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**The Effect of Dietary Phytosphingosine on Cholesterol Levels and Insulin Sensitivity  
in Subjects with the Metabolic Syndrome**

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Running head: Phytosphingosine improves the metabolic syndrome

**Disclosure statement:**

The authors have nothing to disclose

**Keywords:** Sphingolipids, Metabolic Syndrome, Insulin resistance, Cholesterol,  
Intravenous glucose tolerance test.

## **Abstract**

**Background:** Sphingolipids, like phytosphingosine **PS** are part of cellular membranes of yeasts, vegetables and fruits. Addition of phytosphingosine to the diet decreases serum cholesterol and free fatty acid **FFA** levels in rodents and improves insulin sensitivity.

**Objective:** To study the effect of dietary supplementation with phytosphingosine on cholesterol and glucose metabolism in humans.

**Methods:** Twelve men with the metabolic syndrome (according to the IDF criteria; age  $51 \pm 2$  years (mean  $\pm$  SEM); BMI  $32 \pm 1$  kg/m<sup>2</sup>) were randomly assigned to 4 weeks of phytosphingosine **PS** (500 mg t.d.) and 4 weeks of placebo **P** in a double-blind cross-over study, with a 4-week wash-out period between both interventions. At the end of each intervention anthropometric measures and serum lipids were measured and an intravenous glucose tolerance test **IVGTT** was performed.

**Results:** Phytosphingosine did not affect body weight and fat mass compared to placebo. Phytosphingosine decreased serum total cholesterol ( $5.1 \pm 0.3$  (PS) vs.  $5.4 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ) and LDL-cholesterol levels ( $3.1 \pm 0.3$  (PS) vs.  $3.4 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ), whereas it did not alter serum triglyceride and HDL-cholesterol levels. In addition, phytosphingosine lowered fasting plasma glucose levels ( $6.2 \pm 0.3$  (PS) vs.  $6.5 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ). Phytosphingosine increased the glucose disappearance rate (K-value) by 9.9% during the IVGTT ( $0.91 \pm 0.06$  (PS) vs.  $0.82 \pm 0.05$  (P) %/min;  $p < 0.05$ ) at similar insulin levels, compared to placebo, implying enhanced insulin sensitivity. Phytosphingosine induced only minor gastrointestinal side effects.

**Conclusion:** Dietary supplementation of phytosphingosine decreases plasma cholesterol levels and enhances insulin sensitivity in men with the metabolic syndrome.

## **Introduction**

Sphingolipids are ubiquitous functional components in the food and, therefore, constituents of our normal daily diet although the amounts are relatively small (Vesper *et al.*, 1999). Sphingolipids belong to the class of amphiphilic membrane lipids. They consist of a long-chain sphingoid base, a polar head group and a fatty acid, which is linked via an amide bond (Merrill, Jr. *et al.*, 1997). Different head groups on the backbone separate the individual sphingolipids from one another. At least 300 different sphingolipids were identified in mammals. Sphingolipids primarily serve as critical components of cell membranes, although they are also present in small amounts in lipoproteins and other lipid-rich structures (Harder & Simons, 1997). Certain complex sphingolipids are involved in specific functions, such as cell growth, division, differentiation, survival and death (Berra *et al.*, 2002).

Sphingolipids in food cross the intestinal membrane, and are biological active (Schmelz *et al.*, 1994). Nevertheless, it is uncertain if they have health benefits in humans.

Phytosphingosine, one of the sphingolipids, is a constituent of plants, fruits and yeasts (Vesper *et al.*, 1999). Normal daily intake of phytosphingosine averages 50 milligrams in humans. In high fat-fed, insulin resistant ApoE3 Leiden mice, phytosphingosine treatment (diet supplemented with 1% phytosphingosine for 5 weeks) decreased plasma cholesterol and triacylglycerol levels by ~ 57%. This was at least in part explained by the intestinal effects of phytosphingosine, since it reduced intestinal absorption of dietary cholesterol and free fatty acids by ~40 % (Duivenvoorden *et al.*, 2006). Phytosphingosine treatment also seemed to positively affect insulin sensitivity in these animals (data not published). The lipoprotein profile of these mice closely resembles the pattern of

dyslipidemia characteristic of the metabolic syndrome **MetS** in humans. At present, it is unclear whether addition of phytosphingosine to the diet is also beneficial for humans. The MetS consists of a constellation of metabolic abnormalities, including glucose intolerance, obesity, dyslipidemia and hypertension, all well-defined cardiovascular risk factors. At present, 25% of adult Americans meet the criteria of the metabolic syndrome (Ford *et al.*, 2002). Having the MetS more than doubles the risk of developing atherosclerotic CVD and type 2 diabetes (Ford, 2005; Isomaa *et al.*, 2001). As for now, the only intervention targeting all aspects of the MetS is lifestyle change, consisting of diet, weight loss and increasing physical activity. The chances of long-term adherence (a prerequisite for success) of such an intervention are low however. The use of drugs that improve individual components of the MetS is likely to cause polypharmacy in patients, which diminishes patient compliance and leads to side effects. Thus, therapeutic tools targeting multiple components of the syndrome simultaneously are needed. This study was meant to elucidate the effects of dietary supplementation with phytosphingosine on blood cholesterol levels and insulin sensitivity in male subjects with the MetS.

## **Patients and Methods**

### *Patients*

Twelve men with the MetS according to the criteria of the International Diabetes Federation **IDF** (Alberti *et al.*, 2006) were recruited via advertisements in local newspapers. Additional inclusion criteria were age between 18 and 65 years; BMI between 27 and 40 kg/m<sup>2</sup>; HOMA-IR > 2.0. Subjects were excluded from the study if they had a history of any chronic disease (including cardiovascular disease and type 2 diabetes mellitus) or if they were smokers. No subject used medication that could affect the investigated metabolic markers. All subjects had a stable body weight for three months prior to participation, and were instructed not to alter lifestyle (eating, drinking and exercise) until the end of the study. Prior to participation the subjects gave written informed consent after oral and written explanation of the study had been given. The study was approved by the Medical Ethical Committee of Leiden University Medical Center.

### *Study design*

Subjects enrolled in a randomized double-blind placebo-controlled cross-over intervention study with a 4 week wash-out period in between the two interventions. Subjects were randomly assigned to placebo **P** or phytosphingosine **PS** as first intervention. They received phytosphingosine (Cosmoferm, Delft, The Netherlands; encapsulated by Utrecht Medical Centre, Utrecht, the Netherlands) in a dosage of 500 mg twice daily **t.d.** and Placebo capsules also **t.d.** for 4 weeks. At the end of each intervention patients were admitted to the research center to perform an intravenous glucose tolerance

test **IVGTT** (LUNDBAEK, 1962). During both intervention periods patients visited the research center weekly for anthropometric measurements, registration of adverse events (both subjective side effects and laboratory abnormalities were recorded) and compliance registration (weekly pill count).

### *Study days*

At the end of each intervention patients were admitted to the clinical research center after an overnight fast for an IVGTT. First, anthropometric measurements (weight, length, waist and hip circumference) were obtained together with measurements of blood pressure and body fat mass by bioelectrical impedance analysis (Bodystat, Bodystat<sup>®</sup>, Bodystat Ltd. Douglas, Isle of Man). Subsequently, an intravenous cannula was placed, to draw a basal blood sample followed by an IVGTT. Twenty-five gram of glucose was infused in 4 minutes by a volumetric pump (Pilot C syringe pump, Fresenius Vial, France), with blood sampling at 0, 2, 4, 6, 8, 10, 12, 20, 30, 40, 50, 60, 90 and 120 minutes from a second cannula in a contralateral arm vein. Glucose, insulin, c-peptide and free fatty acids (FFA) levels were determined in these samples.

### *Assays*

Serum glucose, cholesterol, high density lipoprotein **HDL** cholesterol en triglycerides were measured with a fully automated P-800 module (Roche, Almere, the Netherlands). Low density lipoprotein **LDL** cholesterol was calculated according to the Friedewald equation. Insulin and C-peptide were detected with an immunometrische assay on an automated Immulite 2500 (Siemens, Breda, the Netherlands).

### *Statistical analysis and mathematical calculations*

The glucose disappearance rate (K-value) was determined by log-linear regression of the glucose concentrations against time over the period from 10 to 120 minutes post-glucose loading. Total and incremental areas under the curve **AUC** of glucose, insulin, c-peptide and FFA were determined over the periods from 0-120 min (glucose) and 10 to 120 min (insulin, c-peptide and FFA) post-glucose loading. Baseline levels were defined as plasma glucose, insulin, c-peptide and FFA levels at time 0 min (LUNDBAEK, 1962). Data are presented as mean  $\pm$  SEM. For comparisons between placebo and phytosphingosine treatment a Student's *t*-test for paired samples was used. When appropriate, non-parametric (Wilcoxon signed-rank test) tests for paired samples were performed. All analyses were done using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). A p-value of  $< 0.05$  was considered statistically significant.

## **Results**

### *Patient Characteristics*

Anthropometric parameters are presented in Table 1. There were no differences in anthropometric parameters, fat mass and blood pressure after 4 weeks treatment with placebo vs. phytosphingosine. The patients' compliance was very good; 2 respectively 3 patients missed only 1 capsule of 500 mg during the placebo respectively phytosphingosine treatment period.

### *Fasting Cholesterol levels*

Four weeks of phytosphingosine treatment decreased total cholesterol levels ( $5.1 \pm 0.3$  (PS) vs.  $5.4 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ) and LDL-cholesterol levels ( $3.1 \pm 0.3$  (PS) vs.  $3.4 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ) as compared to 4 weeks treatment with placebo, whereas phytosphingosine did not alter triglyceride and HDL-cholesterol levels (Figure 1 and Table 2).

### *Metabolic parameters*

Phytosphingosine decreased fasting serum glucose levels compared to placebo ( $6.2 \pm 0.3$  (PS) vs.  $6.5 \pm 0.3$  (P) mmol/L;  $p < 0.05$ ). However, phytosphingosine did not alter fasting levels of insulin, c-peptide and FFAs (Table 2).

Phytosphingosine did not affect the total and the incremental areas under the curve (AUC), of glucose, insulin, c-peptide and FFA levels during IVGTT (Table 3). However, phytosphingosine improved the K-value (a parameter of the glucose disappearance rate;

$0.91 \pm 0.06$  (PS) vs.  $0.82 \pm 0.05$  (P) %/min;  $p < 0.05$ ) at equal insulin levels, implying enhanced insulin sensitivity (Figure 2).

#### *Safety and side effects*

Administration of phytosphingosine 500 mg t.d. for 4 weeks was well tolerated. Liver enzymes, creatinin levels and hemoglobin levels were not affected by phytosphingosine treatment (data not shown). Subjects only reported minor side effects, which were all gastrointestinal complaints (PS vs. P: diarrhea: 4 vs. 3; pyrosis: 3 vs. 1; nausea 3 vs. 2; abdominal discomfort 4 vs. 1 subjects).

## Discussion

This study indicates that dietary supplementation with 500 mg phytosphingosine twice daily significantly lowers total and LDL-cholesterol by 6% and 10%, respectively, and enhances insulin sensitivity in men with the metabolic syndrome. Side effects were minimal and of gastrointestinal nature. This study confirms in humans the metabolic effects of dietary phytosphingosine, previously documented in rodents (Duivenvoorden *et al.*, 2006)

Blood cholesterol concentrations can be modulated by changes in the intake of dietary fat and cholesterol. However, implementation of dietary advices reduces total cholesterol levels by only 3 to 6% (Tang *et al.*, 1998). In addition, reductions in LDL-cholesterol and total cholesterol levels can be accomplished by dietary supplementation of plant sterol esters. Plant sterol esters possess the same cholesterol-lowering capacity as phytosphingosine in this dosage. In the performed studies total cholesterol levels decreased by 4-10% and LDL-cholesterol levels by 6-10 % after treatment with 1 to 3.25 grams plant sterol esters for 3.5 to 52 weeks (Hendriks *et al.*, 1999; Hendriks *et al.*, 2003; Miettinen *et al.*, 1995). The maximum cholesterol-lowering effect with plant sterol esters treatment is reached with a dosage of ~ 2.5 grams. Therefore, the cholesterol-lowering capacity of 1 gram phytosphingosine for 4 weeks is greater than that of implementations of dietary advices and equal to that of dietary supplementation with ~ 2.5 grams plant sterol esters. However, we expect a larger cholesterol-lowering effect with a higher dosage of dietary phytosphingosine supplementation.

Several mechanisms could account for the less explicit reduction in cholesterol levels in our study as compared to the previous rodent studies. Firstly, the effects of

phytosphingosine on cholesterol metabolism are dose-dependent and the rodent studies were performed with higher amounts of phytosphingosine in the diet (1% of the diet) than used in the present study (0.2% of the diet) (Duivenvoorden *et al.*, 2006; Imaizumi *et al.*, 1992). Secondly, the study may have been too short to show the full decrease in cholesterol levels. The duration of treatment with phytosphingosine was based on the rodent study, which treated mice with phytosphingosine for 5 weeks (Duivenvoorden *et al.*, 2006). Studies with plant sterol esters-enriched spread observed a maximal cholesterol-lowering effect after 3 months (Miettinen *et al.*, 1995). Further studies should elucidate whether longer treatment with phytosphingosine could extend the magnitude of the cholesterol-lowering effect. The exact mechanism by which phytosphingosine lowers blood cholesterol levels is not fully understood, but includes decreased absorption of dietary cholesterol from the gut (Duivenvoorden *et al.*, 2006; Noh & Koo, 2004).

The observed decrease in fasting plasma glucose levels can be due to decreased intestinal glucose uptake and/or decreased basal endogenous glucose **EGP** production by the liver. In one study sphingomyelin, another sphingolipid, decreases the absorption of glucose in the intestine in mice (Barrenetxe *et al.*, 2006). No data are available on the glucose absorption from the intestine after phytosphingosine treatment. In rodents dietary phytosphingosine leads to an improvement in hepatic steatosis, this is often accompanied by an improvement in hepatic insulin resistance and thus a decreased basal EGP (Petersen *et al.*, 2005; Ravikumar *et al.*, 2008).

The k-value is a measure for the glucose disappearance rate after a glucose load. K-values in patients with type 2 diabetes mellitus treated with oral blood glucose-lowering agents and/or insulin vary between 0.4-0.7 (%/min). Subjects without insulin

resistance have a k-value above 1 (%/min) (LUNDBAEK, 1962). The increase in k-value was found in the absence of an increase in either fasting or glucose-stimulated serum insulin levels. This indicates improved tissue insulin sensitivity and increased peripheral glucose uptake. The underlying mechanism of the improvement in insulin sensitivity is unclear. Possibly phytosphingosine acts like acarbose. Acarbose diminishes the postprandial glucose uptake, thereby decreasing glucotoxicity and its associated inflammation and insulin resistance of muscle and liver (Lieber *et al.*, 2004; Okada *et al.*, 2009; Segal *et al.*, 2005). It is very likely that phytosphingosine diminishes postprandial glucose uptake as well.

A strength of our study was the placebo controlled cross-over design which is an effective method for balancing confounding factors between treatment periods. A possible weakness was the small sample size. Since this was the first study with phytosphingosine in humans, we could not perform a formal power calculation. However, the results were highly significant. Nevertheless, the results of our study should be confirmed in a study with a bigger sample size.

In conclusion, a relatively low-dose of phytosphingosine decreases serum total and LDL-cholesterol levels and fasting plasma glucose and improves glucose disappearance in men with the metabolic syndrome within 4 weeks. Therefore, sphingolipids like phytosphingosine may provide an additional dietary tool to treat the metabolic features of the metabolic syndrome.

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**Table 1.** Anthropometric parameters after 4 weeks treatment with placebo and phytosphingosine (500 mg t.d.) in 12 men with the metabolic syndrome.

	placebo	phytosphingosine
age (years)	50.8 ± 2.1	
height (m)	1.83 ± 0.02	
weight (kg)	105.9 ± 4.6	106.1 ± 4.6
BMI (kg/m <sup>2</sup> )	31.5 ± 1.0	31.6 ± 1.0
waist (cm)	109.6 ± 2.8	109.9 ± 2.6
hip (cm)	110.6 ± 2.1	109.8 ± 1.9
WHR	0.99 ± 0.01	0.99 ± 0.01
fat mass (kg)	32.6 ± 2.6	33.6 ± 2.7
systolic blood pressure (mmHg)	138 ± 5.5	140 ± 4.9
diastolic blood pressure (mmHg)	84 ± 2.0	83 ± 1.6
Heart rate (rate/min)	69 ± 2.7	68 ± 2.7

BMI: body mass index; WHR: waist hip ratio  
mean ± SEM

**Table 2.** Cholesterol levels after 4 weeks treatment with placebo and phytosphingosine (500 mg t.d) in 12 men with the metabolic syndrome.

	placebo	phytosphingosine
cholesterol (mmol/L)	5.38 ± 0.27	5.08 ± 0.29*
triglyceride (mmol/L)	2.28 ± 0.24	2.3 ± 0.21
LDL-cholesterol (mmol/L)	3.43 ± 0.28	3.12 ± 0.29*
HDL-cholesterol (mmol/L)	0.92 ± 0.07	0.92 ± 0.07
cholesterol/HDL ratio	6.08 ± 0.36	5.64 ± 0.27*

mean ± SEM

\* p<0.05

**Table 3.** IVGTT values after 4 weeks treatment with placebo vs. phytosphingosine (500 mg t.d.) in 12 men with the metabolic syndrome.

	placebo	phytosphingosine
basal glucose (mmol/L)	6.5 ± 0.3	6.2 ± 0.3*
total AUC(0-120 min) glucose (mmol/L)	1213 ± 44	1206 ± 52
AUC(0-120 min) from bas. glucose (mmol/L)	349 ± 21	379 ± 25
basal insulin (mU/L)	21.3 ± 2.6	20.8 ± 2.1
total AUC(10-120 min) insulin (mU/L)	5251 ± 490	5394 ± 493
AUC(10-120 min) from bas. insulin (mU/L)	2908 ± 354	3123 ± 377
basal c-peptide (nmol/L)	1.12 ± 0.07	1.12 ± 0.09
total AUC(10-120 min) c-peptide(mU/L)	237 ± 14	247 ± 16
AUC(10-120 min) from bas.c-peptide (mU/L)	114 ± 11	124 ± 11
basal FFA (mmol/L)	0.56 ± 0.05	0.65 ± 0.04
total AUC(10-120 min) FFA (mmol/L)	33.7 ± 2.7	37.3 ± 3.3

AUC: area under the curve; bas: basal; FFA: free fatty acids  
mean ± SEM; \* p<0.05

**Figure 1.** Cholesterol levels (A: total cholesterol; B: LDL-cholesterol) after 4 weeks treatment with placebo and phytosphingosine (500 mg t.d.) in 12 men with the metabolic syndrome. Data are presented as mean  $\pm$  SEM (bars) and individual changes (lines).

**Figure 2.** K-values during the IVGTT after 4 weeks treatment with placebo and phytosphingosine (500 mg t.d.) in 12 men with the metabolic syndrome. Data are presented as mean  $\pm$  SEM (bars) and individual changes (lines).



