Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1753–1757

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Some biochemical studies on *trans* fatty acid-containing diet

Yasmin Ali Abd El-Aal [a,*], Doaa Mohamed Abdel-Fattah [b], Khalifa El-Dawy Ahmed [b]

[a] Biochemistry Department, Faculty of Applied Medical Science, October 6 University, Egypt
[b] Biochemistry Department, Faculty of Veterinary Medicine, Zagazig University, Egypt

ARTICLE INFO

Article history:
Received 4 March 2019
Accepted 14 March 2019

Keywords:
Trans fatty acid
Hydrogenation
Cancer

ABSTRACT

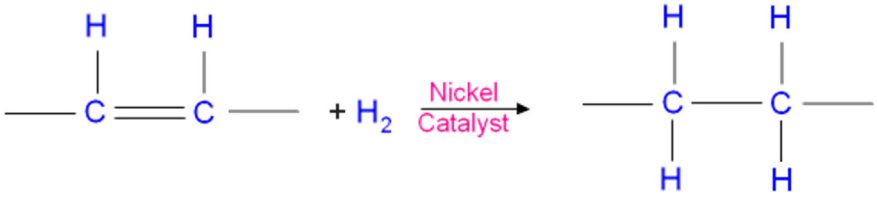
trans fatty acids (TFA's) are unsaturated fatty acid which have one or more double bond, they are present naturally and most of it is artificial, fried, baked food and margarine are major sources of TFA, there are several biological effects of TFAs on body health, various study showed that dietary TFA associated with various health disorders such as Diabetes, cardiovascular disease (CVD), Obesity, breast cancer, prostatic cancer infertility, and coronary artery disease (CAD). The World Health Organization (WHO) in 2015 encourages eliminations of *trans* fatty acids. The diet which related to non-communicable diseases include TFA should be eliminated, WHO's European Food and Nutrition Action Plan 2015–2020 suggested that TFAs should be less than 1% of the daily energy intake include natural origin. So the aim of this review, to know more than about *trans acids*, their nature, sources, and their different effect on health and how can analysis it.

1. Introduction

Trans fatty acids are unsaturated fatty acids maybe have one double bond like elaidic acid (18:1t9) which is the main *trans* unsaturated fatty acid found in partially hydrogenated vegetable oils (PHVOs) or more than one double bond like Rumenic acid(cis-9,trans-11C18:2) which is the major source of ruminant *trans* acids. The physical properties of *trans* acids are difficult than of cis fatty acids configuration. For example *trans* isomers having the higher melting points which made the *trans* acids valuable commercially and made it possible for shortening by hydrogenation of oils e.g soya bean oil, cottonseed oil to produce desirable properties [1].

2. Food sources of *trans* fatty acids

The major source of TFA are commercially produced in the diet by PHVO, because it is not expensive compared with other fats, and gave the food desirable characteristics, and shelf-life of the products. as French fries, fast food, and baked products prepared by PHVO. partially hydrogenated vegetable oils is a chemical process that made vegetable oils semisolid fats by adding hydrogen to liquid oil in the presence of the catalyst to make margarines. Liquid oils are unsaturated which will react with hydrogen in the presence of a catalyst which may be nickel or platinum at about 60 °C. Hydrogenation elevates the melting point above room temperature converting liquid oils to solid in a process called hardening.



While ruminant meats and dairy products participate a small amount of the dietary TFA approximately 2–6%. These natural TFA come from the normal process of bacterial metabolism of

* Corresponding author.
E-mail address: yasminkahk@gmail.com (Y. Ali Abd El-Aal).

https://doi.org/10.1016/j.dsx.2019.03.029
1871-4021/

Abbreviations

TFA	*trans* fatty acid
CVD	cardiovascular disease
CAD	coronary artery disease
WHO	World Health Organization
PHVOs	partially hydrogenated vegetable oils
USFA	unsaturated fatty acids
SFA	saturated fatty acids
FDA	Food and Drug Administration
LDL	Low density lipoprotein
HDL	High density lipoprotein
Lp(a)	lipoprotein (a)
PUFA	poly unsaturated fatty acid

polyunsaturated fatty acid in the rumen called biohydrogenation is a process in which the bacteria convert unsaturated fatty acids (USFA) to saturated fatty acids (SFA). However, some of the TFA intermediaries formed by biohydrogenation (Fig. 1). Linoleic and linolenic acids are the primary substrates for biohydrogenation. The major source in the ruminant fat of *trans* isomer is vaccenic acid (11*t*-18:1), while elaidic acids (9*t*-C18:1) and its isomer (10*t*-18:1) are the major TFA in PHVO. Also, a small portion of TFA found in pork and poultry fat [2–5].

3. Biological effects of TFA on body health*

The diet intake rich in TFA associated with various disorders such as CVD, breast cancer, prostate cancer, diabetes, obesity and others. The World Health Organization debate that the PHVO should be removed from the diet intake as it would come back with health benefits. After deciding that on June 2015 they were no longer 'generally recognized as safe' for involvement in human food, the United States Food and Drug Administration demanded food manufacturers eliminated them from products by June 2018 [6,7].

4. Cardiovascular disease

There are several published studies have shown an association of TFA with risks of CVD. The ratio of LDL cholesterol to HDL cholesterol increased by TFA. The World Health Organization and Agriculture Organization of the United Nations recommended that the amount of TFA should be less than 4% in human dietary fat. It is shown that industrial TFA associated with the enhanced risk of CVD while ruminant TFA not [8]. Jakobsen [9] suggested that ingestion of ruminant TFA is not linked with risk of CVD. For women but

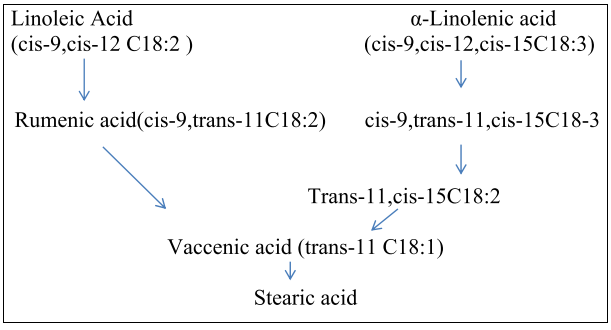


Fig. 1. Biohydrogenation of linoleic and α-linolenic acid in the rumen.

intake of TFA from animal origin should be low. In prospective cohort studies when the intake is below 2.5 g/d of a total, ruminant and industrial TFA no differences in the risk of CAD is reported [10].

5. Effect of TFA on lipid and lipoprotein metabolism

TFA which come from PHOs causing increase of serum total and LDL-cholesterol, the most unfavorable effect in comparison with carbohydrates and other fatty acids is the effect on the ratio of serum total cholesterol to HDL-cholesterol, on apoB, apoA1 concentration, LDL-and HDL-cholesterol, While they do not affect on serum triacylglycerol levels [11]. In several intervention studies lipoprotein (a) [Lp (a)] like LDL is associated with increased risk of CVD. TFA result from PHOs enhanced lipoprotein (a) concentrations [12–14] estimated that in women ruminant TFA increased HDL-cholesterol. For both genders were observed Increased in LDL-cholesterol and triacylglycerol concentrations when compared the effect of 5% of the energy of TFA from hydrogenated with the equal amount from ruminant TFA on lipoprotein metabolism. And no effects on LP (a) were recorded and no change in the serum total to HDL-cholesterol ratio. In another study [15] at two different levels (1.5% and 3.7% of energy) of ruminant TFA only healthy men and intake of 3.6% of energy from hydrogenated sources, It was found that adversely affected cholesterol metabolism from high intake (3.7% of energy) of TFA (ruminant and hydrogenated sources). But no effects were observed at the intake of 1.5% of energy from the ruminant.

6. Type 2 diabetes

Various studies about associations between TFA and Diabetes. One study suggested that there is no link between TFA and diabetes [16] while [17] found that TFA enhance the risk of type 2 diabetes, they estimated that the relative risk was 1.39 (1.15, 1.67; $P < 0.001$when 2% increase in energy from TFA. while the relative risk was 0.63(0.53, 0.76; $P < 0.0001$) from polyunsaturated fatty acid for a 5% increase in energy. Also, they found that 40% lower risk would result when replacing 2% of energy with PUFA. Another study investigates the link between plasma concentrations of the four master TFA isomers (elaidic acid, palmitelaidic acid, and vaccenic acid, linolelaidic acid) and diabetes. Especially elaidic acid even after controlling other risk factors were positively associated with diabetes in US adults. Total TFAs, elaidic acid, palmitelaidic acid, and vaccenic acid were positively associated with biomarkers of changing glucose metabolism in adults with no diabetes [18]. In mice, the diet rich in TFA induces insulin resistance [19] and causes in monkeys weight gain and insulin sensitivity impairment [20]. In US adults [21,22], suggested that *trans* palmitelaidic acid was associated with a lower risk of diabetes while another study reported that neither *trans*-palmitelaidic acid nor elaidic acid was significantly associated with diabetes [23]. Ruminant TFAs had less adverse effects than industrial TFAs was demonstrated by Refs. [24,25] in adults without diabetes were observed a positive and significant association between some plasma TFAs and fasting insulin, fasting glucose, and HbA1c. Identical findings were observed in the study of [26] in which insulin resistance was associated with serum elaidic acid concentration. Also [27], reported harmful effects of TFA intake on insulin sensitivity.

7. Coronary artery disease

The consumption of TFA associated with coronary artery disease. Different clinical investigations have revealed that. Which has been found in obese and cardiac patients in atherosclerotic lesions and adipose tissue [28] [29]. found that patients with CAD had

Triglyceride, ApoB and ApoB/ApoA1 ratio levels higher than in healthy patients while HDL-C and ApoA1 levels in CAD patients were lower. However, No significant differences in cholesterol and LDL-C were observed in healthy and patients. And in the case of CAD patients a high increase of TFA. In mice, the high diet of TFA increased plasma levels of triglyceride but on cholesterol and LDL-C plasma levels did not affect. And the causes of lack effect of LDL raising by TFA unclear [30,31]. The ApoB/ApoA1 ratio is more feature as an index of cardiovascular risk [32]. And in overweight and obesity, It is considered the best thing to predict CAD risk [33]. So in the prediction of CAD risk, Apo B/Apo A1 levels were better than LDL −C levels. The TFA especially elaidic acid and eicosanoic acid raise the LDL/HDL cholesterol ratio [34]. Which also noted in Ref. [29] and presumably, The risk of a CAD. Due to the increased risk of CAD, *trans* isomers of linoleic acid were major adversely linked with total mortality [35].

8. Obesity

A few studies have also been published about the association between TFA consumption and the risk of obesity and weight gain. Conflicting results have been reported from animal and cell studies under the effect of TFA on lipid oxidation, glucose and on body weight and composition. Of adipose tissue in vitro and ex vivo studies have found TFA to reduce lipid deposition and inhibit lipid synthesis. There are two studies measured hormones related to appetite and weight gain showed that lower leptin and higher adiponectin and resistin levels of animals which ate 20%TFA [36,37]. Rodent studies have been shown that in obese animals resistin levels increase and may be included in increase insulin resistance, but adiponectin is linked to improving weight and glycaemic control [38]. Even in the absence of caloric excess and very moderate gains in weight, the dietary TFA increases abdominal obesity and induces abnormalities in glucose metabolism [39].

9. Prostatic cancer

The potentially harmful effects of TFA on cancer risk is not well understood [40,41]. found that there is no association between dietary *trans* fatty acids and prostate cancer measured using food frequency questionnaire (FFQ) as a tool to measure TFA. However [42], suggest that specific TFA isomers (Trans-16:1, trans-18:1, trans-18:2 and total TFA) may increase the risk of advanced prostate cancer by (FFQ) [43]. found that elaidic acid (18:1t9) (trans, trans-18:2 n-6)(cis, trans 18:2n-6),(trans, cis-18:2n-6)TFA by whole blood increase risk in nonaggressive tumors [44]. found that serum phospholipids C18 *trans* fatty acids (vaccenic acid and 9-cis, 12-*trans*-18:2 TFA) were linked to increased prostate cancer risk, not C16 trans fatty acid [45]. suggested that sources of TFA might explain the discrepancy of results, for example, high levels of TFA intake from PHVOs cause increased risk of coronary heart disease not from those come from the ruminant source. Therefore, the source and type of TFA in the food intake may be important considerations as modifiers of health risk. In contrast, studies using an FFQ have not reported a positive association between TFA content and prostate cancer risk, But studies using adipose tissue biopsies and blood serum measurements of TFA have found a positive association. The most tools for cancer control is through cancer prevention programs is to modify dietary habits or nutritional components [46]. Numerous western countries have instituted laws that put assurance on the production of healthy foodstuffs like putting trans-fat content labels on food products, low trans-fat foods, Elimination of partially hydrogenated oils in foods etc [47].

10. Breast cancer

The effect of TFA on breast cancer development has been examined more extensively than other cancers. In postmenopausal women [48] examined that the relationship between the risk of breast cancer and specific TFA isomers in subcutaneous adipose tissue and proliferative benign breast disease. Although both elaidic acid and vaccenic acid were not associated with breast cancer. The trans-9-16:1 fatty acid isomer was significantly associated. Another study analyzed specific TFA isomers and found no association between breast cancer risk and adipose tissue TFA content [49]. Three of five studies that used adipose tissue for TFA exposure as a marker showed a positive relationship with breast cancer [50–52]. However [53,54], in US Nurses Health Study by FFQ from 1980 to 1994 without benign breast disease 44697 postmenopausal subjects reported that no signs of increased the risk of breast cancer from high intake of TFA, fat subtypes and total dietary fat [54].women who work in the human health field more healthier than who in the rest. Proposing that sample may have affected the results. Also [55], not found significant between TFA intake and breast cancer risk. Another FFQ study [56] found in subjects using hydrogenated fat cooking oils an developed risk for breast cancer. The Netherlands Cohort Study [57] found that a higher incidence of breast cancer with intake high levels of TFA (vaccenic acid) via FFQ. However [58], reported that the serum level of vaccenic acid was linked with a decrease in the risk of breast cancer, This discrepancy may be related to conjugated linolenic acid (CLA) formation because vaccenic acid is a precursor to CLA which has been having anticarcinogenic properties [59]. The enzyme which is responsible for the conversion of the vaccenic acid to CLA is D-9-desaturase, this conversion important as they reduce mammary carcinogenesis in rats [60,61]. Many different transcription factors are involved in this enzyme regulation [62,63]. Therefore, the decrease in the function of the D-9-desaturase enzyme will decrease the conversion of the vaccenic acid to the anticancer fatty acid, CLA. The conflicting findings suggest that numerous different factors including intake of polyunsaturated fatty acid (PUFA), hormonal balance, genetic predisposition and D-9-desaturase function which may play a role in change the effect of TFA on breast cancer development.

11. Potential mechanism of actions

The mechanism by that TFA could increase cancer risk is notestablished, However, The incorporation of TFA into the cell membrane phospholipids (PL) could be a possible candidate. Alteration in membrane composition may change the membrane associated function [64]. In the mice which fed TFA reported that a decrease in n-3 PUFA in the plasma membrane of adipose tissue [64]. This decrease associated with develop the risk of cancer and falling in membrane fluidity [64–66]. The decrease of membrane fluidity linked with an increase in the activity of free radicals in the phospholipid bilayer causing oxidative stress [67]. Also, TFA which incorporate into adipocyte and endothelial cell membranes may change membrane-bound receptors function and the signaling cascades linked with inflammatory pathways [68,69].

12. Infertility in women

Eating these unhealthy fats has been associated with an increased risk for several diseases lastly found that it is linked to increasing a woman's risk of infertility. Factors which known to increase insulin resistance as decreased physical activity and increased body weight, Found that associated with an increased risk of infertility due to ovulatory dysfunction [70,71]. Also, biomarkers such as high concentrations of glycated hemoglobin have

been reported linked to decreased fertility [72]. At the Harvard School of Public Health, the nutrition researchers reported that women who have ovulation-fertility problems eat more TFA than fertile women.73% the risk might be expected of ovulation-related infertility from each 2% increase of TFA intake [73,74] found that an increase in a fetal loss when intake TFA energy more than 4.7%. Also [75] reported that TFA might cause fetal development abnormalities. [76] first found no relation between TFA and birth weight and in the same year reported that TFA decreases birth weight.

References

[1] Hagemann JH, Tallent WH, Barve JA, Ismail IA, Gunstone FD. Polymorphism in single acid triglycerides of positional and geometric isomers of octadecenoic acid. J Am Oil Chem Soc 1975;52:204–7.
[2] Martin C, Milinsk M, Visentainer J, Matsushita M, de-Souza N. Trans fatty acid-forming processes in foods: a review. Anais Da Academia Brasileira De CiÃncias. 2007;79(2):343–50.
[3] Dijkstra AJ, Hamilton RJ, Hamm W. Trans fatty acids. Black well Publishing; 2008.
[4] Park Y. Conjugated linoleic acid (CLA): good or bad trans fat? J Food Compos Anal 2009;22:S4–12.
[5] Kodali DR. Trans fats replacement solutions. Illinois: AOCS Press Urbana; 2014.
[6] World Health Organization. Eliminating trans fats in Europe: a policy brief. http://www.euro.who.int/data/assets/pdf_file/0010/288442/Eliminating-trans-fats-in-Europe-A-policy-brief.pdf?ua=1; 2015. accessed April 2016).
[7] Food and Agriculture Organization of the United Nations. Fat and Oils in Human Nutrition, Report of a Joint Expert Consultation. Food and Agriculture Organization of the United Nations and the World Health Organizations, Rome.
[8] Funck LG, Barrera-Arellano D, Block JM. Conjugated linoleic acid (CLA) and its relationship with cardiovascular disease and associated risk factors. Arch Latinoam Nutr 2006;56(2):123–34.
[9] Jakobsen MU, Overvad K, Dyerberg J, Heitmann BL. Intake of ruminant trans fatty acids and risk of coronary heart disease. Int JEpidemiol 2008;37:173–82.
[10] Weggemans RM, Rudrum M, Trautwein. EA Intake of ruminant versus industrial trans fatty acids and risk of coronary heart disease — what is the evidence? Eur J Lipid Sci Technol 2004;106:390–7.
[11] Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;77:1146–55.
[12] Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary cis and trans fatty acids on serum lipoprotein[a] levels in humans. J Lipid Res 1992;33:1493–501.
[13] Nestel P, Noakes M, Belling B, McArthur R, Clifton P, Janus E, Abbey M. Plasma lipoprotein lipid and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. J Lipid Res 1992;33:1029–36.
[14] Chardigny JM, Destaillats F, Malpuech-Brugere C, Moulin J, Bauman DE. Lock, AL et a Do trans fatty acids from industrially produced sources and from natural sources have the same effect on cardiovascular disease risk factors in healthy subjects? Results of the Trans Fatty Acids Collaboration (TRANSFACT) study. Am J ClinNutr 2008;87:558–66.
[15] Motard-Belanger A, Charest A, Grenier G, Paquin P, Chouinard Y, Lemieux S, et al. Study of the effect of *trans* fatty acids from ruminants on blood lipids and other risk factors for cardiovascular disease. Am J Clin Nutr 2008;87:593–9.
[16] Papantoniou K, Fito M, Covas MI, Munoz D, Schroder H. Trans fatty acid consumption, lifestyle and type 2 diabetes prevalence in a Spanish population. Eur J Nutr 2010;49:357–64.
[17] Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–26.
[18] Liu Buyun, Sun Yangbo, Snetselaar Linda G, Sun Qi, Yang Quanhe, Zhang Zefeng, Liu Liegang, Frank B, Bao Wei. Association between plasma trans-fatty acid concentrations and diabetes in a nationally representative sample of US adults. J Diabetes 2018. https://doi.org/10.1111/1753-0407.12652.
[19] Zhao X, Shen C, Zhu H, et al. Trans-fatty acids aggravate obesity, insulin resistance and hepatic steatosis in C57BL/6 mice, possibly by suppressing the IRS1 dependent pathway. Molecules 2016;21:705.
[20] Kavanagh K, Jones KL, Sawyer J, et al. Trans fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. Obesity 2007;15:1675–84.
[21] Mozaffarian D, Cao H, King IB, et al. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: a cohort study. Ann Intern Med 2010;153:790–9.
[22] Mozaffarian D, de Oliveira Otto MC, Lemaitre RN, et al. Trans-palmitoleic acid, other dairy fat biomarkers, and incident diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr 2013;97:854–61.
[23] Takkunen MJ, Schwab US, de Mello VD, et al. Longitudinal associations of serum fatty acid composition with type 2 diabetes risk and markers of insulin secretion and sensitivity in the Finnish Diabetes Prevention Study. Eur J Nutr 2016;55:967–79.
[24] Tardy AL, Morio B, Chardigny JM, Malpuech- Brugere C. Ruminant and industrial sources of trans-fat and cardiovascular and diabetic diseases. Nutr Res Rev 2011;24:111–7.
[25] Liu Buyun, Sun Yangbo, Snetselaar Linda G, Sun Qi, Yang Quanhe, et al. Association between plasma trans-fatty acid concentrations and diabetes in a nationally representative sample of US adults. J Diabetes 2018. https://doi.org/10.1111/1753-0407.12652.
[26] Itcho K, Yoshii Y, Ohno H, et al. Association between serum elaidic acid concentration and insulin resistance in two Japanese cohorts with different lifestyles. J Atheroscler Thromb 2017;24:1206–14.
[27] Angelieri CT, Barros CR, Siqueira-Catania A, Ferreira SRG. Trans fatty acid intake is associated with insulin sensitivity but independently of inflammation. Braz J Med Biol Res 2012;45:625–31.
[28] Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H. High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults. J Nutr 2003;133:1186–91.
[29] Ahmed Samia Hadj, Kharroubi Wafa, Kaoubaa Nadia, Zarrouk Amira, Batbout Fathi, Gamra Habib, et al. Correlation of trans fatty acids with the severity of coronary artery disease lesions. Lipids Health Dis 2018;17:52.
[30] CassagnoN, Palos-Pinto A, Costet P, Breilh D, Darmon M, Berard AM. Low amounts of trans 18:1 fatty acid elevate plasma triacylglycerols but not cholesterol and alter the cellular defense to oxidative stress in mice. Br J Nutr 2005;94:346–52.
[31] Monguchi T, Hara T, Hosokawa M, Nakajima H, Mori K, Toh R, Irino Y, Ishida T, et al. Excessive intake of trans fatty acid accelerates atherosclerosis through promoting inflammation and oxidative stress in a mouse model of hyperlipidemia. J Cardiol 2017;70(2):121–7.
[32] Parish S, Peto R, Palmer A, Clarke R, Lewington S, Offer A, et al. For the international studies of infarct survival ISIS. Collaborator. The joint effects of apolipoprotein B, apolipoprotein A1, LDL cholesterol, and HDL cholesterol on risk: 3510 cases of acute myocardial infarction and 9805 controls. Eur Heart J 2009;30. 2137–46.
[33] Lu M, Lu Q, Zhang Y, Tian G. ApoB/apoA1 is an effective predictor of coronary heart disease risk in overweight and obesity. J Biomed Res 2011;254:266–73.
[34] Brouwer IA, Wanders AJ, Katan MB. Effect of animal and industrial trans fatty acids on HDL and LDL cholesterol levels in humans—a quantitative review. PLoS One 2010;5:e9434.
[35] Wang Q, Imamura F, Lemaitre RN, Rimm EB, Wang M, King IB, et al. Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: the cardiovascular health study. J Am Heart Assoc 2014;27:3–4.
[36] Huang Z, Wang B, Pace RD, Yoon S. Trans fat intake lowers total cholesterol and high-density lipoprotein cholesterol levels without changing the insulin sensitivity index in Wistar rats. Nutrients Res 2009;29:206–12.
[37] Koppe SWP, Elias M, Moseley RH, Green RM. Trans fat feeding results in higher serum alanine aminotransferase and increased insulin resistance compared with a standard murine high-fat diet. Am J Physiol Gastrointest Liver Physiol 2009;297:G378–84.
[38] Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, et al. Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension 2003;42:231–4.
[39] Kavanagh Kylie, Jones Kate L, Sawyer Janet, Kelley Kathryn, Jeffrey Carr J, Wagner Janice D, Rudel Lawrence L. Trans fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. Obesity 7 July 2007;15. 1675.
[40] Schuurman AG, van den Brandt PA, Dorant E, Brants HAM, Goldbohm RA. Association of energy and fat intake with prostate carcinoma risk. Cancer 1999;86:1019–27.
[41] Hodge AM, English DR, McCredie MR, et al. Foods, nutrients, and prostate cancer. Cancer Causes Control 2004;15:11–20.
[42] Liu X, Schumacher FR, Plummer SJ, et al. Trans-fatty acid intake and increased risk of advanced prostate cancer: modification by RNASEL R462Q variant. Carcinogenesis 2007;28:1232–6.
[43] Chavarro JE, Stampfer MJ, Campos H, et al. A prospective study of trans-fatty acid levels in blood and risk of prostate cancer. Cancer Epidemiol Biomark Prev 2008;17:95–101.
[44] King IB, et al. Erum trans-fatty acids are associated with risk of prostate cancer in beta-carotene and retinol efficacy trial. Cancer Epidemiol Biomark Prev 2005;14:988–92.
[45] Willett WC. Trans fatty acids and cardiovascular disease-epidemiological data. Atherosclerosis Suppl 2006;7:5–8.
[46] Cohen JT. FDA's proposed ban on trans fats: how do the costs and benefits stack up? Clin Ther 2014;36:322–7.
[47] Haven N, Tada L, War AW. Mutagens, carcinogens, and tumor promoters in our daily food. Can Fam Physician 1975:1970–84.
[48] London SJ, Sacks FM, Stampfer MJ, et al. Fatty acid composition of the subcutaneous adipose tissue and risk of proliferative benign breast disease and breast cancer. J Natl Cancer Inst 1993;85:785–93.
[49] Petrek JA, Hudgins LC, Levine B, et al. Breast cancer risk and fatty acids in the breast and abdominal adipose tissues. J Natl Cancer Inst 1994;86:53–6.
[50] Bakker N, Van't VP, Zock PL. Adipose fatty acids and cancers of the breast, prostate and colon: an ecological study. EURAMIC Study Group. Int J Cancer 1997;72:587–91.
[51] Kohlmeier L, Simonsen N, van't Veer P, et al. Adipose tissue trans fatty acids and breast cancer in the european community multicenter study on antioxidants, myocardial infarction, and breast cancer. Cancer Epidemiol Biomark

Prev 1997;6:705–10.
[52] Petrek JA, Hudgins LC, Ho M, et al. Fatty acid composition of adipose tissue, an indication of dietary fatty acids, and breast cancer prognosis. J Clin Oncol 1997;15:1377–84.
[53] Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. J Am Med Assoc 1999;281:914–20.
[54] Byrne C, Rockett H, Holmes MD. Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. Cancer EpidemiolBiomarkersPrev 2002;11:261–5.
[55] Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079–85.
[56] Wang J, John EM, Horn-Ross PL, et al. Dietary fat, cooking fat, and breast cancer risk in a multiethnic population. Nutr Canc 2008;60:492–504.
[57] Voorrips LE, Brants HAM, Kardinaal AFM, Hiddink GJ, van den Brandt PA. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: The Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002;76:873–82.
[58] Aro A, Mannisto S, Salminen I, Ovaskainen ML, Kataja V, Uusitupa M. Inverse association between dietary and serum conjugated linoleic acid and risk of breast cancer in post- menopausal women. Nutr Canc 2000;38:151–7. https://doi.org/10.1207/S15327914NC382_2. PMID:1152559.
[59] Pariza MW, Ha YL, Benjamin H, et al. Formation and action of anticarcinogenic fatty acids. Adv Exp Med Biol 1991;289:269–72.
[60] Lock AL, Corl BA, Barbano DM, et al. The anticarcinogenic effect of trans-11 18 : 1 is dependent on its conversion to cis-9, trans-11 CLA by D9-desaturase in rats. J Nutr 2004;134:2698–704.
[61] Turpeinen AM, Mutanen M, Aro A, et al. Bioconversion of vaccenic acid to conjugated linoleic acid in humans. Am J Clin Nutr 2002;76:504–10.
[62] Warensjo E, Ingelsson E, Lundmark P, et al. Polymorphisms in the SCD1 gene: associations with body fat distribution and insulin sensitivity. Obesity 2007;15:1732–40.
[63] Riserus U, Tan GD, Fielding BA, et al. Rosiglitazone increases indexes of stearoyl-CoA desaturase activity in humans: link to insulin sensitization and the role of dominant- negative mutation in peroxisome proliferator-activated receptor-g. Diabetes 2005;54:1379–84.
[64] Ma DW. Lipid mediators in membrane rafts are important determinants of human health and disease. Appl Physiol Nutr Metabol 2007;32:341–50.
[65] Ibrahim A, Natrajan S, Ghafoorunissa R. Dietary trans-fatty acids alter adipocyte plasma membrane fatty acid composition and insulin sensitivity in rats. Metabolism 2005;54:240–6. The American Journal of Clinical Nutrition 85231237.Retrieved from, http://ajcn.nutrition.org/content/85/1/231.long.
[66] Stillwell W, Shaikh SR, Zerouga M, et al. Docosahexaenoic acid affects cell signaling by altering lipid rafts. Reprod Nutr Dev 2005;45:559–79.
[67] Colomer R, Moreno-Nogueira JM, Garcia-Luna PP, et al. n-3 Fatty acids, cancer and cachexia: a systematic review of the literature. Br J Nutr 2007;97:823–31.
[68] Morrow JD, Awad JA, Boss HJ, et al. Non-cyclooxygenase- derived prostanoids (F2-isoprostanes) are formed in situ on phospholipids. Proc Natl Acad Sci U S A 1992;89:10721–5.
[69] Clandinin MT, Cheema S, Field CJ, et al. Dietary fat: exogenous determination of membrane structure and cell function. FASEB J 1991;5:2761–9.
[70] Kummerow FA, Zhou Q, Mahfouz MM. Effect of trans fatty acids on calcium influx into human arterial endothelial cells. Am J Clin Nutr 1999;70:832–8.
[71] Rich-Edwards JW, Goldman MB, Willett WC, et al. Adolescent body mass index and ovulatory infertility. Am J Obstet Gynecol 1994;171:171–7.
[72] Rich-Edwards JW, Spiegelman D, Garland M, et al. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology 2002;13:184–90.
[73] Hjollund NHI, Jensen TK, Bonde JPE, Henriksen NE, Andersson AM, Skakkebaek NE. Is glycosilated haemoglobin a marker of fertility? A follow-up study of first-pregnancy planners. Hum Reprod 1999;14:1478–82.
[74] Chavarro Jorge E, Rich-Edwards Janet W, Rosner Bernard A, Willett Walter C. Dietary fatty acid intakes and the risk of ovulatory infertility.2007. Am J Clin Nutr 2007;85:231–7. Printed in USA. © 2007 American Society for Nutrition.