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REVIEW

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Effectiveness of low-fat diet on the levels of insulin-like growth factor-1 and insulin-like growth factor binding proteins: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background Previous researches on the effect of low-fat diet (LF) on insulin-like growth factor-1 (IGF-1), and its binding proteins (IGFBPs) did not reach a consensus result, and there is no study summarizing these findings. Thus, this systematic review and meta-analysis of randomized control trials (RCTs) was performed to pool available evidence and answer the question whether dietary fat can affect IGF-1 and IGFBPs or not.

Methods PubMed, Scopus, ISI Web of Science, Google, Google scholar, ProQuest, and the Cochrane Library were searched without language restrictions until July 2, 2024 to retrieve related studies. Weighted mean difference and the corresponding variance were considered as the effect size. Standard tools were applied to assess the quality of the studies and evidence.

Results Pooling data of the eligible studies showed no significant effect of LF diet on IGF-1 (six studies; participants = 1029.; pooled mean = 1.63 ng/ml, 95% CI= [-1.34, 4.59], $P = 0.28$, $I^2 = 0.00\%$), and IGFBP-3 (five studies; participants = 969; pooled mean = 65.24 ng/ml, 95% CI= [-169.53, 300.00], $P = 0.59$, $I^2 = 0.0\%$). The results of subgroup analysis for IGF-1 and IGFBP-3 also demonstrated no significant findings. For IGFBP-1, available evidence is insufficient since only two studies have been performed yet and their results are contradictory.

Conclusions This study indicated no significant effect of LF diet on IGF-1, and IGFBP-3 concentrations. Low certainty of evidence indicates that available evidence cannot support to draw a firm conclusion and future researches may change the estimates.

Keywords Insulin-like growth factor I, Insulin-like growth factor binding proteins, Diet, Fat-Restricted, low-fat diet

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Introduction

The insulin-like growth factor I (IGF-1) peptide is mainly produced in the liver in response to the pituitary-derived growth hormone (GH) [1, 2]. This hormone plays an important role in the induction of cell proliferation, and inhibition of apoptosis through endocrine, autocrine and paracrine manners [1, 3]. In the blood stream, IGF-1 is bound with IGFBPs. Six IGFBPs have been identified which are bound with 98% of all circulating IGF-1 (mostly IGFBP-3), and regulate IGF-1 transportation and cellular homeostasis [4].

Epidemiological studies have been shown an association between imbalance concentrations of IGF-1 and IGFBPs and some disorders; including breast, prostate, colon and lung cancers [5], or lower bone mineral density, decreased fat-free mass, increased fat mass, and a higher risk of cardiovascular disease [1]. So, understanding modifiable factors affecting the IGF-1 and its binding proteins is important; and can be used in preventive strategies. In this field, nutritional determinants have been less discussed and the results of the studies are contradictory. Among studies investigating the effect of dietary components on IGF-1 and IGFBPs, dietary fat has been given more attention. In this regard, some trials reported a significant association between lower dietary fat and lower levels of IGF-1 [1] and IGFBPs concentrations [5], while; some others demonstrated lower dietary fat may increase IGF-1 and IGFBPs [1, 6]. Furthermore, several trials showed no significant effects of low-fat (LF) diets on IGF-1 or IGFBPs [5, 7, 8].

The inconsistent results prompted us to conduct a systematic review and meta-analysis study to assess the effect of LF diets compared with high-fat (HF)/usual diets on IGF-1, and IGFBPs in general adult participants using RCTs.

Materials and methods

The present systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

This study was registered in the PROSPERO international prospective register of systematic reviews (: https://www.crd.york.ac.uk/PROSPERO) under registration number CRD42023420978.

Search strategy

PubMed, Scopus, ISI Web of Science, Google, ProQuest, Google scholar and the Cochrane Library were searched until to July 2, 2024, without language restrictions. The search strategy contained a combination of keywords related to LF diet, IGF-1, and IGFBPs to find relevant studies. Furthermore, the reference lists of the eligible articles were manually checked to identify further relevant studies. More details on the search strategy have been provided in supplementary Table 1.

Screening and study selection

Titles and abstracts of the relevant studies were independently screened by three reviewers (KT, MH, MKS) based on the following criteria:

1)RCTs (either parallel or crossover designs), 2) participants aged ≥ 18 years old; 3) compared the effects of a LF dietary intervention (≤ 30% of total energy intake) on IGF-1 and IGFBPs levels versus a HF dietary intervention or usual diet (> 30% of total energy intake); and 4) having sufficient data regarding dietary interventions, IGF-1 or IGFBPs levels.

We excluded trials with follow-up periods less than four weeks and trials did not provide sufficient data to estimate mean changes for the interested outcome. Trials that reported evident deviation of intervention (defined follow-up rate under 70%) were also excluded. In addition, we excluded trials in which co-interventions (e.g. lifestyle modification) were unbalanced between intervention and comparison groups. Eligibility criteria based on the PICOS is shown in Supplementary Table 2.

Data extraction

Two independent reviewers (FM, SZM) extracted relevant information as follows: first author's name; publication year; study location; age, sex, BMI, and health status of participants; study duration; study design; number of participants in each group; the percent of macronutrients in the dietary interventions including LF and HF/usual diet; means and SDs of IGF-1, IGFBPs levels before and after the intervention or mean differences (MDs) and standard deviations (SDs) during the follow-up period.

To minimize potential errors during data extraction, data were cross-checked, and any disagreements were resolved by consensus with the corresponding author (SA).

Risk of bias

The Cochrane risk of bias tool for RCTs (ROB1) was used to assess methodological quality of the included studies; based on the following criteria: selection bias (random sequence generation and allocation concealment), performance/detection bias (blinding of participants and personnel/blinding of outcome assessment), attrition bias (incomplete data outcome), reporting bias (selective reporting), and other bias [10]. We did not consider blinding of participants and personnel domain in assessment of overall quality since generally blinding of participants and personnel regarding dietary intervention are difficult and blinding cannot be appropriately performed due to nature of the interventions.

Eventually, the included studies were categorized as follow: good quality if all the domains rated low risk of bias, unclear quality if they had ≥2 unclear risk of bias regarding the domains, and poor quality if they had a high risk of bias for the main domains (selection bias, performance bias, and detection bias), respectively [10]. The Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach also applied to rate the certainty of the evidence for each outcome.

Data synthesis and statistical analysis

For the measure of each outcome of interest, the mean differences (MDs) and their 95% CIs between LF group and HF/control group were applied as the effect size in the meta-analysis. Moreover, the weighted mean differences (WMDs) and their corresponding SDs were estimated using the DerSimonian and Laird random-effects model [8, 11]. For studies in which SD changes from baseline were missing, standard errors were computed and then converted them into SDs based on the formula provided in the Cochrane Handbook of Systematic Reviews [8, 11]. Moreover, for studies in which had co-intervention with low fat diet, we only considered low fat diet arm in our pooled analysis.

For the study of Young et al. (2013), we entered the low fat dietary interventions as a combined intervention in the main analysis. Regarding the study of Gann et al. (2005), only phase 1 of study was included in the pooled analysis. Furthermore, for the study of Wu et al. (2005), we only considered the soy-free phase, which included only the low fat diet without soy in our main analysis.

Assessment of heterogeneity was performed using the Cochran's Q test and the I^2 test [12]. Predefined subgroup analyses were conducted based on design and duration of study, sex of participants, intervention type, and population to detect source of heterogeneity.

Furthermore, sensitivity analyses were carried out by removing one study at a time. Publication bias was evaluated using funnel plots, and Egger's regression asymmetry and adjusted rank correlation tests [13], if number of the included studies was minimum 10 studies for every outcome [13] (ref). STATA version 16.0 software (STATA Corp) was applied for statistical analyses. Two-sided *P* values < 0.05 were considered as a significant level.

Results

Search and selecting studies

Figure 1 indicates the literature search and screening process. The primary search resulted in 833 studies. After removal duplication and screening six articles [1, 5, 7, 14–16] were eligible to include in the present meta-analysis. The reference list of excluded studies as well as the reasons for exclusion are presented in Supplementary Table 3.

Study characteristics

Table 1 shows the characteristics of the included studies. Parallel design was applied in all the included RCTs, except one study which was cross over [1]. Three studies recruited participants with both sexes [7, 15, 16]; while, other studies were performed on women [1, 5, 14], exclusively. Healthy subjects [1, 5], patients with colorectal adenoma [7], patients with breast cancer [14], overweight/obese persons [16], and patients with severe burning [15] were recruited among the included studies. Duration of intervention ranged from 4 to 208 weeks. The amount of prescribed fat in LF diet al.so ranged from 15 to 30% of total calorie intake. Other characteristics of the included studies have been presented in the Table 1.

Risk of bias

Supplementary Table 4 presents risk of bias of the included studies. Based on the Cochrane risk of bias tool, two studies [15, 16] had unclear risk for random sequence generation domain due to insufficient data for judgment. Except two trials the process of allocation concealment was not explained by all studies [1, 5, 15, 16]. Moreover, all studies had low risk of bias for incomplete outcome domain except two studies [1, 5], as they did not provide sufficient information on withdrawals and missing follow-up of participants. All the studies had also low risk of bias for selective reporting except two studies which were unclear risk of bias [1, 16]. The majority of included studies were rated as high risk of bias for blinding of participants and personnel, as blinding cannot be appropriately performed due to the nature of the interventions. Thus, we did not consider this domain in overall quality assessment. Finally, all the included studies were judged to have a poor quality [1, 5, 16] except two studies, which had a fair quality [7, 15] and one trial which had a good quality [14]. The GRADE framework was used to assess the quality of evidence for each outcome. The evidence for the effects of LFD on IGF-1 and IGFBP-3 were judged as low and very low quality, respectively (Supplementary Table 4).

Meta-analysis

IGF-1

Six studies (participants: 1029) evaluated the effect of a LF diet on IGF-1 levels versus a HF diet [1, 5, 7, 14–16], and no significant effect was found (WMD = 1.63 ng/ml; 95% CI= -1.34, 4.59; P=0.28; I^2=0.00%; P-heterogeneity=0.42) (Fig. 2); which was consistent across subgroups (Supplementary Table 6).

Furthermore, overall sensitivity analysis as well as sensitivity analysis with omitting the study of Flood et al. (2008) showed no significant results.

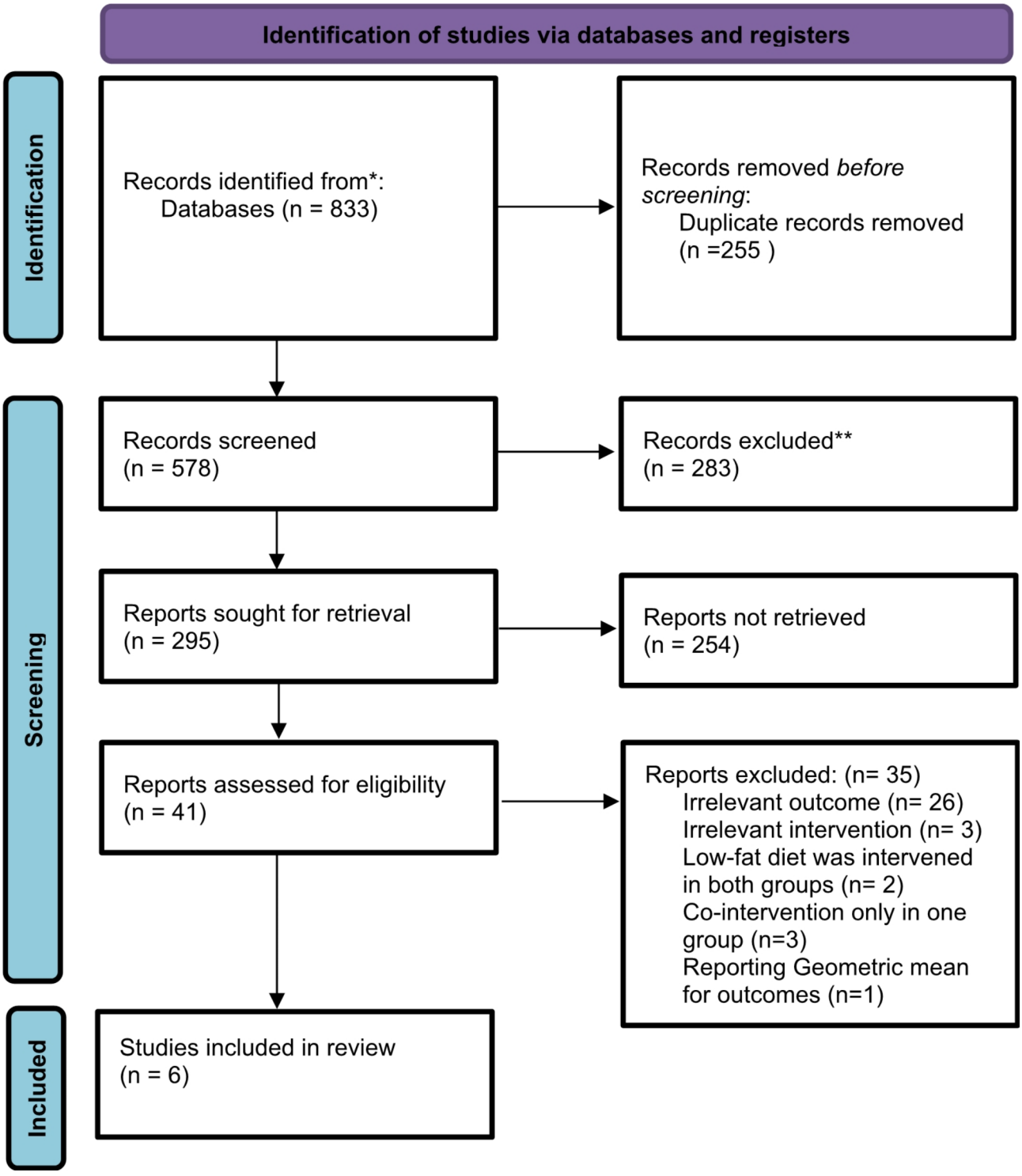

Fig. 1 Flow chart of search and select of studies related to assess effect of low-fat diet on levels of insulin-like growth factor (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and insulin-like growth factor binding protein-1 (IGFBP-1)

Table 1 The characteristics of the studies investigating the effect of low-fat diet on the levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding proteins (IGFBPs)

Author, Year	Country/ Study design (C/*P*)/ (duration, weeks)	Sex [Age, year; Intervention, Control]	Population	Co-intervention in LF group	Macronutrient [Fat/CHO/ Pro] (%)				Results
					Intervention		Control		
					Prescribed	Intake	Prescribed	Intake	
Young et al. (2013)	USA/ C/ (8)	Female [57, 57]	Postmenopause	None	[20%,65%,15%]	NM	[40%, 45%, 15%]	NM	↑IGFBP-3 ↔IGF-1
Gann et al. (2005) Phase 1	Phase 1: USA / P/ (52)	Phase 1: Female [33.5, 33.2]	Premenopause	None	Phase 1: [< 20%, 60–65%, 15–20%]	Phase 1: [22.1%, 64.8%, 14.5%]	NM	Phase 1: [30.4%, 54.8%, 14.1%]	Phase 1: ↔IGF-1 ↔IGFBP-3 ↔IGFBP-1
Flood et al. (2008)	USA / P/ (52), (208)	Both [62.1, 61.0]	colorectal adenoma	None	[20%, NM, NM]	[22.7%, NM, NM]	[NM, NM, NM]	[33.7%, NM, NM]	Week 52: ↔IGF-1 ↔IGFBP-3 Week 208: ↓IGF-1 (in both groups) ↔IGFBP-3
Khodabakhshi et al. (2021)	Iran / P / (12)	Female [45.2, 44.8	Patient with breast cancer	Calorie restriction	[30%, 55%, 15%]	[75%, 6%, 19%]	[29.2%, 49.5%, 17.7%]	[73.1%, 6.7%, 18.5%]	↓IGF-1 (only in LF diet group)
Arciero et al. (2008)	USA / P / 12	Both [44, 42]	Overweight/ obese persons	high-intensity resistance and cardiovascular training			HPEx [28.8%, 41.9%, 26.9%]	MPEx [31.3%, 25.3%, 43.5%]	↑IGF-1 ↑IGFBP-1 (only in HPEx group) ↔IGFBP-3
Garrel et al. (2000)	Canada / P / (4)	Both [38, 34]	severely burned adults	fish oil	[15%, 60%, 25%]	[35%, 40%, 25%]	NM	NM	↑IGF-1 (only in LF diet with fish oil)

CHO, carbohydrates; PRO, proteins; C, cross-over; P, parallel; IGFBP-1, insulin-like growth factor binding protein-1; IGFBP-3, insulin-like growth factor binding protein-3; LFD, low fat diet; HFD/CD, high fat diet/control diet; HPEx, high-protein diet with combined high-intensity resistance and cardiovascular training; MPEx, moderate-protein diet with combined high-intensity resistance and cardiovascular training

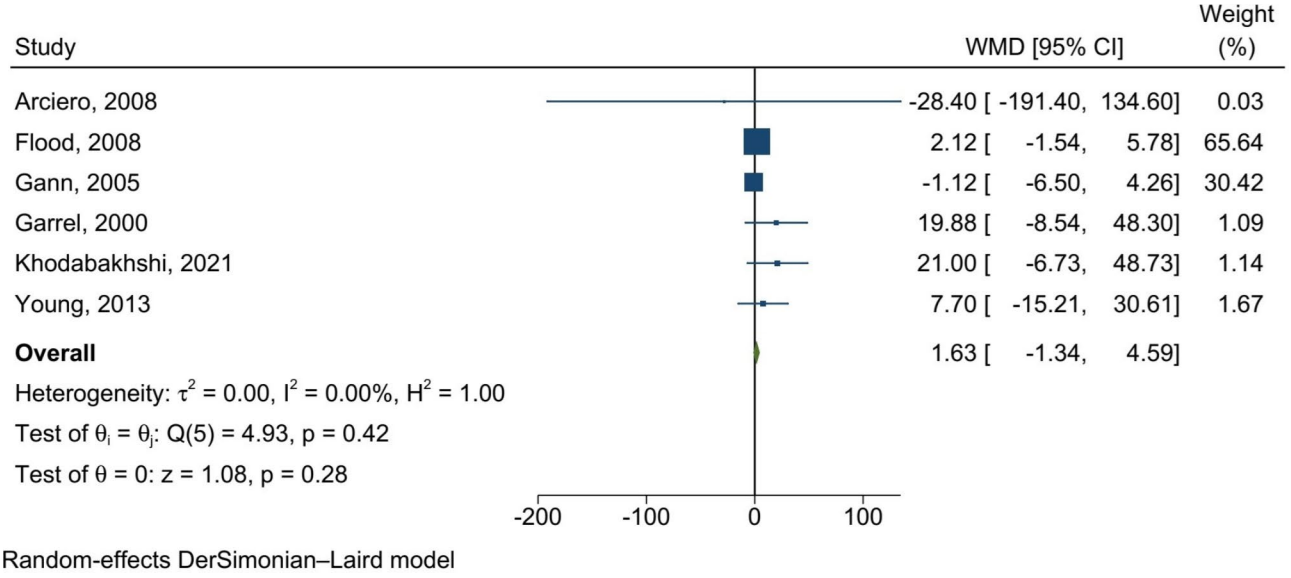

Fig. 2 Forest plot of randomized controlled trials showing weighted mean differences in Insulin-like growth factor I (IGF-1) levels between low fat diet and control groups for all eligible studies. Analysis was conducted using a random-effects model. Solid squares depict the weight assigned to the corresponding study; the black diamond represents the summary effect. ES, effect size

IGFBP-3

The meta-analysis of 5 studies (participants: 969) [1, 5, 7, 15, 16] showed no significant effect of LF diet compared with HF diet on IGFBP-3 concentration (WMD=65.24 ng/ml; 95% CI=-169.53, 300.00; P=0.59;; I^2=0.0%; P-heterogeneity=0.96) (Fig. 3). Subgroup analysis also indicated no significant findings (Supplementary Table 7).

Furthermore, overall sensitivity analysis as well as sensitivity analysis with omitting the study of Gann et al. (2005) showed no significant change in the results.

Qualitative analysis

For IGF-1, most of trials (5 of 6) were at fair and poor quality. Main trial limitations related to IGF-1 were lack of personnel and blinding of outcome assessment. Finally, the level of evidence regarding IGF-1 was low. For IGFBP-3, all of trials were at fair and poor quality. Main trial limitations related to IGFBP-3 were lack of personnel and blinding of outcome assessment. Finally, the level of evidence regarding IGFBP-3 was very low (Supplementary Table 5).

IGFBP-1

We found two studies investigating the effect of LF diet on IGFBP-1. One study was performed among a sample of premenopausal women and compared the impact of LF diet (fat: <20%, CHO: 60–65%, PRO: 15–20%) versus control/usual diet (fat: 30.4%, CHO: 54.8%, fat: 14.1%) on IGF-I and IGFBPs levels after 52 weeks [5]. The results of this study showed no significant change of IGFBP-1. Another study by Arciero et al. (2008), evaluated the effect of a dietary intervention (a high-protein diet; fat: 28.8%, CHO: 41.9%, PRO: 26.9%; or a moderate-protein diet; fat: 31.3%, CHO: 43.5%, PRO: 25.3%) along with a high-intensity resistance and cardiovascular training on body composition, insulin sensitivity, lipid profile, IGF-I and IGFBPs levels during 12 weeks and in overweight/obese individuals [16]. This study reported a significant increase in IGFBP-1 levels in the high-protein diet with training group [16].

Discussion

Our systematic review and meta-analysis of RCTs demonstrated no significant effect of a LF diet (containing≤30% of energy) versus control/usual diet (containing>30% of energy) on IGF-1, and IGFBP 3 concentrations in overall and subgroup analyses. The result of qualitative analysis on IGFBP1 also were inconsistence and more studies are needed.

Previous studies have been reported a significant association between higher IGF-1 levels and risk of some cancers including prostate [17], breast [18] and colorectal [19, 20]. Moreover, some studies showed a significant association between the higher IGF-1 levels and all-cancer mortality [21, 22]. Unbalanced levels of this hormone also has been reported to be involved in many other pathological conditions such as diabetes, obesity and cardiovascular diseases [23].

Dietary intakes have been introduced as a modulator of IGF-1 levels. Although protein intake and calorie manipulation have been investigated, the effect of dietary fat on IGF-1 and IGFBPs levels is still unknown. We tried to answer this question through a systematic review and meta-analysis of previous RCTs, and found no significant effect of LF diet on IGF-1 or IGFBP-3 levels. Moreover,

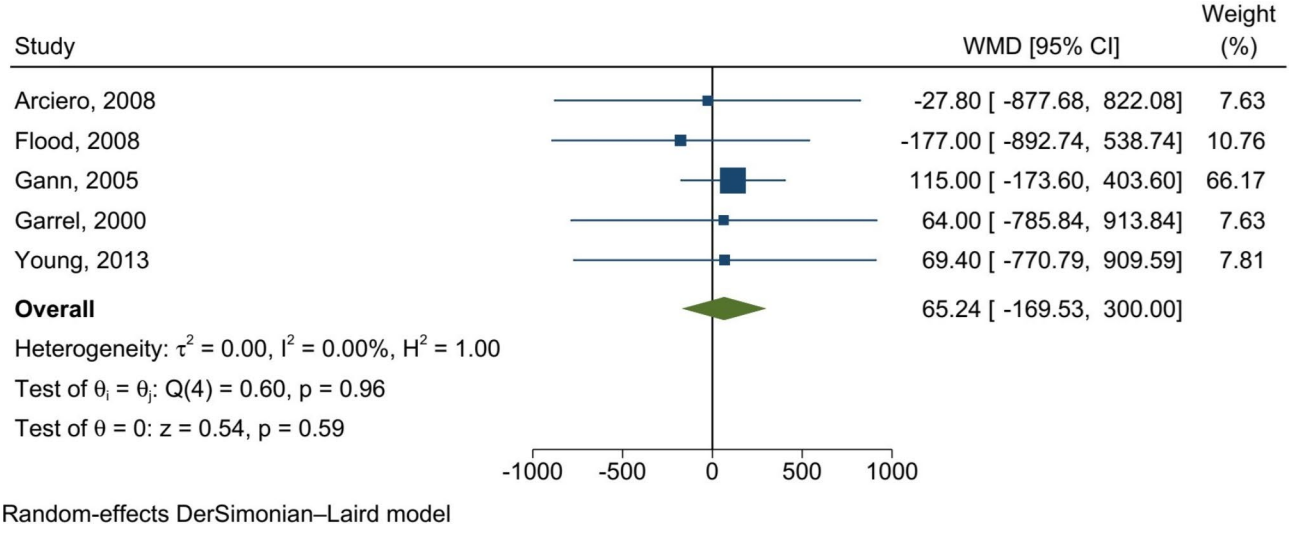

Fig. 3 Forest plot of randomized controlled trials showing weighted mean differences in insulin-like growth factor binding protein-3 (IGFBP-3) levels between low fat diet and control groups for all eligible studies. Analysis was conducted using a random-effects model. Solid squares depict the weight assigned to the corresponding study; the black diamond represents the summary effect. ES, effect size

available evidence for IGFBP-1 was inadequate for analysis and conclusion.

There are several plausible factors for explaining the divergent results between the relevant studies. IGF-1 and IGFBPs are mediated by a complex system, which just a limited number of related factors were controlled in the included studies. One of these factors is amount of macronutrients and the source of them in the diet. For instance, dietary protein intake was ranged 15–20% of calorie in the included studies. Some previous reports demonstrated an association between higher protein intake and higher IGF-1 levels [24, 25]. A meta-analysis study also approved this association [26]. Moreover, data from NHANES III reported that higher carbohydrate intakes are associated with higher IGF-1 levels, in addition to a high-protein diet [22]. The source of macronutrient also seems to be important. The results of some studies indicated a higher dairy product consumption was related to a higher IGF-1 level; while, eggs and egg products intakes were associated with lower IGF-1 levels [22, 27]. Furthermore, some of the previous studies reported higher intakes of fiber were associated with higher IGF-1 levels [25, 28], through colon fermentation and short chain fatty acid production [29, 30].

Some studies also showed a significant association between different edible oils and IGF-1 or IGFBPs. For instance, some researchers reported that fish oil consumption compared with sunflower oil was related to a higher IGF-1 levels [31]; this is while, other studies showed no significant effect [32, 33]. However, we could not assess the effect of different oils on IGF-1 or its binding proteins, due to the insufficient data.

On the other hands, body weight of participants has been found to be associated inversely with IGF-1 [34] or positively with IGFBPs [25]. However, the effect of weight loss intervention on IGF-1 concentration is equivocal in previous trials [35–37], and some studies demonstrated this association disappeared with increasing age [38, 39]. Furthermore, other related factors including sleep restriction [40], depression [41], alcohol intake [42], micronutrients [43], physical activity [44], and co-interventions in some of included studies (fish oil supplementation, Calorie restriction, high-intensity resistance and cardiovascular training) also has been claimed to be associated with IGF-1 levels, which may affect our results.

In addition, the adherence to a dietary intervention and using a standard method to measure compliance is challenging in dietary interventional studies. As well, it is reported LF diets have lower acceptability than low-carbohydrate diets [45]. Also, in the present study, actual dietary intake was not reported at the end of the intervention in most of the included studies, and we had to assume the actual intake is equal to what was prescribed, even though we knew this might not be true.

To the best of our knowledge, our study is the first systematic review and meta-analysis about effect of LF diet on IGF-1 or IGFBPs levels. We also applied a comprehensive search strategy without any limitations on language or time of publication to achieve all the eligible studies. Furthermore, although between study heterogeneity was not identified, subgroup and sensitivity analyses were conducted to determine their effects, as well as, evaluate the impact of a single study on the results.

However, our study had some limitations. The main limitation is related to the confounding factors which no sufficient data has been provided for them in the included studies. Moreover, adherence to the study protocol was not considered in most of the included studies. Finally, the direct effect of LF diet could not be elucidated due to co-interventions in some of the included studies.

Conclusion

The findings of the present study indicated no significant effect of LF diet on IGF-1, and IGFBP-3 concentrations. However, due to the discovered association between high levels of IGF-1 and all-cause mortality, it is suggested to conduct more studies with controlling confounding and minimum deviation of the intervention to achieve more precise evidence in this field. In addition, these associations were judged to be low and very low certainty of evidence meaning that the true effect remained unknown and addition of future studies have a great impact on the present estimates.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-024-00698-x.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Author contributions Concept and design of the study: SS, SAScreening of included articles: KT, MH, MKS. Data extraction: FM, SZM. Quality assessment of included studies: SS. Analysis and interpretation of data: SS, SA, ZS. Writing draft of the manuscript: ZS, SS, SA. SS and SA critically revised the manuscript and approved the final version of manuscript to be submitted. All authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical statement
All data and analyses in this research were based on previous published studies, thus ethical approval and patient consent are not applicable for it.

Competing interests
The authors declare no competing interests.

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References

1. Young LR, Kurzer MS, Thomas W, Redmon JB, Raatz SK. Low-fat diet with omega-3 fatty acids increases plasma insulin-like growth factor concentration in healthy postmenopausal women. Nutr Res. 2013;33(7):565–71.
2. Meshkini F, Abdollahi S, Clark CC, Soltani S. The effect of vitamin D supplementation on insulin-like growth factor-1: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2020;50:102300.
3. Meshkini F, Ramezani-Jolfaie N, Sargazi S, Clark CC, Soltani S. The effects of lycopene supplementation on insulin-like growth factor-1 and insulin-like growth factor binding proteins: a systematic review of randomized controlled trials. Phytother Res. 2022;36(4):1633–43.
4. Bailes J, Soloviev M. Insulin-like growth factor-1 (IGF-1) and its monitoring in medical diagnostic and in sports. Biomolecules. 2021;11(2):217.
5. Gann PH, Kazer R, Chatterton R, Gapstur S, Thedford K, Helenowski I, et al. Sequential, randomized trial of a low-fat, high-fiber diet and soy supplementation: effects on circulating IGF-I and its binding proteins in premenopausal women. Int J Cancer. 2005;116(2):297–303.
6. Aronson WJ, Barnard RJ, Freedland SJ, Henning S, Elashoff D, Jardack PM, et al. Growth inhibitory effect of low fat diet on prostate cancer cells: results of a prospective, randomized dietary intervention trial in men with prostate cancer. J Urol. 2010;183(1):345–50.
7. Flood A, Mai V, Pfeiffer R, Kahle L, Remaley A, Rosen C, et al. The effects of a high-fruit and-vegetable, high-fiber, low-fat dietary intervention on serum concentrations of insulin, glucose, IGF-I and IGFBP-3. Eur J Clin Nutr. 2008;62(2):186–96.
8. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. 2008.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W–65.
10. Higgins J, In JPT, Higgins. & S. Green Cochrane Handb Syst Reviews Interventions. 2011;5(0).
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
13. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
14. Khodabakhshi A, Akbari ME, Mirzaei HR, Seyfried TN, Kalamian M, Davoodi SH. Effects of ketogenic metabolic therapy on patients with breast cancer: a randomized controlled clinical trial. Clin Nutr. 2021;40(3):751–8.
15. Abribat T, Nedelec B, Jobin N, Garrel DR. Decreased serum insulin-like growth factor-I in burn patients: relationship with serum insulin-like growth factor binding protein-3 proteolysis and the influence of lipid composition in nutritional support. Crit Care Med. 2000;28(7):2366–72.
16. Arciero PJ, Gentile CL, Pressman R, Everett M, Ormsbee MJ, Martin J, et al. Moderate protein intake improves total and regional body composition and insulin sensitivity in overweight adults. Metabolism. 2008;57(6):757–65.
17. Travis RC, Appleby PN, Martin RM, Holly JM, Albanes D, Black A, et al. A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk. Cancer Res. 2016;76(8):2288–300.
18. Hormones TE, Group BCC. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010;11(6):530–42.
19. Rinaldi S, Cleveland R, Norat T, Biessy C, Rohrmann S, Linseisen J, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. Int J Cancer. 2010;126(7):1702–15.
20. Renehan AG, Zwahlen M, Minder C, T O'Dwyer S, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004;363(9418):1346–53.
21. Major JM, Laughlin GA, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. Insulin-like growth factor-I and cancer mortality in older men. J Clin Endocrinol Metabolism. 2010;95(3):1054–9.
22. Rahmani J, Montesanto A, Giovannucci E, Zand H, Barati M, Kopchick JJ, et al. Association between IGF-1 levels ranges and all-cause mortality: a meta-analysis. Aging Cell. 2022;21(2):e13540.
23. AsghariHanjani N, Vafa M. The role of IGF-1 in obesity, cardiovascular disease, and cancer. Med J Islamic Repub Iran. 2019;33:56.
24. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng C-W, Madia F, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metabol. 2014;19(3):407–17.
25. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev. 2002;11(9):852–61.
26. Kazemi A, Speakman JR, Soltani S, Djafarian K. Effect of calorie restriction or protein intake on circulating levels of insulin like growth factor I in humans: a systematic review and meta-analysis. Clin Nutr. 2020;39(6):1705–16.
27. Giovannucci E. Nutrition, insulin, insulin-like growth factors and cancer. Horm Metab Res. 2003;35(11/12):694–704.
28. Crowe FL, Key TJ, Allen NE, Appleby PN, Roddam A, Overvad K, et al. The association between diet and serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in the European prospective investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1333–40.
29. Yan J, Charles JF. Gut microbiota and IGF-1. Calcif Tissue Int. 2018;102:406–14.
30. Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, et al. Gut microbiota induce IGF-1 and promote bone formation and growth. Proc Natl Acad Sci. 2016;113(47):E7554–63.
31. Damsgaard CT, Harsløf LB, Andersen AD, Hellgren LI, Michaelsen KF, Lauritzen L. Fish oil supplementation from 9 to 18 months of age affects the insulin-like growth factor axis in a sex-specific manner in Danish infants. Br J Nutr. 2016;115(5):782–90.
32. Damsgaard CT, Mølgaard C, Matthiessen J, Gyldenløve SN, Lauritzen L. The effects of n-3 long-chain polyunsaturated fatty acids on bone formation and growth factors in adolescent boys. Pediatr Res. 2012;71(6):713–9.
33. Pedersen MH, Mølgaard C, Hellgren LI, Matthiessen J, Holst JJ, Lauritzen L. The effect of dietary fish oil in addition to lifestyle counselling on lipid oxidation and body composition in slightly overweight teenage boys. Journal of nutrition and metabolism. 2011;2011.
34. Landin-Wllhelmsen K, Wllhelmsen L, Lappast G, Rosen T, Lindstedt G, Lundberg PA, et al. Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol. 1994;41(3):351–7.
35. Olszanecka-Glinianowicz M, Zahorska-Markiewicz B, Kocełak P, Janowska J, Semik-Grabarczyk E. The effect of weight reduction on plasma

concentrations of ghrelin and insulin-like growth factor 1 in obese women. Endokrynologia Polska. 2008;59(4):301–4.
36. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes. 2011;35(5):714–27.
37. Mason C, Xiao L, Duggan C, Imayama I, Foster-Schubert KE, Kong A, et al. Effects of dietary weight loss and exercise on insulin-like growth factor-I and insulin-like growth factor-binding protein-3 in postmenopausal women: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1457–63.
38. Harris TB, Kiel D, Roubenoff R, Langlois J, Hannan M, Havlik R, et al. Association of insulin-like growth factor-I with body composition, weight history, and past health behaviors in the very old: the Framingham Heart Study. J Am Geriatr Soc. 1997;45(2):133–9.
39. Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women: the Rancho Bernardo Study. Am J Epidemiol. 1997;145(11):970–6.
40. Chennaoui M, Leger D, Gomez-Merino D. Sleep and the GH/IGF-1 axis: consequences and countermeasures of sleep loss/disorders. Sleep Med Rev. 2020;49:101223.
41. Szczęsny E, Ślusarczyk J, Głombik K, Budziszewska B, Kubera M, Lasoń W, et al. Possible contribution of IGF-1 to depressive disorder. Pharmacol Rep. 2013;65(6):1622–31.
42. Liran M, Rahamim N, Ron D, Barak S. Growth factors and alcohol use disorder. Cold Spring Harbor Perspect Med. 2020;10(12).
43. Janjuha R, Bunn D, Hayhoe R, Hooper L, Abdelhamid A, Mahmood S, et al. Effects of dietary or supplementary micronutrients on sex hormones and IGF-1 in middle and older age: a systematic review and meta-analysis. Nutrients. 2020;12(5):1457.
44. Stein AM, Silva TMV, Coelho FGM, Arantes FJ, Costa JLR, Teodoro E, et al. Physical exercise, IGF-1 and cognition a systematic review of experimental studies in the elderly. Dement Neuropsychologia. 2018;12:114–22.
45. Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obes Rev. 2009;10(1):36–50.

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