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Review

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Does Dietary Intake Impact Omentin Gene Expression and Plasma Concentration? A Systematic Review

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Omentin gene expression · Dietary intakes · Hypocaloric diet · Adipose tissue · Adipokines

Abstract
Background: Omentin is an adipokine with anti-inflammatory and insulin-sensitizing effects that can play a protective role against cardiovascular disease and diabetes. The aim was to systematically review and summarize the existing evidence on the association between overall dietary intake and omentin gene expression and circulation. ***Summary:*** A literature search was conducted in PubMed, Scopus, and Web of Science up to September 2019. Of the 1,940 retrieved articles, 20 relevant studies were included, 6 of which were observational, 11 were clinical trials in humans, and 3 were animal studies. Four randomized controlled trials (RCTs) had a high risk of bias (RoB), 1 had "some concerns", and 2 had a low RoB. Among the nonrandomized studies with comparators, 4 had a serious RoB and 2 had a moderate RoB. In the experimental animal studies with a moderate RoB, conflicting results for omentin serum concentration were found for high-fat and low-fat diets. A high-fat diet (HFD) was shown to reduce omentin gene expression in one animal study. In the observational studies, omentin serum concentration was reduced by Ramadan fasting and saturated fatty acid (SFA) intake, and an increase in omentin gene expression was observed with monounsaturated fatty acid (MUFA) intake. There was no association of dietary inflammatory index (DII), macronutrient intake, or total calorie intake with omentin plasma concentrations. In the human interventional studies, omentin plasma concentration increased with a long-term low-calorie, low-fat diet (LFD), and no change was seen with a HFD or a short-term low-calorie diet (LCD). ***Key Messages:*** It seems that a long-term diet with a lower fat content and a balanced distribution of fatty acids, i.e., a higher MUFA and lower SFA intake, may effectively increase omentin plasma concentration, possibly via improved insulin resistance and reduced inflammation, but more research is needed to confirm or refute this.

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Introduction

For decades, it was believed that adipose tissue (AT) was a passive reservoir for fatty acids, and was involved in mechanical and heat insulation, and the regulation of thermogenesis. However, today, it is clear that AT is also an active endocrine organ that secretes a large number of peptides and bioactive mediators called adipokines into the circulation, and that these adipokines have autocrine, paracrine, and endocrine functions. In this context, omentin is one of the adipokines mainly produced by AT and is related to obesity and its comorbidities [1–3].

The omentin gene encodes a 34-kDa adipokine that is expressed and secreted mainly from visceral AT, as well as some other organs such as mesothelial, endothelial, and vascular smooth-muscle cells [4, 5]. In humans, the omentin gene is located on chromosome 1q21.3 and contains 7 introns and 8 exons [4]. A homolog of omentin with a characteristic of omentin/intelectin has been identified, called omentin-2; omentin-2 has 83% amino acid similarity to that in omentin [6].

Several studies have shown that omentin plays an important role in maintaining metabolism and insulin sensitivity. It also has anti-inflammatory and antiatherosclerotic effects, and can help to reduce the risk of cardiovascular disease and diabetes through AMP- and mitogen-activated protein kinase, Akt, and NF-κB [7, 8]. The main form of omentin in human blood is omentin-1. Past reports showed that a low omentin plasma concentration may contribute to the pathogenesis of insulin resistance and type 2 diabetes mellitus (T2DM) [7, 9]. Also, preclinical and clinical studies reported that omentin plasma concentration was inversely associated with various cardiovascular risk factors, such as body mass index (BMI), waist circumference, body fat, insulin concentration, and homeostasis model assessment of insulin resistance [10–12]. However, a cohort study demonstrated that a higher concentration of omentin is associated with a greater risk of experiencing cardiovascular events in subjects with diabetes. This discrepancy may be due to this fact that omentin plasma concentration may increase in a compensatory manner in response to risk factors that increase cardiovascular events in diabetes [13]. Omentin is also inversely correlated with leptin, resistin, and TNF-α, and is positively correlated with adiponectin [8]. The results of these past studies, as well as the many resemblances between omentin and adiponectin, suggests that omentin may be a beneficial adipocytokine [14].

A growing number of studies examining omentin have generated contradictory findings. Some reported that omentin plasma concentration increased after a low-calorie diet (LCD) [12, 15], while others revealed that these diets lead to a reduction in omentin plasma concentration [16, 17]. There was no change in omentin plasma concentration in response to a very low-calorie diet (VLCD) [18], soybean oil [19], or sesame oil [20]. Interestingly, higher omentin plasma concentrations were detected with lower saturated fatty acid (SFA) intake [21]. However, in another study, no association between omentin plasma concentrations and total energy intake and macronutrients was observed [22]. Since omentin is an adipokine that has anti-inflammatory effects and reduces insulin resistance, and can subsequently prevent cardiovascular disease and diabetes, it is important to understand the relationship between omentin and diet. Because of these inconclusive results on the association between dietary factors and omentin plasma concentrations, summarizing what is known about omentin responses to diet will help to identify knowledge gaps and facilitate the design of future intervention studies.

To date, no systematic review has been conducted with a focus on the association of dietary factors with omentin gene expression and plasma concentration. Therefore, we aimed to summarize the available evidence to clarify the effect of micro- and macronutrients and dietary patterns on omentin gene expression and plasma concentration in humans and animals.

Table 1. PICOS and PECO criteria used to define the research question and search the literature

Criteria	Description
Participants	Animals (mammals) and human adults (all races and both sexes)
Interventions /Exposure[1]	Dietary intake; diet; micro- and macronutrients; dietary pattern; enriched food
Comparisons	With or without a control group in animal and human studies
Outcomes	Concentration and gene expression of omentin
Study design	Any interventional trials (animal and human), observational (longitudinal and cross-sectional) design

PICOS: participants, interventions, comparisons, outcomes, study design; PECO: participants, exposure, comparisons, outcomes. [1] Exposure in observational studies.

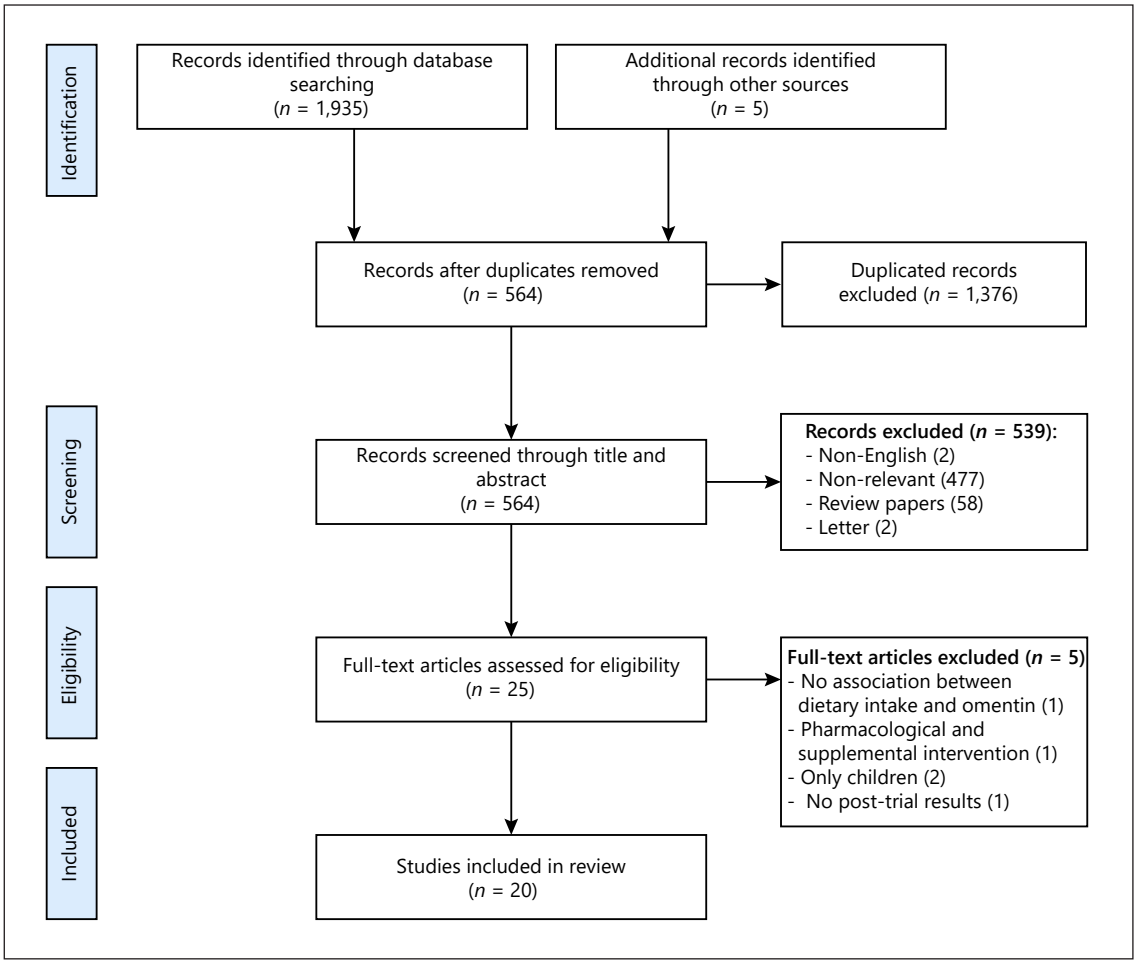

Fig. 1. PRISMA flow diagram for the systematic literature review of the effect of dietary intakes on omentin gene expression and concentration.

Materials and Methods

Literature Search

The online databases PubMed, Scopus, and Web of Science were searched for relevant studies. According to the PICOS (participants, interventions, comparisons, outcomes, study design) and PECO (population, exposure, comparison, outcome) inclusion/exclusion criteria for interventional and observational studies, respectively, we used combinations of terms (including MeSH terms) such as omentin, diet(ary), food, nutrition, nutrient, intake, and pattern to search for relevant publications up to September 2019. Since observational studies were included alongside interventional studies (even without the control group), there was some modification of the PICOS and PECO criteria (Table 1). The reference list of included studies was also checked manually. During the preparation and presentation of this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed [23]. A summary of the review and the reasons for excluding studies are presented in the PRISMA flow chart (Fig. 1).

Study Eligibility

Studies were included in this systematic review if they met the following inclusion criteria: (1) they were interventional and observational studies conducted on animals or humans regardless of their demographic group, BMI, age, and sample size; (2) they investigated the association of micro- and macronutrients, food items, food groups, and dietary pattern as exposure, with circulatory concentration and gene expression of omentin; (3) they were published in English, with full texts and not just abstracts. Studies were excluded if they investigated the effect of herbal supplementations and the effect of weight change due to disease without dietary interventions. Case studies, review articles, in vitro studies, and studies on human or animal cell lines were also excluded.

Selecting the Studies

The screening process commenced with the removal of duplicate articles using EndNote tools. Two researchers independently conducted the literature search and screened the titles, abstracts, and full texts of the identified studies, based on the eligibility criteria detailed above. The final decision regarding the eligibility of articles was made by agreement between the 2 researchers, and any

disagreement was resolved by involving a third researcher. Figure 1 presents the PRISMA flow diagram of the review summary and procedure.

Data Extraction

Two investigators independently extracted the following data for each of the included articles: author names, publication year, location, aim, sample size, age, study design, practice setting, study duration, participants' health status, dietary assessment, omentin assessment method, main results, and any other results related to omentin. In the case of missing data or unclear pieces of information, it was considered that the authors did not report such variables.

Assessment of Risk of Bias

We evaluated the methodological risk of bias (RoB) of the studies using 4 different RoB assessment tools because this review included both human (observational and interventional) and animal studies. The Rob2 tool (revised tool for Risk of Bias in randomized trials) [24] and the ROBINS-I tool (Risk of Bias in Non-Randomized Studies of Interventions) [25] were used for evaluating the RoB of randomized and nonrandomized studies with the comparison between relevant study groups, respectively (online suppl. Fig. 1, 2; see www.karger.com/doi/10.1159/000513885 for all online suppl. material). The RoB of single-arm nonrandomized studies, without evaluating the "comparability" item, was assessed by the Newcastle-Ottawa scale (online suppl. Table 1) [26]. We used the SYRCLE (SYstematic Review Center for Laboratory Animal Experimentation) tool for animal studies (online suppl. Table 2) [27]. Any disagreement was resolved by discussion and consensus. We used the robvis tool (visualization tool for risk of bias assessments in a systematic review) for presenting the data as appropriate [28].

Results

Overview of Included Studies

In this analysis, 1,940 articles were identified. A total of 564 articles were screened after removing duplicate articles. After evaluating title and abstract, 25 articles were selected for full-text assessment, 20 of which were identified as meeting the inclusion criteria. Studies were classified according to type, resulting in 6 observational studies [21, 22, 29–32], 3 animal studies [20, 33, 34], and 11 intervention studies. Of the human intervention studies, 7 were conducted without a control group [12, 15–18, 35, 36] and 4 considered a control group [19, 37–39].

Participants in the included human studies included both genders and comprised adults between the ages of 18 and 65 years. Of the 17 human studies included in our review, 2 recruited healthy subjects, 10 recruited obese or overweight subjects, and the rest included individuals who were pregnant, diabetic, had nonalcoholic fatty liver disease (NAFLD) or NAFLD with T2DM, or were obese with T1DM. The primary studies were conducted in a variety of countries, including Iran, the Czech Republic, Spain, the USA, and Turkey. A summary of the details and findings of the included studies are presented in Tables 2, 3, and 4, categorized by study design. Because of high methodological heterogeneity (duration, population, and intervention), no meta-analysis was performed.

Animal Experimental Studies

Up to now, only 3 studies of moderate RoB have assessed the effect of dietary change on the omentin plasma concentration and gene expression in animals (Table 2) [20, 33, 34]. In these studies, a significant reduction in omentin gene expression was observed after intervention with a normal diet and a high-fat diet (HFD) compared to the control (no induced obesity and diabetes) [33, 34]. However, the results regarding the effects of HFD on omentin plasma concentration were contradictory. Feng et al. [33] showed a reduced omentin plasma concentration in the HFD group compared to the control, but no difference was found between the HFD group and the control in another study [34]. Similarly, sesame oil did not show a significant effect on omentin plasma concentration [20]. Also, there were no significant differences in omentin gene expression and plasma concentration between rats with HFD-induced obesity that were fed a LFD and those fed a HFD [33].

In summary, these experimental animal studies, which examined the effects of dietary fat on omentin gene expression, showed that a HFD could reduce omentin gene expression. However, the results regarding omentin plasma concentrations were not consistent with gene expression changes. Consistent and reliable findings of serum and gene expression will be helpful to better understand the function and mechanism involved, and, ultimately, determine the relationships. Therefore, human studies are needed to consider the effect of dietary intake, especially fat, on obesity and diabetes via the regulation of omentin plasma concentration and gene expression.

Human Observational Studies

Table 3 summarizes the main characteristics and results of the effect of dietary intakes on omentin plasma concentrations. From these studies, we observed that omentin plasma concentrations may be associated with dietary intakes and dietary approaches. The possible effect of Ramadan fasting was demonstrated in 2 moderate RoB studies [29, 30]. We observed a reduction in omentin serum concentration with fasting compared to nonfasting [29, 30]; however, Ramadan fasting did not affect omentin serum concentration compared to baseline [30]. One of

Table 2. Summary of the animal studies that investigated the impact of dietary intake on omentin concentration and gene expression

First author [ref.], year	Sample	Intervention	Duration	Outcome	Main results	Other results
Feng [33], 2013	Male SD rats	Standard chow for 16 weeks (calorie-based components; 65% carbohydrates, 22% proteins, and 13% lipids; $n = 8$) Induced obesity with HFD for 8 weeks (33% carbohydrates, 12% proteins, and 55% lipids; $n = 831$) The HFD group was then divided to receive exenatide ($n = 88$), Avandamet ($n = 88$), LFD ($n = 88$), or HFD ($n = 87$) for 8 more weeks	16 weeks	gene expression and serum concentration of omentin	Decreased expression (visceral) and concentration of omentin in the HFD group compared to control No significant differences in omentin concentration in the LFD group Decreased expression (visceral) of omentin in the LFD group compared to control Increased omentin concentration the exenatide and Avandamet groups compared to the HFD and LFD groups	Suppressed adiponectin in the HFD rats Enhanced leptin in the HFD and diet-change rats compared to control Enhanced TG and FFA levels in HFD rats vs. control Decreased TG in LFD vs. HFD rats
Goodarzi [34], 2019	Male mice ($n = 36$)	Normal chow diet (healthy mice as controls for T1D [$n = 6$] and T2D [$n = 6$]). Mice with T1D on high doses of STZ ($n = 8$) Mice with T2D on a HFD (HFD + STZ; $n = 8$) Mice with T2D on a NPD (NPD + STZ; $n = 8$)	12 weeks	gene expression and serum concentration of omentin	No significant change in omentin concentration in T2D mice on a HFD compared to control Plasma omentin concentration decreased in T2D mice on a NPD and increased in T1D mice Gene expression of omentin was elevated in T1D mice and reduced in T2D mice on a HFD/NPD compared to control	Increased body weight, TG, cholesterol, and plasma glucose in mice on a HFD compared to control Plasma insulin decreased in T1D mice, increased in HFD mice, and showed no difference in the NPD mice
Babaei [20], 2015	Female Wistar rats ($n = 10$)	Sesame oil (3 days a week for 8 weeks)	8 weeks	serum omentin concentration	No significant change in omentin concentration compared to control after the intervention	Increased body weight and BMI after the intervention

HFD, high-fat diet; LFD, low-fat diet; FFA, free fatty acid; NPD, normal pellet diet; STZ, streptozotocin; T1D, type 1 diabetes; T2D, type 2 diabetes; SD, Sprague Dawley; TG, triglyceride.

the limitations of this particular study was the lack of a dietary intake assessment [29]. In another high RoB study, we did not find any differences in omentin serum concentration between high and low dietary inflammatory index (DII) scores. It should be mentioned that participants with higher DII scores had a higher intake of carbohydrate and SFAs, and a lower intake of protein, polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), and fiber [31]. In 2 moderate and high RoB studies, we found no association between omentin plasma concentration and dietary intake of total energy, protein, carbohydrate, and fat [21, 22]. Furthermore, a higher omentin plasma concentration was associated with a lower SFA intake [21]. At the gene expression level, only 1 high RoB study demonstrated a positive association of dietary intake of MUFAs, PUFAs, and omega-6 with omentin gene expression; however, the observed results remained significant only for dietary MUFAs in the final model [32].

Based on high RoB studies, it seems that SFAs are inversely and MUFAs are positively related to omentin plasma concentration and gene expression, respectively, in participants with obesity. On the other hand, the moderate RoB studies demonstrated that Ramadan fasting could decrease omentin plasma concentration when compared to nonfasting [21, 22, 29–32]. Measurement of dietary intake measurement was variable across studies, with 24-h dietary recall, self-reported record, and food frequency questionnaires all being used. It should be noted that studies have been conducted on participants with obesity and these could indicate the impact of excess body fat accumulation on current findings. However, further observational research including cohort studies with longer follow-up of overweight and normal-weight subjects in larger samples of different ethnicities is needed to substantiate these findings and see if differences exist in different body types. Moreover, the role of confounders, such as insulin, should be considered as a factor that would influence the results of abovementioned studies.

Human Interventional Studies

Table 4 summarizes the main characteristics and results of dietary intakes on omentin gene expression and plasma concentration in 11 articles. Several studies investigated the effect of a LCD on omentin plasma concentration [12, 15, 17, 19, 35–37]. In serious RoB studies, we observed that the omentin plasma concentration increased after weight loss from long-term LCDs as well as LCDs within a Mediterranean dietary pattern, in participants with obesity [12, 15, 17]. In studies deemed to be of some concern regarding a RoB, we found similar results with a long-term hypoca-

Table 3. Summary of the observational studies on the association of dietary intake and omentin status

First author [ref.], year	Design; location	Gender, age, and condition of patients	Follow-up duration	Outcome, ng/mL	Results	Changes in other measurements
Kiyak Caglayan [29], 2016	prospective; Turkey	female, 28 years, pregnant (n = 40)	4 weeks	Group with fasting: End 13.11±1.79; Group without fasting: End 18.64±3.48	Serum omentin concentration was lower in the group with fasting than in the nonfasting group	No differences in fasting glucose, TG, HDL-C, and thyroid hormone levels between the 2 groups Increased LDL-C, TC, leptin, and apelin in the group with fasting
Nosrati-Oskouie [32], 2019	cross-sectional; Iran	Obesity group: male + female, 38 years, obese (n = 50) Group without obesity: 46 years, nonobese (n = 47)	–	Obesity group: VAT; 1.23±0.60 SAT; 3.68±2.08 Group without obesity: VAT; 11.06±3.52 SAT; 6.49±2.17	Positive association of omentin gene expression with dietary MUFA intake in VAT of group with obesity after adjustment for confounders[1]	No significant differences in omentin gene expression in SAT between 2 groups Omentin gene expression in VAT was higher in the group without obesity The positive association between omentin gene expression and plasma omega-6:omega-3 ratio in VAT of group without obesity after adjustment for confounders
Ebrahimi [30], 2018	prospective; Iran	Group with fasting: male + female, 37 years, NAFLD (n = 42) Group without fasting: male + female, 35 years, NAFLD (n = 41)	4 weeks	Group with fasting: Baseline 229.78±106.69 End 192.93±75.71 Group without fasting: Baseline 222.82±105.45 End 209.05±99.84	No change in serum omentin concentration in either group at the end of the study Mean differences in serum omentin concentration was higher in the group with fasting (a greater reduction with fasting)	Increased energy, total carbohydrate, total fat intakes and no change in total protein intake in the group with fasting after Ramadan No change in energy and macronutrient intake in the group without fasting Mean differences in weight, BMI, WC, WHR, body fat percent, and serum vaspin concentration were greater in the group with fasting (a greater reduction with fasting)
Zabetian-Targhi [21], 2016	cross-sectional; Iran	male, 37 years, obese (n = 33) female, 39 years, obese (n = 137)	–	male 36.28 ± 14.94 female 33.92 ± 13.24	A negative association between SFA and omentin concentration after adjustment for total energy intake in all subjects A positive association between SFA and omentin concentration in women	Significant association of higher omentin concentration with lower levels of fasting insulin, glucose, TC, IL-6, and TNF-α, and higher levels of IL-13, IL-14, and IL-1β in all subjects.
Bienertová-Vašků [22], 2014	cross-sectional; Czech Republic	male, 50 years, obese (n = 12) female, 51 years, obese (n = 53)	–	all 442.75±159.65; male 467.20 ±160.65 female 437.86±160.63	No association of plasma omentin concentration with total energy intake and macronutrients in all subjects	No significant correlation found between omentin concentration and BMI, weight, WC, HC, WHR, and body fat
Mirmajidi [31], 2019	cross-sectional; Iran	male and female, 18–60 years, healthy obese (n = 171)	–	higher DII score: 72.60 (58.10–80.60) lower DII score: 69.90 (59.50–95.50)	No differences between those below and above the median DII score	Levels of FBS were higher in those above than in those below the median DII score

SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IL, interleukin; TNF, tumor necrosis factor; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; DII, dietary inflammatory index; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio. [1] Adjusted for age, insulin, and total energy intake. [2] Median (IQR).

Table 4. Summary of the intervention studies on the effect of dietary intake on omentin status

First author [ref.], year	Study design; location	Gender, age, and condition of patients	Intervention	Duration	Outcome, ng/mL	Results	Changes in other measurements
Hamnvik [37], 2015	double-blind, randomized, placebo-controlled trial; USA	Study 1: male, 22 years, healthy (n = 6) Study 2: male, 23 years, healthy (n = 68)	Study 1: fed state Study 2: fasting state	Study 1: 4 days Study 2: 8 days	Study 1[b]: Baseline – End – Study 2: Baseline[b] – End 231±38	No change in omentin concentration between baseline and follow-up in the fed state No change in omentin concentration between baseline and follow-up in the fasting state	No change in day-night variation of omentin levels Decreased omentin levels after administration of high-dose metreleptin (0.1 mg/kg)
Vamvini [19], 2016	randomized, placebo-controlled trial; USA	male and female, 35 years, healthy (n = 626)	Group 1: 1.25 g/kg soybean oil at time 0 and 3 h for 6 h (n = 6) Group 2: 20% intralipid i.v. lipid emulsion[a] (n = 6) Group 3: 10% intralipid i.v. lipid emulsion[a] (n = 5) Group 4: control (saline infusion; n = 9)	6 h	Baseline 281.4±86.6 End[b] –	No change in omentin concentration after intervention in any group	Increased glucagon levels in the oral lipid group compared with the control group No change in fetuin-A, irisin, and adiponectin in the lipid group compared with the control group
Arslan [16], 2017	randomized trial; Turkey	male and female, 38 years, T2DM and NAFLD (n = 654)	Diet (no details reported) (n = 25) 2 g/day metformin along diet (n = 29)	3 months	Baseline 5.37±1.31 End 4.00±1.46	Serum omentin was decreased after the intervention	Decreased body weight, BMI, WC, HC, body fat percentage, HOMA-IR, HbA_{1c}, and glucose levels after intervention in the group with diet
Lesná [15], 2015	clinical trial; Czech Republic	male and female, 29–62 years, obesity and T1DM (n = 614)	Phase 1: fasting for 1 week and diet (1,200 kcal/day, 75 g protein, 40 g fat, 150 g saccharides) for 3 weeks Phase 2: diet (1,650 kcal/day, 75 g protein, 50 g fat, 225 g saccharides) for a further 11 months	Phase 1: 1 month Phase 2: 11 months	Baseline[e] 5.31 (3.72–6.49) End of phase 1[e] 5.05 (3.91–7.32) End of phase 2[e] 9.74 (9.11–10.98)	Plasma omentin was stable at baseline and phase 1; increased in phase 2	Decreased BMI, WC, and a daily dose of insulin in baseline vs. phase 1 and 2 Decreased LDL-C and TC in phase 1 vs. baseline Enhanced HbA_{1c} and HDL-C levels in phase 2 vs. baseline
Urbanová [18], 2014	clinical trial; Czech Republic	female, 60 years, obese non-diabetic (n = 637) female, 60 years, obese T2DM (n = 611) female, 43 years, healthy (n = 626)	VLCD with energy intake 600 kcal/day (obese nondiabetic n = 610; obese T2DM n = 611) 3 months of exercise (30 min aerobic exercise 3 times a week)[a] (obese nondiabetic, n = 613) bariatric surgery[a] (obese nondiabetic, n = 613)	2 weeks	Obese nondiabetic: Baseline 403.8±57.68 End 406±54.20 Obese T2DM: Baseline 474.9±44.61 End 485.7±42.88 Healthy Baseline 565.5±27.74 mRNA expression[b]	No change in serum and mRNA expression of omentin after VLCD in any group	Decreased BMI and levels of CRP, glucose, HDL-C and TC, but no change in insulin, LDL-C, TG, leptin, resistin, adiponectin, and HOMA-IR in the group with obesity and T2DM after the intervention Decreased BMI, LDL-C, HDL-C, and TC, but no effect on CRP, insulin, glucose, HOMA-IR, TG, leptin, resistin, and adiponectin levels in obese nondiabetic subjects after the intervention
Jafari [38], 2016	randomized, placebo-controlled, double-blind, parallel-arm; Iran	women, postmenopausal, diabetic (n = 659) group with FY (n = 30) group with PY (n = 29)	1 serving of low-fat FY (2,000 IU vitamin D in 100 g) 1 serving of PY	12 weeks	Group with FY: Baseline 0.08±0.009 End 0.12±0.01 Group with PY: Baseline 0.09±0.01 End 0.09±0.01 Between 2 groups Model 1[c] FY: 0.12±0.008 PY: 0.08±0.008 Model 2[d] FY: 0.12±0.008 PY: 0.09±0.008	Serum omentin increased in the FY group compared to baseline No change in serum omentin in the PY group compared to baseline Omentin concentration in the FY group was higher than in the PY group after intervention	Enhanced 25(OH)D level and decreased fasting insulin, HOMA, PTH, TG, WC, WHR, FM, and hs-CRP in the group with FY compared to baseline Enhanced glycemic markers (except HbA_{1c}), WC, WHR, BMI, FM, and hs-CRP in the group with PY
Moreno-Navarrete [12], 2010	clinical trial; Spain	male and female, 42 years, obese (n = 635) male, 42 years, obese (n = 618) female, 43 years, obese (n = 617)	A deficit of 500–1,000 kcal/day with 30, 54, and 16% of energy from fat, carbohydrates, and protein	4 months	All: Baseline 44.9±9.02 End 53.4±8.8 Males: Baseline 48.6±8.3 End 56.4±8.9 Females: Baseline 41.1±8.3 End 50.2±7.6	Serum omentin increased after intervention in all subjects and both genders	Decreased BMI, weight, FM, WHR, TG, LDL, insulin, HOMA-IR and leptin after the intervention

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Table 4 (continued)

First author [ref.], year	Study design; location	Gender, age, and condition of patients	Intervention	Duration	Outcome, ng/mL	Results	Changes in other measurements
Antonio de Luis [17], 2018	clinical trial; Spain	male and female, 48 years, obese (n = 667) male, 48 years, obese (n = 617) female, 48 years, obese (n = 650)	A deficit of 500 kcal/day; 53% of calorie from carbohydrates, 26% of lipids, and 21% of proteins (Mediterranean hypocaloric diet)	12 weeks	All: Baseline 357.8±55.4 End 366.7±65.1 Males: Baseline 342.6±66.1 End 352.6±49.9 Females: Baseline 360.5±61.4 End 370.4±57.1	Plasma omentin increased after intervention in all subjects and both genders	Decreased BMI, weight, FM, WC, BP, glucose, insulin, and HOMA-IR after the intervention Negative association was observed between omentin and BMI as well as insulin level after weight loss
Kabiri [35], 2017	randomized, cross-over clinical trial; Iran	female, 35 years, healthy premenopausal with overweight (n = 617)	Both groups: a deficit of 500 kcal/day (15% of energy from protein, 51% from carbohydrates, and 34% from fat). Group with olive-oil-rich diet (16% MUFAs and 8% SFAs; n = 68) Group with usual diet (8% MUFAs and 16% SFAs; n = 69)	Two 6-week periods separated by a 2-week washout	Group with olive-oil-rich diet Baseline 619±45.7 End 636.8±39 Group with usual diet Baseline; 647.5±38 End 614±41.3	Serum omentin decreased in the group with usual diet and increased in the group with the olive-oil-rich diet No difference between 2 diets and also after adjustment for PUFA, fiber, and protein intake	Decreased fasting glucose, TG, and TC in the group with olive-oil-rich diet Decreased weight, BMI, and FM after intervention in both groups
De Luis [36], 2018	randomized clinical trial; Spain	male and female, 48 years, obese (n = 6,239) male, 49 years, obese (n = 661) female, 48 years, 178, obese (n = 6,178)	Diet 1: a HFD consisting of 38% carbohydrates, 26% proteins, and 36% fats (n = 6,117); Diet 2: a LFD consisting of 54% carbohydrates, 20% proteins, 26% fats (n = 6,122)	12 weeks	Diet 1: All subjects Baseline 391.9±74.1 End 396.7±67.8 Males: Baseline 404.7±48.8 End 415.1±54.8 Females: Baseline 386.7±58.8 End 388.4±54.1 Diet 2: All subjects Baseline 422.5±74.1 End 447.7±74.1 Males: Baseline 382.2±55.8 End 401.4±35.1 Females: Baseline 427.2±55.8 End 462.4±39.1	No change in plasma omentin after hypocaloric diet 1 in all subjects and both genders Plasma omentin increased in all subjects and both genders after hypocaloric diet 2 Plasma omentin was higher in males than females after hypocaloric diet 2	Decreased BMI, weight, FM, WC, SBP, and LDL-C after intervention in both groups
Zarrati [39], 2019	randomized, double-blind, placebo-controlled trial; Iran	male and female, 36 years, obese or overweight (n = 656)	LCD in both groups Group with probiotic yogurt: 200 g/day containing *Lactobacillus acidophilus* La5, *Bifidobacterium* BB12 and *Lactobacillus casei* DN001 (108 CFU/g each 200 g yogurt; n = 626) Group with regular yogurt: 200 g/day (n = 630)	8 weeks	Group with probiotic yogurt: Baseline 11.45±3. 88 End 11.55±3.14 Group with regular yogurt: Baseline 12.39±4.62 End 10.88±3.81 Between 2 groups[f] (differences): Group with probiotic yogurt 0.09±1.51 Group with regular yogurt −1.5±1.8	No change in omentin concentration after intervention in group with probiotic yogurt Serum omentin decreased in the group with regular yogurt after the intervention Change of omentin concentration was higher in group with probiotic yogurt than regular yogurt even after adjustment for confounder	Decreased fat percent after intervention in the group with probiotic yogurt No significant difference in weight, BMI, and WC after intervention between 2 groups

NAFLD, nonalcoholic fatty-liver disease; VLCD, very-low-calorie diet; LCD, low-calorie diet; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; FY, fortified yogurt; PY, plain yogurt; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; 25(OH)D, 25 hydroxy vitamin D; WC, waist circumference; WHR, waist-to-hip ratio; HC, hip circumference; TC, total cholesterol; FM, fat mass; SBP, Systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid. [a] Part of the study was not reported due to the lack of inclusion criteria for this review. [b] Values were not reported. [c] Adjusted for baseline values. [d] Adjusted for baseline, age, physical activity, diabetes duration, menopausal duration, energy, and protein intake. [e] Median (IQR). [f] Adjusted for age, sex, BMI, and baseline value.

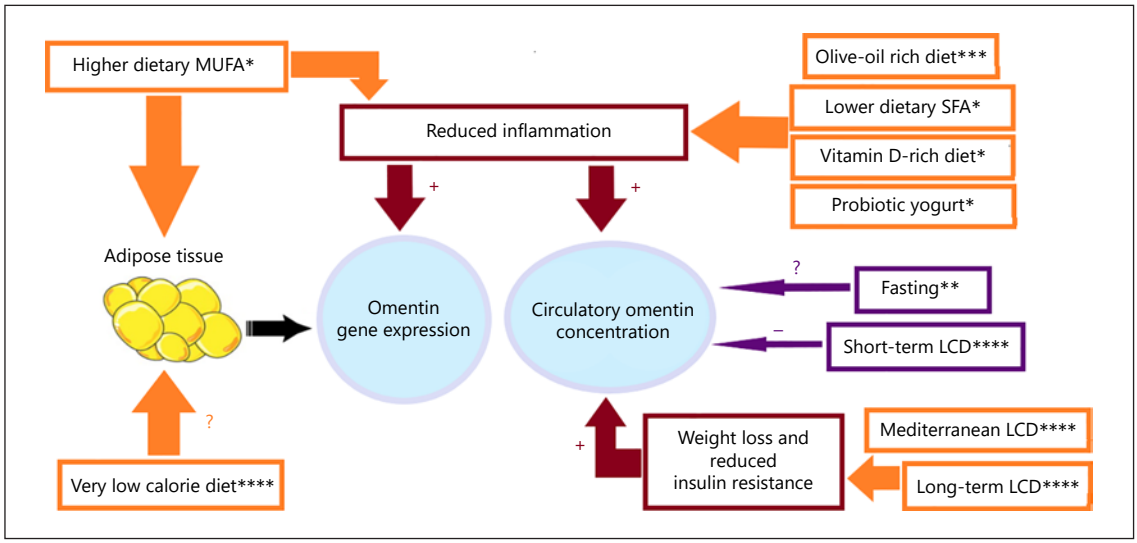

Fig. 2. Schematic representation of dietary impact on omentin status. Red, intermediate mechanism; orange and purple, intervention; +, an increase; –, a decrease; ?, unclear. * a low risk of bias (RoB); ** a moderate RoB; *** a high RoB; **** a serious RoB.

loric low-fat diet (LFD) [36]. No changes were observed in omentin plasma concentration after intervention with a hypocaloric HFD [36], fasting [37], a short-term LCD [15], or the oral consumption of soybean oil [19]. The distribution of dietary fat was similar in both hypocaloric HFDs and LFDs (45% MUFAs, 30% SFAs, and 25% PUFAs), but omentin plasma concentration was not compared between groups [36]. In this line, only a single study with serious RoB examining the effects of dietary intake on omentin gene expression, in addition to plasma concentration, showed that intervention with a short-term VLCD did not affect omentin plasma concentration and mRNA expression [18]. Also, we did not observe any significant effect of an olive-oil-rich LCD on omentin plasma concentration compared to the control [35].

We found 2 low RoB studies that examined the effects of probiotic yogurt and vitamin D-fortified low-fat yogurt on omentin plasma concentration [38, 39]. These studies showed an increase in omentin plasma concentration and a decrease in high-sensitivity C-reactive protein (hs-CRP) [38]. Similarly, a second study showed that the change in omentin plasma concentration was higher with probiotic yogurt consumption compared to the control [39].

Interventional studies on humans varied with regard to conditions and types of disease, and most of them were focused on dietary energy [12, 15, 17, 18, 35] which may subsequently influence weight status and metabolic conditions. Some studies had before-and-after designs without a control group (quasi-experimental) that could affect the validity of the results [12, 15–18, 35, 36]. Other studies reported a change in omentin plasma concentration, while it was better to report the effect size. According to the above studies, we found contradictory results regarding the effects of a LCD on omentin. A long-term LCD could increase omentin plasma concentration [12, 15, 17]; however, a short-term LCD had no effect on omentin gene expression and plasma concentration [15, 18]. Thus, omentin plasma concentration may be potentially affected by dietary fat, the duration of the intervention, and, possibly, the total energy intake, so that omentin increases with a long-term LCD and a LFD. Notably, a long-term LCD that was high in fat, and a short-term LCD rich in MUFAs, did not increase omentin plasma concentration. In general, it can be concluded that short-term dietary interventions do not appear to affect the omentin plasma concentration.

Overall Results

The abovementioned low RoB observational studies demonstrated that omentin plasma concentrations may have no association with macronutrients except dietary fat, especially SFAs and MUFAs. However, to the best of our knowledge, no interventional studies with this aim have yet been conducted and are needed to confirm this finding by high-quality studies. It seems that the duration of the diet, total caloric intake, and dietary fat, including the amount and type of fat, are among the main determining factors that may impact omentin plasma concentration.

Discussion

We systematically reviewed a variety of studies of different designs to address whether dietary intakes affect omentin plasma concentration and/or gene expression. Overall, we found contradictory results regarding the effect of a LCD on the omentin plasma concentrations in humans and animals. In the observational studies, we noted a significant decrease in omentin plasma concentration with fasting and dietary SFA intake, no association with DII, macronutrients, or total calorie consumption, and a positive association between omentin gene expression and dietary intake of MUFAs. The interventional studies reported a significant increase in omentin plasma concentration with the intake of vitamin D-fortified low-fat yogurt, a long-term LCD, and a LFD, but no change with probiotic yogurt, soybean oil, an olive-oil-rich diet, a HFD, a short-term LCD, or a fasting state. In the animal studies, we found that omentin plasma concentration did not change with a HFD (it increased in 1 study), a LFD, and sesame oil intake. Regarding omentin gene expression, a HFD reduced gene expression in animal studies, and a LCD did not affect it in a human study. The results of this review are schematically presented in Figure 2.

The interventional studies showed that a LCD for at least 3 months may be able to increase omentin plasma concentrations in patients with obesity [12, 15, 17, 36]. Also, dietary fat appears to have a synergistic effect on the LCD and has a greater impact on omentin plasma concentrations than a LCD. This hypothesis can be supported by studies showing that a LCD with a Mediterranean dietary pattern (of which a high MUFA content is a feature) and a hypocaloric LFD versus a hypocaloric HFD (which did not change omentin plasma concentration despite decreased fat mass), can have a positive effect on increasing the omentin plasma concentration [17, 36].

Intervention in the form of a weight reduction program that involved a LCD increased the omentin plasma concentration when insulin resistance improved [12, 17, 36, 40]. Therefore, calorie reduction does not appear to have an independent effect on the omentin plasma concentration. Weight loss and insulin sensitivity induced by a LCD may affect omentin plasma concentration. We hypothesize that the higher omentin plasma concentration found in participants with obesity and diabetes may be a compensatory mechanism. This hypothesis is supported by the work of Niersmann et al. [13], who reported that omentin was increased in response to cardiometabolic risk factors and inflammation in individuals with a cardiovascular risk.

However, some studies showed a decrease in omentin plasma concentration with a LCD, despite weight loss and improved fasting glucose [16, 18, 35]. We observed that 2 weeks of a VLCD did not affect omentin plasma concentrations and gene expression [18]. It seems that acute energy deprivation may not affect omentin status. Furthermore, Kabiri et al. [35] demonstrated that omentin plasma concentration was decreased after 6 weeks of a LCD with a high SFA content (16%) compared to a high-MUFA (16%) diet that increased omentin. Furthermore, in a low RoB study, we found an inverse association between omentin plasma concentration and SFA intake [21]. It seems that the change in omentin plasma concentration might be attributable to dietary fat and fatty acid content. A recent study revealed that the quality and quantity of dietary fatty acids were associated with subcutaneous and visceral *AT* gene expression [41]. In agreement with this finding, we showed in a previous study that only dietary MUFA intake was related to omentin gene expression [32]. Another possible explanation for these conflicting results found in the literature may be due to the different weight loss interventions, which included a VLCD (acute weight loss) and a LCD with a high SFA content. Finally, a long-term LCD modulated to have reduced fat content (a high MUFA and low SFA intake) is a nutritional approach that may improve the modifiable risk factors of cardiovascular disease, including insulin resistance and omentin plasma concentration; this requires further investigation [35].

Since some studies have demonstrated an inverse correlation between omentin plasma concentrations and inflammatory markers [42, 43], we propose that an improved inflammatory status is another possibility for reduced omentin plasma concentrations by modified LCDs and LFDs. We found that a short-term VLCD did not affect omentin plasma concentration and gene expression, or CRP levels, in patients with obesity. Moreover, serum insulin and CRP were higher, and omentin was lower, in patients with obesity and T2DM than in healthy participants [18]. Jafari et al. [38] reported that the intake of vitamin D-fortified low-fat yogurt decreased hs-CRP, and improved inflammation and the omentin plasma concentration, independent of a change in body weight or BMI. Similarly, vitamin D supplementation for 16 weeks decreased hs-CRP while increasing IL-10 and omentin plasma concentration [44]. Omentin acts as an anti-inflammatory factor in patients with diabetic obesity [21], as well as one of the mediators of the antioxidant effect of vitamin D [45].

An observational study showed that fasting for 4 weeks could increase the omentin plasma concentration compared to a nonfasting state [30]. Another study reported

that omentin plasma concentration in a fasting state for 4 weeks decreased in comparison to not fasting [29]. It should be mentioned that body weight and leptin (that inversely correlated with omentin) increased in pregnant women after a fasting period; this may provide an explanation for the abovementioned discrepancy. Finally, in healthy participants, the clinical trial did not observe any effect of fasting for 8 days on the omentin plasma concentration [37]. It is possible that the lack of an effect of fasting on omentin status was due to the small sample size and short duration of intervention in this particular study. Overall, it seems that fasting for 4 weeks, as is the case in Ramadan fasting, may affect omentin plasma concentration due to weight loss, and it also increases insulin sensitivity.

Omentin plasma concentration may be affected by the amount of dietary fat, the type of dietary fatty acids, weight loss, insulin resistance, inflammation status, and the duration of a dietary intervention. In addition to the quality and quantity of dietary intake, it has been assumed that a change in omentin plasma concentration changes the parameters of metabolic syndrome and insulin sensitivity. Some articles report that the omentin plasma concentration was lower in patients with insulin resistance, T2DM, and obesity than in healthy controls [5, 9, 34, 46]. Previous studies suggested that increases in omentin plasma concentration and gene expression might play a protective role against insulin resistance [12, 17, 18, 21]. It seems that hyperinsulinemia inhibits omentin secretion [15, 29, 36]. As observed in an animal study, omentin gene expression and plasma concentrations were increased in T1DM mice with low serum insulin [34]. Insulin levels are reduced with weight loss, in association with increased omentin plasma concentrations [11, 12]. Bearing in mind the results of these studies, increased insulin plasma concentrations, typically found in patients with obesity and T2DM, might indeed be an important contributor that precedes a decrease in omentin plasma concentration. Another possible factor contributing to low omentin plasma concentration could be excessive adiposity and obesity-associated metabolic complications. This possibility is supported by increased omentin plasma concentrations found in patients with anorexia nervosa and severely reduced body fat [47, 48].

From the data in the animal study, we observed that omentin gene expression and plasma concentration decreased, and free fatty acids increased, with a HFD [33]. This may be due to the insulin resistance induced by elevated free fatty acids [49]. Also, changing from a HFD to a LFD did not alter the omentin plasma concentration, probably because this intervention did not have any effect on weight loss [33].

Interestingly, among the relevant studies, Hamnvik et al. [37] failed to demonstrate any change in omentin plasma concentration with chronic energy deprivation and weight loss following bariatric surgery. We observed in another study that, although weight did not change, the plasma concentrations of omentin, glucose, and insulin were different in an aerobic-resistance training group, an estrogen replacement therapy group, and a group that undertook aerobic-resistance training plus estrogen replacement therapy [20]. These results suggest that the omentin plasma concentration is not only affected by weight and fat mass but also by the overall reorganization of fat tissue achieved in the long term. This discrepancy may be explained by the greater loss of subcutaneous versus visceral AT (from which omentin is primarily secreted) following bariatric surgery [50]. Further studies are needed, that focus on omentin expression in different fat deposits, to dissect the potentially distinct roles of subcutaneous AT- and visceral AT-produced omentin.

The major limitation of our systematic review was the limited number of existing interventional studies, especially with longer-term follow-up. Only 4 longitudinal studies had a follow-up period >3 months. The follow-up periods of 6 h to 14 days in the 3 short-term randomized controlled trials (RCTs) were most probably too short to result in any measurable and related effect on omentin plasma concentration. A further limitation was that 4 of the included studies had a cross-sectional design. These studies can suggest associations, but not any causal effects, of diet manipulation on omentin status. The included studies varied widely with regard to study design, population demographics, statistical analyses, and adjustments. Because the association between dietary factors and omentin status was often not the primary research question, the selection of adjustment sets for the control of confounders was not theory-driven. Indeed, most of the analyses did not control for possible omentin-related confounders, which were shown to be linked to dietary factors, such as physical activity. Furthermore, we were unable to perform a meta-analysis, due to the substantial methodological heterogeneity (of durations, populations, and interventions) between included studies. The validity of the assessment tool regarding dietary factors was usually not reported. Many studies were underpowered to detect the interactions of dietary factors and omentin plasma concentrations and gene expression between- or within-groups on account of relatively small sample sizes. The lack of statistical power may explain why the results of the analysis on the effect of dietary factors on omentin status did not reach statistical significance.

Conclusions

Based on the current data, there is little compelling evidence that a convincing conclusion can be drawn at present regarding the effect of dietary intake on omentin plasma concentration and gene expression. However, it seems that long-term changes in dietary intake, especially a LFD and a proper distribution of fat content, including a higher MUFA and lower SFA intake, may increase the omentin plasma concentration, possibly via enhanced insulin sensitivity and improved levels of inflammation. However, the evidence remains sparse, mostly due to the lack of high-quality studies. Further research is needed to substantiate these findings, given the noted RoB as well as limitations, inconsistency, and lack of replication of many studies. Longer dietary RCTs which also assess compliance, are necessary to evaluate the efficacy of dietary intake on omentin plasma concentrations and gene expression.

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Statement of Ethics

This study was approved by the Ethics Committee of the Institute of Endocrinology and Metabolism of Shahid Beheshti University of Medical Sciences (Code of Ethics: IR.SBMU.ENDOCRINE.REC.1398.010).

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

M.N.-O., E.Y., and N.S.A.-M. designed the research, conducted the literature search and screening, and drafted, reviewed, and revised the manuscript; G.A., P.M., M.S., and M.Z. critically reviewed and revised the manuscript. All authors read and approved the final version.

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