SUPPLEMENT

The Role of the Novel Lipokine Palmitoleic Acid in Health and Disease[1–3]

María E Frigolet[4]* and Ruth Gutiérrez-Aguilar[4,5]

[4]Metabolic Diseases: Obesity and Diabetes Laboratory, Hospital Infantil de México Federico Gómez, Mexico City, Mexico; and [5]Research Division, Faculty of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico

ABSTRACT

The monounsaturated fatty acid palmitoleate (palmitoleic acid) is one of the most abundant fatty acids in serum and tissues, particularly adipose tissue and liver. Its endogenous production by stearoyl-CoA desaturase 1 gives rise to its *cis* isoform, *cis*-palmitoleate. Although *trans*-palmitoleate is also synthesized in humans, it is mainly found as an exogenous source in ruminant fat and dairy products. Recently, palmitoleate was considered to be a lipokine based on evidence demonstrating its release from adipose tissue and its metabolic effects on distant organs. After this finding, research has been performed to determine whether palmitoleate has beneficial effects on metabolism and to elucidate the underlying mechanisms. Thus, the aim of this work was to review the current status of knowledge about palmitoleate, its metabolism, and its influence on metabolic abnormalities. Results have shown mixed cardiovascular effects, direct or inverse correlations with obesity, and hepatosteatosis, but a significant amelioration or prevention of insulin resistance and diabetes. Finally, the induction of palmitoleate release from adipose tissue, dietary intake, and its supplementation are all interventions with a potential impact on certain metabolic diseases. *Adv Nutr* 2017;8(Suppl):173S–81S.

Keywords: fatty acids, palmitoleate, lipokine, diet, obesity, diabetes, insulin resistance, cardiovascular disease

Introduction

Metabolic syndrome is characterized by the accumulation of visceral adipose tissue, dyslipidemias, hypertension, and high concentrations of fasting plasma glucose, as well as low-grade inflammation (1, 2). Dietary interventions that promote lifestyle changes can be used as an appropriate alternative to reduce metabolic syndrome. Such interventions include modifications of the type and concentration of dietary FAs, which influence metabolism through various pathways. For instance, dietary fat saturation plays a role in lipoprotein metabolism and insulin action. SFAs are associated with a higher risk of ischemic heart disease and insulin resistance, whereas unsaturated FAs have multiple beneficial effects on cardiovascular health (3–5) and insulin sensitivity (6–8) in clinical and animal studies. MUFAs promote a healthy blood lipid profile and improved blood pressure, insulin sensitivity, and glycemic control (9–12). PUFAs positively affect insulin sensitivity, cardiovascular and mental health, and development, and reduce hypertension and inflammation (13, 14).

The MUFA palmitoleic acid or palmitoleate (16:1n–7 or 16:1D9) has received a lot of attention in recent years, even though its metabolism was described in the 1960s (15). Palmitoleate can be found as a *cis* (16:1c9) or a *trans* (16:1t9) isomer (**Figure 1**). The *cis* isoform (*cis*-palmitoleate) has been associated with increased insulin sensitivity and decreased lipid accumulation in the liver (16). In animal models, *cis*-palmitoleate decreased the expression of proinflammatory markers and adipokines, which are related to the establishment of metabolic abnormalities (16–18). *Trans*-palmitoleate (1) is found in dairy products and partially hydrogenated oils and may be associated with favorable metabolic profiles and decreased incident diabetes (19). Typically, *trans* FAs, which are produced for commercial cooking and frying, are related to a higher risk of endothelial dysfunction and coronary heart disease (20). Nevertheless, prospective cohorts have denied the association of plasma *trans*-palmitoleate with stroke (21), and further research is needed to determine whether the proinflammatory effects of *trans*-linoleic acid and *trans*-oleic acid also are attributed to *trans* FAs other than *trans*-palmitoleate.

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*To whom correspondence should be addressed. E-mail: maruf.himfg@gmail.com.

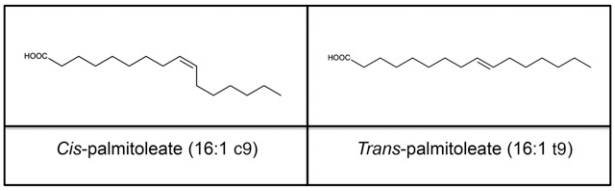

FIGURE 1 Chemical structure of palmitoleate. Palmitoleate (16:1n–7 or 16:1Δ9) is a MUFA with 16 carbons. The double bond is located in the n–7 or Δ9 carbon, counting from the methyl-terminal carbon or the carboxylic acid end, respectively. The 2 isoforms of palmitoleate, *cis* and *trans*, are shown here.

Therefore, considering the evidence of its beneficial effects, it is important to evaluate whether palmitoleate could be used as a strategy for preventing or treating metabolic diseases. Here, we review the current status of knowledge of palmitoleate, including its sources, metabolism, effects on metabolic abnormalities, and underlying mechanisms.

Endogenous Synthesis of Palmitoleate

Palmitoleic acid mainly originates from de novo lipogenesis in humans. Lipogenesis is mediated by stearoyl-CoA desaturase 1 (SCD1)[6], the rate-limiting enzyme catalyzing the synthesis of MUFAs, mainly oleate (18:1c9) and palmitoleate (16:1c9) (22). In addition to palmitate, oleate also can be converted into palmitoleate by chain shortening in human hepatocellular carcinoma cells (23). In humans, *cis*-palmitoleate biosynthesis occurs primarily in the liver, and secondarily in adipose tissue, where it is later incorporated into phospholipids, TGs, waxes, and cholesterol esters.

Because SCD1 is the main pathway for palmitoleate generation, researchers have assumed before that endogenous production of palmitoleate is represented only by *cis*-palmitoleate. However, recent findings show that *trans*-palmitoleate also could be generated endogenously by the shortening of dietary vaccenic acid (18:1t11), with a conversion rate of 17% (24). Because dietary concentrations of palmitoleate are relatively low, and it is rapidly oxidized (15, 25), it is possible that palmitoleate plasma concentrations are affected by endogenous production from dietary vaccenic acid. Vaccenic acid is the most predominant ruminant *trans* FA, and its metabolic effects are either neutral or suggest protection against atherosclerosis and activation of PPARs (23, 26–29). Thus, because vaccenic acid is a precursor of *trans*-palmitoleate, the chance of increased metabolic benefits through dairy consumption arises.

Dietary Palmitoleate

Dietary sources with high palmitoleate content include salmon, cod liver oil, and macadamia oil (6%, 7%, and 17% or g/100 g total FAs, respectively). Currently, the highest reported concentration of palmitoleate in foods corresponds to the shrub sea buckthorn, which is native to Asia and Europe. The oil of its pulp contains palmitoleic acid at 32–42% (30, 31). Other natural sources of palmitoleate are olive oil, chocolate, and eggs.

trans-Palmitoleate can be found in partially hydrogenated oils, but it is principally derived from dairy and ruminant *trans* fats (32). In humans, serum *trans*-palmitoleate concentration ranges from 0.02% to 0.55% of total FAs (33), which means that <1% of FAs are represented by palmitoleate. *trans*-Palmitoleate plasma concentrations are positively correlated with self-reported consumption of whole-fat dairy, butter, margarine, and baked desserts (33). Thus, it has been considered to be a dairy fat biomarker. In a prospective cohort study in 3736 adults [the Cardiovascular Health Study (CHS)], circulating *trans*-palmitoleate concentrations correlated strongly with FA biomarkers of dairy fat intake, but weakly with markers of partially hydrogenated oils (33, 34), suggesting that *trans*-palmitoleate is found mainly in naturally occurring fats.

It has been shown that palmitoleic acid in plasma TG and cholesteryl ester is positively related to carbohydrate intake (35). It is known that carbohydrate intake increases SCD1 expression (36) and, therefore, a direct relation between dietary carbohydrate and palmitoleate concentrations was expected. Various other studies in humans also have exposed a direct association between carbohydrate intake and plasma palmitoleate, indicating upregulation of de novo lipogenesis (37–39). Because *cis*-palmitoleate is synthesized endogenously, diet components modifying SCD1 activity as carbohydrate necessarily change serum *cis*-palmitoleate concentrations, which range approximately from 0.19% to 0.5% of FAs (40). An intervention with distinct groups of carbohydrate content in the diet showed that highest carbohydrate consumption increases *cis*-palmitoleate 1.3 times (35). In addition to carbohydrate consumption, protein intake also was associated with plasma palmitoleate (34). Nevertheless, neither alanine nor arginine supplementation modified plasma or adipose tissue palmitoleic acid in rats (41). Natural sources of *cis*-palmitoleate as fish and macadamia oil could increase the blood concentration of this isoform (42, 43). For instance, a 1.3-fold increase in circulating palmitoleate was achieved in hypercholesterolemic men after they consumed macadamia nuts (43). Controversy exists in terms of serum palmitoleate modifications after fish oil intake because of its distribution in different lipids. The content of palmitoleate in lysophophatidic acid, phopsholipids, and other fractions results increased or decreased in different studies and species (44–46), with no general conclusions.

Thus, although the evidence shows that some dietary components modify palmitoleate concentrations, nutrient distribution and specific nutrients need to be investigated further in order to clarify whether diet and lifestyle changes induce metabolic improvements through palmitoleic acid. Palmitoleate sources and metabolism are summarized in **Figure 2**.

Where Is Palmitoleate Hidden?

Palmitoleate is a major constituent of human muscle, liver, and adipose tissue among miristic, palmitic, stearic, oleic,

[6] Abbreviations used: CHS, Cardiovascular Health Study; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SCD1, stearoyl-CoA desaturase 1.

and linoleic acids (47, 48). In humans, palmitoleic acid is site-specific. For example, the calf adipose depot contains more palmitoleic acid (6%) than the trapezius (3%), perirenal (4%), and mesenteric (4%) depots (49). Also, palmitoleate in subcutaneous adipose tissue in the upper arm and thigh is more abundant than in abdominal subcutaneous fat (50–55). Interestingly, the content of palmitoleic acid in adipose tissue decreases with age. Higher concentrations of palmitoleate are found in the adipose tissue of infants (>10%), lower concentrations are found in children, and the lowest are found in adults (3–7%) (47, 48, 56). Women tend to have more adipose palmitoleate than men, although the meaning of such sexual differences remains to be determined (57).

Serum palmitoleate correlates with human adipose tissue palmitoleate under fasting conditions (58). However, palmitoleate is relatively more abundant in adipose tissue than it is in serum. In animals, infusion of *cis*-palmitoleate increases the content of *cis*-palmitoleate in subcutaneous and mesenteric adipose tissue, longissimus and semitendinosus muscles, and the liver (59). This means that increasing circulating palmitoleate influences tissue abundance. FA composition in tissues has been evaluated extensively and, in many cases, dietary FAs influence its concentration in tissues. Accordingly, the content of palmitoleate in tissues is reflected by diet. In human skeletal muscle, a saturated fat–enriched diet increased palmitoleate phospholipids in comparison with a diet with a high proportion of MUFAs (60). An increase in palmitoleate concentration in white and brown adipose tissues was associated with ethanol consumption in rats (61). In the aorta of obese rats, treatment with vitamin E and selenium decreased the concentration of palmitoleate (62). The liver of rodents was more abundant in palmitoleate after supplementation with live *Lactobacillus rhamnosus* LA68 bacteria (63) and ubiquinone (64). Therefore, the presence of palmitoleate in distinct compartments partly depends on environmental stimuli that modify tissue and systemic concentrations.

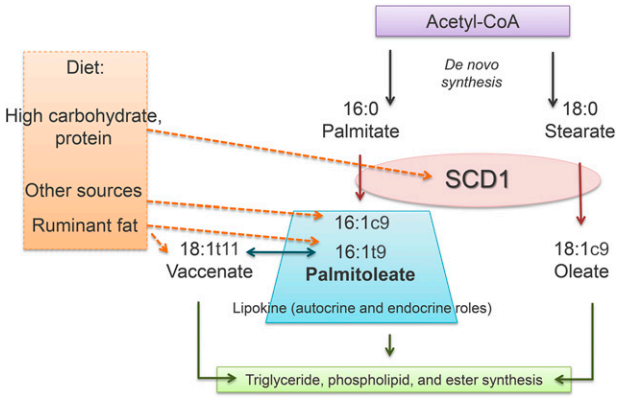

FIGURE 2 Palmitoleate metabolism. De novo lipogenesis leads to FA synthesis and desaturation via SCD1, with consequent production of 18:1c9 (oleate) and 16:1c9 (*cis*-palmitoleate). Dietary carbohydrate and protein increase SCD1 activity and the generation of both oleate and *cis*-palmitoleate. Natural sources of *cis*-palmitoleate include macadamia nuts and fish oil. Dietary sources of palmitoleate are represented mainly by ruminant fat, which contains 16:1t9 (*trans*-palmitoleate) and18:1t11 (vaccenate), a precursor of *trans*-palmitoleate. Palmitoleate, oleate, and vaccenate can be stored in adipose tissue as TGs, cholesteryl esters, or phospholipids. Moreover, palmitoleate is now considered to be a lipokine because of its bioactivity and effects in the liver and muscle. SCD1, stearoyl-CoA desaturase 1.

Is Palmitoleate a Lipokine?

With the use of a mouse model that lacks the adipose chaperones fatty acid–binding proteins (FABPs) 4 and 5, an increased activation of SCD1 and a consequent rise in palmitoleate concentration in adipose tissue were observed. Augmented palmitoleate concentration significantly reduced hepatosteatosis in one study, and promoted glucose transport in skeletal muscle (16). Because palmitoleate was released from adipose tissue and induced these metabolic effects on distant organs, it was referred to as a "lipokine." This study revealed that mobilization of bioactive lipids from adipose tissue regulates systemic metabolic homeostasis. Other works have confirmed that increased palmitoleate production influences metabolism in the absence of FABP and through activation of SCD1 (65, 66).

Because animal models are not always translated to humans, the verity of palmitoleic acid's behaving as a lipokine was questioned in the work of Gong et al. (67). The authors of this paper concluded that palmitoleate is associated with increased SCD1 activity and human obesity. Also, they stratified this association by carbohydrate intake as a way to disentagle liver-derived palmitoleate from adipose palmitoleate. High carbohydrate increases palmitoleate generation in adipose tissue, but decreases de novo lipogenesis in the liver, according to the animal model by Cao et al. (16). However, the connection of palmitoleate and obesity was attenuated when stratifying by carbohydrate consumption. Therefore, the association between adipose-specific palmitoleate and human obesity and lipogenesis was not confirmed in this study (67).

Recently, several works have examined palmitoleate release in humans, Relative release of palmitoleate was higher than that of other FAs, and its release from gluteofemoral adipose tissue was increased compared with that of abdominal adipose tissue, mainly because of greater tissue abundance (55, 57). If palmitoleate is readily mobilized from peripheral subcutaneous adipose tissue, then its role as a lipokine would be consistent with the insulin-sensitizing action of peripheral fat. Other roles of palmitoleate that suggest that it may be a lipokine are cardiac growth (68), endothelial function (69), inhibition of cell gap junction (70), β cell proliferation (71), prevention of endoplasmic reticulum stress (72), reduction of lipogenesis and FA desaturation in adipocytes (73), and suppression of cytokine production (16). The latest studies suggest that palmitoleate could attenuate inflammation in metabolically active tissues. Palmitoleate reverses proinflammatory gene expression in bone marrow cells and macrophage polarization through the activation of AMP-activated protein kinase (74).

Finally, the reasons why palmitoleate fulfills the requirements for being lipokine are explained as follows. Circulating

concentrations are changed in response to distinct metabolic states, concentrations in tissues and cells are low unless biosynthesis is initiated, and bioactivity is achieved at low concentrations. The possibility that palmitoleate may act in an autocrine or endocrine fashion has been proposed because endogenous and exogenous palmitoleate can be converted into phospholipids that contain palmitoleate (palmitoleoylphosphatidylinositol), and both palmitoleate and its phospholipids could be a modulating metabolism (75).

Palmitoleate in Health and Disease

Controversial results have been found with respect to the potential metabolic benefits of palmitoleate in humans. Plasma and adipose tissue concentrations of palmitoleate have been associated with an increased risk of obesity, dyslipidemia, and insulin resistance (34, 76–78). In addition, some studies have established an association between circulating and dietary palmitoleate and decreased diabetes incidence, lower cardiovascular disease risk, and inflammation status (33, 79, 80). However, mixed cardiovascular and insulin-sensitizing effects might be explained by sex, because greater insulin resistance was shown in men but not in women (34). Moreover, different ethnic groups, mean ages, and lifestyle confounders could have influenced metabolic outcomes, because some studies include only white men, mean ages range from 50 to 75 y, and results are not always adjusted for carbohydrate or energy intake. Laboratory techniques were also different between studies, which could lead to diverse FA concentrations. Finally, palmitoleate has been measured in phospholipids, cholesteryl esters, TGs, and nonesterified FAs with different interpretations of its metabolic action. For instance, the abundance of palmitoleate in cholesteryl esters was inversely associated with insulin sensitivity in one study (81), but plasma or VLDL palmitoleate was not different between insulin-resistant and insulin-sensitive individuals in another study (82). Although the concentration of the nonesterified FA palmitoleate in plasma is increased by adipose tissue release, which is consistent with its role as a lipokine, the measurement of the FFA in plasma or its esters in plasma or tissues should be considered and related to its metabolic effects. The role of palmitoleate as a lipokine and its association with metabolic diseases are summarized in **Figure 3**.

Obesity

Some studies have evaluated palmitoleate concentration in plasma or in tissues of obese compared with nonobese subjects. Results in children (77) and adults (78) showed significantly higher palmitoleate content in the plasma of the obese group. Also, a correlation was found between abdominal adiposity and palmitoleate abundance, which was consistent with increased SCD1 activity. Therefore, endogenous lipogenesis causing an increase in palmitoleate could be an important factor involved in the pathogenesis of obesity. In the Diet, Obesity, and Genes study group of subjects, an association between baseline content of palmitoleate and total weight loss was observed, i.e., the lower the initial percentage of palmitoleate, the greater was the weight loss (83). Comparing overweight and morbidly obese individuals, dietary and adipose tissue palmitoleate was higher in the overweight group (84). However, in the prospective cohort of the CHS, circulating *trans*-palmitoleate was associated with slightly lower BMI and waist circumference (33). These contrasting results may be due to the divergent adiposity in the groups of the latter studies. Apparently, obesity is associated with increased palmitoleate, which has been considered to be a negative predictor of weight loss. Therefore, the metabolic beneficial effects of palmitoleate could be lost during obesity despite increased circulating concentrations. This is frequently observed with some adipokines, which are exacerbated in obese conditions, but resistance to its actions has been associated with poor metabolic outcomes (85).

In young adults, a higher intake of palmitoleic acid for 1 d was inversely associated with gastric half-emptying time, which affects gastrointestinal transit and appetite (86). In male rats, administration of palmitoleic acid and a TG form of palmitoleate decreased food intake via increased concentrations of cholecystokinin, but independently of the PPAR-α pathway (87). Thus, it is possible that the short-term effects of exogenous palmitoleate include satiety, although this affirmation and the fact that obese subjects are resistant to its effects should be confirmed in future investigations.

Cardiovascular Disease

Epidemiologic studies suggest that circulating palmitoleate is involved in cholesterol metabolism and hemostasis, although net cardiovascular effects are not clear yet. In the CHS cohort, plasma phospholipid palmitoleate was associated with lower LDL cholesterol and fibrinogen and higher HDL cholesterol, but increased TGs (34, 78). Furthermore, palmitoleic acid has

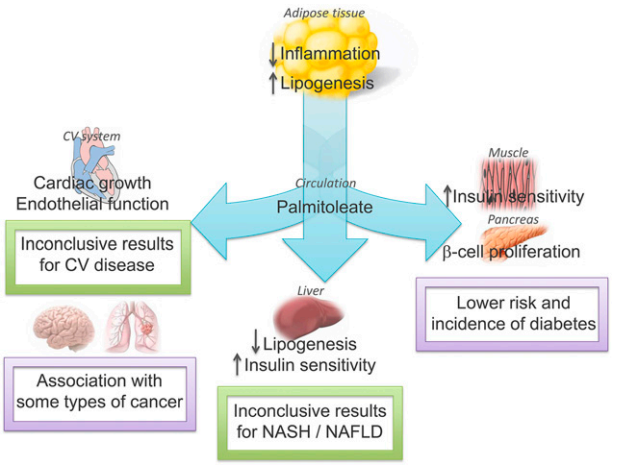

FIGURE 3 The autocrine and endocrine role of palmitoleate and its influence on metabolic diseases. Palmitoleate is produced in adipose tissue and exerts its lipokine actions in adipose tissue, the cardiovascular system, the liver, muscle, the pancreas, and other organs. These effects are associated with health or disease, or are as yet inconclusive with no connection to improvement in metabolic abnormalities. CV, cardiovascular; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ↓, decreased; ↑, increased.

been correlated with multiple cardiometabolic risk factors, including high blood pressure, total cholesterol, TGs, apoA-I, apoB, and endothelial dysfunction (69, 88). In a middle-aged and elderly Chinese population, the content of palmitoleate in erythrocytes correlated with higher retinol-binding protein 4, hypertriglyceridemia, reduced HDL cholesterol, and elevated blood pressure, and inversely correlated with adiponectin (89). In a group of healthy male physicians, *cis*-palmitoleate concentration in the membrane of erythrocytes was positively associated with coronary heart disease, whereas vaccenic acid in the same compartment was inversely related to coronary heart disease (90). However, FA concentration in red blood cells does not necessarily represent circulating or tissue concentrations in the short term, which would reflect its synthesis and its contribution to metabolism (91). Also, the effects of palmitoleate as a lipokine would be attained as free palmitoleate and not esterified or linked to the membrane of an organelle.

Supplementation with palmitoleate or enriched diets shows decreased plasma cholesterol and plasma TG concentrations (92, 93). When dyslipidemic subjects received capsules with 220.5 mg *cis*-palmitoleate for 30 d, there were significant reductions in C-reactive protein, TGs, and LDL cholesterol and a significant increase in HDL cholesterol (79). Also, the consumption of *trans*-palmitoleate from dairy was associated with lower amounts of inflammation, but mixed relations with serum lipids (19, 33). In various studies (42, 43, 92), but not all studies (93), the consumption of macadamia nuts (which contain high *cis*-palmitoleate concentrations) was related to favorable serum lipid profiles.

Overall, contrasting results in humans could be due to heterogeneous populations, which include healthy subjects and patients with pre-existing dyslipidemia. Apparently, healthy subjects have no metabolic advantages with increased circulating palmitoleate, whereas supplementation in dyslipidemic subjects could be a strategy for the improvement of the serum lipid profile, although further research is needed to support this statement.

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

The role of palmitoleate in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) is controversial. In animals, increased serum palmitoleate has been associated with reduced hepatosteatosis and adipokine expression (16), Also, dietary or orally administered palmitoleate decreased plasma cholesterol, atherogenic risk, and total lipids in the liver (94, 95). In KK-Ay mice (a model of obesity and type 2 diabetes), palmitoleate consumption reduced body weight, ameliorated development of hypertriglyceridemia, and decreased lipogenesis in the liver (96). Antidiabetic thiazolidinediones changed the liver lipid profile by increasing palmitoleate due to the upregulation of SCD1 in this tissue, which was related to the insulin-sensitizing effects of thiazolidinediones in mice (97). In human and mouse primary hepatocytes, palmitoleate was cytoprotective, preventing endoplasmic reticulum stress–induced apoptosis (72). However, other studies showed that hepatic steatosis was caused by palmitoleate in mice, even though liver inflammation was attenuated (17). In rats fed sucrose, which is typically associated with the development of NASH, palmitoleic acid was increased in the plasma and liver (98). In humans, plasma palmitoleate was found to be increased in patients with either NAFLD or NASH (99, 100).

Taken together, these results indicate that liver and serum concentrations of palmitoleate change inconsistently in NAFLD and NASH, possibly due to study design, i.e., dietary palmitoleate, supplementation, or endogenously produced, time of exposure, existing metabolic abnormalities, or different conclusions for distinct species.

Diabetes and Insulin Resistance

After results indicating that palmitoleate could be acting as a lipokine, several groups examined this FA in the context of insulin resistance and type 2 diabetes. A substantial decreased risk of diabetes in the CHS and Multi-Ethnic Study of Atherosclerosis was associated with increased serum *trans*-palmitoleate. Each 0.05% higher *trans*-palmitoleate concentration was related to a 32% and 28% lower risk of diabetes in the Multi-Ethnic Study of Atherosclerosis and the CHS, respectively (33). In a study that recruited 100 Caucasian subjects, circulating palmitoleate predicted insulin sensitivity, estimated by euglycemic–hyperinsulinemic clamp and oral glucose tolerance tests, independent of age, sex, and adiposity (80).

The abundance of palmitoleate in cholesteryl esters has been associated with insulin sensitivity in most studies (101, 102). For instance, palmitoleate in this same fraction was greater in women living in the Amazonian rain forest than in urbanized women, and less body fat and HOMA-IR also was found in the former group (81). Similarly, nonesterified palmitoleate was associated with lower HOMA-IR in healthy subjects (103). Relative release of palmitoleate was markedly higher from gluteofemoral adipose tissue than from abdominal subcutaneous adipose tissue (57). This implies that lower body adipose tissue is the major source of palmitoleate that serves as a lipokine (nonesterified form) and protects against metabolic disease risk. This is consistent with findings showing that central adiposity, but not peripheral fat, is related to metabolic abnormalities (1, 104). One work confirms that increased production of palmitoleate is associated with insulin sensitivity. Here, the authors concluded that rosiglitazone improved insulin sensitivity by increasing adipose SCD1 activity measured by the desaturation index 16:1/16:0, and that this process was dependent on PPAR-γ transcriptional activity (105).

Only 2 early investigations from the Uppsala Longitudinal Study of Adult Men associated adipose tissue palmitoleic acid with insulin resistance assessed by the clamp. In these studies, only elderly white men with a mean age of 71 were included, which limits external validity (81, 106).

In summary, palmitoleic acid has been associated with increased insulin sensitivity in most studies and consistently with lower incident diabetes in humans. Animal models have been useful to explore mechanisms by which palmitoleate induces insulin sensitivity. Palmitoleic acid from adipose tissue promotes insulin sensitivity in muscles and suppresses

the expression of monocyte chemoattractant protein 1 (MCP-1) and TNF-α in adipose tissue (16). Other studies corroborate the favorable effects of palmitoleic acid on insulin action (71, 107, 108) through translocation of glucose transporter 4 (GLUT-4) to the plasma membrane (109). Cellular studies found that palmitoleate induces β cell proliferation and secretory function (110, 111), regulates the expression and degradation of metabolic enzymes (16), and prevents endoplasmatic reticulum stress and apoptosis mediated by palmitate (65, 72). Thus, endogenously produced or dietary palmitoleate has been related to a reduced onset of diabetes; therefore, it could be a potential strategy for preventing this disease in humans.

Cancer

Palmitoleate concentrations have been found to be associated with some cancer types. In clinical studies, breast and prostate cancer risk and incidence were increased with augmented palmitoleate concentration in blood and tissues (51, 112–117). In addition, gallbladder carcinoma and brain tumors have been associated with increased palmitoleate content in erythrocyte membranes and membrane phospholipids of the tumors, respectively (118, 119). The proportion of palmitoleate in serum and variance of the SCD1 gene was associated with cancer mortality in Swedish men (120). In 3T3-L1 cells, SCD1 promotes cell survival through palmitoleate production (121). In cancer cells, inhibition of SCD1 blocks cell cycle progression, and this is reversed by palmitoleate, which is linked to cancer cell proliferation (122). Thus, mechanistically, SCD1-augmented activity and the consequent production of palmitoleate is apparently connected with cancer. It is plausible that the endogenous production of palmitoleate is the underlying cause of cell proliferation and survival in cancer progression. However, dietary palmitoleate and supplementation should be considered and investigated in order to rule out its possible association with cancer.

Conclusions

Palmitoleate is considered to be a lipokine, because it is released from adipose tissue and exerts its actions on distant organs. In humans, subcutaneous lower body fat releases significantly more palmitoleate than other fat depots linking beneficial effects of palmitoleate with fat distribution. Although its role in obesity development and its contribution to liver or cardiovascular health is not clear, decreased incident diabetes is certainly associated with higher palmitoleate concentrations. In animals, an improved lipid profile and increased insulin sensitivity are explained through increased transcriptional activity, improved insulin signaling, and modulation of enzymes and cytokines. The rationale of inconsistencies observed between animals and humans is unknown. However, free palmitoleate concentrations or its incorporation in phospholipids or TGs for metabolic actions or for storage possibly could explain different metabolic outcomes among species. Further research is needed to clarify the effects of palmitoleate in humans with distinct ethnicities, ages, and pre-existing diseases, and the molecular mechanisms that explain such effects. Clinical studies that reveal such information will help to resolve whether palmitoleate represents a valid strategy to prevent or treat diabetes, along with other metabolic abnormalities integrated in metabolic syndrome.

Acknowledgments

Both authors read and approved the final manuscript.

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