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Revisión

Safety in the hypertriglyceridemia treatment with n-3 polyunsaturated fatty acids on glucose metabolism in subjects with type 2 diabetes mellitus

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Abstract

Introduction: **Type 2 diabetes mellitus increases the risk of hypertriglyceridemia and is an independent risk factor for cardiovascular diseases. Current literature reveals the beneficial effects of n-3 polyunsaturated fatty acids (n-3 PUFA) in hypertriglyceridemia treatment, however the safety for type 2 diabetic subjects are still debatable. This literature review discusses the safety on glucose metabolism of n-3 PUFA supplementation in the treatment of hypertriglyceridemia in subjects with type 2 diabetes mellitus.**

Methods: **A literature review was conducted on EMBASE and MEDLINE database to investigate clinical trials published since 1990 until June 2014 that investigated the effects of dietary/supplementation n-3 PUFA intake in hypertriglyceridemia treatment in subjects with type 2 diabetes mellitus.**

Results and Discussion: **Fourteen clinical trials (n = 2,105) were included in this review. All trials reported a reduction in triglycerides levels between 12 - 34% in intra-group and 15 - 36% in between-groups analysis. Four trials showed a significant increase in LDL-c (6 - 18%) and another four in HDL-c levels (4 - 15%). No significant changes were found to total cholesterol, VLDL-c, fasting glucose, HbA1C, and insulin sensitivity index.**

Conclusions: **The n-3 PUFA supplementation leads an improvement on TG levels and did not result in any impairment on glucose metabolism in hypertriglyceridemic patients with type 2 diabetes mellitus being a safe option to treat the diabetic population.**

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Key words: *N-3 PUFA. Diabetes mellitus. Triglycerides. Lipid profile. Cardiovascular diseases.*

SEGURIDAD EN EL TRATAMIENTO DE LA HIPERTRIGLICERIDEMIA CON N-3 ÁCIDOS GRASOS POLIINSATURADOS EN EL METABOLISMO DE LA GLUCOSA EN PACIENTES CON DIABETES MELLITUS TIPO 2

Resumen

Introducción: **Diabetes mellitus tipo 2 aumenta el riesgo de hipertrigliceridemia y es un factor de riesgo independiente para las enfermedades cardiovasculares. La literatura actual revela efectos beneficiosos de n-3 ácidos grasos poliinsaturados (n-3 AGPI) en el tratamiento de la hipertrigliceridemia, sin embargo, la seguridad de este tratamento en los sujetos diabéticos tipo 2 es discutible. Esta revisión de la literatura discute la seguridad del n-3 PUFA la suplementación sobre el metabolismo de la glucosa en el tratamiento de la hipertrigliceridemia en pacientes con diabetes mellitus tipo 2.**

Métodos: **Se ha realizado una revisión de la literatura en la base de datos MEDLINE y EMBASE del los ensayos clínicos publicados con fecha posterior al 1990 hasta Junio de 2014 sobre los efectos de la ingesta / suplementos del n-3 AGPI en el tratamiento de la hipertrigliceridemia en pacientes con diabetes mellitus tipo 2.**

Resultados y Discusión: **Catorce estudios clínicos (n = 2105) se incluyeron en esta revisión. Del estudios informaron una reducción en los niveles de triglicéridos entre 12 a 34% en interior del grupo comparación y de 15 a 36% en entre grupos análisis. Cuatro estudios mostraron un aumento significativo en el LDL-c (6-18%) y otros cuatro en los niveles de HDL-c (4 - 15%). No se encontraron cambios significativos en el colesterol total, VLDL-c, la glucosa, HbA1c y el índice de sensibilidad a la insulina.**

Conclusión: **El n-3 AGPI suplementación lleva una mejora en los niveles de triglicéridos y no arrojaron deterioro en el metabolismo de la glucosa en pacientes con hipertrigliceridemia con diabetes mellitus tipo 2 siendo una opción segura para el tratamiento de la población diabética.**

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Palabras clave: *N-3 PUFA. Diabetes mellitus. Triglicéridos. Perfil de lípidos. Enfermedades cardiovasculares.*

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Abbreviations

CVD: Cardiovascular diseases.
DHA: Docosahexaenoic acid.
EPA: Eicosapentaenoic acid.
FPG: Fasting plasma glucose.
HbA1c: Glycated hemoglobin.
HDL-c: High-density lipoprotein cholesterol.
HOMA: Homeostasis model assessment.
IGT: Impairment glucose tolerance.
ISI: Insulin sensitivity index.
LDL-c: Low-density lipoprotein cholesterol.
n-3 PUFA: n-3 polyunsaturated fatty acids.
OGTT: Oral glucose tolerance test.
PUFA: Polyunsaturated fatty acid.
QUICKI: Quantitative insulin sensitivity check index.
T2DM: Type 2 diabetes mellitus.
TAG: Triglyceride.
TC: Total cholesterol.
VLDL-c: Very low-density lipoprotein cholesterol.

Introduction

Intake of n-3 polyunsaturated fatty acids (n-3 PUFA) has been shown to produce a favorable effect on many markers of the metabolic syndrome and decrease the risk of cardiovascular diseases (CVD). Increasing the consumption of n-3 PUFA promotes metabolic modulation of proinflammatory cytokines, prostaglandins and leukotriene generating substances with less inflammatory activity[1]. Furthermore n-3 PUFA is efficient to lower triglycerides levels, leading a reduction on cardiovascular risk diseases[2].

The increased occurrence of type 2 diabetes mellitus (T2DM) is followed by increased risk factors for CVD, dyslipidemia[3] and hypertriglyceridemia[4]. Evidence shows that high concentration of triglycerides (TG) is an independent risk factor for cardiovascular diseases[5,6]. In this context, nutritional interventions are a new strategy to reduce TG levels and help to prevent and treat dyslipidemia and CVD[7,8].

The triacylglycerol-lowering effect of n-3 PUFA supplementation is recognized in T2DM subjects[9-11], but the safety on the glucose metabolism is controversial[12]. Some research shows an increase in blood glucose levels, which would contradict its use by this population[13-16]. Furthermore, Wu et al. (2012), in a systematic review and meta-analysis (n = 481,489) shown that n-3 PUFA consumption (seafood and plant sources) are associated to 12% of increased risk of T2DM[17].

Therefore, the aim of this literature review is discuss the safety of n-3 PUFA supplementation on glucose metabolism in the treatment of hypertriglyceridemia in subjects with type 2 diabetes mellitus.

Methods

Data Sources

An extensive English and Spanish-language literature review was conducted to investigate recent clinical trials published between 1990 – June 2014 on the electronic database EMBASE and MEDLINE. The search and cross-referenced terms used were: omega 3, omega 3 fatty acids, n-3 polyunsaturated fatty acids, n-3 PUFA AND hypertriacylglycerolemia, hypertriglyceridemia, triglyceridemia, triacylglycerolmia, triacylglycerol, triglycerides AND diabetes, diabetes mellitus, and Type 2 diabetes mellitus; and their respective terms in Spanish. In order to broaden the search, additional trials were sought from the references cited in the selected trials.

Study selection

Were included clinical trials that investigated the effects of dietary / supplementation of n-3 PUFA in hypertriglyceridemia treatment in subjects with T2DM. The trials were accepted only with protocol design approved by a human ethics committee. The inclusion criteria were assessed by reading the summary and methodology of the trials.

Trials were discarded if they were deemed irrelevant to the review's objectives, duplicate publications, reported an inappropriate population type, did not report defined outcomes, used an alternative study design or were not published in the English and Spanish language.

Data synthesis

The following information were explored in each trial and were presented in this study: country and year of publication, study design, n–3 PUFAs treatment, sample size, statistical analyses, trial outcomes and proposed mechanisms discussed. When necessary, additional data were requested to the corresponding author. The following trial results were verified: the n-3 PUFA effects on triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c), high density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c) and insulin sensitivity index (ISI).

The data were synthesized by constructing descriptive summary and main results tables. The data shown in the results section were extracted from the results of the selected trials. A meta-analysis was not performed given the heterogeneity in the data due to the differences at studies design and variables: (i) follow-up period (2 weeks to 1 year); (ii) dose of the n-3 PUFA

per day (840mg to 10g); (iii) type of the treatment (n-3 PUFA, fish oil, Eicosapentaenoic acid – EPA + Docosahexaenoic acid – DHA); (iv) different methods to analyse the variables becoming unable to summarize the data of the trials.

Results

We identified 244 citations in the electronic search, of which 36 abstracts were relevant. From these abstracts included 14 clinical trials[18-31] were included in the review.

Characteristics of the studies

the trials analyzed are heterogeneous in the country, gender and age of the population, study design, sample size, follow-up period, type of the n-3 PUFA supplementation (EPA and DHA) and fish oil and linseeds oil).

A total of 14 trials included, three were from Italy and France, two from Australia, and one from Sweden, USA, Canada, Iran, Spain and Brazil. There were four randomized double-blind crossover clinical trial (high quality experimental design), six randomized double-blind clinical trial (good quality), one randomized single-blind clinical trial (low quality), and three clinical trials (poor quality). The trials ranged in duration from 2 weeks to one year. The individual trial sample size ranged from 8 to 935 and the ages between 21 and 80 years. A total of 2105 hypertriglyceridemic patients with T2DM were included in the 14 trials. The source of n-3 PUFA supplementation were isolated n-3 PUFA, fish oil, EPA or DHA, and the dosage ranged from 840mg of EPA plus DHA to 10g n-3 PUFA. The characteristics of these trials are summarized in table I.

Metabolic Implications

There was a reduction in TG levels range from 12 to 34% ($p<0.05$) between the initial and final values (intra-group), and from 15 to 36% ($p<0.05$) when placebo and intervention groups were compared (between-groups). Two trials reported non-significant effects on TG levels.[22,31] Concerning the total cholesterol levels, four trials reported improvement but just one shown a significant reduction of 4% ($p<0.05$).[23] Two trials that evaluated the VLDL-c levels showed significant reductions ranging from 26 to 36.0%.[18,19] Regarding to LDL-c all significative results showed an increase from 6 to 18%.[18-20,27] Twelve trials evaluated the effects of n-3 PUFA on the HDL-c levels, and it was observed a significant increase in intra and between-groups analysis (5 to 15%[27,30] and 4 to 7%[21,23], respectively).

Regarding the effects of n-3 PUFA on glucose metabolism the results are clear. Twelve trials evaluated the HbA1c levels and only Axelrod et al. (1994) reported a small significant increase of 0.72% compared with safflower oil ($p<0.05$).[20] Regarding to fasting plasma glucose, thirteen trials showed a non-significative modification on fasting plasma glucose after n-3 PUFA supplementation. Woodman et al. (2002) reported a significant increase of 12% and 19% after the consumption of the DHA and EPA treatment, respectively.[25] Seven trails assessed insulin sensitivity indices (euglycemic, hyperinsulinemic clamp, hyperglycemic clamp, homeostasis model assessment - HOMA, and quantitative insulin sensitivity check index – QUICKI) and no significant changes were observed. These results are described in table II.

Discussion

The literature data confirm the hypotriglyceridemic effect of the n-3 PUFA in subjects with T2DM, mainly in hypertriglyceridemic subjects. This effect is dose-dependent, but do not indicate the levels of optimal intake, the ideal source of n-3 PUFA supplementation (isolated n-3 PUFA, fish oil, EPA or DHA) and the duration of the intervention period. However, the data suggest that an intake of 3-4g n-3 PUFA per day can be effective in the reduction of TG levels without adverse effects[32]. Therefore, more randomized controlled trials are extremely important to evaluate the response to different sources and to define the optimal amount for safe and efficient supplementation.

Despite the benefits of n-3 PUFA consumption on hypertriglyceridemia treatment, the role of its effects on glucose metabolism (fasting glucose, HbA1C, and insulin sensitivity index) in T2DM subjects is controversy. While some old studies (before 1990) with high dose used (≥10g/day fish oil) have reported an unfavorable effect of n-3 PUFA on glucose metabolism[13-16] the recent studies (after 1990) using low doses (2 – 4g/day) have shown no deleterious effects (Table II).

The n-3 PUFA intake has many beneficial physiological effects, can reduce insulin response to oral glucose without altering the glycemic response in healthy humans[33]. Regarding T2DM people, Hartweg et al., (2008) reported in a review study (n = 1,075) that n-3 PUFA supplementation has no significant change in HbA1c, fasting glucose and fasting insulin[11]. Akintunde et al., (2011), in a meta-analysis study (n = 618) showed that n-3 PUFA intervention had no effects on insulin sensitivity compared to placebo in a T2DM subjects[34]. These results are consistent with our findings, but we have also identified more recent clinical trials.

The present review pools the results from 14 clinical trials of n-3 PUFA supplementation studying a total of 2,105 hypertriglyceridemic patients with T2DM. As the main results, n-3 PUFA supplementation had a statistically significant improvement on TG and VLDL

Table I
Characterization of the studies analyzed

Author, year	*Country*	*Study desing*	*N°*	*Gender*	*Age (y)*	*Treatment/day*	*Follow-up*
Annuzzi et al., 1991[18]	Italy	RCT double-blind crossover	8	M	45-57	10g n-3 PUFA	2x (2 wks)
Boberg et al., 1992[19]	Sweden	RCT double-blind crossover	14	M + F	55-75	3g n-3 PUFA	2x (8 wks)
Axelrod et al., 1994[20]	USA	RCT double-blind	18	M + F	21-65	2.5g n-3 PUFA	6wks
Sirtori et al., 1997[21]	Italy	RCT double-blind	868	M + F	45-80	(1.53g EPA + 1.05g DHA) and 2g n-3 PUFA	2 and 4 months
Goh et al., 1997[22]	Canada	RCT double-blind crossover	28	DNS	54-62	7-8g fish oil / linseed	3 months
Sirtori et al., 1998[23]	Italy	RCT double-blind	935	M + F	45-80	(1.53g EPA + 1.05g DHA) and 2g n-3 PUFA	6 and 6 months
Luo et al., 1998[24]	France	RCT double-blind crossover	12	M	49-60	6g fish oil	2 months
Woodman et al., 2002[25]	Australia	RCT double-blind	51	M + F	40-75	4g EPA and 4g DHA	6 wks
Ouguerram et al., 2006[26]	France	CT	5	DNS	36-65	6g fish oil	8 wks
Garg et al., 2007[27]	Australia	CT	13	M + F	DNS	1.3-1.4g n-3 PUFA	2 wks
Kabir et al., 2007[28]	France	RCT double-blind	26	F	40-60	3g Fish oil	2 months
Shidfar et al., 2008[29]	Iran	RCT double-blind	56	M + F	35-75	2g n-3 PUFA	10 wks
De Luis et al., 2009[30]	Spain	CT	30	M + F	42-72	465mg EPA and 375mg DHA	12 wks
Crochemore et al., 2012[31]	Brazil	RCT single-blind	41	F	DNS	1.5 g fish oil and 2.5 g fish oil	30 days

CT: Clinical trial; RCT: Randomized clinical trial; M: Male; F: Female; n-3 PUFA: n-3 polyunsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; DNS: Data not shown; Wks: Weeks.

Table II
Observed changes in lipid profile and glucose metabolism

Author, year	*TG*	*TC*	*VLDL-c*	*LDL-c*	*HDL-c*	*HbA1c*	*FPG*	*ISI*
Annuzzi et al., 1991[18]	↓16%§	N/C	↓26%§	↑18%§	NA	NA	↓5%ns	N/C
Boberg et al., 1992[19]	↓27%¥	N/C	↓36%§	↑6%§	↑8%ns	↑16%ns	↑6%ns	N/C
Axelrod et al., 1994[20]	↓29%§	↓8%ns	NA	↓8%ns	N/C	↑0.7%¥	N/C	NA
Sirtori et al., 1997[21]	↓21.5%¥	N/C	NA	↑6%§	↑4%§	N/C	N/C	NA
Goh et al., 1997[22]	↓15%ns	↓8%ns	NA	↓9%ns	↑16%ns	N/C	N/C	NA
Sirtori et al., 1998[23]	↓25.2%*	↓4%*	NA	N/C	↑7%§	N/C	N/C	NA
Luo et al., 1998[24]	↓27%*	N/C	NA	↑14%ns	N/C	N/C	N/C	N/C
Woodman et al., 2002[25]	↓19%§ ↓15%§	N/C N/C	NA NA	N/C N/C	N/C N/C	N/C N/C	↑19%§ ↑12%§	N/C N/C
Ouguerram et al., 2006[26]	↓24%*	N/C	NA	NA	NA	↓4%ns	↓6%ns	↓16%ns
Garg et al., 2007[27]	↓34%*	N/C	NA	↑10.5%*	↑5%*	↑4%ns	N/C	NA
Kabir et al., 2007[28]	↓12%*	N/C	NA	N/C	N/C	N/C	N/C	↑8%ns
Shidfar et al., 2008[29]	↓31.5%* ↓36%§	↓4%ns	NA	N/C	↓5%ns	N/C	N/C	NA
De Luis et al., 2009[30]	↓34%*	N/C	NA	N/C	↑15%*	NA	N/C	NA
Crochemore et al., 2012[31]	↓7%ns ↓20%ns	N/C N/C	NA NA	↑4%ns N/C	N/C ↑4%ns	N/C N/C	↑5%ns ↑7%ns	↓6%ns N/C

n-3 PUFA: n-3 polyunsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; TG: Triglycerides; TC: Total cholesterol; VLDL-c: Very low density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; HDL-c: High density lipoprotein cholesterol; HbA1c: Glycated hemoglobin A1c; FPG: fasting plasma glucose; ISI: insulin sensitivity index; ↑: Increase; ↓: Decrease; NA: Not analyzed; N/C: No change (< 3%, $p > 0.05$); §: $p < 0.05$ between-groups; ¥: $p < 0.01$ between-groups; *: $p < 0.05$ intra-group (pre vs post); ns: difference non-significant.

cholesterol and deleterious effect in LDL cholesterol. Furthermore, n-3 PUFA supplementation did not result in any statistically significant increase in HbA1c, fasting glucose and impairment on insulin sensitivity indices. The dietary supplementation with n-3 PUFA in hypertriglyceridemic T2DM patients leads to a reduction of TG without any side effect on glycemic control proving the safety of the n-3 PUFA treatment.

Conclusion

The n-3 PUFA supplementation leads an improvement on TG levels and did not result in any impairment on glucose metabolism markets (fasting glucose, HbA1C, and insulin sensitivity index) in hypertriglyceridemic patients with type 2 diabetes mellitus. These results show a safety use of n-3 PUFA in the hypertriglyceridemic treatment of T2DM population.

Further studies are needed to be able to clarify the action mechanisms of n-3 PUFA on glucose metabolism, verifying, especially in a long-term, if these hypotriglyceridemic treatment will affect the glycemic control.

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Author disclosure statement

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