decreased when SFAs were replaced by MUFAs or PUFAs [77]. Many of these ceramides also contributed to a reduced multi-lipid score (rMLS), a biomarker predictive of cardiometabolic risk across independent cohorts, highlighting the potential of ceramide profiling as a precision nutrition tool to assess fat quality-driven metabolic effects.

Although several studies report reductions in circulating ceramides following PUFA supplementation, findings remain heterogeneous, likely reflecting differences in intervention duration, tissue specificity, and baseline metabolic status. Overall, MUFA and PUFAs promote a more favorable sphingolipid profile through modulation of synthesis and degradation pathways, while SFAs favor the accumulation of ceramide species associated with IR and hepatic lipid deposition.

Of note, while the preponderance of evidence suggests a beneficial remodeling of the ceramide profile towards less deleterious species (e.g., increasing C24:0/C16:0 ratio), the effects on total ceramide concentrations are inconsistent. These inconsistencies can be attributed to factors like intervention duration, specific ceramide species measured, tissue compartment (circulating vs. tissue), and the baseline metabolic status of the population.

### 3.3.2. Polyphenols

Although current evidence remains limited, some studies suggest that polyphenols may play a significant role in regulating ceramide metabolism and its cardiometabolic effect. Polyphenols are a broad class of plant-derived bioactive compounds characterized by multiple phenolic rings, recognized for their antioxidant and anti-inflammatory properties [78,79]. Common dietary sources include green tea, coffee, red wine, fruits and vegetables, and

higher habitual intake has consistently associated with improved lipid metabolism and reduced cardiometabolic risk [80].

In a randomized controlled study, Rodríguez-Morató et al. (2021) demonstrated that white wine enriched with tyrosol significantly reduced ceramide ratios associated with endothelial dysfunction (C16:0/C24:0, C18:0/C24:0, and C24:1/C24:0) and simultaneously attenuated diacylglycerol accumulation in adults at high cardiovascular risk [81].

The lipidomic shifts were also accompanied with enhanced nitric oxide-related vasodilatory biomarkers, that could be derived by wine-phenolics that leads to vascular lipid remodeling by attenuating ceramide accumulation in the endothelial tissue.

The study also noted baseline variability in several ceramide species by sex, smoking status, and BMI, that are potential metabolic modifiers of the polyphenol response [81]. Importantly, the conversion of tyrosol to hydroxytyrosol, mediated by polymorphisms in CYP2A6 and CYP2D6, may also underlie interindividual differences [82]. This nutrigenetic effect of the lipidomic effects of Mediterranean dietary components, enhances antioxidant capacity and contributes to improved endothelial function.

Similar evidence from an RCT by Zhao et al. (2021) [83] showed that 12-week supplementation with anthocyanins (320 mg/day) led to reductions in plasma Cer(d18:1/16:0) and Cer(d18:1/24:0), accompanied by improved lipid profiles and increased cholesterol efflux capacity. Since the observed changes in ceramides correlated positively with reductions in non-HDL-C and ApoB, its hypothesis that anthocyanins could enhance lipoprotein catabolism and hinder the secretion and transport of sphingomyelin- and ceramide-rich ApoB-containing particles.

While the magnitude of ceramide lowering was smaller than that achieved with pharmacological lipid-lowering agents (fibrate or statins), anthocyanins were well tolerated even at high doses, supporting their potential as a safe dietary strategy for ceramide modulation. Moreover, the doses used in the present study are attainable through regular dietary intake, as berry fruit such as blueberries and raspberries contain particularly high anthocyanin levels, up to 487 mg and 687 mg per 100g of fresh fruit, respectively [83].

### 3.3.3. Fructose

High-carbohydrate diets are widely associated with the development of metabolic diseases. However, complex carbohydrates such as amylose and resistant starch, derived from sources like brown rice, lentils, and sweet potatoes, have long been part of traditional human diets without triggering the widespread prevalence of chronic conditions observed today. Notably, the sharp rise in metabolic disorders—including obesity, type 2 diabetes, and non-alcoholic fatty liver disease—has paralleled the mass introduction of simple sugars and high-fructose corn syrup (HFCS) into processed foods [84]. This evidence indicates that simple sugars and HFCS, rather than carbohydrates in general, are a key dietary contributor to the current epidemic of chronic metabolic diseases.

High fructose intake is increasingly recognized as a potent contributor to metabolic dysfunction through its impact on hepatic lipid metabolism and de novo lipogenesis (DNL). Recent studies have shown that fructose, particularly high fructose syrup, increases hepatic ceramide accumulation by driving de novo lipogenesis through the upregulation of the sterol regulatory element-binding protein (SREBP1) transcription factor, thereby generating abundant palmitoyl CoA. The excess palmitoyl-CoA combines with serine via SPT to form ceramide through the de novo pathway [15,22,85]. Furthermore, emerging data demonstrate that fructose intake induces the expression of thioredoxin-interacting protein (TXNIP), a multifunctional regulator of

cellular redox state and carbohydrate metabolism. TXNIP directly interacts with fructose transporters GLUT2 and GLUT5, promoting their activity and thereby facilitating increased fructose absorption in the small intestine and transport into peripheral tissues. An elevated TXNIP enhances fructose uptake and its shuttling to the liver, increasing substrate availability for de novo lipogenesis and lipotoxic ceramide generation. As a result, excessive fructose intake may increase ceramide generation, thereby promoting lipotoxicity, endoplasmic reticulum (ER) stress, and insulin resistance [86].

Evidence suggests that fructose restriction, even over a short duration, leads to favorable remodeling of ceramide profiles, reduction of hepatic lipogenesis, and improvement in insulin sensitivity. Olson et al. (2022) reported that a short-term reduction in fructose intake in children with obesity and metabolic syndrome led to decreased circulating ceramides and improved insulin sensitivity [60]. Despite maintaining total caloric intake, fructose reduction from 12 % to 4 % of total energy led to significant decreases in hepatic DNL and marked reductions in multiple ceramide species, including Cers C14:0, C20:0, C22:0, and C24:0.

Similarly, findings from the Framingham Offspring Cohort provide large-scale epidemiological support for the link between chronic fructose exposure and sphingolipid dysregulation. In this study, Walker et al. (2020) reported that higher cumulative intake of sugar-sweetened beverages (SSBs) (the principal dietary source of fructose) was positively associated with circulating concentrations of Cer(d18:1/16:0) and Cer(d18:1/22:0), as well as higher Cer(d18:1/24:0) levels among individuals with prediabetes or type 2 diabetes [87]. As previously mentioned, these ceramide species have been consistently implicated in the pathogenesis of insulin resistance, hepatic steatosis, and cardiometabolic disease, reinforcing the hypothesis that dietary sugars contribute to metabolic deterioration through the activation of ceramide biosynthetic pathways [87].

### 3.4. Dietary patterns and their impact on ceramide modulation

Dietary patterns—combinations of foods and nutrients habitually consumed—play a major role in shaping health outcomes. Research consistently shows that what people eat as a whole, rather than individual foods or nutrients, is strongly linked to the risk of chronic diseases, mental health, and overall quality of life [88]. Alongside calorie restriction as a dietary strategy, the most extensively studied healthy dietary patterns include the Mediterranean diet, the Nordic diet, and vegetarian diets (Fig. 5).

#### 3.4.1. Calorie restriction

Calorie restriction (CR) has been associated with improved insulin sensitivity and reduced risk of T2D in individuals with obesity. Although reductions in long-chain Cer, such as Cer C24:0 and C18:0 have been linked to favorable metabolic outcomes, direct evidence on Cer modulation by CR in humans remains limited [89]. In a 16-week intervention, CR significantly enhanced insulin sensitivity, as shown by increased glucose infusion rates during hyperinsulinemic-euglycemic clamps. However, these improvements occurred without changes in skeletal muscle Cer, suggesting that other mechanisms, like the suppression of thioredoxin-interacting protein (TXNIP) (a regulator of oxidative stress), may mediate the metabolic benefits of CR [89]. While CR has been recognized for its benefits in metabolic regulation (improve insulin sensitivity in absence of detectable reductions in skeletal muscle ceramides), the macronutrient distribution could have a more pronounced effect in modulating Cer levels due to the complexity of lipid-metabolism interactions [89].

#### 3.4.2. Mediterranean diet, Nordic diet, and vegetarian diet

Different dietary patterns rich in plant-based foods and unsaturated fats, such as the Mediterranean (MedDiet), Nordic, and vegetarian diets, are known for their cardiometabolic benefits, and it is suggested that part of these effects involve the modulation of Cer metabolism [90–92].

The MedDiet, characterized by a high intake of fruits, vegetables, olive oil, legumes, and whole grains, has shown consistent associations with favorable shifts in Cer profiles. Studies have reported reductions in Cer species such as C24:0 and C18:0 and increases in the C24:0/C16:0 ratio—changes associated with lower cardiovascular risk, improved vascular function, and reduced inflammation [90–92]. These effects were observed both in clinical trials and in population-based cohorts. Additionally, adherence to the MedDiet has been associated with improvements in endothelial function, lipid profiles, and adipokines [91].

A similar trend has been observed in the Nordic diet, which emphasizes whole grains, berries, vegetables, fish, and plant oils. In a randomized trial, adherence to a healthy Nordic diet for 12–24 weeks led to transient reductions in circulating Cer such as Cer d18:1/22:0 and d18:1/24:0, as well as increases in plasmalogens (lipids associated with antioxidant function) [93].

Vegetarian diets, typically low in SFAs and centered around fruits, vegetables, and legumes, have been linked to reduced systemic inflammation and improved metabolic markers. In a small study comparing vegetarians and omnivores with obesity and similar body composition, vegetarians consumed less saturated fat, had lower plasma palmitic acid levels, and showed reduced inflammatory activity in adipose tissue. Although no differences in muscle Cer abundance were observed, these findings suggest that vegetarian diets may support a metabolic profile less conducive to Cer accumulation [94].

The studies reviewed indicate that nutritional interventions do not merely modify total ceramide levels, but rather reshape the composition and balance individual ceramide species, reflecting specific regulatory effects on sphingolipid metabolism [93]. Overall, Mediterranean, Nordic, and plant-based dietary patterns have been associated with improved insulin sensitivity and lipidomic profiles, partly through reductions in deleterious ceramide species and enrichment in protective long-chain lipid species.

### 3.5. Clinical and translational perspectives

Distinct dietary components modulate specific ceramide synthase (CerS) isoforms and their associated ceramide species: diets enriched in saturated fatty acids tend to up-regulate CerS5 and CerS6, leading to higher synthesis of C16:0 and C18:0 ceramides, which are, as previously described, drivers of IR and mitochondrial dysfunction. In contrast, monounsaturated and polyunsaturated fatty acids (MUFA and PUFA) down-regulate these isoforms while favoring the production of very-long-chain ceramides such as C22:0–C24:0.

Despite growing evidence that diet can modulate ceramide metabolism, translating the current results into clinical practice remains a challenge. Intervention trials suggest that measurable changes in ceramide profiles typically require 6–12 weeks of sustained dietary modification (Supplementary Table 1). For instance, Ottestad et al. (2012) observed that a 7-week intervention with fish oil providing 1.6 g/day of EPA + DHA in healthy adults did not significantly alter total ceramide levels, suggesting that longer or more intensive interventions may be necessary to remodel sphingolipid metabolism [68].

But interventions involving Mediterranean diets or higher habitual intake of polyunsaturated fatty acids (PUFAs) tend to produce more consistent improvements in ceramide ratios,

particularly an increase in the C24:0/C16:0 ratio, over longer periods. For bioactive compounds such as polyphenols, evidence indicates that regular dietary consumption (rather than short-term supplementation) may have a more meaningful role in long-term lipidome remodeling.

From a biomarker perspective, ceramides show potential as early indicators of metabolic risk and response to intervention, however the clinical implementation is still limited. Compared with established markers such as HOMA-IR or HbA1c, lipidomic assays are costly, less standardized, and not yet widely accessible [95] so ceramide profiling should currently be viewed as a *complementary research biomarker* in metabolic diseases.

Inter-individual variability is another factor that may explain the variability in ceramide responses to diet. These may include genetic differences in key enzymes of sphingolipid metabolism, such as *ASAH1*, *ASAH2*, and *ACER3* gene variants, which influence the balance between ceramide synthesis and degradation and are essential for systemic sphingolipid regulation [96].

#### 4. Conclusion

Ceramides can be potential lipidomic biomarkers for early metabolic dysfunction and as tools for monitoring nutritional response. Future research should prioritize longitudinal and interventional studies integrating lipidomics and dietary assessment to translate these results into precision nutrition strategies and clinical practice.

Evidence summarized in this review supports the role of specific nutrients—particularly MUFAs, PUFAs, and polyphenols—as well as dietary strategies as CR and dietary patterns such as the Mediterranean, Nordic, and vegetarian diets, in modulating circulating and tissue-specific ceramide levels. These dietary components may contribute to preserving metabolic homeostasis in healthy individuals, preventing the development of chronic metabolic diseases, and as therapeutic strategies for individuals with metabolic diseases by attenuating ceramide-driven mechanisms of IR and inflammation. Finally, as a structured narrative review, this work provides an integrative perspective while recognizing the need of greater methodological standardization and harmonization in future studies.

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Not applicable.

#### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Grammarly and ChatGPT, in order to improve readability. After using

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#### Conflict of interest

The authors declare no conflict of interest.

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#### Appendix A. Supplementary data

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