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Editorial

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# Sphingolipids: Friends or Foes?

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Sphingolipids play a physiologically major role in the human body. They not only serve as essential constituents of the membrane but also make microdomains called lipid rafts with cholesterol on the cell surface for transporting substances in and out of the cells. Sphingomyelin constitutes myelin sheath and red blood cell membrane. In contrast, if sphingomyelin is abnormally stored in the reticuloendothelial system and neurons of the body, lethal damage can occur after birth. This situation occurs in Niemann–Pick disease type A and B genetically lacking sphingomyelinase, which degrades sphingomyelin. In plasma, about 20% of lipoprotein phospholipids is sphingomyelin, most of which exists in VLDL and LDL[1]. Sphingomyelin on the surface of LDL particles interferes in the reaction between LDL and LDL receptors[2, 3] and promotes LDL aggregation[2]. Aggregated LDL is captured by scavenger receptors of macrophages. These phenomena mean that sphingomyelin in LDL has pro-atherogenicity. As reported previously, the ingestion of plant stanol decreased the amount of sphingomyelin in LDL and lowered the aggregation susceptibility of LDL particles[4].

Sphingomyelin consists of ceramide (N-acyl sphingosine) and phosphoryl choline. Ceramide consists of sphingosine and a fatty acid **(Fig. 1)**. Ceramide and sphingosine also belong to sphingolipid. Ceramide is related to atherosclerosis. Meeusen *et al.* demonstrated that the number of plasma ceramides was associated with major adverse cardiovascular events in their cohort of 495 participants[5]. Concerning the molecular species of ceramides, they showed that N-palmitoyl sphingosine [Cer(16:0)], N-stearoyl-sphingosine [Cer(18:0)], and N-nervonoyl-sphingosine [Cer(24:1)] are significantly predictive of a major cardiovascular outcome at 4 years of follow-up. Recently, ceramide has also been reported to be involved in the pathogenesis of type 2 diabetes mellitus. Neeland *et al.* reported that plasma ceramides, especially bound to saturated fatty acids, are related to visceral adiposity, insulin resistance, and the development of type 2 diabetes[6]. Fretts *et al.* also reported that plasma ceramide, especially Cer(16:0), Cer(18:0), N-arachidoyl-sphingosine [Cer(20:0)], and N-behenoyl-sphingosine [Cer(22:0)], are associated with a higher risk of diabetes[7].

In this issue of Journal of Atherosclerosis and Thrombosis, Kurano *et al.* reported that they measured ceramides and sphingosine, including dihydrosphingosine, a molecule that is closely related to sphingosine **(Fig. 1)**, in each serum lipoprotein and lipoprotein-deleted fraction of healthy controls and patients with diabetes and compared the distribution of these sphingolipids between the two populations[8]. Some of their patients with type 2 diabetic mellitus had complications related to cardiovascular diseases and diabetic nephropathy. They separated lipoproteins from the serum of all participants using sequential ultracentrifugation and measured sphingolipids in each fraction using the LC-MS/MS system. Although several researchers have mentioned the relationship between serum ceramides and atherosclerosis or metabolic deterioration in humans, the distribution of sphingolipids among lipoproteins is rarely observed. Therefore, the research of Kurano *et al.* is well noted. The important points they found are as follows: 1) the levels of ceramide, sphingosine, and dihydosphingosine in HDL were lower, whereas those in lipoprotein-depleted fractions were higher in patients with diabetes; 2) the contents of sphingosine, Cer(16:0) and N-lignoceroyl-sphingosine [Cer(24:0)] in the LDL fraction were higher in the group with diabetes, and levels of ceramides in LDL were negatively associated with the presence of cardiovascular diseases

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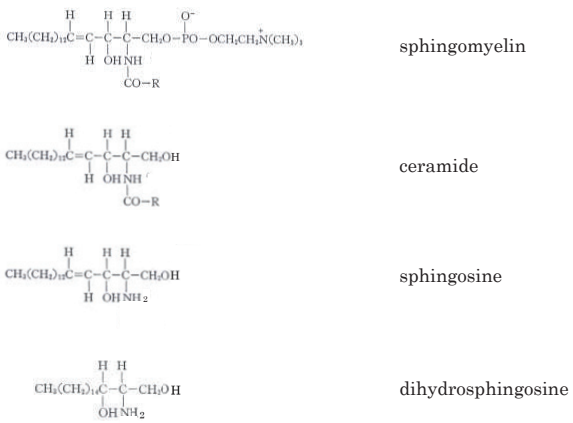


**Fig. 1.** The structures of sphingolipids are shown.
CO-R denotes an acyl residue.

and stage 4 diabetic nephropathy in the group with diabetes; 3) each ceramide did not necessarily behave in the same mode, that is, the levels of N-oleoyl-sphingosine [Cer(18:1)] in HDL were not significantly decreased in the group with diabetes.

The amount of ceramides measured in serum is related to atherosclerosis and type 2 diabetes, as mentioned above. Kurano *et al.* revealed a significant difference in the distribution of ceramides among lipoproteins and lipoprotein-deleted fractions of serum when comparing patients with diabetes to healthy subjects[8]. Moreover, in patients with diabetes, ceramides increase in LDL, but they decrease in HDL compared to normal subjects. Surprisingly, the level of ceramides in the LDL of patients with diabetes is negatively related to cardiovascular events and diabetic nephropathy. Ceramides contained in lipoproteins behave differently in atherogenesis and metabolic conditions than those existing in lipoprotein-deleted fractions or bound to albumin. Kurano *et al.* described an interesting finding in their previous research that sphingosine 1-phosphate (S1P), a sphingolipid, is anti-atherogenic when it is bound to HDL via apoprotein M, but it exerts harmful effects on atherosclerosis when it is bound to albumin[8]. So, do the ceramides have the same effect as S1P? They calculated the ratio of ceramides to phospholipids, apolipoprotein B, or apolipoprotein A-I in each lipoprotein to elucidate the role of ceramides in lipoproteins but did not reach a definite conclusion in this research. This is an inevitable and important question and deserves further investigation. Kurano *et al.* found that Cer(18:1) behaves a differently from other ceramides in the HDL of patients with diabetes[8]. It is reasonable to speculate that each ceramide affects metabolism differently depending on its molecular species not only in the whole serum but also in lipoproteins. More observations are expected.

Although the research of Kurano *et al.* is noteworthy, there are some concerns in their study. Some patients in the group with diabetes were prescribed statins. Statins naturally affect lipoprotein metabolism and may affect sphingolipid metabolism. They analyzed the data using various statistical methods and tried to cancel the confounding effects of statins, but it complicated the interpretation of the results. The number of subjects they measured was relatively small considering the mixed characters of the group. If they included more subjects for analysis, the results could become much clearer.

In conclusion, Kurano *et al.* opened the door to a new research field of sphingolipids, but the question of physiological and pathological roles of sphingolipids remains.

## Conflict of Interest

None.

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