UNIVERSIDADE DE BRASÍLIA

Faculdade de Ciências da Saúde (FS)

Programa de Pós-Graduação em Nutrição Humana

DISSERTAÇÃO DE MESTRADO

EFEITO DO CONSUMO DE ÁCIDOS GRAXOS N-3 NO PERFIL DE EICOSANOIDES DE INDIVÍDUOS COM OBESIDADE E SOBREPESO: REVISÃO SISTEMÁTICA E METANÁLISE

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Brasília, Dezembro de 2020

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Dissertação apresentada ao Programa de Pós-Graduação em Nutrição Humana da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito à obtenção do título de Mestre em Nutrição Humana.

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Dissertação aprovada como requisito para a obtenção de grau de Mestre em Nutrição, Programa de Pós-Graduação em Nutrição Humana da Faculdade de Ciências da Saúde da Universidade de Brasília.

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RESUMO

Introdução: Na obesidade, é comum a presença de inflamação crônica de baixo grau, caracterizada, em partes, pela alteração no perfil de eicosanoides, com aumento na síntese de suas variedades pró-inflamatórias. Os ácidos graxos poliinsaturados n-3 da dieta apresentam efeitos benéficos na redução do estado de inflamação crônica, exibindo um papel anti-inflamatório, o que pode auxiliar na manutenção da homeostase fisiológica na obesidade. O objetivo desta revisão sistemática foi avaliar o efeito da ingestão de ácidos graxos n-3 no perfil de eicosanóides séricos de pessoas adultas com obesidade e sobrepeso. **Metodologia**: A elaboração deste trabalho seguiu as diretrizes proposta pelo PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-analyses*). Foram analisados os artigos publicados até julho de 2020 em 7 bases de dados distintas, entre elas: PubMed, Scopus, Embase, Web of Science e Cochrane Library. Para a literatura cinzenta, utilizou-se as bases ProQuest e Google Acadêmico. Não foram aplicadas restrições em relação à data de publicação ou idioma de publicação. Os estudos foram selecionados de maneira independente por dois avaliadores, assim como a extração e análise dos dados. A avaliação do risco de viés seguiu os critérios estabelecidos pelo Joanna Briggs Institute. O efeito do consumo de ácido graxo n-3 na síntese das prostaglandinas foi estimado por Δ de Glass, tipo 1 em um modelo de efeito aleatório para a metanálise. **Resultados**: De um total de 2941 artigos selecionados na busca, 39 atendiam aos critérios de inclusão. Após a leitura completa dos artigos, 7 artigos foram incluídos ao final do processo de seleção. O consumo de ácidos graxos n-3 promoveu a redução nos níveis séricos da maioria dos eicosanoides pro-inflamatórios analisados em indivíduos com obesidade e/ou sobrepeso. No grupo das prostaglandinas pró-inflamatórias, foi encontrado redução significativa após o consumo de ácidos graxos n-3 (Glass' Δ-0.35; CI -0.62, -0.07, $i^2 = 31,48$). As análises de subgrupo mostraram maior efeito em períodos de consumo até 8 semanas (Glass' Δ-0.51; CI -0.76, -0.27) e doses superiores a 0.5 g de ácidos graxos n-3 (Glass' Δ -0.46; CI -0.72, -0.27). **Conclusão**: O consumo de ácidos graxos n-3 contribui na redução dos níveis séricos de eicosanoides pro-inflamatórios, além de reduzirem os níveis séricos de prostaglandinas pró-inflamatórias em indivíduos com obesidade e/ou sobrepeso.

Palavras-chave: Eicosanoides, inflamação, ácidos-graxos ômega-3, obesidade

ABSTRACT

Introduction: In the context of obesity, low-grade chronic inflammation is a common feature, partly characterized by a modification in eicosanoid profile, with an increase in pro-inflammatory varieties. Dietary long chain polyunsaturated omega-3 fatty acids show benefits in the chronic inflammatory state, exerting an anti-inflammatory effect, which can assist physiological homeostasis in obesity. The objective of the present systematic review is to evaluate the effect of omega-3 fatty acid intake in serum eicosanoid profile of adult individuals with obesity and/or overweight. **Methods**: The elaboration of the present study followed PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-analyses)*. Articles published in 7 different databases until July 2020 were analyzed. For indexed databases, PubMed, Scopus, Embase, Web of Science and Cochrane Library were selected. For grey literature, ProQuest and Google Scholar were chosen. No restrictions were applied in terms of publication date or language. Studies were selected independently by two reviewers, as well as data extraction and analysis. Risk of bias evaluation followed the criteria proposed by Joanna Briggs Institute. The effect of omega-3 fatty acid consumption over prostaglandin synthesis were estimated by Δ Glass type 1 in a random-effects model for the meta-analysis. **Results**: A total of 2941 articles were selected and 39 of them attended inclusion criteria. After complete reading of the remaining articles, 7 studies were included in the end of the selection process. The intake of omega-3 fatty acids promoted a reduction in serum levels of the majority of pro-inflammatory eicosanoids in individuals with obesity and/or overweight. A significant reduction was found in pro-inflammatory prostaglandins after omega-3 intake (Glass' Δ-0.35; CI -0.62, -0.07, $i^2 = 31,48$). Subgroup analysis showed greater effects in periods up to 8 weeks (Glass' Δ-0.51; CI -0.76, -0.27) and in doses higher than 0.5 g omega-3 fatty acids (Glass' Δ -0.46; CI -0.72, -0.27). **Conclusion**: Omega-3 fatty acid intake contributes to a reduction in serum levels of pro-inflammatory eicosanoids. It also reduces serum level of pro-inflammatory prostaglandins in individuals with obesity and/or overweight.

Key-words: Eicosanoids, Inflammation, omega-3 fatty acids, obesity.

LISTA DE FIGURAS

LISTA DE ABREVIATURAS E SIGLAS

15-LOX – 15-lipooxigenase

5-LOX – 5-Lipooxigenase

ALA – Alpha Linolenic Acid

ARA – Arachidonic Acid

COX-1 – Ciclooxigenase 1

COX-2 – Ciclooxigenase 2

DAMPs - Damage-Associated Molecular Patterns

DCVs – Doenças Cardiovasculares

DHA – Docosaexaenoic Acid

DMT2 e DM2 – Diabetes Mellitus Tipo 2

DPA – Docosapentaenoic Acid

EPA – Eicosapentaenoic Acid

FABP4 – Fatty Acid Binding Protein 4

HDL-c – High density lipoprotein cholesterol

HETEs – Hydroxyeicosatetraenoic Acids

HOMA1-IR – Homeostatic Model Assessment 1 – Insulin Resistance

IL-18 – Interleukin 18

IL-1β – Interleukin 1 beta

IL-1ra – Interleukin 1 beta receptor antagonist

IMC – Índice de Massa Corpórea

LDL-c – Low density lipoprotein cholesterol

LPS – Lipopolissacarídeo ou Lipopolissacharide

LTB4 – Leukotriene B4

MCP-1 – Monocyte Chemoattractive Protein 1

mRNA – messenger RNA

NALP3 - NACHT, LRR And PYD Domains-Containing Protein 3

NFk-B - Nuclear Factor Kappa B

NLRs - NOD-like Receptors

PCR-us – Proteína C Reativa ultra-sensível

PGE2 – Prostaglandin E2

PGF2 – Prostaglandin F2

PGI3 – Prostaglandin I3

PLA2 – Phospholipase A2

RhoA-Rock - Rho/Rho-Associated Coiled-Coil Containing Protein Kinase

SPMs – Specialized Pro-Resolvin Mediators

TLRs – Toll-like Receptors

TNF-alpha – Tumor Necrosis Factor Alpha

TXB2 – Thromboxane B2

SUMÁRIO

APRESENTAÇÃO DA DISSERTAÇÃO

Este trabalho consiste na dissertação de mestrado intitulada "***O efeito da ingestão de ácidos graxos n-3 no perfil de eicosanoides de indivíduos com obesidade e sobrepeso: revisão sistemática e meta-análise*****"** realizada pelo Programa de Pós-Graduação em Nutrição Humana da Universidade de Brasília (UnB). O trabalho divide-se da maneira apresentada a seguir:

1. Introdução, Revisão de Literatura, Objetivos e Metodologia
2. Artigo Científico
3. Considerações Finais **e** Materiais complementares

1.1. INTRODUÇÃO

A obesidade é descrita pelo acúmulo excessivo de gordura no organismo, capaz de perturbar o estado de saúde, tendo o seu diagnóstico realizado no momento que um indivíduo atinge um Índice de Massa Corpórea (IMC) igual ou superior a 30 kg/m². O sobrepeso, de maneira similar, também denota um aumento ponderal, em maior parte gerado pela expansão do tecido adiposo, entretanto, seu ponto de corte é o valor de 25 kg/m² (BLÜHER, 2019). Embora a causa principal envolvida na patogênese da obesidade seja o superávit calórico prolongado, a condição também pode ser atribuída a fatores ambientais, tais como sedentarismo, estresse mental, perturbações no ciclo circadiano e exposição a poluentes ambientais (GHOSH; BOUCHARD, 2017). Na perspectiva fisiológica, um dos componentes observados na obesidade é a presença de uma resposta inflamatória, processo gerenciado pelo sistema imune e utilizado como mecanismo de defesa e também como um importante regulador metabólico (SHOELSON; LEE; GOLDFINE, 2006). Entretanto, na obesidade, essa resposta inflamatória encontra-se cronicamente ativada por intermédio do excesso de tecido adiposo, revelando o termo amplamente conhecido na literatura científica como "inflamação crônica de baixo grau" (*low-grade chronic inflammation,* do inglês). A presença de um ambiente inflamatório está intimamente relacionada a uma série de doenças, tais como resistência insulínica, diabetes mellitus tipo 2, câncer e doenças cardiovasculares (ELLULU *et al.*, 2016).

Bioquimicamente, a resposta inflamatória é composta por uma ampla variedade de substâncias, que vão desde hormônios, citocinas e proteínas de fase aguda, até moléculas denominadas eicosanoides, convergindo para um propósito comum de interromper ou minimizar eventos nocivos ao organismo (TSOUPRAS; LORDAN; ZABETAKIS, 2018). Particularmente, eicosanoides são um grupo de substâncias compreendidas dentro do grupo dos autacoides e são originados por meio do processo de oxidação de ácidos graxos poli-insaturados de cadeia longa presentes nas membranas celulares, tais como o ácido araquidônico (AA) proveniente da família n-6, e os ácidos graxos da família n-3, EPA e DHA (ácido eicosapentaenoico e docosaexaenoico, respectivamente) (DE CATERINA; BASTA, 2001). Estes eicosanoides são comumente nomeados de acordo com sua origem, sejam eles provenientes de ácidos graxos n-9, n-6, ou mesmo de ácidos graxos n-3, e algumas classes tradicionalmente estudadas são leucotrienos, tromboxanos,

prostaglandinas, prostaciclinas, lipoxinas e ácidos hidroxieicosatetraenoicos (HETEs) (SOBERMAN; CHRISTMAS, 2003).

Em um ponto de convergência entre a resposta inflamatória e a geração de eicosanoides, é possível inserir o padrão dietético, em especial no que diz respeito ao consumo de gorduras. O padrão de consumo denominado Dieta Ocidental (*"Western Diet"*), predominante na sociedade moderna, é caracterizado por um alto consumo de gorduras saturadas e poli-insaturadas da série n-6, em detrimento a um baixo consumo de gorduras da série n-3, sendo esta característica intimamente ligada a um estado pro-inflamatório (CALDER, 2015b). Isso acontece porque a proporção entre ácidos graxos n-6:n-3 é capaz de determinar a composição de fosfolipídios da membrana celular e, consequentemente, modificar o perfil de eicosanoides secretados a partir destes ácidos graxos. Prostaglandinas, tromboxanos e leucotrienos de série par (PGE2, TXB2, LTB4, por exemplo) estão associadas a gênese e/ou manutenção de um ambiente inflamatório e, consequentemente, associados às doenças crônicas (SIMOPOULOS, Artemis P., 2008a; SIMOPOULOS, Artemis P, 2008c). Por outro lado, ácidos graxos n-3, em especial o EPA e o DHA possuem uma ação inflamatória menos potente e, até mesmo, ligeiramente anti-inflamatória e estão ligados a manutenção de um estado inflamatório fisiológico, e não patológico. Os mediadores eicosanoides desta classe são representados pelas prostaglandinas, tromboxanos e leucotrienos de série ímpar, em especial as séries 3 e 5 (CRUVINEL *et al.*, 2010; HEADLAND; NORLING, 2015). Sugere-se, desta forma, que um maior consumo de ácidos graxos n-3 poderia auxiliar na resolução do estado pró-inflamatório (SERHAN; SAVILL, 2005).

Pelos pontos citados nos parágrafos anteriores, torna-se importante contribuir para a consolidação das informações acerca do impacto do consumo de ácidos graxos da série n-3 no perfil de eicosanoides de pacientes com sobrepeso e/ou obesidade, uma vez que o aumento no consumo deste nutriente pode refletir na atenuação da resposta inflamatória e, consequentemente, reduzir a incidência de agravos de saúde comumente relacionados a obesidade.

1.2. REVISÃO DE LITERATURA

1.2.1. Obesidade e Inflamação

A epidemia global da obesidade está associada ao aumento no número de doenças crônicas, tais como esteatose hepática, esteatoepatite, câncer, asma, diabetes mellitus tipo 2 (DMT2), doenças neurodegenerativas e cardiovasculares (REILLY; SALTIEL, 2017). Atualmente, a ciência busca esclarecer os mecanismos que seriam capazes de justificar a ocorrência destes eventos de maneira conjunta. Estudos publicado nas últimas duas décadas sugerem a inflamação crônica de baixo grau como o fenômeno metabólico capaz de conectar cada uma destas condições com a obesidade propriamente dita (DAS, 2001; HOTAMISLIGIL, 2006; LUMENG; SALTIEL, 2011).

Muitos podem ser os gatilhos para o início da resposta inflamatória, desde poluentes ambientais, antígenos oriundos do intestino (a exemplo da molécula de lipopolissacarídeo, LPS), manifestações alérgicas, e até mesmo a morte de diferentes tipos celulares (HOTAMISLIGIL, 2006). No entanto, um importante gatilho a ser considerado é o consumo excessivo de calorias proveniente da dieta, o que resulta em estado hiper-anabólico, especialmente nas células adiposas. Este direcionamento ao ambiente anabólico induz a expansão dos estoques de ácidos graxos na forma de triglicerídeos, no interior dos adipócitos, que respondem por meio da secreção de moléculas sinalizantes, como as quimiocinas, dando início a resposta inflamatória adaptativa (ELLULU *et al.*, 2016; LUMENG; SALTIEL, 2011).

Em um primeiro momento, o processo de expansão adipocitária na obesidade é capaz de preservar o equilíbrio homeostático, mas com o prolongamento do superávit calórico e a contínua expansão dos estoques intracelulares de ácidos graxos, este equilíbrio apenas consegue ser mantido por meio do estabelecimento de novos padrões de secreção hormonal, glicose sanguínea, neurotransmissores e peso. A estes novos padrões, atribui-se a coexistência dos processos de resistência a ação da insulina, resistência a ação das catecolaminas, fibrose e remodelamento do tecido adiposo (REILLY; SALTIEL, 2017).

Acredita-se que este mesmo processo de expansão dos adipócitos está associado ao aumento da resposta inflamatória, por meio do fenômeno chamado de estresse mecânico. Este estresse é proveniente da expansão volumétrica do adipócito, uma vez que existe incorporação excessiva de triglicerídeos, fazendo com que exista uma interação entre adipócitos e células subjacentes da matriz extracelular. Os adipócitos são circundados por uma densa rede de glicoproteínas e colágeno que sofrem impacto direto da compressão gerada pela expansão adipocitária. Uma vez que isto ocorra, existe ativação do fator de transcrição *Nuclear Factor Kappa B* (NFk-B), molécula associada a expressão de citocinas e quimiocinas pro-inflamatórias. Esta ativação induz o recrutamento de células imunitárias, tais como neutrófilos e monócitos, e a polarização destas mesmas células para um fenótipo pró-inflamatório, como o que é classicamente observado na transição entre macrófagos do tipo M2 para o tipo M1 (HARA *et al.*, 2011; MCBEATH *et al.*, 2004).

Outro mecanismo que parece estar associado ao estado inflamatório gerado pela obesidade é o aumento na incidência de morte adipocitária, fenômeno presente em maior escala no tecido adiposo de indivíduos com obesidade (CINTI *et al.*, 2005). Adipócitos mortos, ou mesmo aqueles que estão prestes a morrer, são capazes de disparar sinais que contribuem para a dissipação da inflamação, tais como a atração de monócitos e a polarização de macrófagos para o fenótipo M1, como citado no parágrafo anterior. Esta conformação de células mortas e células imunitárias presentes no tecido adiposo é visto, histologicamente, como estruturas denominadas "*crown-like*", ou do português, "similares a coroa". Ademais, as substâncias liberadas por estes adipócitos são caracterizadas como padrões moleculares associados ao dano celular (do inglês, *damage-associated molecular patterns* – DAMPs), capazes de sensibilizar os receptores do tipo NOD (NLRs) e, consequentemente, ativar via do NALP3 inflamassoma, responsável pela síntese de algumas citocinas inflamatórias, tais como as interleucinas IL-1β e IL-18 (VANDANMAGSAR *et al.*, 2011).

Estudos que avaliaram a resposta inflamatória associada a perda de peso em indivíduos obesos, mostraram resultados significativos na redução de marcadores pró-inflamatórios como interleucina-6 (IL-6), Proteína C-Reativa (PCR) e Proteína Quimioatrativa de Monócitos (MCP-1) quando a magnitude da perda de peso alcançou valores entre 5 a 16% de perda de peso total

(JENSEN *et al.*, 2014; MAGKOS *et al.*, 2016). Estes resultados corroboram a ideia de que a obesidade se associa ao padrão pró-inflamatório descrito acima.

1.2.2. Obesidade e Perfil de eicosanoides

Ao considerar a inflamação do tecido adiposo e todas as moléculas envolvidas neste processo, é necessário enfatizar a síntese dos eicosanoides, lipídios bioativos responsáveis por uma importante rede de sinalização, não só no tecido adiposo, mas em todo o organismo. Os eicosanoides são originados, principalmente, por meio de uma ação enzimática coordenada pelas enzimas ciclooxigenase (COX-1 e COX-2), lipooxigenase (5-LOX e 15-LOX) e epoxigenases (Cytocromo P450) que usam como substrato os ácidos graxos poli-insaturados, em especial o ácido araquidônico (ARA), o ácido eicosapentaenoico (EPA) e o ácido docosaexaenoico (DHA) (SAINI; KEUM, 2018). De acordo com a família de ácido graxo metabolizado, sejam eles ácidos graxos n-3 (EPA e DHA) ou n-6 (ARA), um diferente arranjo de eicosanoides será originado. Para a primeira família, haverá predominância na formação de prostaglandinas e leucotrienos de série ímpar, processo auxiliado pela ação COX-2 e 5-LOX, respectivamente. Já para a família n-6, a formação de eicosanoides de série par ocorrerá mediante ação das enzimas das mesmas enzimas citadas anteriormente. Em adição a isso, algumas enzimas da família Citocromo P450, epoxigenase e epoxido hidrolase, conseguem originar ácidos epoxieicosatrienoicos (SCHMITZ; ECKER, 2008).

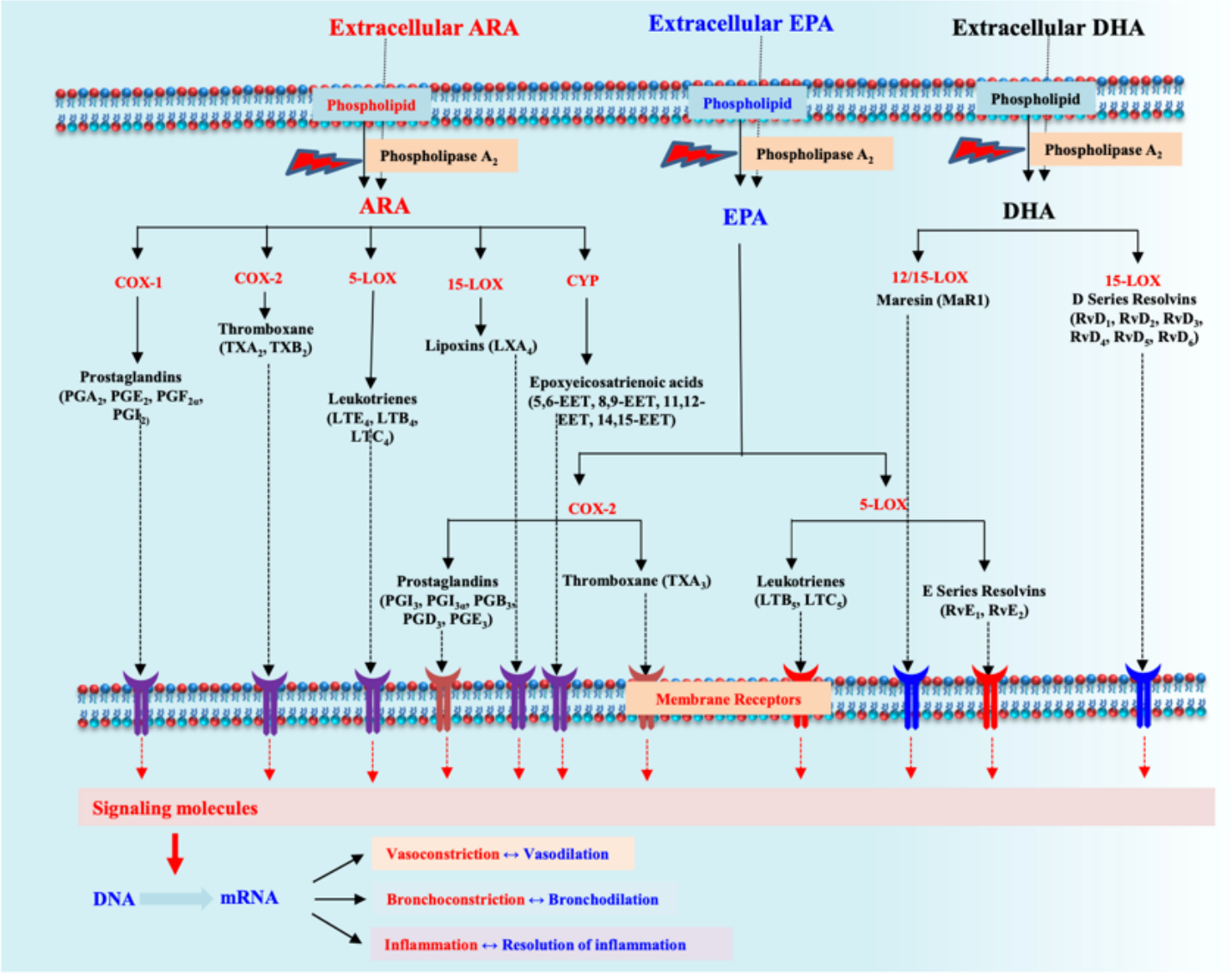

Figura 1. Ácidos graxos e subprodutos eicosanoides (Saini, 2018).

A formação de eicosanoides é importante, não somente no contexto imunológico, enquanto reguladores da inflamação, mas também no contexto metabólico, enquanto reguladores de distintos processos fisiológicos, como regulação da função renal (IMIG, 2015), da pressão arterial (IMIG, 2010), e até mesmo defesa contra microorganismos (WAN *et al.*, 2014). Entretanto, quando sintetizados em excesso, eicosanoides são capazes de gerar desequilíbrio na resposta inflamatória, estando associados a fisiopatologia da aterosclerose, trombose, câncer e asma (ARAÚJO; WHEELOCK; HAEGGSTRÖM, 2018).

Alguns trabalhos em modelos animais são capazes de estabelecer conexão entre a expansão do tecido adiposo e ação dos eicosanoides. Um dos principais representantes da classe das prostaglandinas, a Prostaglandina E2 (PGE2), tem sido mencionada como elemento importante no recrutamento de células do sistema imune para o tecido adiposo, bem como no processo de diferenciação de macrófagos M1, características marcantes no processo inflamatório deflagrado pela obesidade (ARAÚJO; WHEELOCK; HAEGGSTRÖM, 2018). Na classe dos leucotrienos, o Leucotrieno B4 (LTB4) parece ter grande associação com a inflamação do tecido adiposo, sendo capaz de ativar o NF-kB e aumentar a produção de IL-6, TNF-alfa e MCP-1 em culturas de adipócitos de camundongos obesos (HORRILLO *et al.*, 2010). Li e colaboradores mostraram o papel do LTB4 na promoção de resistência insulínica no tecido muscular e adiposo, e no acúmulo de gordura hepática em camundongos obesos, corroborando seu papel na indução do ambiente inflamatório encontrado na obesidade (LI *et al.*, 2015).

Estudos em humanos são mais escassos, porém apresentam resultados que corroboram com os dados apresentados em modelos experimentais. Baek e colaboradores submeteram um total de 86 crianças asmáticas ao exercício físico e mensuraram, entre outros parâmetros, os níveis de LTB4 e PGF2 urinários. Seus achados revelaram que os níveis destes eicosanoides pro-inflamatórios em crianças asmáticas e obesas eram superiores aos seus níveis em crianças asmáticas não-obesas, inclusive após a realização do exercício (BAEK *et al.*, 2013). Em indivíduos adultos com obesidade os níveis de LTB4 urinários foram associados a circunferência de cintura aumentada, um clássico marcador antropométrico de obesidade (BÄCK *et al.*, 2014). García-Alonso e colaboradores compararam amostras de tecido adiposo de indivíduos eutróficos e saudáveis, encontrando maiores níveis de PGE2 e 6-Keto prostaglandina F1 alfa (6-Keto-PGF1

alfa) em obesos quando comparado aos eutróficos. Como análise adicional, avaliou-se a expressão de mRNA da enzima COX-2 entre os dois grupos de participantes, com resultados propondo maior atividade da enzima em pacientes obesos. Tal fato é congruente com o aumento na produção de prostaglandinas pró-inflamatórias, embora estudos mais robustos precisem ser realizados acerca deste tema (GARCÍA-ALONSO *et al.*, 2016).

Alterações nos níveis de eicosanoides observados na obesidade se correlacionam com comorbidades e agravos de saúde encontrados em pacientes com excesso de peso, a exemplo de aterosclerose, esteatose hepática não alcoólica e diabetes tipo 2 (ARAUJO *et al.*, 2018). Os principais, mas não exclusivos, eicosanoides envolvidos no processo são elencados na imagem abaixo, de acordo com suas respectivas condições metabólicas.

	COX	LOX	CYP
Obesidade/DM2	↑ PGE2	↑ 12-HETE, 15-HETE	↑ 20-HETE
DCV	↑ PGE2 PGE2 – TXA2 (desequilíbrio)	↑ Cys-LTs, LTB4	20-HETE, EEts (desequilíbrio)
Esteatose Hepática	↑ PGD2, LXA2 ↑ PGE2	↑ 5-HETE, 15-HETE	↑ 8,9-DHET ↑ 11, 12-DHET

Figura 2. Alterações nos níveis de eicosanoides em diferentes condições metabólicas. Adaptado de Araújo, 2018.

1.2.3. O papel dos ácidos graxos ômega-3 e 6 na inflamação e no perfil de eicosanoides

Diversos tipos de lipídios dietéticos são relevantes e podem contribuir para o processo pró-inflamatório existente na obesidade. Um mecanismo clássico que já vem sendo elucidado é a ligação de alguns ácidos graxos, em especial os ácidos graxos saturados e os *trans*, com os receptores do tipo Toll-Like (TLRs), a exemplo dos TLR4 e TLR2. Ao efetivar esta conexão, estes ácidos graxos são capazes de ativar a via de sinalização do NFk-B, consequentemente ativando a

secreção de citocinas e quimiocinas, e estimulando o recrutamento de macrófagos M1 para o tecido adiposo (REILLY; SALTIEL, 2017). Outras proteínas seriam capazes de agir como "sensores lipídicos", a exemplo da *Fatty Acid Binding Protein 4* (FABP4), também associada a ativação de macrófagos (MAKOWSKI *et al.*, 2012).

Entretanto, um dos principais mecanismos estudados no âmbito da inflamação é o papel dos ácidos graxos poli-insaturados n-3 e n-6 na modulação da resposta inflamatória. Isso ocorre pois o conteúdo de lipídios dietéticos consumidos, em especial quando nos referimos a proporção entre n-6 por n-3, determina a constituição dos fosfolipídeos de membrana, substrato para a formação de eicosanoides. Diferentes composições destes fosfolipídios geram diferentes padrões de resposta inflamatória , uma vez que ácidos graxos n-6, representados pelo ácido araquidônico (ARA), são precursores de eicosanoides com característica pró-inflamatória , ao passo que ácidos graxos n-3, estão associados a geração de eicosanoides de menor potência inflamatória e, até mesmo, com característica anti-inflamatória (HEADLAND; NORLING, 2015). Os fosfolipídeos de membrana são submetidos a ação da enzima fosfolipase A2 (PLA2), ficando suscetíveis a ação das enzimas (COX-1 e COX-2), (5-LOX e 15-LOX) e da família citocromo P450 formando diferentes conjuntos de eicosanoides, a depender do ácido graxo que compunha o fosfolipídio de membrana em questão (CALDER, 2003; FLACHS *et al.*, 2009).

De maneira geral, o consumo de ácidos graxos poli-insaturados é associado com efeitos benéficos a saúde, entretanto, atribui-se participações opostas aos ácidos graxos n-6 e 3, uma vez que são responsáveis pela geração de mediadores antagônicos, na perspectiva inflamatória (SAINI; KEUM, 2018). Dietas ricas em n-6 estão associadas a manutenção do quadro de inflamação crônica, o que se associa, consequentemente, a doenças cardiovasculares, câncer e diabetes. Do contrário, dietas ricas em n-3 estão associadas a resolução do processo inflamatório e proteção contra doenças metabólicas crônicas (ADKINS; KELLEY∗, 2010; KANG; LIU, 2013; SERHAN; SAVILL, 2005). Uma das primeiras evidências que estabeleceu conexão entre o consumo de n-3 e desordens crônicas foi a avalição do consumo destes ácidos graxos em esquimós da Groenlândia. O consumo dietético desta população era baseado em alimentos de origem animal com alto teor de gorduras do tipo n-3, e apresentavam pequenas taxas de doenças cardíacas, diabetes tipo 1, asma e esclerose múltipla (SIMOPOULOS, Artemis P., 2011).

Diferente da Groênlandia, o padrão de consumo predominante nas sociedades ocidentais, é caracterizado pela ingestão elevada de n-6 e gorduras saturadas, em detrimento a um baixo consumo de gorduras n-3, padrão alimentar chamado de “Western Diet”, ou “Dieta Ocidental”. Acredita-se que populações ancestrais há cerca de 40 a 50 mil anos atrás, consumiam proporções equitativas entre os dois ácidos graxos, próximas a 1:1, entretanto, o padrão de consumo Western Diet acentuou diferenças entre eles, revelando que países como Estados Unidos e do ocidente europeu chegam a atingir proporções de 40-50:1. Esta desproporção é capaz de gerar um ambiente celular substancialmente mais propenso a formação de eicosanoides pró-inflamatórios. (PELLA *et al.*, 2003; SIMOPOULOS, Artemis P.; DINICOLANTONIO, 2016). A figura 3 exemplifica a modificação do consumo de gorduras dietéticas ao longo do tempo.

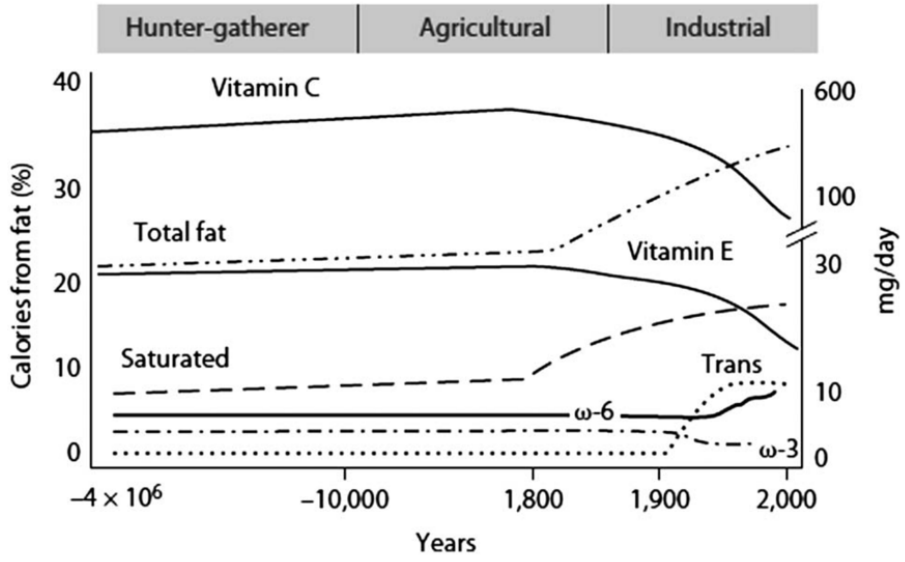

Figura 3. Evolução histórica do consumo de ácidos graxos ômega-6, ômega-3 e outros nutrientes. (Simopoulos, 2016).

Uma vez que os lipídios dietéticos são precursores dos eicosanoides, o consumo de EPA ou DHA está associado a redução na síntese de PGE2 e de TXB2, importantes agregantes plaquetários e vasoconstrictores. Da mesma forma, são capazes de reduzir a síntese de LTB4, potente indutor inflamatório, responsável por processo de quimiotaxia e aderência leucocitária (JIANG *et al.*, 2016). Celada e colaboradores forneceram 2 g de ácidos graxos n-3 (ALA, EPA e DHA) por meio de alimentos fortificados para 18 indivíduos com sobrepeso e obesidade, em um

protocolo com duração de 4 semanas. Seus achados revelaram uma redução significativa ($p<0.05$) nos níveis de TXB2 séricos ao término do protocolo (CELADA *et al.*, 2019a). Uma possível justificativa para esta resposta, reside na capacidade dos ácidos graxos EPA e DHA agirem como inibidores competitivos da enzima prostaglandina sintetase, responsável por gerar as moléculas supracitadas por meio da reação com o ARA (MARTÍNEZ-FERNÁNDEZ *et al.*, 2015). Os ácidos graxos n-3 associam-se, também, a uma ampla gama de eicosanoides anti-inflamatórios (TXB3, PGI3, LTB5), responsáveis por processos de vasodilatação, inibição da agregação plaquetária e amenização da resposta inflamatória (SIMOPOULOS, Artemis P., 2008b). O trabalho conduzido por Nielsen e colaboradores propôs que a suplementação de cápsulas oleosas na quantidade de 1.12 g de ácidos graxos n-3 (EPA e DHA) aumentou significativamente os níveis de LTB5 ao final de 6 semanas de protocolo ($p<0.001$), em 50 indivíduos adultos com sobrepeso (NIELSEN *et al.*, 2012a). Também estão relacionados a formação de mediadores específicos relacionados a resolução da inflamação aguda (*Specialized Pro-Resolvin Mediators*, SPMs) (a exemplo das maresinas, lipoxinas, protectinas e resolvinas). Estas moléculas, estão associadas ao processo de resolução da inflamação e reestabelecimento das propriedades nativas do tecido alvo (DOYLE; SADLIER; GODSON, 2018). Ferrucci e colaboradores analisaram os níveis plasmáticos dos marcadores pró-inflamatórios TNF-alfa, PCR, IL-6 e IL-1ra em um total de 1123 pessoas entre 20 e 90 anos, com média de IMC 27,5 kg/m² (± 4,4). As níveis plasmáticos de n-3 foram associados, de forma independente, com menores níveis destes marcadores, atribuindo importância a estes ácidos graxos não somente na perspectiva dos eicosanoides, mas na modulação de todo o ambiente inflamatório (FERRUCCI *et al.*, 2006). Coletivamente, estes fatos atribuem grande importância a razão entre os ácidos graxos ômega-6 e 3, e não somente a suas quantidades absolutas.

A partir do entendimento de estudos prévios que mostram a influência dos ácidos graxos n-3 na síntese dos eicosanoides, e que estes marcadores estão associados a resposta inflamatória em indivíduos com obesidade, torna-se importante contribuir para aumentar o nível de evidências científicas sobre esta relação. Ainda não há na literatura científica nenhuma publicação analisando de maneira sistemática as evidências disponíveis sobre o efeito do consumo de ácidos graxos n-3 sobre e as classes de eicosanoides em pessoas com excesso de peso. Esta lacuna de conhecimento motivou a elaboração deste trabalho, cujo objetivo consistiu em conduzir uma revisão sistemática

e meta-análise de ensaios clínicos avaliando o efeito do consumo de ácidos graxos n-3 no perfil de eicosanoides em pacientes com obesidade e/ou sobrepeso.

1.3 OBJETIVOS

1.3.1 OBJETIVOS GERAIS

- Avaliar o impacto do consumo de ácidos graxos n-3 no perfil de eicosanoides em indivíduos adultos com obesidade e/ou sobrepeso.

1.3.2 OBJETIVOS ESPECÍFICOS

- Avaliar o efeito do consumo de ácidos graxos n-3 nas variedades pró-inflamatórias e anti-inflamatórias de eicosanoides em indivíduos adultos com obesidade e/ou sobrepeso por meio de revisão sistemática com meta-análise
- Analisar o efeito da fonte (suplemento ou alimento), dose e tempo de suplementação dos ácidos graxos n-3 na modificação do perfil de eicosanoides;
- Avaliar a qualidade dos estudos publicados sobre suplementação de ácidos graxos n-3 e perfil inflamatório de eicosanoides indivíduos adultos com obesidade e/ou sobrepeso.

1.4. METODOLOGIA

A presente revisão sistemática com meta-análise foi conduzida conforme recomendações do PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) e seu protocolo foi registrado na plataforma PROSPERO (Prospective Register of Systematic Reviews) sob o código CRD42020153362.

1.4.1. Fonte das informações e estratégias de busca

O procedimento de busca foi executado nos seguintes bancos de dados: PubMed, biblioteca Cochrane, Embase, Scopus e Web of Science. Também foram buscados estudos na literatura

cinzenta, como Google Acadêmico e ProQuest. Publicações até a data de 7 de novembro de 2019 foram analisadas e as buscas atualizadas na data de 14 de julho de 2020.

A estratégia de busca foi revisada por um pesquisador com experiência em revisões sistemáticas, de acordo com o *checklist* PRESS (Peer Review of Electronic Search Strategies).

A estratégia de busca utilizada no PubMed foi adaptada de acordo com o respectivo banco de dados: (“Morbid obesity” OR “Severe obesity” OR “Abdominal obesity” OR “Central obesity” OR “Visceral obesity” OR “Obese men” OR “Obese women” OR “Overweight” OR “Overweight men” OR “Overweight women” OR “Excess weight” OR “obese” OR “obesity” OR “Fat accumulation” OR “fatness” OR “body fatness” for population main characteristic and combined with intervention keywords "N3 fatty acids" OR "n-3 Fatty Acids" OR "n 3 Fatty Acids" OR "n3 Fatty Acids" "W3 fatty acids" OR "w-3 fatty acids" OR "w 3 fatty acids" OR "N3 Polyunsaturated Fatty Acid" OR "n-3 Polyunsaturated Fatty Acid" OR "n 3 Polyunsaturated Fatty Acid" OR "n3 Polyunsaturated Fatty Acid" OR "n-3 PUFA" OR "N 3 PUFA" OR "N3 PUFA" OR "N-3 oils" OR "N3 oils" OR "N 3 oils" OR "Omega 3 Fatty Acids" OR "Eicosapentanoic Acid" OR "omega 3 Eicosapentaenoic Acid" OR "omega-3-Eicosapentaenoic Acid" OR "Timnodonic Acid" OR "Docosahexenoic Acid" OR "omega 3 Docosahexenoic Acid" OR "Docosahexaenoate" OR "alpha Linolenic Acid" OR "Linolenate" OR "Linolenic Acid" OR “EPA and DHA supplementation” OR EPA OR DHA OR “omega 3” OR “omega-3” OR “fish oil” OR “arachidonic acid” OR “arachidonate”) AND (“eicosatetraenoic acid” OR eicosanoid OR Icosanoid OR Prostanoid OR Lipoxin OR Prostaglandin OR Thromboxane OR Leukotriene OR "hydroxyeicosatetraenoic acid" OR "Isoprostane" OR “dinoprostone”). A busca realizada no Google Acadêmico se limitou aos primeiros 200 artigos mais relevantes. Nenhum dos filtros de idioma, data de publicação ou status foram aplicados aos resultados de cada banco de dados. Mais informações acerca das estratégias de busca podem ser visualizadas no Apêndice 1.

Uma consulta no portal *ClinicalTrials.gov* foi conduzida (U.S. National Library of Medicine) de forma a verificar se havia algum outro estudo finalizado ou em andamento com dados não publicados que pudesse ser incluído em nossa revisão sistemática. A lista de referências foi manualmente revisada para identificar potenciais estudos que não puderam ser localizados por

meio das buscas nos bancos de dados. As duplicatas foram removidas e o processo de seleção de artigos foi realizado com auxílio do software Rayyan.

1.4.2. Critério de eligibilidade

Ensaios clínicos e estudos observacionais conduzidos em adultos com sobrepeso e/ou obesidade com mais de 18 anos e menos de 65 anos de idade foram considerados elegíveis. O critério de inclusão consistiu em estudos que avaliassem o consumo de ácido graxos poli-insaturados da série ômega-3 por meio da alimentação ou suplementação.

Os critérios de exclusão foram: 1) Estudos com indivíduos submetidos a cirurgia metabólica/bariátrica; 2) Consensos, revisões, cartas ao editor, resumos de conferência e editoriais; 3) Estudos que envolvessem indivíduos com doenças inflamatórias pré-existentes; 4) Utilização de fármacos ou suplementos de característica anti-inflamatória; 5) Mensuração de eicosanoides ausentes ou realizadas em locais diversos do soro ou plasma.

1.4.3. Extração de dados

A seleção dos trabalhos foi realizada de forma independente por dois revisores. Os estudos foram alocados em um dos três grupos a seguir: “incluídos”, “excluídos” ou “conflitantes”, e respostas conflitantes foram posteriormente resolvidas entre os revisores. Os dados foram extraídos e selecionados por um autor (G. S.). Todas as informações obtidas foram conferidas por um segundo autor (I. R.).

A informação extraída foi categorizada da seguinte maneira: 1) Autor, Ano de publicação, e País; 2) Desenho do estudo; 3) Período do Estudo; 4) Fonte dos ácidos graxos ômega-3; 5) Protocolo do Estudo; 6) Protocolo de adesão para alimentos/suplementos; 7) Idade; 8) IMC inicial; 9) Marcadores inflamatórios Pré e Pós-intervenção; 10) Resultados principais.

1.4.4. Risco de viés em estudos individuais

O risco de viés dos artigos incluídos foi realizado de acordo com a ferramenta *Joanna Briggs Institute Critical Appraisal Tools*. Um checklist de 9 questões (“*Checklist of quasi-experimental studies*”) foi utilizado para determinar o risco de viés em ensaios clínicos não randomizados e um checklist de 13 questões (“*Checklist of randomized controlled trials*”) para

determinar o risco de viés nos ensaios clínicos randomizados. O risco de viés de cada estudo incluído foi determinado de forma independente por dois revisores (G. S. e I. R.) e pode ser visualizado na Figura 2.

1.4.5. Medidas sumário e síntese dos resultados

De acordo com os dados de desfechos primários coletados a partir da extração dos dados, foi possível conduzir a meta-análise para investigar a magnitude de efeito do consumo de ácidos graxos ômega-3 nos níveis séricos de prostaglandinas pro-inflamatórias. Para isso, realizamos um modelo de efeitos aleatórios (*random-effect model*) utilizando o método de estimativa por máxima verossimilhança restrita (*restricted maximum likelihood, REML*). O modelo de efeitos aleatórios aplicado a meta-análise parte do princípio que diferentes estudos estão estimando diferentes, porém relacionados, efeitos de intervenção, o que está de acordo com os dados obtidos na extração.

O valor entre a diferença dos marcadores inflamatórios investigados do momento inicial (*baseline*) ao momento final (*endpoint*) foi estimado pelo modelo Glass Tipo 1, utilizando 95% de intervalo de confiança. O delta (Δ) de Glass é adequado pois permite comparar as alterações de desvios-padrão e sua inferência sobre a variância, além de padronizar as diferentes medidas analisadas criando a medida sumário. Da mesma forma, o Delta de Glass é oportuno para aqueles trabalhos cuja comparação com o grupo controle não é possível, fato que ocorreu em nosso estudo em virtude da ausência de parte dos dados basais em um dos estudos incluídos. Houve tentativa de contato com os autores do respectivo estudo para aquisição dos dados faltantes, entretanto não obtivemos resposta. Para os estudos com mais de um grupo de intervenção, o grupo com a maior dosagem de ácidos graxos n-3 consumida foi levada em consideração para a análise. Para o estudo com o desenho *crossover*, a alteração média no nível dos marcadores inflamatórios ao fim dos períodos de intervenção foi utilizada.

A heterogeneidade dos efeitos do tratamento entre os estudos foi testada utilizando o teste Qui-Quadrado ($p<0.10$) e a magnitude de seus efeitos utilizando o I^2. Quando o I^2 era inferior a 40% atribuía-se pouca relevância, de acordo com as recomendações da Colaboração Cochrane. De forma a investigar os parâmetros capazes de influenciar a heterogeneidade, foram realizadas análises de subgrupo, considerada os seguintes estratos: i) doses de ácidos graxos n-3 (maior ou menor que 0.5 g EPA + DHA , conforme recomendado pela ISSFAL, para população geral) (CUNNANE, 2004); ii) fontes dos ácidos graxos ômega-3 (alimentos ou suplemento por via oral);

iii) tempo de intervenção (mais de 8 semanas ou até 8 semanas). Em virtude do pequeno número de estudos incluídos na meta análise, não foi possível realizar meta-regressão e análise de viés de publicação.

2. RESULTADOS

2.1 Artigo original

Artigo Original

Effect of n-3 long chain polyunsaturated fatty acid intake on eicosanoid profile of individuals with obesity and overweight: a systematic review and meta-analysis of clinical trials

Manuscrito submetido ao periódico *Prostaglandins, Leukotrienes and Essential Fatty Acids*

(Periódico classificado pelo QUALIS CAPES como A2 na área de Nutrição)

Title Page

Title: Effect of n-3 long chain polyunsaturated fatty acid intake on eicosanoid profile of individuals with obesity and overweight: a systematic review and meta-analysis of clinical trials

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KEY WORDS

Eicosanoids, Inflammation, n-3, PUFA, obesity, systematic review

1. INTRODUCTION

Obesity is one of the most prevalent chronic conditions currently seen in western society (WHO, 2000) and can interfere in a balanced inflammatory response through eicosanoid metabolism modulation (PICKENS *et al.*, 2017). In individuals with obesity, visceral adipose tissue presents a dysfunctional phenotype when compared to lean individuals' tissue. Excessive adipose tissue accumulation can potentially modify phospholipase A2 (PLA2), cyclooxygenase 2 (COX-2) and 5-lipooxygenase (5-LOX) activity, thereby increasing eicosanoid mediators such as prostaglandins (PG) and leukotrienes (LT) (DJURIC *et al.*, 2017; LANG; DUAN; HO, 2019). This metabolic modification seems to determine a state of chronic low-grade inflammation, which is recognized as a critical factor for the establishment and progression of metabolic dysfunction associated with obesity (HOTAMISLIGIL, 2006). The pro-inflammatory eicosanoids synthesis is associated with several obesity manifestations, such as insulin resistance (YING *et al.*, 2017), tissue inflammation (WANG, D.; DUBOIS, 2012), renal injury (NASRALLAH; HASSOUNEH; HÉBERT, 2016) and increased cardiovascular maladaptations (VIANELLO *et al.*, 2020).

Inflammation and dietary fat, especially n-6/n-3 polyunsaturated fatty acids (PUFA) ratio, have a tight correlation (NETTLETON; KATZ, 2005), since there is enzymatic competition by the use of these PUFAs as substrates for synthesis of inflammatory mediators (PICKENS *et al.*, 2017). The unbalanced PUFA intake can be directly associated with markers of inflammation and augmentation in COX and LOX-derived proinflammatory eicosanoids (MAS *et al.*, 2012; SIMOPOULOS, A P, 2006) such as prostaglandin E2 (PGE2), leukotriene B4 (LTB4) and thromboxane A2 (TXA2), derived from n-6 fatty acids such as arachidonic acid (AA)(GROPPER, S. S.; SMITH, J. L.; GROFF, 2013).

A higher intake of n-3 PUFA, such as eicosapentaenoic acid (EPA) and docosaexaenoic acid (DHA) has the capability to modulate eicosanoid profile in COX and LOX dependent pathways, generating 3-series prostaglandins and thromboxanes, and 5-series leukotrienes and lipoxins (FISCHER *et al.*, 2014; LEUNG; ZHANG, 2014). Also, because of enzymatic competition, a higher EPA and DHA consumption might shift eicosanoid metabolism from AA

metabolites (pro-inflammatory activity) to EPA and DHA metabolites (less pro-inflammatory activity and even modestly anti-inflammatory activity) (CALDER, 2015a). Besides COX and LOX enzyme, cytochrome P450 enzyme family also synthetize eicosanoid mediators as 5-HEPE (EPA-derived) and 5-HETE (AA-derived) contributing to modulate inflammation (ONODERA *et al.*, 2017; WANG, W. *et al.*, 2016).

Significant modifications on inflammatory signaling and eicosanoid profile in human have been seen during intervention with EPA and DHA fatty acids (BROWNING, 2003; CALDER, 2003) (), suggesting a protective effect of n-3 PUFA on chronic diseases. A previous study (JIANG *et al.*, 2016) showed that marine-derived n-3 PUFA had a beneficial effect on reducing the concentration of major pro-inflammatory eicosanoids in unhealthy subjects. However, there has been no study conducted to summarize the available evidence of the effects of n-3 PUFA supplementation on pro- and anti-inflammatory eicosanoids markers on individuals with obesity and overweight. Therefore, the aim of this study was to evaluate the effects of n-3 PUFA intake on a variety of pro-inflammatory and anti-inflammatory eicosanoids on adults with obesity and overweight, through systematic review and meta-analysis of controlled trials.

2. MATERIALS AND METHODS

The current systematic review and meta-analysis was conducted as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (MOHER *et al.*, 2015), and the protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO - CRD42020153362).

2.1. Information sources and search strategies

A comprehensive search was executed in the following databases: PubMed, Cochrane library, Embase, Scopus and Web of Science, and grey literature (Google Scholar and ProQuest). Publications up to November 7, 2019 were examined, and updated on July, 14th, 2020.

The search strategy was reviewed by an investigator with experience in systematic reviews in accordance with the Peer Review of Electronic Search Strategies checklist criteria (MOHER *et al.*, 2015). The following strategy was adapted for the databases: (“Morbid obesity” OR “Severe obesity” OR “Abdominal obesity” OR “Central obesity” OR “Visceral obesity” OR “Obese men” OR “Obese women” OR “Overweight” OR “Overweight men” OR “Overweight women” OR “Excess weight” OR “obese” OR “obesity” OR “Fat accumulation” OR “fatness” OR “body fatness” for population main characteristic and combined with intervention keywords "N3 fatty acids" OR "n-3 Fatty Acids" OR "n 3 Fatty Acids" OR "n3 Fatty Acids" "W3 fatty acids" OR "w-3 fatty acids" OR "w 3 fatty acids" OR "N3 Polyunsaturated Fatty Acid" OR "n-3 Polyunsaturated Fatty Acid" OR "n 3 Polyunsaturated Fatty Acid" OR "n3 Polyunsaturated Fatty Acid" OR "n-3 PUFA" OR "N 3 PUFA" OR "N3 PUFA" OR "N-3 oils" OR "N3 oils" OR "N 3 oils" OR "Omega 3 Fatty Acids" OR "Eicosapentanoic Acid" OR "omega 3 Eicosapentaenoic Acid" OR "omega-3-Eicosapentaenoic Acid" OR "Timnodonic Acid" OR "Docosahexenoic Acid" OR "omega 3 Docosahexenoic Acid" OR "Docosahexaenoate" OR "alpha Linolenic Acid" OR "Linolenate" OR "Linolenic Acid" OR “EPA and DHA supplementation” OR EPA OR DHA OR “omega 3” OR “omega-3” OR “fish oil” OR “arachidonic acid” OR “arachidonate”) AND (“eicosatetraenoic acid” OR eicosanoid OR Icosanoid OR Prostanoid OR Lipoxin OR Prostaglandin OR Thromboxane OR Leukotriene OR "hydroxyeicosatetraenoic acid" OR "Isoprostane" OR “dinoprostone”). The Google search was limited to the first 200 most relevant articles. No filters on language, publication date, or status were applied to the results found in each database. More information about search strategies is provided in Appendix 1.

A consultation was carried out on the ClinicalTrials.gov Database portal (U.S. National Library of Medicine) in order to verify if there was any on-going or non-published data that could be included in our systematic review. Reference lists of included records were manually reviewed to identify potentially studies not retrieved from databases. The duplicates were removed, and the screening procedure was applied using Rayyan software (OUZZANI, 2017).

2.2. Eligibility criteria

Clinical trials studies that were conducted on adults with obesity and overweight (more than 18 years old and less than 65 years old) were eligible. The intervention criteria were n-3 polyunsaturated fatty acid intake either through oral supplements or foods.

Exclusion criteria were: 1) Studies with subjects that underwent bariatric/metabolic surgery; 2) Consensus, management, reviews, letters, conference abstracts, editorials; 3) Studies evaluating subjects with inflammatory diseases; 4) Use of non-steroidal anti-inflammatory drugs or anti-inflammatory supplements; 5) Absent eicosanoid measurement or measurements other than serum or plasma eicosanoids.

2.3. Data extraction

Study selection was undertaken independently by two reviewers. Studies were allocated in one of the three following groups: “included”, “excluded” or “conflict” and discrepant answers were resolved between reviewers. Data were extracted from selected studies by one author (G. S.). All the retrieved information was cross checked by a second author (I. R.).

The extracted information was categorized as follows: 1) Author, Year of publication, and Country; 2) Study design; 3) Study Period; 4) n-3 PUFA source; 5) Study Protocol; 6) Food or supplement adherence protocol; 7) Age; 8) Baseline BMI; 9) Baseline and Post-Intervention Inflammatory markers; 10) Main results.

2.4. Risk of bias in individual studies

The risk of bias of included articles was performed according to the Joanna Briggs Institute Critical Appraisal Tools. A 9-question checklist ("*Checklist of quasi-experimental studies*") was used to assess risk of bias in non-randomized clinical trials and a 13-question checklist ("*Checklist of randomized controlled trials*") in order to evaluate randomized clinical trials. The risk of bias of each included study was assessed independently by two reviewers (G. S. and I. R.).

2.5. Summary measures and Synthesis of results

The primary outcomes were the identified measures of association between the n-3 PUFA intake and serum inflammatory markers levels for the qualitative analysis.

Due to available data collected regarding the primary outcomes, we were able to conduct a meta-analysis to investigate the effect size of the n-3 PUFA intake on prostaglandins pro-inflammatory eicosanoid levels. For this, we built random-effect models using the restricted maximum likelihood (REML) method (RAUDENBUSH, 2009). The random-effects meta-analysis approach incorporates an assumption that the different studies are estimating different, yet related, intervention effects (DEEKS; HIGGINS; ALTMAN, 2019; DERSIMONIAN, REBECCA; LAIRD, 1986), which agrees with our data.

The difference between the parameters investigated from baseline to endpoint was estimated by Glass's, type 1, with its respective 95% CI (SMITH; GLASS, 1977). The Glass's Δ is suitable for studies whose comparison with a control group is not possible (KLINE, 2013), which happened in this study due to the absence of part of the data and the non-response of the authors to the attempts to contact them to request them. In studies with more than one intervention group, the highest n-3 PUFA dose group was considered for analysis. For the study with a crossover design, mean changes between the levels of markers at the end of two intervention periods were used (HIGGINS JPT, 2011).

Heterogeneity of treatment effects between studies was tested using the Chi-square method ($p<0.10$) and its magnitude using I^2. When I^2 was less than 40% it was not considered important, according to Cochrane's collaboration recommendation (HIGGINS JPT, THOMAS J, CHANDLER J, CUMPSTON M, LI T, PAGE MJ, 2020). In order to investigate parameters

influencing heterogeneity, we performed subgroup analyzes, considering the following strata: doses of n-3 (higher or lower than 0.5 g EPA + DHA n-3 PUFA as recommended by ISSFAL for general people (SPECTOR, 2004); source of administration of n-3 (food or oral supplement); and intervention time (more than 8 weeks or up to 8 weeks). Due to the small number of studies included in the meta-analysis, it was not possible to perform meta-regression and analysis of publication bias (DEEKS; HIGGINS; ALTMAN, 2019).

3. RESULTS

The initial search identified a total of 2941 articles from seven databases, and after removing duplicates, 39 potential studies met the eligibility assessment and complete full-text reading. Thirty-two articles were excluded and the reasons are presented in Appendix 2. At the end, seven articles (CELADA *et al.*, 2019b; DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016; RAMEL *et al.*, 2010) were selected for this systematic review. After selection, the full reference list of each article was checked in order to identify possible additions and no article was potentially eligible. In addition, the *Clinicaltrials.gov* registers were consulted and no protocol associated with eligible articles has been identified. Flow diagram of the screening process is shown in Figure 1.

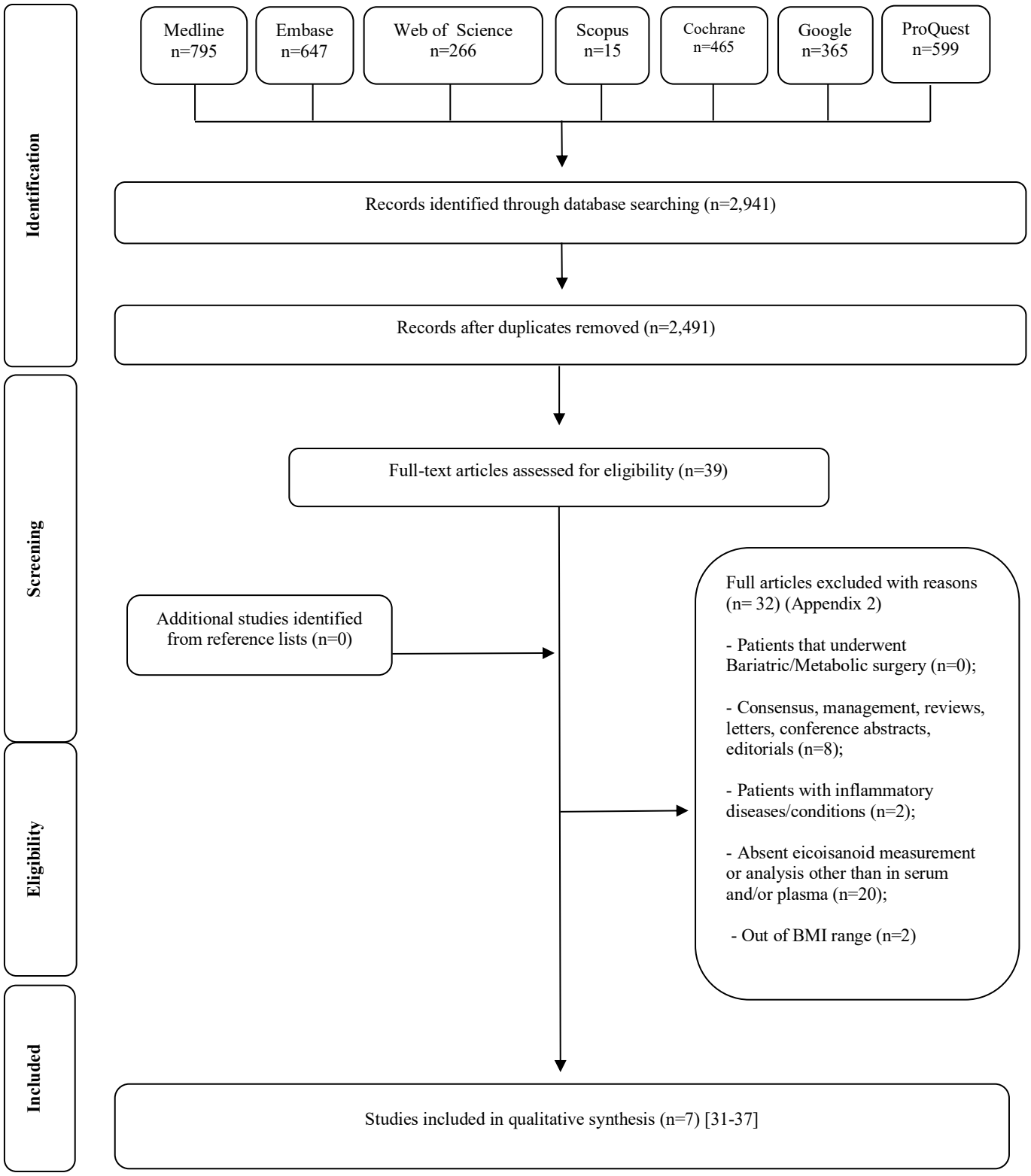


Figure 1. Flow Diagram of Literature Search and Selection Criteria.[1]

[1] Adapted from PRISMA.

3.1. Characteristics of included studies

In total, seven clinical trials included 610 individuals with obesity and/or overweight published between 2010 (RAMEL *et al.*, 2010) and 2019 (CELADA *et al.*, 2019b) (Table 1). Among them, six studies (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016; RAMEL *et al.*, 2010) are randomized trials and only one study (CELADA *et al.*, 2019b) is a non-randomized trial. The studies were conducted in different countries which included Spain (CELADA *et al.*, 2019b; DE LUIS *et al.*, 2016), Germany (DAWCZYNSKI *et al.*, 2013), Denmark (NIELSEN *et al.*, 2012b), Poland (POLUS *et al.*, 2016). Ramel et al was a multicenter study that included Spain, Iceland and Ireland (RAMEL *et al.*, 2010).

The lower BMI between studies was 25.91 ± 3.67 (DAWCZYNSKI *et al.*, 2013) and the higher BMI was 34.4 ± 2.69 (POLUS *et al.*, 2016). The mean age ranged from 31 ± 5.9 years old (RAMEL *et al.*, 2010) to 61.82 ± 7.13 (DAWCZYNSKI *et al.*, 2013). The majority of studies analyzed both men and women (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; RAMEL *et al.*, 2010), except by Celada et al and Polus et al, which included only men and only women, respectively. The intervention period ranged from 4 weeks (CELADA *et al.*, 2019b) to 24-week (DE LUIS *et al.*, 2016).

The n-3 PUFA content of the protocol interventions was provided by oral oil supplements (DE LUIS *et al.*, 2016; NIELSEN *et al.*, 2012a; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016; RAMEL *et al.*, 2010) or by food such as n-3 enriched frankfurters and patés (CELADA *et al.*, 2019b), n-3 enriched yogurt (DAWCZYNSKI *et al.*, 2013) and salmon, a fatty fish (RAMEL *et al.*, 2010). N-3 enriched-food were provided as a mixture of different n-3 long chain PUFA family, including EPA, DHA, DPA (docosapentaenoic acid) (CELADA *et al.*, 2019b) and ALA (alpha linolenic acid) (DAWCZYNSKI *et al.*, 2013). One study supplemented individuals using exclusively DHA fatty acid capsules (DE LUIS *et al.*, 2016) and three other studies supplemented with EPA plus DHA capsules (NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016). Only one study presented total fat amount and did not mention which specific fatty acids were included in the intervention protocol (RAMEL *et al.*, 2010). The control group were supplemented with olive oil (NIELSEN *et al.*, 2012b), corn/soybean oil (O'SULLIVAN *et al.*,

2014) or sunflower oil capsules (RAMEL *et al.*, 2010) and one study did not specify which oil was used (POLUS *et al.*, 2016). Studies that utilized food as PUFAs source presented conventional fruit yoghurt (DAWCZYNSKI *et al.*, 2013) and normal-fat frankfurters and pates as control groups (CELADA *et al.*, 2019b).

The lower amount of fatty acid dosage observed was 0.25 g of DHA (DE LUIS *et al.*, 2016) and the higher amount was 3 g of n-3 PUFA (including ALA, EPA, DPA and DHA)(DAWCZYNSKI *et al.*, 2013; O'SULLIVAN *et al.*, 2014).

Each study measured a particular subset of eicosanoids, varying from leukotrienes, prostaglandins, thromboxanes, lipoxins to PUFA metabolites such as HEPEs and HETEs (Table 1). Five of seven studies measured both pro- and anti-inflammatory eicosanoids (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016), and two studies were measured only the pro-inflammatory ones (CELADA *et al.*, 2019b; RAMEL *et al.*, 2010) .

Table 1 – Data Extraction

Author, Year and Country	**Study Design**	**Study Period**	**n-3 PUFA Source**	**Study Protocol**	**Food or supplement adherence protocol**	**Age (mean±SD)**	**Baseline BMI (kg/m^2)**	**Marker**	**n-3 Intervention Group (mean±SD)**		**Significance***
									Baseline Values (pg/mL)	Post Intervention Values (pg/mL)	
Celada, 2019 – Spain [31]	Non-randomized crossover clinical trial	4 weeks	Enriched Frankfurters and pâtés	**n-3 Intervention group (n=18)**: 15.5% total fat; 2 g of ALA plus EPA plus DHA/d **Control Group (n=18)**: 18% total fat for frankfurters and 30% total fat for patés)	Seventy-two-hour dietary registers	Both groups: 44.9 ± 10.3	Both groups: 28.6 ± 2.5	6-keto PGF1a	747±452	563±336	**p < 0.001**
								TXB2	309±158	254±75.7	**p < 0.05**

Dawczynski, 2013 – Germany [32]	Placebo-controlled, randomized double-blind parallel clinical trial	10weeks	Enriched Yogurt	**n-3 Intervention group (n=16):**. 5.5 % total fat; 1.59 g EPA/d, 1.12 g DHA/d, 0.07 g ALA/d and 0.23 g DPA/d **Control Group (n=14):** 3.5% total fat	Food Frequency Protocol	**Intervention group** 61.82± 7.13 **Control Group** 58.23 ±7.38	**Intervention group** 25.91± 3.67 **Control Group** 26.14± 3.87	5-HEPE	6.16±6.80	3.19±4.02	p = 0.063
								8-HEPE	0.20±0.21	0.18±0.24	p = 0.646
								9-HEPE	0.44±0.38	0.31±0.30	p = 0.284
								11-HEPE	0.22±0.19	0.21±0.23	p = 0.570
								12-HEPE	0.76±0.82	1.01±0.83	p = 0.312
								15-HEPE	0.29±0.26	0.37±0.38	p = 0.507
								18-HEPE	0.58±0.41	0.70±0.73	p = 0.406
								5-HETE	22.68 ± 19.96	11.60 ± 27.82	**p = 0.030**
								8-HETE	0.97±0.77	0.57±1.16	**p = 0.030**
								9-HETE	0.82±0.90	0.53±1.18	**p = 0.041**
								11-HETE	0.89±0.78	0.52±1.29	**p = 0.030**
								12-HETE	2.92±2.70	2.24±1.62	p = 0.305
								15-HETE	1.26±0.97	0.87±1.68	p = 0.422
								PGE3	0.01±0.00	0.08±0.19	**p = 0.008**
								PGE2	0.07±0.05	0.06±0.07	p = 0.148
								PGD2	0.52±0.52	0.29±0.79	**p = 0.041**
								PGE1	0.06±0.07	0.03±0.06	p = 0.213
								TXB2	0.06±0.08	0.09±0.11	p = 0.397
								LTB4	0.18±0.39	0.07±0.05	p = 0.176

DeLuis, 2016 – Spain [33]	Single-blinded, randomized, controlled, prospective clinical trial	24 weeks	Oral oil supplement	**n-3 Intervention group (n=14):** DHA 0.5 g/day during the first 60 days and 0.25 g/day till 180 days **Control Group (n=15):** placebo capsules with the same scheme (composition not mentioned)	Not informed	**Intervention group:** 47.4±9.1 **Control Group:** 44.3±11.7	**Intervention group:** 33.4±1.4 **Control Group:** 32.95±1.9	15-HETE	23.76±38.35	72.95±51.50	**p<0.05**
								12 -HETE	5359.26± 3431.47	3226.87± 1431.22	**p<0.05**
								8-HETE	57.85±51.38	82.88±36.02	**p<0.05**
								5-HETE	369.63± 106.82	369.10± 149.68	p>0.05
								TXB2	131.26± 95.62	148.01± 71.79	p>0.05
								PGE2	0.14±0.34	13.31±15.46	**p<0.05**
								LTB4	Not detectable	16.31±18.99	**p<0.05[b]**
								PD1	3.80±5.27	6.31±3.03	p>0.05
Nielsen, 2012 – Denmark [34]	Parallel double-blinded randomized controlledclinical trial	6 weeks	Oral oil Supplement	**n-3 Intervention group (n=25):** 0.64 g EPA/d and 0.48 g DHA/d. **Control Group (n=25):** 2 g of olive oil/d.	Food Frequency Questionnaire	**Intervention group:** 58.0 ± 7.4 **Control Group:** 55.4 7 9.5	**Intervention group:** 30.8 ± 4.2 **Control Group :** 29.5 ±3.3	5-HETE[a] 350 ± 18		5-HETE: 328 ± 18	**p = 0.46[b]**
								5-HEPE 58 ± 6		5-HEPE: 117 ± 6	**p<0.001[b]**
								LTB4 240 ± 12		LTB4 205 ± 12	**p = 0.26[b]** **p = 0.005[c]**
								LTB5: 9 ± 1		LTB5: 14 ± 1	**p<0.001[b]**

O'Sullivan, 2014 - United States [35]	Double-blind, placebo controlled randomized clinical trial	6 weeks	Oral oil Supplement	**N-3 intervention group (n=28):**5g fish oil with 2 g EPA/d and 1 g DHA/d **Control Group (n=42):** 5 g soybean oil/d.	Food-frequency questionnaires	**Intervention group:** 37.2 ± 12 **Control Group:** 34.1 ± 12	**Intervention group:** 27.0 ± 4.3 **Control Group:** 27.7 ± 4.6	5- HEPE [d] LTB4 [e]	Slope = 11, r2 = 0.55 (n=28) Slope = - 2.0, r2 = 0.25 (n=29)		**p<0.0001** **p = 0.005**
Polus, 2016 – Poland [36]	Randomized placebo-controlled double-blind clinical trial	12 weeks	Oral oil Supplement	**n-3 Intervention group (n=24):**1.29 g DHA and 0.27-0.45 g EPA/d. **Control Group (n=35):** Not informed	No adherence protocol was informed	**Intervention group:** 45.9 ± 9.3 **Control Group:** 47.3 ± 12	**Intervention group:** 34.4± 2.69 **Control Group:** 34.7±3	LXA4 LXA5	50.29 ± 19.10 62.3 ± 24.38	57.63 ± 17.83 79.8 ± 31.16	p=0.069 p=0.058

Ramel, 2010 - Iceland, Spain and Ireland [37]	Randomized, controlled dietary intervention trial	8 weeks	Salmon and oral oil supplement	**Food intervention group (n=84):**150 g salmon, 3 times per week. 2,1 g LC n-3 PUFA; **Fish oil intervention group (n=80):** 1.3 g EPA plus DHA (6 cápsules per day) **Control Group (n=80):** no seafood (6 sunflower oil capsules per day);	Food Frequency Questionnaire	**Food intervention group** Male: 31.6±5.6 Female: 30.9±5.0 **Fish oil intervention group** Male: 31.0±5.9 Female: 30.9±5.0 **Control Group** Male: 32.6±4.9 Female: 31.7±5.6	**Food intervention group** Male: 30.5±1.3 Female: 30.3±1.5 **Fish oil intervention group** Male: 29.5±1.2 Female: 30.1±1.7 **Control Group** Male: 30.1±1.5 Female: 29.9±1.5	PGEF2	Salmon Male: 188±182 Female: 202±199 Fish oil Male: 270±451 Female: 228±321	Salmon Male: 170±197 Female: 148±184 Fish oil Male: 189±141 Female: 139±199	**p<0.05**[f] **p<0.05**[f]

Abbreviators: RF: reduced-fat, EPA: Eicosapentaenoic acid, DHA: docosahexaenoic acid, PG: Prostaglandin, LT: Leukotriene, n-3 PUFAs: omega-3 polyunsaturated fatty acids, 6-Keto PGF2a: 6-Keto Prostaglandin F2 Alpha; PGI2: prostacyclin I2, HODE: hydroxyoctadecaenoic, HEPE: hydroxy eicosapentaenoic acid, HETE: hydroxyeicosatetraenoic acid, HETrE: 15-hydroxyeicosatrienoic acid, PG: prostaglandin, LXA: Lipoxin A; TXB2: thromboxane B2, LtB4: leukotriene B4, LA: linoleic acid, ALA: a-linolenic acid, LC-PUFA: long chain polyunsaturated fatty acid, LtB5: leukotriene B5,LOX: lipooxygenase enzymes; COX: Cyclooxygenase enzymes; CYP450: Cytochrome P450.

[*] p values without letters represents significant difference or not from within groups
[a] All results are presented in pg/mL, except for Nielson et al (ng/10^7 cells) and O'Sullivan et al with association analysis.
[b] Compared to control group
[c] Compared within n-3 intervention groups
[d] 5-HEPE (nM) vs Red Blood Cells EPA (mol%) Linear regression analyses
[e] LTB4 (nM) vs Red Blood Cells EPA (mol%) Linear regression analyses
[f] Significant before–after differences when the data were viewed for all subjects together

3.2. Adherence Protocols and Analysis of cell fatty acid content

Different protocols were used in each of the studies in order to verify adherence to the intervention. Food frequency questionnaires (DAWCZYNSKI *et al.*, 2013; NIELSEN *et al.*, 2012b; O'SULLIVAN *et al.*, 2014; RAMEL *et al.*, 2010) and Dietary Register (CELADA *et al.*, 2019b) were used. Two studies did not mention the specific adherence protocol used (DE LUIS *et al.*, 2016; POLUS *et al.*, 2016).

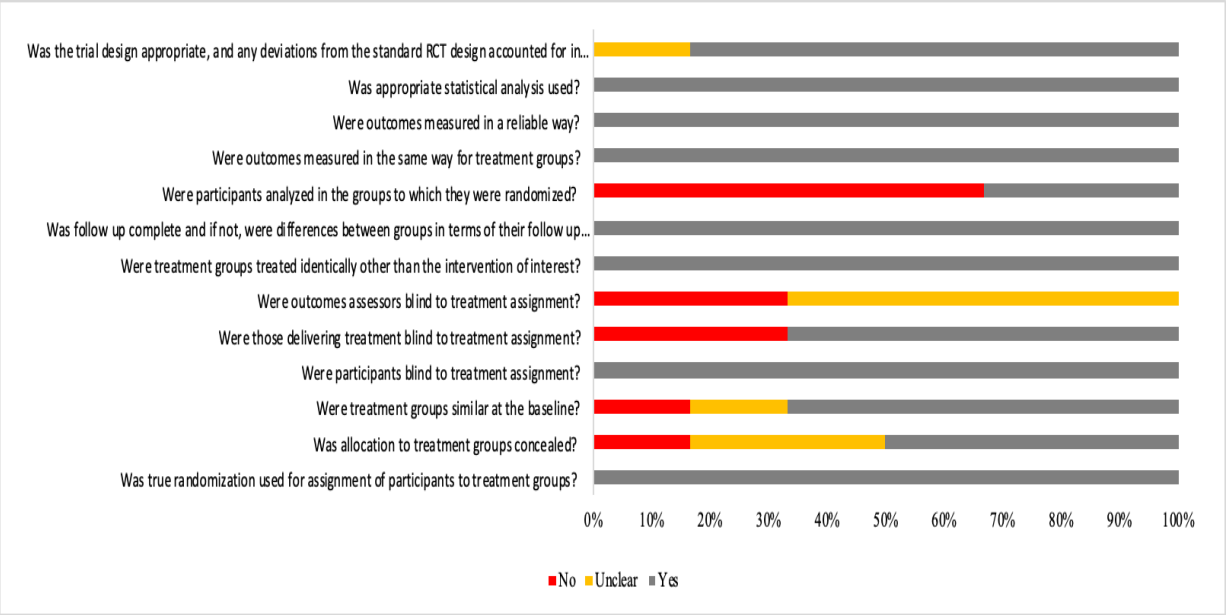
To confirm the n-3 oil supplement or n-3 enriched food intake after the intervention period, five of the seven studies analyzed the fatty acid content, four of them in red blood cells membrane (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016) and one in neutrophils membrane (NIELSEN *et al.*, 2012b), all of them using gas chromatography (GC) as the standard technique. All studies proposed that n-3 PUFA intake led to a significant membrane fatty acid incorporation, further suggesting compliance with the n-3 PUFA intervention protocol.

3.3. Risk of bias within individual studies

The Joanna Briggs Institute appraisal tools were used to assess risk of bias in individual studies. Among the RCT two were categorized as "low-risk of bias" (DAWCZYNSKI *et al.*, 2013; NIELSEN *et al.*, 2012b). The non-randomized trial (CELADA *et al.*, 2019b) and the other four RCT (DE LUIS *et al.*, 2016; O'SULLIVAN *et al.*, 2014; POLUS *et al.*, 2016; RAMEL *et al.*, 2010) were considered as a "high risk of bias" study.

The included trials reported low-risks of bias of assessed domains in the trials regarding randomization, blindness, outcomes measured. Considering the randomized trials, only the following criteria were completely fulfilled: randomization of participants to treatment group, blinding of participants to treatment assignment, identical groups other than the intervention of interest, complete follow-up, outcome measured in an equal and reliable way for treatment groups

and appropriate statistical analysis. In all RCT assessed, the one domain judged with total high risk for bias was regarding intention-to-treat analysis, resulting in one "unclear" (NIELSEN *et al.*, 2012b) and six "no" answers (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016; O'SULLIVAN



et al., 2014; POLUS *et al.*, 2016; RAMEL *et al.*, 2010). In two studies the individuals delivering the treatment and the outcome assessors were not blind to treatment assignment (DE LUIS *et al.*, 2016; RAMEL *et al.*, 2010). In only one study the allocation of treatment groups was not concealed (RAMEL *et al.*, 2010). In all trials assessed, there was at least one domain judged with unclear risk for bias, resulting in overall low quality of trials. Risk-of-bias graph is shown in Figure 2.

Figure 2. Risk of bias in the included studies according to The Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials

3.4. Results of individual studies

Five of seven studies presented an overall reduction in pro-inflammatory markers after n-3 PUFA intervention, and a less pronounced effect on anti-inflammatory eicosanoids (Table 1). Only DeLuis et al. [33] showed enhanced effects in eicosanoids levels after n-3 PUFA intake.

In COX-derivatives pro-inflammatory markers as 6-keto-PGF1a (CELADA *et al.*, 2019b), PGE2 (DAWCZYNSKI *et al.*, 2013; DE LUIS *et al.*, 2016), PGD2 (DAWCZYNSKI *et al.*, 2013)

and PGEF2a (RAMEL *et al.*, 2010) and TBX2 (CELADA *et al.*, 2019b) presented lower serum levels after n-3 PUFA intervention. DeLuis et. al. (DE LUIS *et al.*, 2016) was the only study that presented opposite effects with an increase in PGE2 and TBX2 levels after EPA plus DHA supplementation. The anti-inflammatory marker PGE3 levels reduced after n-3 enriched yogurt (DAWCZYNSKI *et al.*, 2013).

Concerning the LOX-5-derivatives, lower serum levels of the pro-inflammatory marker LTB4 was observed after n-3 PUFA supplementation in one study (NIELSEN *et al.*, 2012b), and the opposite result was observed by De Luis et. al (DE LUIS *et al.*, 2016). The HETE family, such as 5-HETE, 8-HETE, 9-HETE, 11-HETE (DAWCZYNSKI *et al.*, 2013) and 12-HETE (DE LUIS *et al.*, 2016), arachidonic acid derived pro-inflammatory markers, showed reduced serum levels after supplementation. However, 15-HETE and 8-HETE presented increased serum levels after n-3 PUFA intervention in the study conducted by DeLuis et. al. (DE LUIS *et al.*, 2016). In terms of anti-inflammatory markers, only the 5-HEPE EPA-derived eicosanoid, presented higher serum levels after intervention (NIELSEN *et al.*, 2012b).

3. 5 Synthesis of results

Due to the available data, we were able to conducted a subgroup analysis with the prostaglandin eicosanoid group. Meta-analysis presented an overall reduction in pro-inflammatory PG series (Glass' Δ -0.35; 95% CI: -0.62, -0.07) (Figure 3).

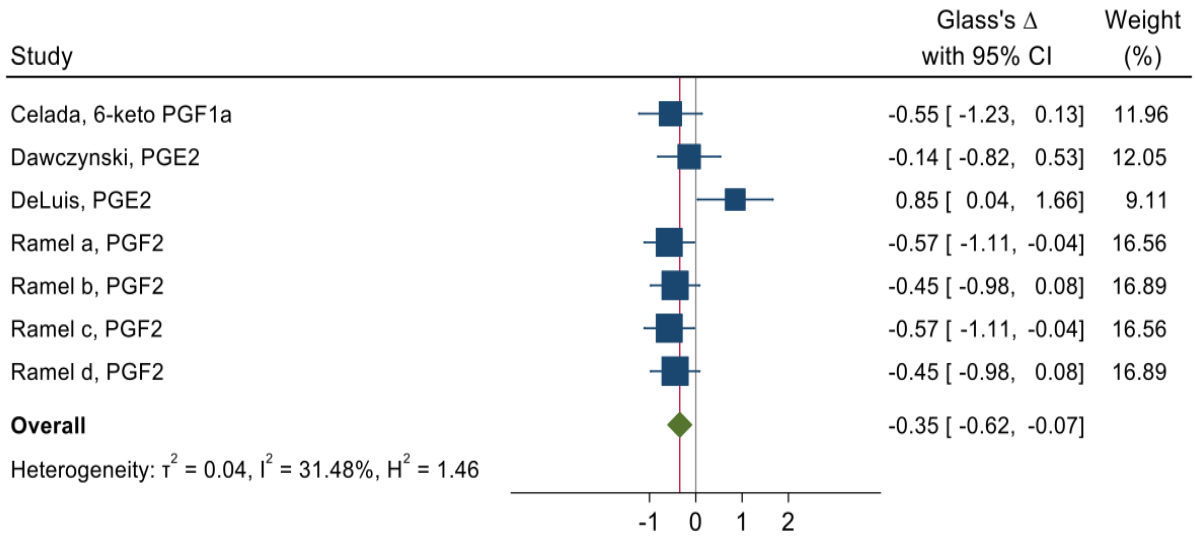


Figure 3. Pooled effect size of n-3 PUFA on prostaglandins markers in subjects with obesity and overweight (standard mean difference).

3.6. Subgroup analysis

Subgroup analysis showed significant effects on PG when n-3 PUFA was consumed in higher doses (Glass' Δ -0.46; 95% CI: -0.72, -0.27) and with period of intervention less than 8 weeks (Glass' Δ -0.51; 95% CI: -0.76, -0.27). There was no difference on PG levels in serum of adults with obesity and overweight when either food (Glass' Δ -0.34; 95% CI: -0.83, 0.13) or supplement source (Glass' Δ -0.31; 95% CI: -0.73, 0.12) was taken into consideration. More details are shown in Table 2.

Subgroups	N	Glass's Δ	95% CI	I^2 (%)	*p* (Chi-squared)
Overall	7	-0.35	-0.62, -0.07	31.48	-
n-3 PUFA dose					
High	5	-0.46	-0.72, -0.27	0.00	0.88
Low	2	0.13	-1.24, 1.50	85.16	0.01
Time of intervention					
More than 8 weeks	2	0.33	-0.65, 1.30	70.74	0.06
Up to 8 weeks	5	-0.51	-0.76, -0.27	0.00	0.99
n-3 PUFA source					
Food	2	-0.34	-0.83, 013	0.00	0.41
Oil Supplement	5	-0.31	-0.73, 012	63.17	0.04

Table 2 – Subgroup analysis for the effect of and n-3 PUFA intake on prostaglandins profile on subjects with obesity and overweight

4. DISCUSSION AND CONCLUSIONS

The studies presented in this systematic review showed a reduction in pro-inflammatory markers after n-3 PUFA intervention in the serum of adults with obesity and overweight, and a minor effect in anti-inflammatory markers. Regarding PG markers, the meta-analysis results supported that pro-inflammatory PG markers are reduced after n-3 PUFA supplementation in doses higher than 0.5g/day of EPA + DHA and with duration of intervention less than 8 weeks.

The daily supply of n-3 PUFAs either by supplementation or enriched-food by diet are recommend by several agencies and organizations since previous studies suggest their protective effect on cardiovascular diseases (HARRIS; POSTON; HADDOCK, 2007; KARK *et al.*, 2003) and cancer (GOODSTINE *et al.*, 2003; ZOCK; KATAN, 1998). World Health Organization (WHO, 2002) recommends 1-2% of daily energy consumption from ômega-3 PUFAs for general population and the International Society for the Studies of Fatty Acids and Lipids (SPECTOR, 2004) recommend at least 500 mg/day of EPA+DHA for general adult population aiming for cardiovascular health. However, there is no current daily recommendation for adults with obesity and overweight, but it is notice that the excess of fat, especially the visceral fat, increases risk for cardiovascular diseases and other comorbidities (GAAL; MERTENS; BLOCK, 2006; SIMOPOULOS, Artemis P; A.P.; SIMOPOULOS, 2016). In addition, in the context of obesity, several immune cells infiltrate in adipose tissue introducing a process known as chronic low-grade inflammation (RICCIOTTI E. & FITZGERALD G. A., 2012), and this sustained inflammatory process can contribute to the pathophysiology of chronic diseases (LIBBY, 2007). Dietary fatty acids play an important role in the inflammatory response, since long-chain n-6 and n-3 PUFAs act as substrates for LOX and COX enzymes to generate several classes of eicosanoids. In fact, three families of eicosanoids (prostaglandins, hydroxyeicosatetraenoic acids and leukotrienes), especially those from n-6 PUFAs metabolism, have key functions in obesity-associated adipose tissue inflammation. When pro-inflammatory eicosanoids are enhanced, they unbalance the inflammatory signal and enhance recruitment of M1-polarized macrophages, increasing proinflammatory adipokines and cytokines secretion by adipose tissue (GARCÍA-ALONSO *et al.*, 2016; HSIEH *et al.*, 2009).

The n-6/n-3 ratio intake in developed and under development countries has been changing over the past century since n-6 PUFA consumption has dramatically risen due to increased

consumption of vegetable edible oils like soybean, corn, sunflower, safflower and cottonseed, known as Western dietary pattern (SIMOPOULOS, Artemis P; A.P.; SIMOPOULOS, 2016). Furthermore, the n-3 PUFAs (ALA, EPA, and DHA) intake has simultaneously decreased in Western diets (SIMOPOULOS, A.P., 2000). Based on the understanding that n-6 FAs induce a more potent inflammatory response, whereas n-3 PUFAs are thought to have a less potent inflammatory effect, the fluctuation in n-6/n-3 ratio intake may contribute to eicosanoid release from adipose tissues. Long chain fatty acids presented the highest rate of mobilization from phospholipase A2 enzyme activity (CONNOR; LIN; COLVIS, 1996) and n-3 long chain PUFAS, especially EPA, are mobilized and metabolized more rapidly than the others (HERZBERG; SKINNER, 1997), and may also help reducing inflammatory response in individuals with obesity (BUCKLEY; HOWE, 2010; LORENTE-CEBRIÁN; COSTA, 2013).

Investigation about mechanisms underlying the attenuation of inflammatory response and metabolic dysfunction in individuals with obesity by n-3 PUFA intake are progressing on the last decades. Effect in obese animal models (high-fat diet-induced obesity and genetic obesity) are promising, but the proposed mechanisms still require further confirmation in humans. Evidence from in vitro and in vivo studies suggests that EPA and DHA can reduce pro-inflammatory adipokine synthesis, decreasing the inflammatory crosstalk between adipocytes and infiltrative immune cells (CALDER, 2003), murine macrophages (DE BOER; MONK; ROBINSON, 2014) and mice CD8 lymphocytes cells (LIDDLE *et al.*, 2019).

White adipocytes have an important role in the orchestrating inflammatory response in white adipose tissue, by releasing several pro-inflammatory molecules and activating and recruiting immune cells. This pro-inflammatory response can be mediated by several transcription factors, including NF-κB, a major complex that stimulates pro-inflammatory response through transcription processes. It regulates inflammatory adipokine gene transcription (STAT3), releasing mediators like monocyte chemoattractant protein 1 (MCP-1), interleukin 6 and IL-1β, alpha tumor necrosis factor (TNF-α), interferon gamma (IFN-γ) and leptin. Also, IL-1β and TNF-α stimulate IL-1 Receptor (IL-1R) and TNF Receptor 1 (TNFR1), respectively, promoting TAK1/TAB1 binding and subsequent NF-κB activation, contributing to perpetuate the pro-inflammatory environment in white adipose tissue (LIDDLE *et al.*, 2017). The COX-1 and COX-2 enzymes are

involved in the inflammation regulatory process, being mainly regulated by growth factors and cytokines, such as IL-1 β, IL-6, or TNF-α (BOWERS; DEGRAFFENRIED, 2015). The COX-2 gene is situated on chromosome 1 and its promoter region displays both an NF-κB and an IL-6 response element (KAWAHARA *et al.*, 2015). Thus, a pro-inflammatory microenvironment leads to a higher release of pro-inflammatory eicosanoids from AA, especially from the prostaglandin family. PG plays an important role in cell proliferation and differentiation, vascular tone and energy metabolism. During an inflammatory response, the levels of PG can dramatically rise with the recruitment of infiltrated immune cells. In the breast tissue of women with obesity, was demonstrated that a higher concentration of pro-inflammatory cytokines promotes greater macrophage COX-2 expression and produces more PGE2 (SUBBARAMAIAH *et al.*, 2013). This study clearly links obesity and low-grade chronic inflammation, processes mediated by COX-2 and aromatase expression in human breast tissue.

Different studies have demonstrated that n-3 PUFA may replace AA and shift eicosanoid profile. An in vitro study with macrophage cells, EPA and DHA replaced 25 to 50% of AA in membrane cellular lipids, and that fatty acids modification significantly reduced 50 to 65% of prostaglandin E2 (PGE2), thromboxane B2 (TXB2) and 6 keto prostaglandin F1α (6 keto PGF1α) synthesis, when stimulated with opsonized zymosan (LOKESH; KINSELLA, 1987). Also, healthy subjects were supplemented with n-3 long chain PUFA (3.2 g EPA + 2.2g DHA) and presented significantly decreased by 37% the AA proinflammatory eicosanoid generated by neutrophils after 6 weeks period (LEE *et al.*, 1985). De Luis et. al. (2016) (DE LUIS *et al.*, 2016) supplemented subjects with obesity with DHA 0.5 g/day during the first 60 days and 0.25 g/day till 180 days and the intervention group reduced serum levels of 15, 12 and 8-HETE, PGE2 and LTB4 when compared to control. During 6 weeks of oral supplementation, n-3 EPA + DHA were effective in reducing LTB4 serum levels when compared to controls. These results were seen in individuals with obesity with 0.64g EPA/d and 0.48g DHA/d supplementation (NIELSEN *et al.*, 2012b) and with 2g EPA/d and 1g DHA/d in overweight subjects (O'SULLIVAN *et al.*, 2014). Besides the inflammatory mediators derived from n-3 PUFA, in vitro and in vivo studies also have demonstrated the potential effects of n-3 PUFA in suppressing proinflammatory mediators such as cytokines in healthy women (MEYDANI *et al.*, 1991) and NFκB in vitro studies (BOER *et al.*,

2016; NOVAK *et al.*, 2003; ZHAO *et al.*, 2005) which may reflect on reducing proinflammatory PG mediators.

Regarding prostaglandins, our meta-analysis presented a significant reduction in pro-inflammatory PG in studies that utilized more than 0.5 g/day EPA + DHA, and when provided by food source then oil supplement. This is in accordance with previous studies that stated a dose-dependent immunological response with n-3 intake on prostaglandin E2 (PGE2) and Prostaglandin E3 (PGE3) (FISCHER *et al.*, 2014; REES *et al.*, 2006). The better bio-utilization of lipids from foods can be attributed to the larger amount of fat as part of the natural composition of food, favoring lipid absorption and conferring a higher bioavailability (VISIOLI *et al.*, 2003). There are also evidence in humans suggesting that an intake between 1.35 g and 2.7 g n-3 PUFA would be required to affect PGE2 production by mononuclear cells in healthy younger and older men (REES *et al.*, 2006) and that could be part of the reason why most anti-inflammatory markers and some pro-inflammatory markers included in our primary analysis did not present altered serum levels.

Time is a critical factor when it comes to n-3 effectiveness, since the benefits over inflammation appear to be dependent on incorporation of fatty acids in the cell membrane (MOCELLIN *et al.*, 2015) and that process might take about 3 weeks to reach its peak (COCKBAIN; TOOGOOD; HULL, 2012). It is important to mention that the studies included in our meta-analysis started from a 4-week period intervention, which comprehend sufficient time to incorporate n-3 fatty acids on cell membrane. Our subgroup analysis showed a significant reduction in pro-inflammatory prostaglandins when the time of intervention was less than 8 weeks, a pattern that could not be seen for more prolonged periods (more than 8 weeks). One reason that could be related to such result is that the majority of our included studies with periods shorter than 8 weeks offered higher quantities of n-3 PUFA, even greater than 2 g per day, an amount that appears to be an immunologic checkpoint in order to affect the inflammatory process in humans (CALDER, 2010). Studies specifically measuring prostaglandins after n-3 PUFA supplementation in periods shorter than 8 weeks are scarce, but exist. Tecklenburg-Lund et. al (TECKLENBURG-LUND *et al.*, 2010) showed that a high dose n-3 PUFA fish oil supplementation (3.2 g EPA plus 2.0 g DHA) taken daily for 3 weeks was effective in reducing 11β-prostaglandin F (2) in asthmatic individuals. However, a reasonable amount of evidence also show beneficial effects of n-3 PUFAs

for more prolonged periods, with reductions in prostaglandins being observed even at the third (FORTIN *et al.*, 1995; GOLDBERG; KATZ, 2007) and sixth month (VEDIN *et al.*, 2010) of intervention.

There are many confounding factors and limitations in human studies, which may difficult the understanding of n-3 PUFA in inflammatory response. Those include dose, source of n-3 PUFA, distribution and amounts of total and subtypes fatty acids in the n-3 PUFA source, population evaluated, genetic backgrounds, environmental conditions, quality and quantity of the diet, etc. Besides that, the baseline values of anti-inflammatory markers may mask the real effect of PUFA supplementation. Also, individual responsiveness to n-3 fatty acids should be taken into account as another major limitation to assess the effect on the inflammatory process and to suggest an optimal dose for n-3 PUFA. One practical example of these difficulties can be observed in one of our included studies (DE LUIS *et al.*, 2016), where unexpected results appeared, such as a significant increase in the pro-inflammatory markers LTB4, PGE2, 8-HETE and 12-HETE ($p<0,05$) after n-3 PUFA intake. In that particular protocol, participants were submitted to a ketogenic diet during an initial period of 45-60 days and according to the author that could interfere in both anti-inflammatory and pro-inflammatory eicosanoid secretion.

The present study has strengths, such as: (I) an effort was made to search for data in seven different databases and rigorously following PRISMA directions in order to minimize publication bias; (II) utilization of validated tools to characterize included studies in terms of methodological quality; (III) the summarized analysis focused on studies measuring comparable outcomes with similar protocols, reducing methodological heterogeneity. Additionally, there are limitations in the present study. Firstly, our meta-analysis results were constructed based on the before-and-after values within a same group, and not in between groups. Secondly, different types of n-3 fatty acids could be observed in intervention groups, and that may influence the final results, since there is a discrepant rate of interconversion in between ALA, EPA, DPA and DHA (INNES; CALDER, 2018). Lastly, due to the limited amount of evidence, our study included a small number of clinical trials (n=7) and therefore a greater number of controlled trials are required to strengthen our findings.

In conclusion, our systematic review and meta-analysis evidence the anti-inflammatory role of n-3 PUFAs through diet or supplementation on eicosanoid synthesis, especially prostaglandins markers, on adult individuals with obesity and overweight. Further clinical trials with high quality are needed to confirm these effects and explore optimal n-3 PUFA doses and period of intake in individuals with overweight and obesity. Finally, is imperative to remember that obesity is a complex condition, directly and indirectly influenced by environmental and genetic factors, thus the interaction of nutrients, especially n-3 fatty acids, with the inflammatory process may be considered as an important anti-inflammatory strategy by healthcare professionals in obesity treatment.

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Author contributions

1) GRBS, INMSR, VSSG and NP contributed significantly to the work's conception, design, data collection, interpretation and analysis; 2) GRBS, INMSR, VSSG, KGM and NP participated in the writing and critical revision of the article in a manner sufficient to establish ownership of the intellectual content; and 3) GRBS, INMSR, VSSG, KGM and NP read and approved the version of the manuscript being submitted.

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Conflict of interest

Declarations of interest: None.

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COMPLEMENTARY CONTENT

Appendix 1 – Database Search Strategy

Pubmed	(("Morbid obesity"[All Fields] OR "Morbid obesities"[All Fields] OR "Severe obesity"[All Fields] OR ("obesity, morbid"[MeSH Terms] OR ("obesity"[All Fields] AND "morbid"[All Fields]) OR "morbid obesity"[All Fields] OR ("severe"[All Fields] AND "obesities"[All Fields])) OR "Abdominal obesities"[All Fields] OR "Abdominal obesity"[All Fields] OR "Central obesities"[All Fields] OR "Central obesity"[All Fields] OR "Visceral obesity"[All Fields] OR ("obesity, abdominal"[MeSH Terms] OR ("obesity"[All Fields] AND "abdominal"[All Fields]) OR "abdominal obesity"[All Fields] OR ("visceral"[All Fields] AND "obesities"[All Fields])) OR "Obese men"[All Fields] OR "Obese women"[All Fields] OR "Overweight"[All Fields] OR "Overweight men"[All Fields] OR "Overweight women"[All Fields] OR "Excess weight"[All Fields] OR "obese"[All Fields] OR "obesity"[All Fields] OR "Fat accumulation"[All Fields] OR "fatness"[All Fields] OR "body fatness"[All Fields]) AND ("N3 fatty acids"[All Fields] OR "n-3 Fatty Acids"[All Fields] OR "n 3 Fatty Acids"[All Fields] OR "n3 Fatty Acids"[All Fields] AND "W3 fatty acids"[All Fields] OR "w-3 fatty acids"[All Fields] OR "w 3 fatty acids"[All Fields] OR "N3 Polyunsaturated Fatty Acid"[All Fields] OR "n-3 Polyunsaturated Fatty Acid"[All Fields] OR "n 3 Polyunsaturated Fatty Acid"[All Fields] OR "n3 Polyunsaturated Fatty Acid"[All Fields] OR "n-3 PUFA"[All Fields] OR "N 3 PUFA"[All Fields] OR "N3 PUFA"[All Fields] OR "N-3 oils"[All Fields] OR ("fatty acids, omega-3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega-3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR ("n3"[All Fields] AND "oils"[All Fields])) OR "N 3 oils"[All Fields] OR "Omega 3 Fatty Acids"[All Fields] OR "Eicosapentanoic Acid"[All Fields] OR "omega 3 Eicosapentaenoic Acid"[All Fields] OR "omega-3-Eicosapentaenoic Acid"[All Fields] OR "Timnodonic Acid"[All Fields] OR "Docosahexenoic Acid"[All Fields] OR (("fatty acids, omega-3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega-3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR "omega 3"[All Fields]) AND Docosahexenoic[All Fields] AND ("acids"[MeSH Terms] OR "acids"[All Fields] OR "acid"[All Fields])) OR "Docosahexaenoate"[All Fields] OR "alpha Linolenic Acid"[All Fields] OR "Linolenate"[All Fields] OR "Linolenic Acid"[All Fields] OR "EPA and DHA supplementation"[All Fields] OR EPA[All Fields] OR DHA[All Fields] OR "omega 3"[All Fields] OR "omega-3"[All Fields] OR "fish oil"[All Fields] OR "arachidonic acid"[All Fields] OR "arachidonate"[All Fields] OR "eicosatetraenoic acid"[All Fields])) AND (("eicosanoids"[MeSH Terms] OR "eicosanoids"[All Fields] OR "eicosanoid"[All Fields]) OR ("eicosanoids"[MeSH Terms] OR "eicosanoids"[All Fields] OR "icosanoid"[All Fields]) OR ("prostaglandins"[MeSH Terms] OR "prostaglandins"[All Fields] OR "prostanoid"[All Fields]) OR ("lipoxins"[MeSH Terms] OR "lipoxins"[All Fields] OR "lipoxin"[All Fields]) OR ("prostaglandins"[MeSH Terms] OR "prostaglandins"[All Fields] OR "prostaglandin"[All Fields]) OR ("thromboxanes"[MeSH Terms] OR "thromboxanes"[All Fields] OR "thromboxane"[All Fields]) OR ("leukotrienes"[MeSH Terms] OR "leukotrienes"[All Fields] OR "leukotriene"[All Fields]) OR "hydroxyeicosatetraenoic acid"[All Fields] OR "Isoprostane"[All Fields] OR "dinoprostone"[All Fields])

Web of science	("Morbid obesity" OR "Severe obesity" OR "Abdominal obesity" OR "Central obesity" OR "Visceral obesity" OR "Obese men" OR "Obese women" OR "Overweight" OR "Overweight men" OR "Overweight women" OR "Excess weight" OR "obese" OR "obesity" OR "Fat accumulation" OR "fatness" OR "body fatness") AND TÓPICO: ("N3 fatty acids" OR "n-3 Fatty Acids" OR "n 3 Fatty Acids" OR "n3 Fatty Acids" "W3 fatty acids" OR "w-3 fatty acids" OR "w 3 fatty acids" OR "N3 Polyunsaturated Fatty Acid" OR "n-3 Polyunsaturated Fatty Acid" OR "n 3 Polyunsaturated Fatty Acid" OR "n3 Polyunsaturated Fatty Acid" OR "n-3 PUFA" OR "N 3 PUFA" OR "N3 PUFA" OR "N-3 oils" OR "N3 oils" OR "N 3 oils" OR "Omega 3 Fatty Acids" OR "Eicosapentanoic Acid" OR "omega 3 Eicosapentaenoic Acid" OR "omega-3-Eicosapentaenoic Acid" OR "Timnodonic Acid" OR "Docosahexenoic Acid" OR "omega 3 Docosahexenoic Acid" OR "Docosahexaenoate" OR "alpha Linolenic Acid" OR "Linolenate" OR "Linolenic Acid" OR "EPA and DHA supplementation" OR EPA OR DHA OR "omega 3" OR "omega-3" OR "fish oil" OR "arachidonic acid" OR "arachidonate" OR "eicosatetraenoic acid") AND TÓPICO: (eicosanoid OR Icosanoid OR Prostanoid OR Lipoxin OR Prostaglandin OR Thromboxane OR Leukotriene OR "hydroxyeicosatetraenoic acid" OR "Isoprostane" OR "dinoprostone")
Scopus	TITLE-ABS-KEY (("Morbid obesity" OR "Morbid obesities" OR "Severe obesity" OR "Severe obesities" OR "Abdominal obesities" OR "Abdominal obesity" OR "Central obesities" OR "Central obesity" OR "Visceral obesity" OR "Visceral obesities" OR "Obese men" OR "Obese women" OR "Overweight" OR "Overweight men" OR "Overweight women" OR "Excess weight" OR "obese" OR "obesity" OR "Fat accumulation" OR "fatness" OR "body fatness" AND "N3 fatty acids" OR "n-3 Fatty Acids" OR "n 3 Fatty Acids" OR "n3 Fatty Acids" "W3 fatty acids" OR "w-3 fatty acids" OR "w 3 fatty acids" OR "N3 Polyunsaturated Fatty Acid" OR "n-3 Polyunsaturated Fatty Acid" OR "n 3 Polyunsaturated Fatty Acid" OR "n3 Polyunsaturated Fatty Acid" OR "n-3 PUFA" OR "N 3 PUFA" OR "N3 PUFA" OR "N-3 oils" OR "N3 oils" OR "N 3 oils" OR "Omega 3 Fatty Acids" OR "Eicosapentanoic Acid" OR "omega 3 Eicosapentaenoic Acid" OR "omega-3-Eicosapentaenoic Acid" OR "Timnodonic Acid" OR "Docosahexenoic Acid" OR "omega 3 Docosahexenoic Acid" OR "Docosahexaenoate" OR "alpha Linolenic Acid" OR "Linolenate" OR "Linolenic Acid" OR "EPA and DHA supplementation" OR epa OR dha OR "omega 3" OR "omega-3" OR "fish oil" OR "arachidonic acid" OR "arachidonate" OR "eicosatetraenoic acid" AND eicosanoid OR eicosanoid OR prostanoid OR lipoxin OR prostaglandin OR thromboxane OR leukotriene OR "hydroxyeicosatetraenoic acid" OR "Isoprostane" OR "dinoprostone"))

Embase	('morbid obesity' OR 'severe obesity' OR 'abdominal obesity' OR 'central obesity' OR 'visceral obesity' OR 'obese men' OR 'obese women' OR 'overweight' OR 'overweight men' OR 'overweight women' OR 'excess weight' OR 'obese' OR 'obesity' OR 'fat accumulation' OR 'fatness' OR 'body fatness') AND (('n-3 fatty acids' OR 'n 3 fatty acids' OR 'n3 fatty acids') AND 'w3 fatty acids' OR 'w-3 fatty acids' OR 'w 3 fatty acids' OR 'n-3 polyunsaturated fatty acid' OR 'n 3 polyunsaturated fatty acid' OR 'n3 polyunsaturated fatty acid' OR 'n-3 pufa' OR 'n 3 pufa' OR 'n3 pufa' OR 'n-3 oils' OR 'n3 oils' OR 'n 3 oils' OR 'omega 3 fatty acids' OR 'eicosapentanoic acid' OR 'omega 3 eicosapentaenoic acid' OR 'omega-3-eicosapentaenoic acid' OR 'timnodonic acid' OR 'docosahexenoic acid' OR 'omega 3 docosahexenoic acid' OR 'docosahexaenoate' OR 'alpha linolenic acid' OR 'linolenate' OR 'linolenic acid' OR 'epa and dha supplementation' OR epa OR dha OR 'omega 3' OR 'omega-3' OR 'fish oil' OR 'arachidonic acid' OR 'arachidonate' OR 'eicosatetraenoic acid') AND (eicosanoid OR icosanoid OR prostanoid OR lipoxin OR prostaglandin OR thromboxane OR leukotriene OR 'hydroxyeicosatetraenoic acid' OR 'isoprostane' OR 'dinoprostone')
Cochrane	Title Abstract Keyword “Morbid obesity” OR “Severe obesity” OR “Abdominal obesity” OR “Central obesity” OR “Visceral obesity” OR “Obese men” OR “Obese women” OR “Overweight” OR “Overweight men” OR “Overweight women” OR “Excess weight” OR “obese” OR “obesity” OR “Fat accumulation” OR “fatness” OR “body fatness” in Title Abstract Keyword AND "N3 fatty acids" OR "n-3 Fatty Acids" OR "n 3 Fatty Acids" OR "n3 Fatty Acids" "W3 fatty acids" OR "w-3 fatty acids" OR "w 3 fatty acids" OR "N3 Polyunsaturated Fatty Acid" OR "n-3 Polyunsaturated Fatty Acid" OR "n 3 Polyunsaturated Fatty Acid" OR "n3 Polyunsaturated Fatty Acid" OR "n-3 PUFA" OR "N 3 PUFA" OR "N3 PUFA" OR "N-3 oils" OR "N3 oils" OR "N 3 oils" OR "Omega 3 Fatty Acids" OR "Eicosapentanoic Acid" OR "omega 3 Eicosapentaenoic Acid" OR "omega-3-Eicosapentaenoic Acid" OR "Timnodonic Acid" OR "Docosahexenoic Acid" OR "omega 3 Docosahexenoic Acid" OR "Docosahexaenoate" OR "alpha Linolenic Acid" OR "Linolenate" OR "Linolenic Acid" OR “EPA and DHA supplementation” OR EPA OR DHA OR “omega 3” OR “omega-3” OR “fish oil” OR “arachidonic acid” OR “arachidonate” OR “eicosatetraenoic acid” in Title Abstract Keyword AND eicosanoid OR Icosanoid OR Prostanoid OR Lipoxin OR Prostaglandin OR Thromboxane OR Leukotriene OR "hydroxyeicosatetraenoic acid" OR "Isoprostane" OR “dinoprostone” in Title Abstract Keyword - (Word variations have been searched)

Appendix 2. Excluded articles and reasons for exclusion (n = 32).

Author, Year	Reason for exclusion
Aronson et al. (2011)	3
Allaire et al. (2016)	5
Denzlinger et al. (1995)	5
Djuric et al. (2017)	5
Gammelmark et al. (2012)	5
Huerta et al. (2014)	5
Holt et al. (2017)	5
Lang et al. (2019)	5
Murphy et al. (2007)	5
Newman et al. (2014)	5
Peres et al. (2018)	5
Petersson et al. (2010)	5
Pickens et al. (2015)	5
Shearer et al (2018)	5
Trebble et al. (2004)	3
Young et al. (2011)	5
Celada et al (2014)	2
Bohm et al (2013)	5
Itariu et al (2012)	2
Fisk et al (2018)	2
Lengfelder et al (2016)	2
Quach et al (2017)	2
Uach et al (2017)	2
Hill et al (2007)	5
Gruslova et al (2017)	2
Pickens et al. (2017)	5
Qin et al. (2015)	6
Nieman et al. (2012)	5
Kaatz et al (2004)	6

Garcia et al (2016)	5
Garcia-Ravelo et al (2018)	5
Brenner et al (2017)	2
Stephensen et al (2011)	5

1) Patients that underwent bariatric/metabolic surgery;
2) Consensus, management, reviews, letters, conference abstracts, editorials
3) Studies evaluating subjects with inflammatory diseases
4) Use of non-steroidal anti-inflammatory drugs or n-3 PUFA supplements
5) Absent eicosanoid measurement or measurements other than serum or plasma eicosanoids
6) Participants out of BMI range

3. CONSIDERAÇÕES FINAIS

Este trabalho resultou na elaboração de revisão sistemática de ensaios clínicos com meta-análise acerca do efeito do consumo de ácidos graxos n-3 no perfil de eicosanoides de pacientes com obesidade e/ou sobrepeso, mas sem quaisquer outras condições crônicas de caráter inflamatório. O objetivo foi auxiliar na consolidação do conhecimento científico na área de lipídios e resposta inflamatória, e até o presente momento ainda não há trabalhos publicados no tema desta revisão sistemática.

A inflamação constitui um importante pilar no surgimento e agravamento de diversas doenças, motivo este pelo qual a consolidação de estratégias nutricionais focando o consumo saudável de lipídios com características anti-inflamatórias é de grande valia para a prática de profissionais de saúde, em especial para pacientes portadores de obesidade, cuja inflamação manifesta-se de forma crônica.

Com o presente trabalho, torna-se possível concluir que tanto medidas nutricionais, (estímulo ao consumo de alimentos fontes de ômega-3), como estratégias de suplementação (utilização de óleo de peixe em cápsulas), são capazes de modificar o perfil de eicosanoides de pessoas com obesidade, assim como reduzir os níveis séricos das prostaglandinas pró-inflamatórias.

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