Lipids in Health and Disease

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Omega-3 fatty acids coordinate glucose and lipid metabolism in diabetic patients

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Abstract

Omega 3 polyunsaturated fatty acids (n-3 PUFA) are known to have beneficial effects on cardiovascular and metabolic health. However, whether different sources of n-3 PUFA, for instance fatty fish vs vegetable oils, could elicit different effects on glucose and lipid metabolism, remains to be determined. Herein we examine recent findings showing that while a plant-based n-3 PUFA supplementation for six months can reduce fasting blood glucose, marine-based n-3 PUFA can instead reduce serum levels of triglycerides. We also discuss the potential molecular mechanisms that could underlie these different effects on the regulation of glycolipid metabolism.

Keywords: Fish oil, Omega-3 fatty acids, PUFA, T2DM, Vegetable oils

Introduction

Type 2 Diabetes Mellitus (T2DM) is commonly associated with dyslipidemia, leading to a higher risk of atherosclerosis and cardiovascular diseases [1, 2]. Hypertriglyceridemia represents an important risk factor for atherosclerosis, especially in diabetic patients [3]. Henceforth, nutraceutical supplementations might help reduce the risk of adverse events and/or improving the quality of life of these subjects [4], in combination with improved lifestyle habits and pharmacological intervention, to prevent/delay the onset of cardiovascular complications.

Hyperglycemia and hyperlipidemia are known to strongly impact the pathophysiology of coronary artery disease, also by driving endothelial dysfunction [3, 5–7]. Moreover, endothelial dysfunction remains among the main mechanisms underlying the onset of cardiovascular adverse events and outcomes in people with Type 1 Diabetes Mellitus (T1DM) or T2DM [7–12]. A dietary intervention with 500 g/week of fatty fish, equivalent to ~ 1 g/day of omega 3 polyunsaturated fatty acids (n-3 PUFA), like eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), have been shown to have a cardioprotective effect by inhibiting platelet-monocyte aggregation, and a higher dietary intake can also improve endothelial function [13].

Discussion

The potential different effects of diverse sources of n-3 PUFA (e.g. fish vs vegetable [14, 15]) on glycolipid metabolism have not been fully investigated. A known difference between vegetable and marine n-3 PUFA is the cholesterol lowering effect vs triglyceride lowering effect, respectively; nevertheless, whether vegetable n-3 PUFA may have an effect on blood glucose has not been established [15–18]. In an elegant double-blind clinical trial, Liu and colleagues evaluated the different effects of marine-derived and plant-derived omega-3 PUFA on the fatty acids of erythrocytes and glycolipid metabolism in patients with diabetes [19]. The study was conducted on 150 patients with a diagnosis of T2DM, of which 52 were randomly assigned to the fish oil group, 50 to the perilla oil group, and 48 to the linseed and fish oil group. All patients were followed up for six months.

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Intriguingly, while the supplementation with perilla oil (a vegetable oil rich in alpha-linolenic acid [20]) significantly decreased fasting blood glucose compared to baseline, fish oil supplementation prompted a marked reduction of serum triglycerides (TG) levels. Therefore, marine-based and plant-based n-3 PUFAs exhibited different effects on the regulation of glycolipid metabolism (Fig. 1). Intriguingly, the administration of all types of n-3 PUFA significantly reduced insulin and C-peptide concentrations compared to baseline. Similarly, serum total cholesterol, apolipoprotein A1, and IL-6 levels significantly decreased in all the treatment groups compared to baseline values (Fig. 1).

These findings are noteworthy inasmuch as the association of diabetes mellitus and dyslipidemia is known to significantly increase the risk of cardiovascular complications [1, 21, 22], particularly coronary artery disease [23, 24]. Furthermore, the diverse impact on glucose and lipid homeostasis shown by the different sources of n-3 PUFA might help explain numerous controversial results in studies examining the effects on n-3 PUFA consumption in people with T2DM [14, 15, 25–29].

The molecular mechanisms underlying the different effects of plant-based vs marine-based n-3 PUFAs are not explored by the Authors and deserve further dedicated investigation. Potential mechanisms include the existence of different receptors for n-3 PUFA, which could trigger different glucometabolic responses. For instance, G-protein coupled receptor 120 (GPR120) is a functional receptor for alpha-linolenic acid [30] expressed on endocrine L-cells lining the gut which has been shown to directly mediate PUFA-induced increases in glucagon like peptide-1 (GLP-1) [31]. Other receptors activated by free fatty acids include GPR40, mostly engaged by long chain fatty acids, GPR84 engaged by medium chain fatty acids, and GPR41 and GPR43, engaged by short chain fatty acids [32–34]. An action on pancreatic islets (direct or mediated by GLP-1 [35–37]), or on hepatic and adipose tissue, represent other, not mutually exclusive possibilities. Supporting the latter hypothesis, marine n-3 PUFA have been shown to lower plasma levels of proprotein convertase subtilisin kexin type 9 (PCSK9) [38]; since PCSK9 inhibitors are used as a medication to reduce hypercholesterolemia, this finding could have major implications for CVD treatment [7, 39, 40].

The study by Liu and collaborators is not exempt from limitations. For instance, the sample size was relatively small. Additionally, many patients had a high body mass index and the mean systolic blood pressure at baseline was above 140 mmHg in all three groups, suggesting that most of the patients in the study were hypertensive. These aspects imply that the findings should not be extended to normotensive and non-overweight patients. Some concerns on the blinding process are mentioned by the Authors ("the assessors who gathered the information and analysts were not fully blinded") but not

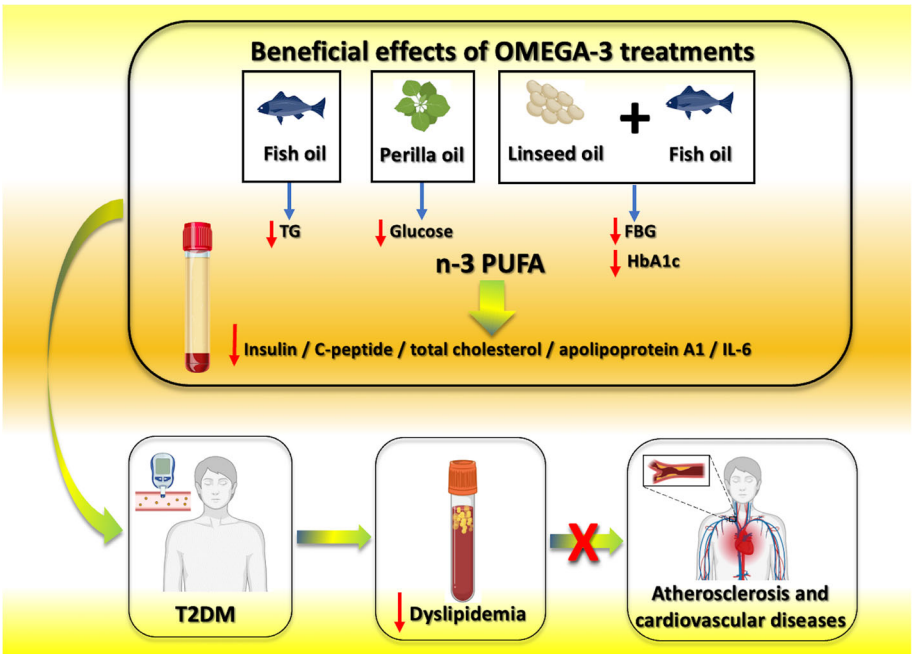

Fig. 1 Different effects of marine-derived and plant-derived n-3 PUFA on lipid and glucose metabolism in people with T2DM. FBG: fasting blood glucose; Hb1Ac: glycated hemoglobin; IL-6: interleukin-6; n-3 PUFA: long chain polyunsaturated fatty acids; T2DM: type 2 diabetes mellitus; TG: triglycerides. Some images have been created with biorender.com

better addressed. Therefore, further studies in larger populations, ideally not limited to T2DM patients, and with a longer follow-up are warranted. Nevertheless, the result of this clinical trial shed light on the importance of the source of n-3 PUFA in the evaluation of glucose and lipid metabolism.

Abbreviations

n-3 PUFA: Omega-3 polyunsaturated fatty acid; EPA: Eicosapentaenoic acid, 20:5n-3; DHA: Docosahexaenoic acid, 22:6n-3; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; TG: Triglycerides

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Authors' contributions

PM, SF, and GS evaluated the literature and drafted the manuscript. FV, UK, CI, and AL performed a literature search, analyzed the literature, and edited the manuscript; AdD and GS made the figure. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Kaze AD, Santhanam P, Musani SK, Ahima R, Echouffo-Tcheugui JB. Metabolic dyslipidemia and cardiovascular outcomes in type 2 diabetes mellitus: findings from the look AHEAD study. J Am Heart Assoc. 2021;10(7):e016947. https://doi.org/10.1161/JAHA.120.016947.
2. Jankauskas SS, Kansakar U, Varzideh F, Wilson S, Mone P, Lombardi A, et al. Heart failure in diabetes. Metabolism. 2021;154910:154910. https://doi.org/10.1016/j.metabol.2021.154910.
3. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Residual hypertriglyceridemia and estimated atherosclerotic cardiovascular disease risk by statin use in U.S. adults with diabetes: National Health and nutrition examination survey 2007-2014. Diabetes Care. 2019;42(12):2307–14. https://doi.org/10.2337/dc19-0501.
4. Giosue A, et al. Relations between the consumption of fatty or lean fish and risk of cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Adv Nutr. 2022. https://doi.org/10.1093/advances/nmac006.
5. Mone P, Gambardella J, Minicucci F, Lombardi A, Mauro C, Santulli G. Hyperglycemia drives stent restenosis in STEMI patients. Diabetes Care. 2021;44(11):e192–e3. https://doi.org/10.2337/dc21-0939.
6. Sawada T, et al. Effects of 6-month eicosapentaenoic acid treatment on postprandial hyperglycemia, hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded, prospective randomized controlled trial. Cardiovasc Diabetol. 2016;15(1):121.
7. Catry E, Bindels LB, Tailleux A, Lestavel S, Neyrinck AM, Goossens JF, et al. Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction. Gut. 2018;67(2):271–83. https://doi.org/10.1136/gutjnl-2016-313316.
8. Wilson S, Mone P, Kansakar U, Jankauskas SS, Donkor K, Adebayo A, et al. Diabetes and restenosis. Cardiovasc Diabetol. 2022;21(1):23. https://doi.org/10.1186/s12933-022-01460-5.
9. Mone P, et al. Cognitive Impairment in Frail Hypertensive Elderly Patients: Role of Hyperglycemia. Cells. 2021;10(8):2115.
10. Lespagnol E, et al. Early Endothelial Dysfunction in Type 1 Diabetes Is Accompanied by an Impairment of Vascular Smooth Muscle Function: A Meta-Analysis. Front Endocrinol (Lausanne). 2020;11:203.
11. Ladeia AM, Sampaio RR, Hita MC, Adan LF. Prognostic value of endothelial dysfunction in type 1 diabetes mellitus. World J Diabetes. 2014;5(5):601–5. https://doi.org/10.4239/wjd.v5.i5.601.
12. Bertoluci MC, Cé GV, da Silva AM, Wainstein MV, Boff W, Puñales M. Endothelial dysfunction as a predictor of cardiovascular disease in type 1 diabetes. World J Diabetes. 2015;6(5):679–92. https://doi.org/10.4239/wjd.v6.i5.679.
13. Din JN, Harding SA, Valerio CJ, Sarma J, Lyall K, Riemersma RA, et al. Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man. Atherosclerosis. 2008;197(1):290–6. https://doi.org/10.1016/j.atherosclerosis.2007.04.047.
14. Nguyen QV, et al. Enhancing Omega-3 Long-Chain Polyunsaturated Fatty Acid Content of Dairy-Derived Foods for Human Consumption. Nutrients. 2019;11(4).
15. Telle-Hansen VH, et al. Polyunsaturated Fatty Acids and Glycemic Control in Type 2 Diabetes. Nutrients. 2019;11(5).
16. Imamura F, Micha R, Wu JHY, de Oliveira Otto MC, Otite FO, Abioye AI, et al. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and Meta-analysis of randomised controlled feeding trials. PLoS Med. 2016;13(7):e1002087. https://doi.org/10.1371/journal.pmed.1002087.
17. Gaundal L, Myhrstad MCW, Leder L, Byfuglien MG, Gjøvaag T, Rud I, et al. Beneficial effect on serum cholesterol levels, but not glycaemic regulation, after replacing SFA with PUFA for 3 d: a randomised crossover trial. Br J Nutr. 2021;125(8):915–25. https://doi.org/10.1017/S0007114520003402.
18. Leslie MA, Cohen DJA, Liddle DM, Robinson LE, Ma DWL. A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. Lipids Health Dis. 2015;14(1):53. https://doi.org/10.1186/s12944-015-0049-7.
19. Liu H, Wang F, Liu X, Xie Y, Xia H, Wang S, et al. Effects of marine-derived and plant-derived omega-3 polyunsaturated fatty acids on erythrocyte fatty acid composition in type 2 diabetic patients. Lipids Health Dis. 2022;21(1):20. https://doi.org/10.1186/s12944-022-01630-0.
20. Kangwan N, et al. Perilla Seed Oil Alleviates Gut Dysbiosis, Intestinal Inflammation and Metabolic Disturbance in Obese-Insulin-Resistant Rats. Nutrients. 2021;13(9).
21. Gupta M, Tummala R, Ghosh RK, Blumenthal C, Philip K, Bandyopadhyay D, et al. An update on pharmacotherapies in diabetic dyslipidemia. Prog Cardiovasc Dis. 2019;62(4):334–41. https://doi.org/10.1016/j.pcad.2019.07.006.
22. Sokola-Wysoczanska E, et al. Polyunsaturated Fatty Acids and Their Potential Therapeutic Role in Cardiovascular System Disorders-A Review. Nutrients. 2018;10(10).
23. Schiele F, et al. Coronary artery disease: Risk stratification and patient selection for more aggressive secondary prevention. Eur J Prev Cardiol. 2017;24(3_suppl):88–100.
24. Jin JL, Cao YX, Zhang HW, Sun D, Hua Q, Li YF, et al. Lipoprotein(a) and cardiovascular outcomes in patients with coronary artery disease and prediabetes or diabetes. Diabetes Care. 2019;42(7):1312–8. https://doi.org/10.2337/dc19-0274.
25. Delpino FM, Figueiredo LM, da Silva BGC, da Silva TG, Mintem GC, Bielemann RM, et al. Omega-3 supplementation and diabetes: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2021:1–14. https://doi.org/10.1080/10408398.2021.1875977.
26. Khalili L, et al. Effect of n-3 (Omega-3) Polyunsaturated Fatty Acid Supplementation on Metabolic and Inflammatory Biomarkers and Body

Weight in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of RCTs. Metabolites. 2021;11(11).
27. Murru E, et al. Different Dietary N-3 Polyunsaturated Fatty Acid Formulations Distinctively Modify Tissue Fatty Acid and N-Acylethanolamine Profiles. Nutrients. 2021;13(2).
28. O'Mahoney LL, et al. Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: a meta-analysis and meta-regression of randomized controlled trials. Cardiovasc Diabetol. 2018;17(1):98. https://doi.org/10.1186/s12933-018-0740-x.
29. Griffo E, di Marino L, Patti L, Bozzetto L, Annuzzi G, Cipriano P, et al. Test meals rich in marine long-chain n-3 polyunsaturated fatty acids increase postprandial chylomicron response. Nutr Res. 2014;34(8):661–6. https://doi.org/10.1016/j.nutres.2014.07.005.
30. Paulsen SJ, Larsen LK, Hansen G, Chelur S, Larsen PJ, Vrang N. Expression of the fatty acid receptor GPR120 in the gut of diet-induced-obese rats and its role in GLP-1 secretion. PLoS One. 2014;9(2):e88227. https://doi.org/10.1371/journal.pone.0088227.
31. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat Med. 2005;11(1):90–4. https://doi.org/10.1038/nm1168.
32. Ookawara M, Matsuda K, Watanabe M, Moritoh Y. The GPR40 full agonist SCO-267 improves liver parameters in a mouse model of nonalcoholic fatty liver disease without affecting glucose or body weight. J Pharmacol Exp Ther. 2020;375(1):21–7. https://doi.org/10.1124/jpet.120.000046.
33. Kiepura A, et al. Anti-Atherosclerotic Potential of Free Fatty Acid Receptor 4 (FFAR4). Biomedicines. 2021;9(5).
34. Kim MH, et al. Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. Gastroenterology. 2013;145(2):396–406–e1–10.
35. Santulli G. Tirzepatide versus Semaglutide once weekly in type 2 diabetes. N Engl J Med. 2022;386(7):e17. https://doi.org/10.1056/NEJMc2114590.
36. Wei D, Li J, Shen M, Jia W, Chen N, Chen T, et al. Cellular production of n-3 PUFAs and reduction of n-6-to-n-3 ratios in the pancreatic beta-cells and islets enhance insulin secretion and confer protection against cytokine-induced cell death. Diabetes. 2010;59(2):471–8. https://doi.org/10.2337/db09-0284.
37. Matarese A, et al. miR-7 Regulates GLP-1-Mediated Insulin Release by Targeting beta-Arrestin 1. Cells. 2020;9(7):1621.
38. Graversen CB, Lundbye-Christensen S, Thomsen B, Christensen JH, Schmidt EB. Marine n-3 polyunsaturated fatty acids lower plasma proprotein convertase subtilisin kexin type 9 levels in pre- and postmenopausal women: a randomised study. Vasc Pharmacol. 2016;76:37–41. https://doi.org/10.1016/j.vph.2015.07.001.
39. Santulli G, Jankauskas SS, Gambardella J. Inclisiran: a new milestone on the PCSK9 road to tackle cardiovascular risk. Eur Heart J Cardiovasc Pharmacother. 2021;7(3):e11–e2. https://doi.org/10.1093/ehjcvp/pvab014.
40. Yu Z, Huang T, Zheng Y, Wang T, Heianza Y, Sun D, et al. PCSK9 variant, long-chain n-3 PUFAs, and risk of nonfatal myocardial infarction in Costa Rican Hispanics. Am J Clin Nutr. 2017;105(5):1198–203. https://doi.org/10.3945/ajcn.116.148106.

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