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REVIEW

The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies

F. Roshanzamir[1,2,3] · M. Miraghajani[4] · M. H. Rouhani[2,5] · M. Mansourian[6] · R. Ghiasvand[2,5] · S. M. Safavi[2,3]

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Abstract

Background and objective Fetuin-A is a liver-derived circulating protein that is associated with insulin resistance and diabetes. The objective of this systematic review and meta-analysis of published observational studies was to investigate mean levels of fetuin-A in T2D patients and the relationship between blood fetuin-A levels and T2D risk.

Materials and methods PubMed, Embase, Google Scholar, Web of Science, and The Cochrane Library were systematically searched for potential relevant studies up to 1 December 2016. Natural logarithm-transformed estimate risks, standard mean differences on the basis of Hedges's adjusted g, and 95% confidence intervals (CIs) were calculated for all eligible studies and were combined to measure the pooled data using random-effects model.

Results A total of 32 studies including 27 case–control and 5 cohort studies were included in the current study. Fetuin-A levels in T2D patients were significantly higher than control groups [Hedges' $g = 1.73$, 95% CI (1.25–2.22), $P < 0.001$], with significant heterogeneity across studies ($P < 0.001$, $I^2 = 98.46\%$). Findings from meta-analyses of cohort studies showed a statistically significant association between fetuin-A levels and T2D risk [rate ratio = 1.62, 95% CI (1.26–2.08), $P < 0.001$], with no significant heterogeneity ($P = 0.10$, $I^2 = 46.06\%$).

Conclusion We found a significant relationship between the fetuin-A levels with T2D risk. Although fetuin-A may be as a potential screening and prediction biomarker or a therapeutic target in T2D patients, further studies are required in this regard.

Keywords Fetuin-A · Type 2 diabetes · Meta-analysis

Introduction

Type 2 diabetes (T2D), which accounts 90–95% of all diabetes, is a growing epidemic associated with many adverse complications [1], including cardiovascular disease, retinopathy, neuropathy, and nephropathy [2]. Therefore, identifying the T2D predictors may be more helpful in the planning T2D prevention.

Several studies showed that hepatokines, liver-derived hormones, can regulate systemic energy metabolism and insulin sensitivity through integrated organ crosstalk [3, 4].

Among hepatokines, fetuin-A is a circulating plasma glycoprotein, which secretes mainly from liver and to lesser extent from other organs such as tongue, placenta,

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✉ S. M. Safavi
safavimorteza@yahoo.com

1 Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran

2 Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

3 Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

4 Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

5 Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

6 Department of Biostatistics and Epidemiology, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

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and adipose tissue [5, 6]. Fetuin-A-knockout mice demonstrate improved insulin sensitivity and also are resistance to weight gain induced by high-fat diet and aging [7, 8]. Human studies also provided evidence that higher fetuin-A level influences obesity, metabolic syndrome, insulin resistance, and T2D [9, 10].

Other well-studied mechanisms have been suggested that fetuin-A exacerbates insulin resistance by inhibiting the insulin receptor tyrosine kinase, reducing the adiponectin expression, and increasing some inflammatory cytokine [11–13]. Thus, high levels of fetuin-A may be correlated with the pathogenesis of T2D. Although many studies showed relationship between fetuin-A, insulin resistance, and diabetes, it has not emphasized by others [14–19].

Since the conflicting data, this systematic review and meta-analysis conducted to summarize the existing observational evidences about mean levels of fetuin-A in T2D patients and clarify the relationship between this hepatokines concentration and T2D risk.

Methods

This study was performed based on a predefined protocol and according to the meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Table 1) [20]. Study identification and selection, data extraction, and quality assessment were performed independently by two investigators, in duplicate. Any disagreements were resolved by discussion and by consultation with the senior author, if necessary.

Data sources and search strategy

We searched the five electronic databases PubMed, Embase, Google Scholar, Web of Science, and Cochrane Library to 1 December 2016 by the following key words: ("diabetes," OR "diabetes mellitus"[MeSH]) AND ("fetuin-A" OR "fetuins"[Mesh] OR "alpha-2-HS-glycoprotein"[Mesh]), without any restriction. The search strategy is revealed in details in Table 1. In addition, reference lists of identified articles and pertinent reviews were manually searched.

Study selection

All retrieved articles from the literature search were screened for the following inclusion criteria: (1) case–control or cohort studies, (2) studies assessing the association between serum or plasma fetuin-A and T2D, (3) studies that reported sufficient information to calculate standardized mean differences (SMDs) and 95% confidence intervals (CI), or studies provided or allowed calculation of a relative risk estimate (odds ratio, relative risk, rate ratio, or hazard ratio), and (4) studies published in English. We excluded editorials, letters, nonhuman studies, and conference abstracts. When several articles were from the same group, the study with the largest sample size or the most

Table 1 Search strategy to identify studies on the association of fetuin-A levels and T2D

PubMed

1. Search strategy to identify relevant exposures:
"Fetuins"[Mesh] OR "fetuins"[All Fields] OR "alpha-2-HS-Glycoprotein"[Mesh] OR "alpha-2-HS-Glycoprotein"[All Fields] OR "AHSG protein, human"[All Fields] OR "AHSG"[All Fields] OR "fetuin-A"[All Fields] OR "fetuin A"[All Fields] OR "alpha-2 HeremansSchmid glycoprotein"[All Fields] OR "alpha2-HS-glycoprotein"[All Fields]
2. Search strategy to identify relevant outcomes:
"diabetes mellitus"[MeSH Terms] OR "diabetes"[All Fields] OR "NIDDM"[All Fields] OR "MODY"[All Fields]

Embase

1. Search strategy to identify relevant exposures:
'fetuin'/exp OR 'fetuin a'/expOR 'fetuin*' OR 'fetuins' OR 'alpha-2-hs-glycoprotein' OR 'ahsg protein, human' OR 'ahsg' OR 'alpha2-hs-glycoprotein' OR 'alpha-2 HeremansSchmid glycoprotein'
2. Search strategy to identify relevant outcomes:
'insulin dependent diabetes mellitus'/exp OR 'non-insulin dependent diabetes mellitus'/exp OR 'diabetes mellitus'/exp OR 'diabetic patient'/exp OR 'diabetes' OR 'niddm' OR 'mody'

Web of Science

1. Search strategy to identify relevant exposures:
"fetuins" OR "alpha-2-HS-Glycoprotein" OR "alpha-2-HS-Glycoprotein" OR "AHSG protein, human" OR "AHSG" OR "fetuin-A" OR "fetuin A" OR "alpha-2 HeremansSchmid glycoprotein" OR "alpha2-HS-glycoprotein" OR "Alpha-2 HeremansSchmid Glycoprotein"
2. Search strategy to identify relevant outcomes:
"diabetes mellitus" or "diabetes" OR "NIDDM" or "Ketosis Resistant" OR "MODY"

Search strings (all inclusive)

Parts 1 and 2 were combined using 'AND'

adjusted estimated effect from multivariable models was included.

Data extraction

The following information was extracted from eligible studies: first author, publication year, country, study design, study name, duration of follow-up, sample size, gender and age of subjects, blood sample type, methods for diagnosis of T2D, methods of fetuin-A detection, mean fetuin-A levels in case and control groups, adjusted effect estimate for most covariates and corresponding 95% CIs, and adjusted or matched variables. When insufficient data were published, we contacted the corresponding author for required data. If a case–control study that reported its results in both matched and unmatched subjects, we used results from matched subjects.

Quality assessment

Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses [21]. This instrument uses a star system (range 0–9 stars) to evaluate a study based on three main domains: selection of study groups (0–4 stars), comparability of groups (0–2 stars), and ascertainment exposure or outcome (0–3 stars). Each study received that seven or more stars were considered to be of high quality.

Statistical analysis

Case–control and prospective studies were analyzed separately. Fetuin-A levels in each case–control study were extracted as mean ± standard deviation (SD). If a study reported the median and the interquartile range of fetuin-A levels, we calculated mean and SD using formulas recommended by Hozo et al. [22]. Standard errors of means (SEM) were transformed into SD by multiplying SEM by the square root of the sample size. To evaluate the association between fetuin-A level and T2D risk, the SMD and 95% CI on the basis of Hedges's adjusted g were used. For studies that reported a measure of association, natural logarithm-transformed estimate risks were used to calculate effect sizes.

Pooled data were calculated using random-effect models (DerSimonian and Laird method) and presented as forest plots with 95% CI. Heterogeneity was investigated using Cochran's Q statistic and I-squared test ($I^2 > 50\%$ was considered as significant heterogeneity). To assess the impact of possible factors on pooled effect size and heterogeneity, subgroup and meta-regression analyses were performed for categorical and continues variables, respectively. A sensitivity analysis was conducted to evaluate the stability of this meta-analysis by deleting each study, one by one. Publication bias was assessed using the funnel plot method, classic fail-safe N, and Begg's and Egger's test. The influence of a potential publication bias on findings was explored using the Duval and Tweedie trim-and-fill procedure. All the P values were two-sided, and $P < 0.05$ was considered significant. Comprehensive meta-analysis (CMA) version 2 was used for this meta-analysis.

Results

Study selection

The initial literature search identified 1116 papers from PubMed, Embase, Web of Science, and The Cochrane Library. After screening the titles and the abstracts, 1028 articles were excluded. The remaining 88 articles were reviewed in full text for eligibility. Of these, 30 studies and 2 additional articles identified from Google scholar searching met the inclusion criteria and were included in the meta-analysis. The selection process of the studies is illustrated in Fig. 1.

Study characteristics

Finally, 32 articles involving 16,982 participants (with mean age 55.01 years) were included in this meta-analysis. Among 32 included observational papers, 27 studies were retrospective case–control studies [14, 16–19, 23–44], which involved 3470 cases (41.1%) and 4574 controls; and 5 studies were prospective studies [9, 10, 45–47], which involved 1993 (29.3%) cases and 8333 none-cases. In total 5463, 18 of them were conducted in Asia [16, 17, 24, 25, 28, 30–39, 41–44], 9 in Europe [10, 18, 19, 23, 27, 29, 40, 46], 4 in North America (USA) [9, 14, 45, 47], and 1 in Australia [26]. They were published between 2008 and 2016.

The assay methods used to determine fetuin-A concentrations were enzyme-linked immunosorbent assay in 25 case–control [14, 16–19, 23–28, 30–41, 43, 44] and 4 prospective studies [9, 45–47], immunoturbidometry in 1 prospective study [10], immunonephelometry in 1 case–control study [29], and Luminex in 1 case–control study [42]. About blood sample type, there were 21 case–control studies [16–18, 23–32, 34–36, 38–41, 44] and 3 prospective studies [45–47] on serum, and 6 case–control [14, 19, 33, 37, 42, 43] and 2 prospective studies [9, 10] on plasma. The key characteristics of the included studies are summarized in Tables 2 and 3.

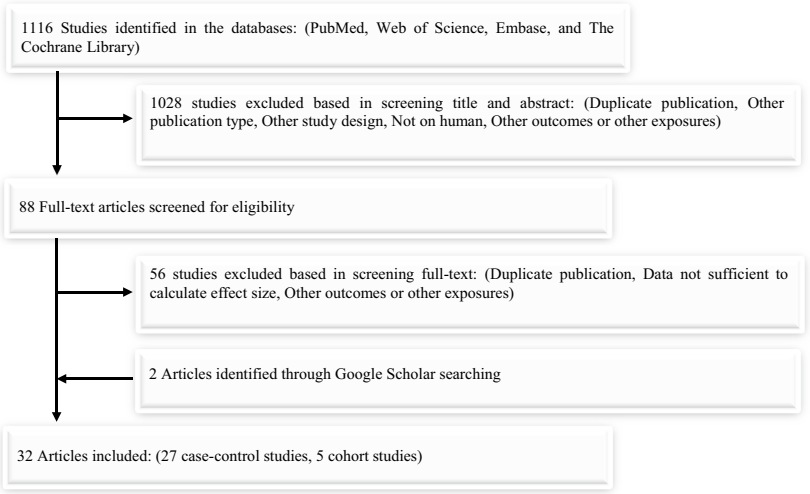

Fig. 1 Flow diagram of study selection

Quality assessment

The results of the quality assessment are provided in Tables 2 and 3. All prospective studies were judged to be of high quality [9, 10, 45–47]. In case–control studies, quality scores ranged from 3 to 9; 13 studies scored ≥7 (high quality) [23–30, 34, 36, 37, 40, 43] and 14 studies scored <7 (low quality) [14, 16–19, 31–33, 35, 38, 39, 41, 42, 44]. The methodological quality assessment according to NOS is shown in Supplementary Tables 2 and 3.

Fetuin-A levels among type 2 diabetes patients

The meta-analysis results revealed that the mean level of fetuin-A in T2D patients was higher than those in controls [Hedges' $g = 1.73$, 95% CI (1.25–2.22), $P < 0.001$] (Fig. 2). There was evidence for high heterogeneity across studies ($Q = 1688.062$ on 26 degrees of freedom, $P < 0.001$, $I^2 = 98.46\%$). Publication bias was observed by Begg's test (Tau = 0.39, P = 0.004) and Egger's test [intercept = 5.19, 95% CI (0.73–0.964), $P = 0.02$]. Duval and Tweedie's trim-and-fill analysis suggested that eight studies were missing in the left side of the mean effect. The pooled effect size using the trim-and-fill procedure was lower than our estimation [Hedges' $g = 0.33$, 95% CI (−0.20 to 0.87)]. The fail-safe N indicated that we would need to locate 4404 null studies to exceed the p value above 0.050. The results of the publication bias assessment are present in Supplementary Fig. 1.

Subgroup analyses based on geographic location, sample size, age, BMI, gender, recruitment method (matched/unmatched), sample type, and study quality showed that the fetuin-A levels in all subgroups were significantly higher in T2D patients than in controls. Further subgroup analyses revealed a significant association between fetuin-A levels and T2D in studies that only T2D cases and healthy controls were included and subjects did not have any other diseases [Hedges' $g = 2.22$, 95% CI (1.65–2.80), $P < 0.001$] but not in studies that T2D cases and/or controls had other diseases [Hedges' $g = 0.47$, 95% CI (−0.42 to 1.36), $P = 0.30$]. Since heterogeneity existed in all subgroups, no factors explain source of the heterogeneity. The summary of the results of subgroup analyses is shown in Table 4. Meta-regression analysis using unrestricted maximum-likelihood method indicated that the no potential variable is the main source of heterogeneity and only BMI is positively associated with the effect sizes in diabetic individuals [slope = 1.26, 95% CI (0.31–2.21), $P = 0.009$]. Outcomes from the meta-regression analysis are presented in Supplementary Fig. 2. Sensitivity analyses showed that the conclusions did not change significantly after each single study was omitted (Supplementary Fig. 3).

Fetuin-A levels and risk of type 2 diabetes

The relation between fetuin-A level and T2D risk is shown in Fig. 3. Findings from meta-analyses that compared patients in the highest quantile versus lowest quantile of fetuin-A concentration showed a statistical significant association between fetuin-A level and T2D risk [rate ratio = 1.62, 95% CI (1.26–2.08), $P < 0.001$] with no significant heterogeneity ($Q = 9.27$ on 5 degrees of freedom, $P = 0.10$, $I^2 = 46.06\%$). Publication bias was observed by Begg's test (Tau = 0.67, $P = 0.06$) and Egger's test [intercept = 4.76, 95% CI (−0.02 to 9.55), $P = 0.05$]. Duval and Tweedie's trim-and-fill analysis suggested that two studies were missing in the left side of the mean effect. The pooled effect size using the trim-and-fill procedure was lower than our estimation [rate ratio = 1.38, 95% CI (1.03–1.85)]. The fail-safe N indicated that we would need to locate and include 38 null or nil studies to exceed the P value above 0.050. The

Table 2 Characteristics of the identified case–control studies included in the meta-analyses on circulating fetuin-A and T2D

Lead author (reference) Year of publication	Country	Sample size Case Control	Other disease of subjects Case Control	Mean age (years) Case Control	Gender (men/women) Case Control	Mean BMI (kg/m^2) Case Control	Mean fetuin-A (unit) Case Control	Assay method Sample	Matching for variables	Quality score
Axelsson et al. [18] 2008	Germany	46 119	CKD CKD	59 52	32/14 70/49	26.4 24.1	0.212 0.260 (g/l)	ELISA Serum	–	5
Ford et al. [19] 2010	UK	19 73	CKD CKD	68.8 67.4	15/4 60/13	30.6 28.4	0.280 0.230 (g/l)	ELISA Plasma	–	3
Tonjes et al. [23] 2010	Germany	56 43	– –	62.4 61.3	24/32 20/23	33.9 29.6	334.6 275.4 (μg/ml)	ELISA Serum	–	7
Ishibashi et al. [24] 2010	Japan	15 194	– –	57 51	57/0 51/0	24.5 23.3	30.4 27.2 (mg/dl)	ELISA Serum	–	7
Song et al. [25] 2011	China	1598 2008	– –	63.8 59.3	705/893 711/1297	26.3 24.5	308.77 290.4 (mg/l)	ELISA Serum	–	7
Lorant et al. [26] 2011	Austria	55 44	PAD PAD	62.2 61.1	38/17 28/16	29.6 26.1	411.19 356.45 (μg/ml)	ELISA Serum	Age, gender	9
Krajnc et al. [27] 2011	Slovenia	45 45	– CKD	59 59	23/22 26/19	31 24	26.2 17.5 (ng/ml)	ELISA Serum	Age, gender	7
Ou et al. [28] 2011	Taiwan	94 94	– –	62 62	51/43 52/42	23.4 22.3	341.0 300.0 (μg/ml)	ELISA Serum	Age, gender	9
Gunduz et al. [17] 2011	Turkey	40 23	– –	49.75 55.04	11/29 8/15	30 32	298.5 391.0 (μg/ml)	ELISA Serum	–	4
Erdmann et al. [29] 2012	Germany	136 168	– –	NG	NG	38.2 38.4	29.1 26.5 (mg/dl)	INA Serum	Age, BMI, baseline insulin	8
Kim et al. [16] 2013	Korea	45 36	CKD CKD	NG	NG	NG	115.48 122.20 (μg/ml)	ELISA Serum	–	3
Zhao et al. [30] 2013	China	112 69	– –	62.46 62.93	81/31 35/34	24.52 24.51	348.89 308.30 (μg/ml)	ELISA Serum	Age, gender	8
Khalil et al. [31] 2013	Syria	60 28	– –	50.4 40.2	7/33 7/21	31.02 30.3	4.11 2.76 (mg/l)	ELISA Serum	–	5
Fatima et al. [32] 2013	Pakistan	50 50	– –	53.8 53.9	24/26 26/24	26.5 23.6	357.3 319.3 (μg/ml)	ELISA Serum	–	6
Scialla et al. [14] 2014	USA	340 261	ESRD ESRD	59.2 55.9	174/166 146/115	NG	0.467 0.532 (g/l)	ELISA Plasma	–	5

Table 2 continued

Lead author (reference) Year of publication	Country	Sample size Case Control	Other disease of subjects Case Control	Mean age (years) Case Control	Gender (men/women) Case Control	Mean BMI (kg/m^2) Case Control	Mean fetuin-A (unit) Case Control	Assay method Sample	Matching for variables	Quality score
Obuchi et al. [33] 2014	Japan	56 603	– –	NG	NG	NG	262.1 257.2 (μg/ml)	ELISA Plasma	–	5
Dutta et al. [34] 2014	India	66 50	– –	41.83 39.98	30/36 29/21	25.5 24.52	497.71 418.66 (μg/ml)	ELISA Serum	–	8
Ahmed et al. [35] 2014	Egypt	40 40	– –	47.45 45.03	20/20 20/20	NG	339.59 284.33 (μg/ml)	ELISA Serum	Age, gender	6
Beigi et al. [44] 2015	Iran	75 75	– –	55.50 53.18	NG	NG	2261.34 1476.93 (NG)	ELISA Serum	Age, gender	6
Zhao et al. [36] 2015	China	68 68	– –	57.49 56.6	39/29 32/36	25.96 25.68	289.21 259.14 (ng/ml)	ELISA Serum	Age, gender, BMI	9
Yin et al. [37] 2015	China	100 100	– –	55.11 13.79	54/46 44/56	25.32 24.38	368. 152.7 (mg/l)	ELISA Plasma	–	7
Akin et al. [38] 2015	Turkey	78 97	– –	48.8 42.1	23/55 56/41	NG	667.55 535.8 (mg/l)	ELISA Serum	–	5
Zhou et al. [39] 2016	China	95 65	– –	58.95 58.71	51/44 30/35	25.35 24.87	286.1 235.8 (μg/ml)	ELISA Serum	–	6
Reinehr et al. [40] 2016	Germany	74 74	– –	15.5 15.2	43/31 43/31	32 32.2	0.300 0.280 (g/ml)	ELISA serum	Age, BMI, gender	8
Ali et al. [41] 2016	Egypt	18 18	HCV HCV	42.43 36.6	14/4 10/8	23.8 23.7	5.34 4.03 (mg/ml)	ELISA Serum	–	6
Sindhu et al. [42] 2016	Kuwait	53 72	– –	NG	30/23 28/44	29.7 28.2	677.10 612.30 (pg/ml)	Luminex MAP Plasma	–	5
Eleftheriadou et al. [43] 2016	Greece	36 57	– –	65.4 62.6	20/16 19/38	29.7 26.6	562.3 435.0 (μg/ml)	ELISA Plasma	–	7

CKD chronic kidney disease, *PAD* peripheral arterial disease, *ESRD* end-stage renal disease, *HCV* chronic hepatitis C virus infection, *NG* not given, *ELISA* enzyme-linked immunosorbent assay, *ITA* immunoturbidimetry assay, *INA* immunonephelometry assay

Table 3 Characteristics of the identified prospective studies included in the meta-analyses on circulating fetuin-A and T2D

Lead author (reference) Year of publication	Name of the study Country	Design	Follow-up (years)	All participants (men/women)	Baseline age (years)	Sample size, cases/non-cases	Assay method Sample	Risk estimate (95% CI)	Ascertainment of type 2 diabetes	Maximum adjusted covariates	Quality score
Ix et al. [45] 2008	Health, aging, and body composition Study USA	Prospective case-cohort	6	3075 (1491/1584)	Range: 70–79	135/406	ELISA Serum	2.41 (1.28–4.53)	Self-report, new use of diabetes medications, or a fasting glucose level 126 mg/dl or greater	Age, sex, race, physical activity score, body weight, WC, SBP, DBP, fasting glucose level, HDL, triglyceride concentration, CRP	9
Ix et al. [46] 2012	The Cardiovascular Health Study Germany	Prospective cohort	10.6	3710 (2239/537)	Mean: 74.8	305/3405	ELISA Serum	1.37 (0.95–1.96)	New use of diabetes medications, or a fasting glucose level 126 mg/dl or greater	Age, sex, race, field center site, physical activity, smoking, alcohol use, estimated glomerular filtration rate, prevalent cardiovascular disease, BMI, WC, hypertension, triglycerides, HDL, serum albumin, CRP	9
Sun et al. [9] 2013	Nurses' Health Study (NHS) USA	Prospective nested case–control	6.5	18,717 (0/18,717)	Range: 53–79	470/470	ELISA Plasma	1.81 (1.07–3.06)	Self-report confirmed by medical records according to American Diabetes Association 1998 criteria	Age, race, fasting status, time of blood drawing, BMI, WC, smoking status, postmenopausal hormone use, physical activity, alcohol use, family history of diabetes, AHEI, coffee consumption, history of hypercholesterolemia or hypertension, CRP, ALT, GGT	8
Stefan et al. [10] 2014	EPIC-Potsdam study Germany	Prospective case-cohort	7	27,548 (10,904/16,644)	Range: 35–65	628/2095	ITA Plasma	1.23 (0.88, 1.72)	Self-report confirmed by a physician	Age, sex, education, occupational activity, sport activity, cycling, smoking, alcohol intake	9

Table 3 continued

Lead author (reference) Year of publication	Name of the study Country	Design	Follow-up (years)	All participants (men/women)	Baseline age (years)	Sample size, cases/non-cases	Assay method Sample	Risk estimate (95% CI)	Ascertainment of type 2 diabetes	Maximum adjusted covariates	Quality score
Aroner et al. [47] 2016	Multi-Ethnic Study of Atherosclerosis (MESA) USA	Prospective case-cohort	11	6500 (3250/3250)	Range: 45–84	455/1957	ELISA Serum	Women 2.61 (1.59–4.26) Men 1.32 (0.84–2.08)	New use of diabetes medications, or a fasting glucose level 126 mg/dl or greater	Age, race/ethnicity,BMI, smoking status, alcohol drinking status and income, menopausal status/postmenopausal hormone, liver fat content	9

ITA immunoturbidimetry, *EPIC* European Prospective Investigation into Cancer and Nutrition, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high-density lipoprotein cholesterol, *CRP* C-reactive protein level, *BMI* body mass index, *AHEI* Alternate Healthy Eating Index score, *ALT* alanine transaminase, *GGT* gamma-glutamyl transpeptidase

results of publication bias assessment are presented in Supplementary Fig. 4. Sensitivity analysis showed that the conclusions did not change significantly after each single study was omitted (Supplementary Fig. 5).

Discussion

Summary of findings

We found that plasma or serum fetuin-A level in T2D patients was significantly higher compared to the controls. In addition, high concentration of fetuin-A was inversely associated with T2D risk. These results did not alter after sensitivity analysis. In the case–control studies, a significant heterogeneity was observed that could not be explained by subgroup and meta-regression analyses. The association between high fetuin-A level and T2D risk did not vary by sample size, age, BMI, gender, study location, recruitment method, sample type, and study quality. However, this association did not observe in studies that T2D cases and/or controls had other diseases.

Comparison of results with the previous studies

To our knowledge, this systematic review and meta-analysis are the first to synthesize evidence from retrospective case–control and prospective cohort studies on the association between fetuin-A and T2D. Findings of our meta-analysis were in line with several non-systematic review studies that explain the roles of fetuin-A in the metabolism and the pathogenesis of metabolic disorders such as T2D [3, 4, 48–51]. In a systematic review, Mukhopadhyay et al. [52] concluded that fetuin-A is a novel hepatokine that modulates cardiovascular and glycemic outcomes and contributes to insulin resistance. Sun et al. [9] combined the results of NHS with three prospective studies; Health ABC Study [45], EPIC-Potsdam study [53], and CHS [46]. They observed positive association between high fetuin-A levels and diabetes risk [RR = 1.69, 95% CI (1.39–2.05)]. Sun et al. [9] included relative risk estimated of EPIC-Potsdam study [53], in which only age was adjusted multivariate, but we included relative risk estimated from the fully adjusted multivariate of EPIC-Potsdam study [10]. In another original article, Aroner et al. pooled the results from MESA with four prospective studies: The Rancho Bernardo Study [54], CHS [46], EPIC-Potsdam study [10], and NHS [9]. Pooled random-effects analysis indicated each 0.10 g/l increment in fetuin-A was associated with a 22% higher risk of diabetes [RR = 1.22, 95% CI (1.07–1.39)]. In this meta-analysis, RR of incident diabetes according to an SD (0.10 g/l) in fetuin-A concentration were combined. We cannot include

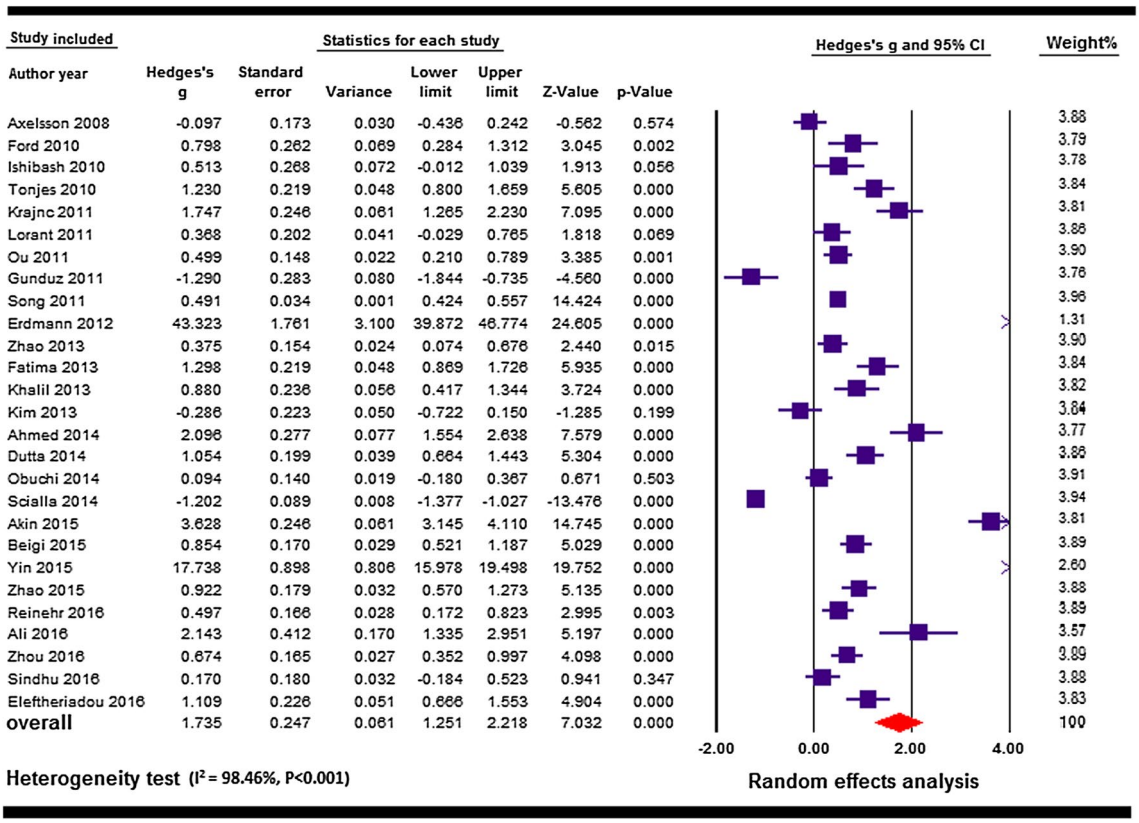

Fig. 2 Forest plot for the relationship between circulating fetuin-A levels and T2D

The Rancho Bernardo Study [54], because risk of incident diabetes was only reported per SD (0.10 g/l) greater fetuin-A level, but we used estimate risks comparing the highest versus lowest quantile of fetuin-A concentration. In the other hand, some studies were inconsistent with our meta-analysis results. This could be due to effects of different drugs intake [55–57] individuals age [51], physical activity [58], genetic factors [59], presence of diseases, and complications of T2D [43–60].

Heterogeneity in study results

Although the results of our analyses is in accordance with most of the included articles in this meta-analysis, the significant heterogeneity observed across 27 case–control studies ($P < 0.001$, $I^2 = 98.46\%$) reduces the reliability of the results. Thus, to explore the sources of the observed heterogeneity, we conducted several subgroup and meta-regression analyses according to the possible variables. However, this heterogeneity remained unexplained by the study design, geographic location, year of publication, sample size, age, BMI, gender, recruitment method, measurement methods (ELISA kits), specimen type (serum/plasma), study quality, and subjects' diseases (Table 4; Supplementary Fig. 2).

Meta-analysis of the five prospective studies revealed no statistically significant between-study heterogeneity ($P = 0.10$), although the I^2 test was 46.06%, suggesting moderate heterogeneity among these studies. We enabled to perform subgroup analysis to identify the causes of heterogeneity because of the limited number of studies.

Heterogeneity between studies which is common in meta-analyses can be due to any potentially relevant differences between the study designs and methodologies and/or characteristics of included subjects [61]. Consequently, we tried to do exhaustive subgroup and meta-regression analyses to investigate discrepancy, but we could not check all confounding factors. The reasons for the observed heterogeneity may be explained by other unevaluated variables that might interfere with the association fetuin-A and T2D. The included studies had differences in inclusion and exclusion criteria, ways of diagnosing T2D, methods of measurement of fetuin-A, adjusted or matched variables, choice of included subjects, and follow-up duration. In addition, the differences in the baseline characteristics of populations such as genetics, diet, physical activity, medication use, degree of hyperglycemia and clinical abnormalities, health status, and diabetic complications might affect heterogeneity. These differences could influence on the results, which, subsequently, in future studies, should be considered.

Table 4 Subgroup analyses of the association of circulating levels of fetuin-A and T2D

Variable	No. of studies	Effect size			Heterogeneity	
		Hedges' *g*	95% CI	*P* value	I^2 %	*P* value
Geographic location						
Asia	18	1.36	(0.90–1.83)	<0.001	97.47	<0.001
Europe	7	4.99	(3.21–6.77)	<0.001	99.05	<0.001
USA	1	–	–	–	–	–
Austria	1	–	–	–	–	–
Age (years)						
<50	5	1.87	(0.72–3.03)	0.001	96.76	<0.001
50–60	11	1.68	(0.70–2.67)	0.001	98.69	<0.001
>60	7	0.64	(0.44–0.85)	<0.001	70.82	0.002
NG	4	–	–	–	–	–
BMI (kg/m^2)						
<25	5	0.56	(0.06–1.05)	0.03	85.72	<0.001
25–29.9	10	1.70	(1.04–2.35)	<0.001	97.84	<0.001
>30	7	5.06	(3.08-7.05)	<0.001	99.09	<0.001
NG	5	–	–	–	–	–
Recruitment method						
Matched	9	3.41	(2.23–4.58)	<0.001	98.75	<0.001
Unmatched	18	1.27	(0.73–1.82)	<0.001	98.32	<0.001
Cases						
<50	9	0.73	(0.03–1.43)	0.04	94.57	<0.001
50–99	13	0.92	(0.52–1.33)	<0.001	93.79	<0.001
>100	5	9.04	(7.09–10.99)	<0.001	99.69	<0.001
Study quality score						
<7	14	0.68	(0.02–1.35)	0.04	97.85	<0.001
≥7	13	3.25	(2.44–4.07)	<0.001	98.81	<0.001
Subjects' diseases						
No	20	2.22	(1.65–2.80)	<0.001	98.48	<0.001
Yes	7	0.47	(−0.42 to 1.36)	0.30	97.43	<0.001
ELISA kits						
Biovendor	9	3.22	(2.05–4.39)	<0.001	98.74	<0.001
Other kits	18	1.36	(0.80–1.92)	<0.001	98.40	<0.001
Gender ratio						
M/F ≤1	11	2.11	(1.30–2.91)	<0.001	98.41	<0.001
M/F >1	12	0.63	(0.05–1.21)	0.03	96.94	<0.001
NG	4	–	–	–	–	–

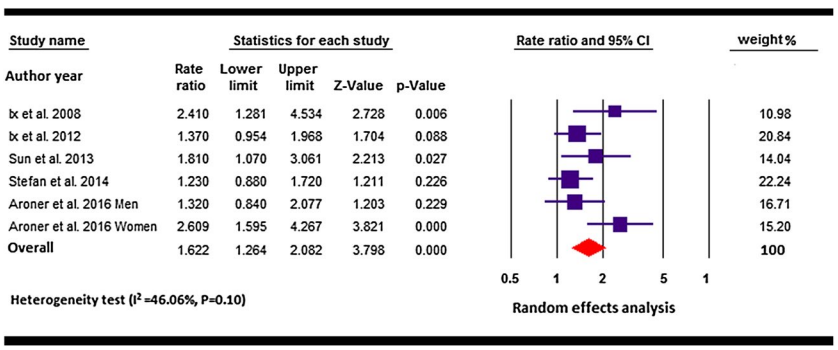

Fig. 3 Forest plot for the relationship between circulating fetuin-A levels and T2D risk

Alternative explanation of subgroup and meta-regression analyses findings

Fetuin-A is largely known as a hepatokine. It has recently been reported fetuin-A as an adipokine secreting from adipose tissue [62]. Recent data have shown that white adipose tissue from obese animals can express and secrete fetuin-A that this secretion is reduced after fasting, exercise voluntary training, and in anorectic animals [63]. Fetuin-A–knockout mice demonstrate not only improved insulin sensitivity but also resistance to weight gain induced by high-fat diet [7]. In humans, fetuin-A level is higher in obese and overweight individuals and is an early marker of adiposity in prepubertal children that lifestyle intervention programs can reduce this increased level [64–67]. Herein, subgroup and meta-regression analyses based on the BMI revealed that the association of fetuin-A with T2D became stronger with increasing BMI (Table 3; Supplementary Fig. 2). These findings suggest correlation between fetuin-A with weight-related insulin resistance and T2D risk.

There is an ethnic susceptibility to obesity and diabetes because of differences in lifestyle and genetic factors among various ethnic groups [68]. In a meta-analysis, the significant relationship between fetuin-A and cardiovascular disease was observed among Caucasians but not Asians [69]. We conducted a subgroup analysis based on geographic location that revealed no statistically significant difference between subgroups, but we observed a stronger association between fetuin-A and T2D from studies conducted in Europa [$n = 7$, Hedges' $g = 4.99$, 95% CI (3.21–6.77), $P < 0.001$] compared with studies conducted in Asia [$n = 18$, Hedges' $g = 1.36$, 95% CI (0.90–1.83), $P < 0.001$]. Although this result can be explained by differences ethnic groups [68], this finding may be due to the fact that participant in most included studies was obese European people.

There may be a sex-specific association of fetuin-A with T2D. Plasma levels of fetuin-A in female rats after a high-fat diet were significantly higher, but were significantly lower in males [70]. It is shown a stronger association between fetuin-A and T2D in women than men in two independent cohort studies: EPIC-Potsdam study [47] and The Rancho Bernardo Study [54]. Consistent with these results, our subgroup analysis based on gender showed the stronger association between fetuin-A and T2D among women than men. This trend may partly be explained by differences in biological (such as BMI, sex hormones, sex chromosomes, sex-specific gene expression of autosomes body, and fat distribution), psychosocial stress (such as sleep deprivation and work stress), and lifestyle factors (such as nutrition and physical activity) [71].

For sample size-stratified analysis, a stronger relationship between fetuin-A and T2D risk was found in the large sample subgroup [cases <50: $n = 9$, Hedges' $g = 0.73$, 95% CI (0.03–1.43), $P = 0.4$; $50 \leq$ cases ≤ 90: $n = 13$, Hedges' $g = 0.92$, 95% CI (0.52–1.33), $P < 0.001$; Cases >100: $n = 5$, Hedges' $g = 9.04$, 95% CI (7.09–10.99), $P < 0.001$]. In fact, larger sample size may indicate more actual relationship between fetuin-A and T2D risk.

As fetuin-A is an inhibitor of tissue and vascular calcification, it is paramount to understand the interaction between vascular diseases and fetuin-A that might affect our results. In the subgroup analysis based on the presence of comorbidities other than T2D, the observed relationship was not significant [$n = 7$, Hedges' $g = 0.47$, 95% CI (-0.42 to 1.36), $P = 0.30$]. This may be due to the reason that in Karajic et al.'s study, the control group was non-diabetic chronic kidney disease (CKD) patients on hemodialysis [27]. However, the sensitivity analysis showed that this study had no effect on the results.

In the current analysis, all the participants in four studies had chronic kidney disease [14, 16, 18, 19]. Although in a study with peripheral artery disease (PAD) subjects, the fetuin-A level was higher in diabetic people [26], others showed that fetuin-A level is lower in diabetic patients with PAD [43, 72, 73].

Smith et al. compared plasma fetuin-A measurements made with two commercial fetuin-A ELISA kits (Biovendor and Epitope) and showed poor agreement between methods [74]. Although SMD was calculated on the basis of Hedges's adjusted g, technical differences of ELISA kits and high variability in the values and units of fetuin-A could affect our results [51]. Biovendor kit was used in the nine included case–control studies and other kits were used in the others. Therefore, we did subgroup analysis based on the use of Biovendor kits or other kits. Although the results did not change statistically, in The Biovendor subgroup, the relationship was stronger than other kit (Table 3).

Mechanisms connecting fetuin-A to T2D

The proposed underlying mechanisms of the interaction between fetuin-A and the T2D development are discussed. It is shown that fetuin-A is involved in insulin resistance, a primary abnormality leading to the development of T2D [75, 76].

Fetuin-A inhibits insulin receptor tyrosine kinase activity through blocking the autophosphorylation of tyrosine kinase and insulin receptor substrate-1 (IRS-1) resulting in the impaired insulin signaling and reduced insulin sensitivity in the liver and muscle [13, 77]. Indeed, it can directly induce muscle insulin resistance through decreasing skeletal muscle glucose uptake by decreasing glucose transporter-4 (GLUT-4) translocation to the plasma membrane [78]. In fatty tissue, fetuin-A acts as an adaptor between

free fatty acids and Toll-like receptor 4 (TLR4) resulting in the production of inflammatory cytokines [11, 79].

Interestingly, the genes encoding fetuin-A and adiponectin, an important insulin sensitizer and anti-inflammatory adipokine, are located next to each other on chromosome 3q27 which is a T2D-susceptibility gene which is suggestive of a possible connection between fetuin-A, adiponectin, and T2D [80]. In fact, an inverse correlation between fetuin-A and adiponectin levels with opposite properties against insulin resistance is well known [81, 82]. Elevated levels of circulatory fetuin-A and hypoadiponectinemia that associate with the increased hepatic insulin resistance and hepatic fat content occur in subjects with nonalcoholic fatty liver disease (NAFLD) [83, 84]. These data suggest that adiponectin and NAFLD may play a main role in the association between fetuin-A and pathogenesis of diabetes [10, 47].

Strengths of study

The present study has several strengths. It may be the first meta-analysis focused on the relationship between fetuin-A and T2D. The comprehensive search was conducted on multiple databases and was carried out and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We included prospective studies, which could explain the causal relationship between fetuin-A and T2D and reduce recall bias and selection bias.

Limitations of study

Some limitations also need to be considered. One of the most important limitations of this study was the high significant heterogeneity and moderate heterogeneity observed in case–control and prospective studies, respectively. Second, in subgroup of geographic location of the case control studies, 18 studies were performed in Asia, 7 in Europe, 1 in Australia, and 1 in America. Therefore, we have problem in generalizability of the results. Third, because some studies did not report the needed data, we could not evaluate the effect of some distracting factors. The duration of diabetes was reported in only 6 studies (ranged between 2.8 to 10 years). Diabetes duration can distract our results, because the patients with more duration of diabetes will suffer from more macrovascular and microvascular complications. The fetuin-A level in diabetic patients with or without these complications may be different. In addition, we could not evaluate the effect of using the drugs, because in the included studies, less attention was paid to the kind of the drug consumed. Fourth, in both analyses, publication bias was present. This publication bias may be due to that negative data may not be reported in observational studies. In addition, some studies could not be included in the meta-analysis because of the different used methods in the reporting. In addition, we only included English and published studies. Finally, we included low-quality studies too. However, stratified analysis showed that there was still significant relationship in low-quality subgroup (Table 3).

Implications for future studies

It is suggested to consider the following points for future studies. First, some genetic polymorphisms on fetuin-A gene can influence fetuin-A expression [59, 85]. Single-nucleotide polymorphisms were identified that associate with insulin-mediated inhibition of lipolysis and stimulation of lipogenesis in adipocytes [86], T2D [87], and fetuin-A level [59, 88].

Second, since fetuin-A is a multifunctional glycoprotein and interacts with variety of receptors, it relates with several disorders and pathologic conditions [52, 89]. In addition, fetuin-A is an inflammatory molecule and also a negative acute-phase protein that reduces in inflammatory conditions [42, 52]. In vitro, some pro-inflammatory cytokines can downregulate the expression of fetuin-A gene [90]. Moreover, plasma fetuin-A level was correlated negatively with a large number of inflammatory cytokines/chemokines in T2D individuals [42]. Therefore, every change in these inflammatory mediators or the presence of any inflammation or stress can affect the fetuin-A level.

Third, lack of reference values, standard unit of fetuin-A, and existence of multiple commercial ELISA kits yield inconsistent values that are methodological challenges to studying human fetuin-A level [51].

Therefore, residual confounding due to genetic background, presence of any inflammation disease, and methodological disparities due to measurement of fetuin-A level can be excluded in the future studies.

Conclusions

Our meta-analysis findings provide evidence to support a significant inverse association between the fetuin-A concentration and T2D risk. In addition, mean levels of fetuin-A in T2D patients were prominently higher than healthy subjects. However, overall conclusions should interpret with caution due to significant heterogeneity between the case–control studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical disclosure All included studies have been reviewed by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards.

Human and animal rights This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent All persons gave their informed consent prior to their inclusion in the studies.

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