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Role of Ceramide in Acute Coronary Syndrome and Type 2 Diabetes Mellitus

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Abstract:

Ceramides are a class of bioactive sphingolipids that play a crucial structural and regulatory role within cell membranes. They are essential components of the stratum corneum, where they contribute to maintaining skin barrier integrity, preventing excessive transepidermal water loss, and protecting against environmental irritants and pathogens. Beyond their structural function, ceramides act as signaling molecules involved in cellular processes such as apoptosis, inflammation, cell differentiation, and response to stress. Alterations in ceramide metabolism or reduced ceramide levels have been implicated in various dermatological and systemic disorders. For example, decreased ceramide content in the epidermis is strongly associated with skin barrier dysfunction, as seen in atopic dermatitis, psoriasis, and xerosis. Additionally, ceramide dysregulation has been linked to metabolic diseases, insulin resistance, and neurodegenerative conditions due to its role in cell signaling pathways and inflammation. Therapeutically, topical ceramide-containing formulations are widely used to restore skin hydration and barrier function, while systemic modulation of ceramide pathways is being explored for broader clinical applications.

Keywords: Ceramide; Sphingolipids; Skin barrier; Stratum corneum; Apoptosis; Inflammation; Atopic dermatitis; Psoriasis; Moisturizers; Transepidermal water loss (TEWL).

Introduction:

Sphingolipids are structural components of cell membranes, and signaling molecules involved in the regulation of a range of cellular functions including cell growth and differentiation, proliferation, and cell death **(1, 2).** Sphingolipids are a diverse category of lipid molecules, which contain a backbone of sphingoid bases, which are aliphatic amino alcohols that include sphingosine or a structurally similar molecule. The sphingoid base is attached to a head group, and N-acylated with numerous variations of fatty acids forming diverse sphingolipid species. Ceramide, the central molecule in sphingolipid metabolism, serves as the main precursor in sphingolipid biosynthesis and can be synthesized through various pathways **(3).**

Ceramides are a type of sphingolipid, the major lipid component of cell membranes **(4).** Ceramides not only act as the second messenger molecule in the sphingolipid signaling pathway, but also take part in the formation process of the stratum corneum. The stratum corneum, which is the primary portion of the intercellular matrix containing 40-50% of intercellular lipids, plays a crucial function in maintaining the water balance of the skin **(5).**

Ceramides can be divided into several types according to their chemical composition. Different chemical structures correspond to different biological functions **(6).**

Ceramides and their metabolites can decrease insulin sensitivity, blood vessel reactivity and pancreatic cell function, as well as maintaining the skin's barrier function, regulating hydration, exerting anti-aging effects and acting as future therapeutic targets for some diseases, such as insulin resistance, obesity, type 2 diabetes,

Parkinson's disease, autoimmune rheumatic disease, ventilator-induced lung injury and cancer (especially breast cancer) **(7).**

Some studies have found that ceramides can inhibit glucose uptake and increase adipose ectopic deposition, while inhibiting the enzymes required for ceramide synthesis can improve the progression of diabetes **(8).**

Biosynthesis and Degradation of Ceramide:

Bioactive ceramides can be produced in three ways **(4).** First, the de novo pathway produces 3-keto-dihydrosphingosine by condensation of serine and palmitate catalyzed by serine palmityl transferase (SPT) **(9).** Next, sphinganine is N-acylated by six distinct ceramide synthases (CerSs) to form various dihydroceramides. The dihydroceramides are oxidized by dihydroceramide desaturase into corresponding ceramides. This is the main method of ceramide production **(5).** Second, in the sphingomyelinase (SMase) pathway, ceramides are produced by hydrolysis of sphingomyelin (SM) catalyzed by SMases, which are divided into neutral SMases (nSMases 1, 2 and 3), acid SMases (aSMase) and alkaline SMases **(10).**

When cellular stress occurs in a particular compartment, the level of ceramide is quickly increased multiple times through this pathway **(11).** The third pathway is the salvage pathway, in which sphingolipids degraded to sphingosine (Sph) are reutilized by reacylation to produce ceramides. Lipid phosphate phosphatases or Sph-1-phosphate (S1P) phosphatase are used to obtain Sph **(12)**. CerSs may acylate Sph to form ceramides. Ceramides can be digested by ceramidases in the opposite direction, resulting in Sph. Sph kinase (SphK) phosphorylates Sph, resulting in S1P, which then reenters sphingolipid metabolism by the SphK and/or one of the six CerSs **(13)** (Fig. 1). Each CerS controls the production of endogenous ceramides from scratch. Although certain CerSs are found throughout the body, other isoforms create tissue-specific synthesis of ceramides. CerS1 specifically synthesizes C18 ceramide, and while it is highly expressed in the skeletal muscles, it is nearly undetectable in other tissues **(14)**. CerS2 is mostly expressed in the kidneys and liver, and synthesizes C22-24 ceramides **(15).** Ceramides with varying acyl chain lengths may trigger diverse cell responses; hence, different CerS isoforms may create different ceramide species **(16).**

CerS3 is most highly expressed in the skin and synthesizes C28-C32 ceramides **(17)**, CerS4 expression is not specific to any tissue and synthesizes C14-C16 ceramides, while CerS5 is primarily expressed in the epithelia of the lungs and CerS6 has been found in almost all tissues in the body, except in the intestines, spleen, lymph nodes and thymus **(18).**

CerS5 and 6 specifically synthesize C14-C16 ceramides. CerS6 is primarily responsible for the production of C16 ceramides, which have been linked to a number of diseases, including insulin resistance and obesity **(19)**. Ceramides are broken down into free fatty acids (FFAs) and Sph by ceramidases. Five distinct ceramidases have been previously reported in humans, each with a different catalytic pH optimum, namely, acid ceramidase, neutral ceramidase, and alkaline ceramidases 1, 2 and 3, which are encoded by five separate genes (ASAH1, ASAH2, ACER1, ACER2 and ACER3, respectively) **(20).**

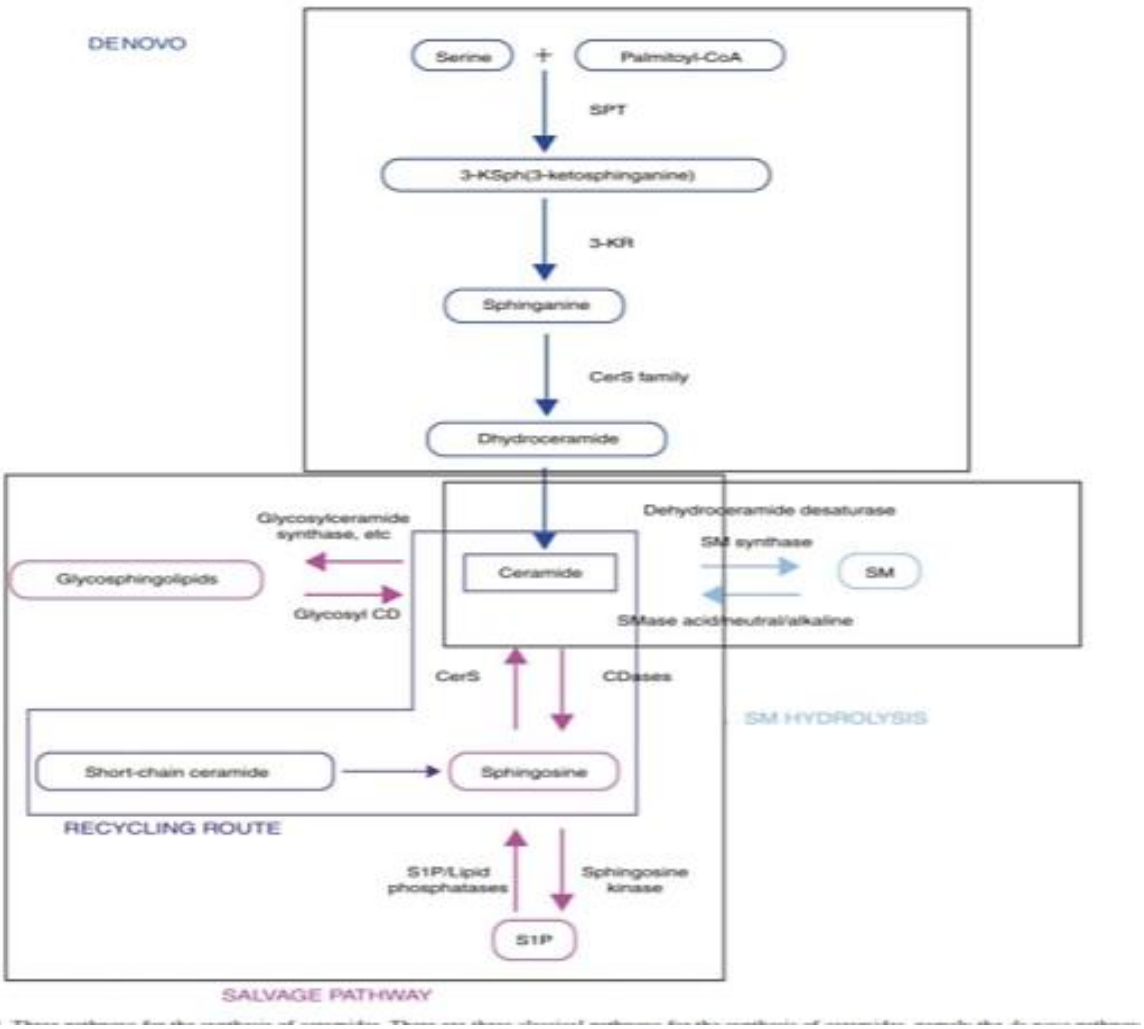

Figure (1): Three pathways for the synthesis of ceramides. There are three classical pathways for the synthesis of ceramides, namely the de novo pathway, the hydrolysis of sphingomyelin pathway and the salvage pathway. CerS, ceramide synthase; SM, sphingomyelin; SMase, sphingomyelinase; CD, ceramidase; S1P, sphingosine-1-phosphate; SPT, serine palmitoyltransferase; 3-KR, 3-ketosphinganine reductase.

Ceramides and diabetes mellitus: is there any verified relationship?

In addition to primary b-cell dysfunction as an underlying cause, Type 2 diabetes mellitus is well recognized as a metabolic disorder in which insulin resistance in peripheral cells is a central feature. Insulin resistance interferes with cellular consumption of glucose as a first order substrate for metabolism and adenosine triphosphate (ATP) generation **(21).** Whilst it has been suggested that insulin resistance serves as a physiological defence against metabolic stress and overfeeding, insulin resistance is also recognized as a hallmark of disease in many people with Type 2 diabetes **(22)**.

The exact pathophysiology of insulin resistance is as yet unknown, but strong evidence points to the involvement and interplay of a variety of factors: a defect in glucose transporter type 4 (GLUT4) expression, a defect in muscle glucose transport, impaired muscle glycogen synthesis, deviations in insulin receptor isoform expression or insulin/ insulin-like growth factor (IGF)-I hybrid receptor abundance and defects in the insulin signalling pathway. Where any defect in this pathway may contribute to the development of insulin resistance **(23).** A body of evidence also suggests that other factors, such as a high fat diet overfeeding, inflammatory cytokines, free radical species and insulin signalling inhibitors, can induce insulin resistance and, ultimately, in the presence of B-cell dysfunction, type 2 diabetes mellitus **(24).**

Ceramide and B cell dysfunction:

- **Ceramide and pancreatic b-cell apoptosis:**

Apoptotic death of b cells residing in pancreatic islets is a hallmark of pancreatic dysfunction in people with diabetes. Loss of b-cell mass reduces the intrinsic capacity for insulin production, secretion and, therefore, release **(25).**

Apoptosis of b cells in islets is a feature of both Type 1 and Type 2 diabetes. b cells are affected by metabolic factors that induce protein misfolding and/or induce inflammatory responses **(25).**

Loss of b cells through apoptosis reduces the total effective b-cell mass and results in inadequate secreted insulin in response to a glucose load **(26).**

B cells are sensitive to a variety of pro-apoptotic stimuli, including ceramides **(27).** Various clinical and experimental studies have demonstrated that sphingolipid metabolites, such as sphingosine 1-phosphate, glycosphingolipids and ceramides, can induce signalling pathways involved in b-cell apoptosis **(28).** This can be accomplished either by inducing ER stress, enhancing lipotoxicity or disrupting mitochondrial function with subsequent development of oxidative damage **(25).**

Grosch et al. (29) found that ceramides can stimulate cytochrome-C release and trigger downstream apoptotic-related pathways in b cells. Further, the apoptotic potency of ceramides was reported by **Zhang et al. (30)** who suggested that ceramides induce b-cell apoptosis through inhibition of ion channel activity. Thus, induction of b-cell apoptosis is a direct diabetogenic consequence of high circulating plasma levels of ceramides.

- **Ceramides and pancreatic cell inflammation:**

Pancreatic inflammation is strongly correlated to b-cell dysfunction and, accordingly, inadequate insulin secretion **(31).** Much work has shown that upregulation of cytokines and marked inflammatory responses are induced in an animal model of Type 1 diabetes mellitus **(32).**

Major et al. (33) demonstrated that ceramides can mimic the cytotoxic effects of TNF-a, IL-1b and IFN-c cytokines in pancreatic b cells and trigger related inflammatory responses.

Sjoholm (34) also found that ceramides mimic IL-1B activity and promote its cytotoxic and cytostatic influence in islet b cells.

Moreover, **Norris and Blesso (35)** recently reported the same effects of sphingolipids and found that they are involved in chronic inflammation in different tissues, including pancreatic islets. Consequently, induction of inflammation is another possible effect of ceramides in diabetes development.

- **Ceramides and pancreatic oxidative stress:**

Oxidative stress has a pivotal role in the pathophysiology of many diseases, including the development of diabetes as a result of b-cell stress **(36).** Excess free radicals in b cells, resulting from hyperglycaemia or toxicity, can impair insulin gene expression and insulin secretion, and induce b-cell apoptosis **(37).**

Ceramide production enhances free radical generation and oxidative damage**.** High levels of circulating ceramides are associated with mitochondrial dysfunction, thereby leading to further free radical generation **(38).**

Jazvinscak Jembrek et al. (38) in 2014 showed that ceramides induce poly[ADP-ribose] polymerase-1 (PARP-1) activity, free radical generation and oxidative damage in neuronal cells. While no direct evidence shows ceramide induced oxidative damage in b cells, indirect evidenceindicates that oxidative stress attributable to ceramide accumulation can play a significant role in islet dysfunction, impaired insulin secretion and diabetes development, and this relationship clearly requires further investigation.

- **Ceramides and defects in insulin expression:**

Some studies have proposed that insulin mRNA/gene expression is under the influence of plasma levels of ceramide **(39).** A number of different sphingolipid metabolites, in addition to ceramides, are strongly implicated in insulin gene expression and may exert inhibitory effects upon it **(28).**

Kelpe et al. (39) in 2003 demonstrated that prolonged exposure to higher ceramide levels downregulates insulin gene expression in a model of isolated islets in culture.

Guo et al. (40) later demonstrated that accumulation of ceramides in plasma inhibits proinsulin gene expression through protein phosphatase 2A (PP2A) activity; therefore, we conclude that ceramide induced insulin gene downregulation can be considered another potential effect of ceramides in diabetes development.

- **Ceramide and defects in insulin secretion:**

Reduced insulin secretion is a central element in the pathogenesis of diabetes mellitus which may be attributable to lower b-cell mass or failure of the b-cell secretory machinery **(41).**

Free fatty acids, as well as ceramides, can affect insulin secretion in different ways, including via intracellular trafficking, intracellular storage in the Golgi complex or by inhibiting secretory machinery **(28).** Ceramides disrupt the apparatus transporting insulin from the ER to the Golgi complex and so disrupt intracellular trafficking of insulin and its subsequent secretion from b cells **(28).**

Karunakaran et al. (42) reported that ceramide accumulation is involved in both b-cell failure and disturbed insulin secretion.

Lang et al. (43) reported that any defect in sphingomyelin synthase 1 activity, which naturally converts ceramides to sphingomyelin, leads to accumulation of ceramides and impairment of insulin release; therefore, it can logically be concluded that impairment of the insulin secretion machinery is another mechanism by which ceramides may induce diabetes mellitus.

- **Ceramides and insulin resistance:**

1- Ceramide and glucose metabolism:

As stated earlier, insulin resistance is a hallmark of Type 2 diabetes mellitus in which the b cells are unable to secrete adequate levels of insulin into the circulation to overcome the resistance to this hormone; therefore, the entry of glucose into cells for use as a first line substrate is disturbed **(44).**

Any agent that interferes with the insulin signalling pathway can therefore induce insulin resistance and, ultimately, in the presence of b-cell failure lead to Type 2 diabetes mellitus **(44).**

Available evidence suggests that higher levels of plasma ceramides promote insulin resistance and the development of metabolic syndrome **.** Additionally, pharmacological or genetic disruption of ceramide synthesis has been shown to improve glucose metabolism and enhance insulin sensitization **(45).**

Haus et al. (46) in 2009 showed that plasma ceramide level is directly associated with insulin resistance in obese people with Type 2 diabetes. They found that insulin sensitivity in such individuals is inversely correlated to the ceramide species C18:0, C20:0, C24:1 and to the total plasma ceramide level.

The accumulation of ceramides produced from palmitate (through the de novo pathway)has been found to induce an inhibition of insulin signalling (in vitro) and diabetes (in vivo) **(47).**

Chavez and Summers (48) in 2012 also emphasized the role of ceramides in insulin resistance and presented a new hypothesis that implicated ceramides as a key agent in the development of insulin resistance. Another possible mechanism for ceramide-induced insulin resistance is via insulin receptor substrate-1 (IRS-1) phosphorylation.

IRS-1 is a mediator protein with signalling activity that links the binding of insulin and IGF-1 to related intracellular receptors of the insulin pathways, thus triggering associated downstream signalling pathways**.** IRS-1 has ~232 Ser/Thr residues which are mainly subjected to phosphorylation **(49).**

Previous work has shown that Ser/Thr residue phosphorylation of IRS-1 decreases its ability to respond to insulin and negatively modulates insulin signalling pathways, thus contributing to insulin resistance**.** Other reports indicate that ceramides may be involved in IRS-1 phosphorylation and can therefore negatively modulate insulin signalling and induce insulin resistance **(49)**.

Ceramides inhibit IRS-1 through activation of the PKR/JNK axis **(50).**

The accumulation of ceramides via different mechanisms blocks the activation of the Akt pathway, a protein kinase that is essential for insulin signalling and insulin-mediated stimulation of glucose metabolism, with consequent inhibition of the Akt-mediated GLUT4 translocation and glucose uptake, and glycogen synthesis **(50).** Intriguingly, ceramides were found to play a role in insulin resistance induced by saturated fatty acids**.** It has also been shown that ceramides can impair glucos200e metabolism by acting on Akt signalling pathways through PP2A and/or PKCf mediators **(51).**

Chen et al. (51) showed that ceramides impair glucose metabolism and induce insulin resistance through PP2A- and PKCf-dependent mechanisms.

Mahfouz et al. (52) also found that ceramides induce insulin resistance through a PP2A-dependent pathway in skeletal muscles of animals.

Insulin resistance in skeletal muscle plays a key role in Type 2 diabetes development. Various studies support the importance of specific muscle ceramides in the development of lipid-induced skeletal muscle insulin resistance **(53).**

The degradation of ceramides both in the liver and in fat tissue improved glucose metabolism, suggesting a major contributing role for both these tissues in regulating circulating ceramide levels, and, in addition, confirming the role of these substances on glucose homeostasis **(54).**

2- Ceramides and endoplasmic reticulum stress:

Endoplasmic reticulum stress is defined as any disturbance in proper function of the ER which may be attibutable to improper folding or ER overloading**.** ER stress is a prominent marker of insulin-resistant cells which, in turn, further impair glucose homeostasis**.** Ceramides can induce ER stress and impair glucose homeostasis in a number of experimental models in several cell lines, such as islet b cells **(55).**

For example, **Liu et al. (56)** found that exogenous application of ceramides induces severe ER stress by impairing ER Ca2+ homeostasis in human adenoid cystic carcinoma cells.

Yano et al. (57) showed that ceramides can cause ER stress by inducing protein misfolding in the ER as a result of Ca2+ depletion in pancreatic b cells.

Moreover, **de la Monte et al. (58)** demonstrated that ceramide-induced ER stress impaired the IGF signalling pathway and enhanced insulin resistance in post mortem brain tissue of human Alzheimer disease models.

Specifically in muscle cells, however, ceramide-induced insulin resistance is mediated mainly by impairment of the insulin signalling pathway (IRS1 and Akt)**.** Rather than by ceramide-induced ER stress, which probably plays a major role in the liver and adipose tissue **(59).**

3- Ceramide and adipokines expression/release:

The adipokines, also known as adipocytokines, are adipose tissue-driven cytokines with pro-inflammatory properties that are mainly released by adipocytes. Since the recognition of leptin as the first adipokine, hundreds of these cytokines have been discovered, such as resistin, TNF-a and IL-6; this effectively implies that adipose tissue is a major endocrine organ**.** Adipokines can exert diabetogenic effects by enhancing

insulin resistance in peripheral tissues of people with obesity**.** Although some adipokines, such as leptin and adiponectin, are involved in control of feeding behaviour and balance of energy, more recent evidence confirms that they are also involved in inflammatory response-induced insulin resistance **(60).**

Some evidence suggests that ceramides increase both adipokine expression and its level in the circulation **(45).**

Available data indicate a strong link between ceramides and adipokines **(45).**

Hamada et al. (61) showed that ceramides stimulate pro-inflammatory adipokine secretion as well as IL-6 and monocyte chemo-attractant protein-1 in mature 3T3-L1 adipocytes.

In addition, **Chavez and Summers (48)** showed that ceramide production is directly correlated to leptin, TNF-a, adiponectin and resistin levels in tissues. Furthermore, the adiponectin receptor is linked to ceramidase activity and induced activation of this activity enhances ceramide catabolism, formation of its anti-apoptotic metabolite sphingosine-1-phosphate, and subsequent reduction of tissue ceramide levels, thus contributing to the pleiotropic metabolic actions of adiponectin**.** Ceramide-induced adipokine secretion can therefore be considered to be another pathophysiological pathway involved in insulin resistance and Type 2 diabetes mellitus development.

Role of ceramides in chronic complications of diabetes mellitus:

Ceramides may accumulate in tissues other than the pancreas, adipose tissue, muscle, liver and brain, such as the kidney, eye, heart and vessels, thus contributing to chronic diabetes complications. Elevated ceramide levels and specific ceramide ratios have been reported to be associated with an increased risk of death and negative outcomes in people with cardiovascular disease **(62).**

Ceramides may contribute causally to impaired vasoreactivity, dyslipidaemia, aggregation of lipoproteins, uptake and retention of oxidized lipids in the vascular wall, and, ultimately, to atherosclerotic plaque formation **(63).**

Ceramides have been associated with lipotoxic and diabetic cardiomyopathy in animal models **(64).**

Furthermore, these substances have been implicated in mesangial cell apoptosis and in retinal pericyte apoptosis **(65)** which are associated with diabetic nephropathy and retinal pericyte apoptosis, respectively Tissue accumulation of ceramides may not only have a pathogenic, but also a prognostic significance in diabetes mellitus, being associated with the risk of development of diabetes-related complications.

Ceramide and Acute coronary syndrome:

The serum concentration of lipids is used to assess the risk of atherosclerotic heart disease. The level of low-density lipoprotein cholesterol (LDL-C) is closely related to atherosclerosis and acute coronary events. Previous studies have indicated that distinct ceramide species are closely related to cardiovascular death in patients with coronary heart disease (CHD). Ceramide molecules Cer(d18:1/16:0), which is abbreviated to Cer16:0; Cer(d18:1/18:0), which is abbreviated to Cer18:0; Cer(d18:1/24:1), which is abbreviated to Cer24:1; and their ratios to Cer(d18:1/24:0), which is abbreviated to Cer24:0, have been investigated as new risk stratification factors in patients with CHD**).** In patients with CHD, a high level of Cer16:0, low level of Cer24:0, and a high Cer16:0/Cer24:0 ratio in plasma are related directly to cardiovascular mortality **(66).**

Accumulating evidence has shown that ceramides are closely related to the pathological process of type 2 diabetes mellitus (DM) and its complications **(67).**

Ceramides: A New Player in Cardiovascular Disease:

The pathogenesis of atherosclerosis is the result of a complex interplay between metabolic and inflammatory risk factors. Despite cholesterol, in particular LDL-C, carrying most of the blame as a driver of CVD, ceramides are emerging as a novel independent factor able to predict cardiovascular risk. Indeed, the crucial role of ceramides in the pathophysiology of CVD has been described both in animal and human studies**,** with

peculiar ceramide subspecies (C16:0, C18:0, C24:0, and C24:1) being reported as independent predictors of cardiovascular events **(68).**

Ceramides appear to play a direct role in promoting atherosclerosis. In this regard, ceramides have been detected in atherosclerotic plaques where they facilitate the transport and entry of oxidized LDL-C into intimal cells, the initial step in atheroma formation**.** Moreover, the tendency of oxidized LDL-C to aggregate is influenced by the lipidome of these lipoproteins themselves, with an increase in ceramide content in LDL enhancing their aggregation capacity **(69).**

In terms of the mechanisms underpinning the involvement of ceramides in the pathogenesis of atherosclerosis, oxidative stress and inflammation may be pivotal. Indeed, while on one hand these pathophysiological processes intervene in atherosclerosis onset and progression, they are also triggered by ceramides **(8).**

In line with this, ceramides influence the activity of the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein 3 (NLRP3) inflammasome in macrophages and adipocytes, increasing the synthesis of pro-inflammatory cytokines**.** Additionally, ceramides are involved in triggering endothelial dysfunction by promoting the formation of ROS and interfering with the production of nitric oxide by the endothelial nitric oxide synthase **(70),** thereby determining an increase in oxidative stress and hampering vasodilation (Figure 2).

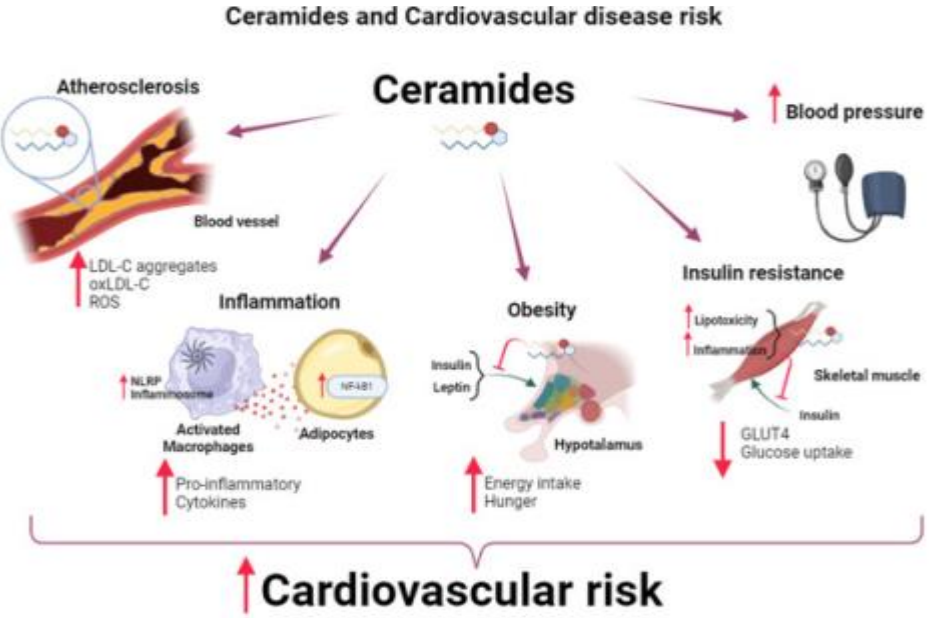

Figure (2): Circulating ceramides and their implications in cardiovascular disease risk.

Ceramides offer a good predictive capability for cardiovascular mortality, allowing to identify patients requiring further therapeutic interventions**.** Elevated ceramide ratios (C16:0/C24:0, C18:0/C24:0, C24:1/C24:0) display an association with CVD mortality in CHD **(18).**

Indeed, higher levels of C16:0, C20:0, C20:1 and C24:0 ceramides in cardiovascular tissue have been observed in both acute and chronic CHD and are positively correlated with the severity of coronary stenosis **(71).** This also held true for major adverse cardiovascular events (MACE) which were independently associated with the plasma levels of C16:0, C18:0, and C24:1 ceramides in patients with and without CHD **(62),** whereas C24:0 displayed an inverse relationship with MACE **(66).** Furthermore, the same ceramides were associated with vulnerable coronary plaque in subjects with acute coronary syndrome **(72)** and in patients with ST-segment–elevation myocardial infarction, C16:0, C18:0, and C24:10 ceramides were all predictors of thin-cap fibroatheroma **(73).** This novel ceramide score was then validated in the FINRISK 2002 cohort, determining a

model with a better predictive capability when including ceramides along with traditional risk factors, such as C-reactive protein, even in patients without previous history of CVD **(74).**

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