Ital J Gender-Specific Med 2021; 7(1): 54-57

Omega-3 fatty acids supplementation in type 2 diabetes: the lack of a sex/gender approach

Massimo D'Archivio, Claudio Giovannini, Roberta Masella

Center for Gender-Specific Medicine, Unit of Gender-Specific Prevention and Health, Italian National Institute of Health, Rome, Italy

Received 22 November 2019; accepted 26 March 2020

Summary. Many randomized controlled trials indicate that the supplementation with omega-3 polyunsaturated fatty acids (n-3 PUFA) in type 2 diabetes mellitus (T2D) patients can lower glucose levels, as well as positively affect cardiometabolic biomarkers. Unfortunately, many of these trials do not take in account sex/gender analysis. We carried out a search in PubMed, aimed at evaluating whether randomized controlled trials on n-3 PUFA supplements in T2D patients have been carried out while taking into account the sex/gender analysis. We showed that much work remains to be done to integrate the sex/gender analysis into trials, especially when a wider knowledge of the influence of sex/gender on specific metabolic responses could positively affect the effectiveness of the therapy or supplementation, such as in T2D patients.

Key words. Type 2 diabetes mellitus, omega-3 fatty acids, sex/gender differences.

Integrazione di acidi grassi omega-3 nel diabete di tipo 2: la mancanza di un approccio sesso/genere specifico

Riassunto. Molti studi randomizzati hanno evidenziato come la supplementazione con acidi grassi n-3 in pazienti con diabete di tipo 2 possa sia abbassare i livelli di glucosio sia influenzare positivamente i biomarcatori cardiometabolici. Purtroppo molti di questi studi non prendono in considerazione l'analisi sesso/genere specifica. Abbiamo effettuato una ricerca in PubMed, al fine di valutare se gli studi randomizzati sull'integrazione di acidi grassi n-3 in pazienti diabetici abbiano tenuto in considerazione l'analisi per sesso/genere. Abbiamo dimostrato come ci sia ancora molto lavoro da fare per integrare l'analisi sesso/genere negli studi clinici, soprattutto quando una conoscenza più ampia dell'influenza del sesso/genere su specifiche risposte metaboliche potrebbe influenzare positivamente l'efficacia della terapia o della supplementazione, come nei pazienti con diabete di tipo 2.

Parole chiave. Diabete mellito tipo 2, acidi grassi omega-3, differenze di sesso/genere

Type 2 diabetes mellitus (T2D) is a metabolic disorder characterized by elevated blood glucose levels in conditions of insulin resistance and insulin deficiency. It is a complex chronic disease, associated with the social, economic, and obesogenic environments of the industrialized Countries. The prevalence of T2D was estimated to be 8.8% of the world population in 2017, with a slightly higher prevalence among men than women (9.1% vs 8.4%).[1]

Many randomized controlled trials (RCTs) indicate that the supplementation with omega-3 polyunsaturated fatty acids (n-3 PUFA) in T2D patients can lower glucose levels, as well as positively affect the cardiometabolic biomarkers, including lipid parameters, inflammatory markers and blood pressure.[2-8] Systematic reviews and meta-analyses investigating the effects of n-3 PUFA in T2D patients established a positive impact of this treatment in lowering triglycerides and improving the inflammatory markers profile.[9,10] Conversely, some studies show that n-3 treatment does not improve these biomarkers in T2D,[11,12] and controversial results are reported on the effects on glycaemic homeostasis and cholesterol levels.[13-15] In addition, the very recent ASCEND study – probably the largest and longest placebo-controlled trial ever conducted on n-3 PUFA supplements in T2D patients[16] – established that there is no significant difference in the risk of serious vascular events between subjects receiving n-3 PUFA supplementation and those receiving placebo.

Clarifying these points should be of utmost importance, since cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in T2D patients.[17]

Unfortunately, the systematic reviews and meta-analyses which addressed this issue show several limits, due to the absence of a sex/gender analysis; this lack is a major bias, since many data suggest that T2D affects the risk of CVD in a differential way, according to sex. Indeed, while in the absence of diabetes the risk for CVD is generally lower in women compared to men, this kind of female 'advantage' seems to diminish or disappear in the presence of T2D.[18-21] Therefore, the integration of the sex/gender analysis into the experimental designs could improve our understanding of how sex affects health and diseases, thus interfering with the development of therapeutics.

We carried out a search in PubMed, aimed at evaluating whether RCTs on n-3 PUFA supplements in T2D patients have been carried out while taking into account the sex/gender analysis. The search was conducted in PubMed on October 28, 2019. The search syntax was 'type 2 diabetes', 'T2D', 'omega-3 fatty acids' and 'n-3

fatty acids', in the human species. Publication dates were considered from October 1, 2009, to October 28, 2019 (ten years). The flow chart of the study screening is showed in Figure; the number of studies included or excluded in each step is also mentioned.

The reasons for the exclusion based on the titles were: review articles; *in vitro*/*ex vivo* studies; letters to Editor; author's replies; type 1 diabetes patients; proposed study protocol. The reasons for the exclusion based on the abstracts were: non-clinical trial; participants not suffering from diabetes; n-3 fatty acids (FA) treatment missing; no relevant markers; language. The reasons for the exclusion based on the full texts were: gender differences not analysed in the results; participants not suffering from diabetes.

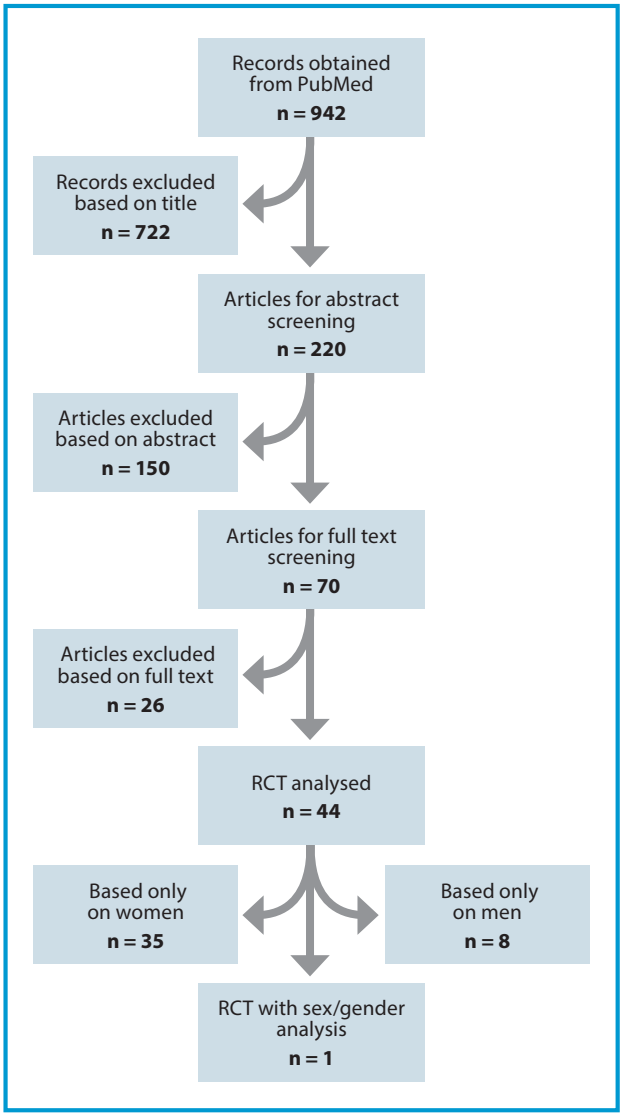
In total, 942 titles were found through our database search; of these 44 RCTs were eligible, and consequently their full text was analysed. Forty-three papers out of 44 studied only men or women; therefore, quite surprisingly, only one study took into account a gender analysis.[22] In that paper, Lyons et al. evaluated the impact of sex on the heart's metabolic and functional responses to different diabetes therapies, among which the FA treatment. The authors studied 78 T2D patients (43 women and 35 men), showing that different therapeutic regimens affect the myocardial metabolism and the diastolic function in a sex-specific manner. In particular, the subjects treated with metformin plus n-3 FA showed that the increase in the diastolic function was the result of an improvement in male patients only. The study provided strong evidence that sex effects should be considered an important factor in defining the optimal therapy for T2D patients.

We decided to better analyse the full text of the 43 studies assessing women (n = 35) and men (n = 8) independently. Thirteen out of the 43 studies (11 on women and 2 on men) met the inclusion criteria (RCTs on n-3 PUFA supplements in T2D patients). The results indicated that n-3 PUFA supplementation has no beneficial effects in men, either on the postprandial triglyceride-rich lipoprotein levels[23] or on the intestinal pro-inflammatory gene expression;[24] conversely, the results obtained were more convincing in women.

Brinton et al.[25] investigated 146 T2D women on stable statin therapy randomized to take EPA (4 g/day) or placebo for 12 weeks. EPA significantly reduced plasma triglycerides without increasing LDL, and lowered other potentially atherogenic parameters, such as non-HDL-C, VLDL-C, Apo B and Apo C-III. Importantly, the Authors stated that the safety and tolerability of EPA were generally similar to placebo. These findings suggest that EPA 4 g/day could be a potentially beneficial treatment for the reduction of the CVD risk in T2D female patients. Moreover, the Authors stated that the potential benefits of this treatment would be tested in 8,000 men and women at high CVD risk, on statin therapy, in an on-going interventional trial.

Other studies showed that a moderate DHA supplementation (400-600 mg/day) in T2D women had a beneficial effect on the platelet function and the oxidative stress associated with T2D,[26] and was effective in improving the red cell membrane lipid anomaly.[27]

Seven studies were designed to investigate the effects of omega-3 FA supplementation in women with gestational diabetes (GDM): all these studies showed a wide spectrum of beneficial effects. In particular, there was an improvement in insulin function, serum triglycerides levels and total antioxidant capacity, as well as an attenuation of the inflammatory markers.[28-33] Moreover, it was also shown that a daily supplementation with 600 mg DHA enhances the maternal, but not fetal, DHA status in GDM-complicated pregnancies. The ineffective-



Flow chart illustrating the study selection process conducted in PubMed.

ness of the supplement to improve the fetal status suggests that the transfer of DHA across the placenta may be impaired in GDM women.[34] Conversely, it should also be noted that an interventional study carried out on 42 T2D women only showed that n-3 PUFA supplementation did not affect body composition, insulin resistance, and lipaemia, suggesting that omega-3 PUFA supplements are not advisable.[35]

It is important to point out that other human studies reported differences between males and females in the response to PUFA treatment.[36] These findings might be due to a different n-3 metabolism or to an interaction among dietary nutrients,[37,38] as well as to a sex-driven modulation of gene-nutrient interactions.[39] Furthermore, other patho-physiological mechanisms could most likely be involved to explain the gender differences in the effects of omega-3 PUFA. This is still an up-and-coming field, and therefore little evidence is currently available.

The importance of integrating the sex/gender analysis in research studies is now well established: the most important funding agencies – including the European Commission and the US National Institutes of Health – signed a policy change concerning this issue. In addition, many peer-reviewed journals changed their editorial guidelines, evaluating the presence and the strength of the sex and gender analysis.[40] Sex/gender differences should be investigated in-depth, in order to allow a better development of therapies custom-tailored according to sex/gender. Much work remains to be done to systematically integrate the sex/gender analysis into clinical trials, especially when a wider knowledge of the influence of sex/gender on specific metabolic responses could positively affect the effectiveness of the therapy or supplementation, such as in T2D patients. Finally, further studies on the molecular mechanisms regulating the interactions among nutrients, sex and gene expression are needed.

In conclusion, our PubMed search suggests that the actual effectiveness of therapies and supplementation could be frequently unrecognized, when sex/gender differences in the metabolic responses are not taken into account.

References

1. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271-81.
2. Nomura S, Taniura T, Shouzu A, et al. Effects of sarpogrelate, eicosapentaenoic acid and pitavastatin on arterioslcerosis obliterans-related biomarkers in patients with type 2 diabetes (SAREPITASO study). Vasc Health Risk Manag. 2018;14:225-32.
3. Golzari MH, Javanbakht MH, Ghaedi E, Mohammadi H, Djalali M. Effect of eicosapentaenoic acid (Epa) supplementation on cardiovascular markers in patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Diabetes Metab Syndr. 2018;12:411-5.
4. Jacobo-Cejudo MG, Valdes-Ramos R, Guadarrama-Lopez AL, Pardo-Morales RV, Martinez-Carrillo BE, Harbige LS. Effect of n-3 polyunsaturated fatty acid supplementation on metabolic and inflammatory biomarkers in type 2 diabetes mellitus patients. Nutrients. 2017;9.
5. Liu K, Wang B, Zhou R, et al. Effect of combined use of a low-carbohydrate, high-protein diet with omega-3 polyunsaturated fatty acid supplementation on glycemic control in newly diagnosed type 2 diabetes: a randomized, double-blind, parallel-controlled trial. Am J Clin Nutr. 2018; 108:256-65.
6. Mazaherioun M, Djalali M, Koohdani F, et al. Beneficial effects of n-3 fatty acids on cardiometabolic and inflammatory markers in type 2 diabetes mellitus: a clinical trial. Med Princ Pract. 2017;26:535-41.
7. Toupchian O, Sotoudeh G, Mansoori A, et al. Effects of DHA-enriched fish oil on monocyte/macrophage activation marker sCD163, asymmetric dimethyl arginine, and insulin resistance in type 2 diabetic patients. J Clin Lipidol. 2016;10:798-807.
8. Zheng JS, Lin M, Fang L, et al. Effects of n-3 fatty acid supplements on glycemic traits in chinese type 2 diabetic patients: a double-blind randomized controlled trial. Mol Nutr Food Res. 2016;60:2176-84.
9. Farimani AR, Hariri M, Azimi-Nezhad M, Borji A, Zarei S, Hooshmand E. The effect of n-3 PUFAs on circulating adiponectin and leptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Acta diabetol. 2018;55:641-52.
10. Hartweg J, Farmer AJ, Holman RR, Neil A. Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes. Curr Opin Lipidol. 2009;20:30-8.
11. Siniarski A, Haberka M, Mostowik M, et al. Treatment with omega-3 polyunsaturated fatty acids does not improve endothelial function in patients with type 2 diabetes and very high cardiovascular risk: a randomized, double-blind, placebo-controlled study (Omega-FMD). Atherosclerosis. 2018;271:148-55.
12. Poreba M, Rostoff P, Siniarski A, et al. Relationship between polyunsaturated fatty acid composition in serum phospholipids, systemic low-grade inflammation, and glycemic control in patients with type 2 diabetes and atherosclerotic cardiovascular disease. Cardiovasc Diabetol. 2018;17:29.
13. Hartweg J, Farmer AJ, Perera R, Holman RR, Neil HA. Meta-analysis of the effects of n-3 polyunsaturated fatty acids on lipoproteins and other emerging lipid cardiovascular risk markers in patients with type 2 diabetes. Diabetologia. 2007;50:1593-602.
14. Chen C, Yu X, Shao S. Effects of omega-3 fatty acid supplementation on glucose control and lipid levels in type 2 diabetes: a meta-analysis. PloS One. 2015;10:e0139565.
15. O'Mahoney LL, Matu J, Price OJ, 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;17:98.
16. Group ASC, Bowman L, Mafham M, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med. 2018;379:1540-50.

17. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the Who multinational study of vascular disease in diabetes. Diabetologia. 2001;44(Suppl 2):S14-21.
18. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858.507 individuals and 28.203 coronary events. Diabetologia. 2014;57:1542-51.
19. Al-Salameh A, Chanson P, Bucher S, Ringa V, Becquemont L. Cardiovascular disease in type 2 diabetes: a review of sex-related differences in predisposition and prevention. Mayo Clin Proc. 2019;94:287-308.
20. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3:105-13.
21. Dong X, Cai R, Sun J, et al. Diabetes as a risk factor for acute coronary syndrome in women compared with men: a meta-analysis, including 10.856.279 individuals and 106.703 acute coronary syndrome events. Diabetes Metab Res Rev. 2017;33.
22. Lyons MR, Peterson LR, McGill JB, et al. Impact of sex on the heart's metabolic and functional responses to diabetic therapies. Am J Physiol Heart Circ Physiol. 2013;305: H1584-91.
23. Tremblay AJ, Lamarche B, Hogue JC, Couture P. n-3 polyunsaturated fatty acid supplementation has no effect on postprandial triglyceride-rich lipoprotein kinetics in men with type 2 diabetes. J Diabetes Res. 2016;2016:2909210.
24. Labonte ME, Couture P, Tremblay AJ, Hogue JC, Lemelin V, Lamarche B. Eicosapentaenoic and docosahexaenoic acid supplementation and inflammatory gene expression in the duodenum of obese patients with type 2 diabetes. Nutr J. 2013;12:98.
25. Brinton EA, Ballantyne CM, Guyton JR, et al. Lipid effects of icosapent ethyl in women with diabetes mellitus and persistent high triglycerides on statin treatment: ANCHOR trial subanalysis. J Womens Health. 2018;27:1170-6.
26. Vericel E, Colas R, Calzada C, et al. Moderate oral supplementation with docosahexaenoic acid improves platelet function and oxidative stress in type 2 diabetic patients. Thromb Haemost. 2015;114:289-96.
27. Min Y, Djahanbakhch O, Hutchinson J, et al. Effect of docosahexaenoic acid-enriched fish oil supplementation in pregnant women with type 2 diabetes on membrane fatty acids and fetal body composition-double-blinded randomized placebo-controlled trial. Diabet Med. 2014;31:1331-40.
28. Jamilian M, Samimi M, Mirhosseini N, et al. A randomized double-blinded, placebo-controlled trial investigating the effect of fish oil supplementation on gene expression related to insulin action, blood lipids, and inflammation in gestational diabetes mellitus-fish oil supplementation and gestational diabetes. Nutrients. 2018;10.
29. Jamilian M, Samimi M, Ebrahimi FA, et al. The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes. J Clin Lipidol. 2017;11:459-68.
30. Jamilian M, Hashemi Dizaji S, Bahmani F, et al. A randomized controlled clinical trial investigating the effects of omega-3 fatty acids and vitamin e co-supplementation on biomarkers of oxidative stress, inflammation and pregnancy outcomes in gestational diabetes. Can J Diabetes. 2017; 41:143-9.
31. Taghizadeh M, Jamilian M, Mazloomi M, Sanami M, Asemi Z. A randomized-controlled clinical trial investigating the effect of omega-3 fatty acids and vitamin E co-supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes. J Clin Lipidol. 2016;10:386-93.
32. Jamilian M, Samimi M, Kolahdooz F, Khalaji F, Razavi M, Asemi Z. Omega-3 fatty acid supplementation affects pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. J Matern Fetal Neonatal Med. 2016;29:669-75.
33. Samimi M, Jamilian M, Asemi Z, Esmaillzadeh A. Effects of omega-3 fatty acid supplementation on insulin metabolism and lipid profiles in gestational diabetes: randomized, double-blind, placebo-controlled trial. Clin Nutr. 2015;34:388-93.
34. Min Y, Djahanbakhch O, Hutchinson J, et al. Efficacy of docosahexaenoic acid-enriched formula to enhance maternal and fetal blood docosahexaenoic acid levels: randomized double-blinded placebo-controlled trial of pregnant women with gestational diabetes mellitus. Clin Nutr. 2016;35:608-14.
35. Crochemore IC, Souza AF, de Souza AC, Rosado EL. Omega-3 polyunsaturated fatty acid supplementation does not influence body composition, insulin resistance, and lipemia in women with type 2 diabetes and obesity. Nutr Clin Pract. 2012;27:553-60.
36. de Goede J, Verschuren WM, Boer JM, Kromhout D, Geleijnse JM. Gender-specific associations of marine n-3 fatty acids and fish consumption with 10-year incidence of stroke. PloS One. 2012;7:e33866.
37. Baker EJ, Miles EA, Burdge GC, Yaqoob P, Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res. 2016;64:30-56.
38. Jin H, Nicodemus-Johnson J. Gender and age stratified analyses of nutrient and dietary pattern associations with circulating lipid levels identify novel gender and age-specific correlations. Nutrients. 2018;10.
39. Coltell O, Sorli JV, Asensio EM, et al. Genome-wide association study for serum omega-3 and omega-6 polyunsaturated fatty acids: exploratory analysis of the sex-specific effects and dietary modulation in mediterranean subjects with metabolic syndrome. Nutrients. 2020;12.
40. Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger L. Sex and gender analysis improves science and engineering. Nature. 2019;575:137-46.

Author contribution statement: all Authors have contributed equally to this work and to submit the manuscript.

Conflict of interest: the Authors declare no conflicts of interest.

Correspondence to:
Massimo D'Archivio
Center for Gender-Specific Medicine
Italian National Institute of Health
Viale Regina Elena 299
00161 Rome, Italy
email: massimo.darchivio@iss.it