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REVIEW

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Insulin-like growth factor-1 and non-alcoholic fatty liver disease: a systemic review and meta-analysis

Yang Yao[1] · Xiangxia Miao[2] · Donglie Zhu[3] · Dongmin Li[4] · Ying Zhang[5] · Chengyan Song[5] · Kaige Liu[6]

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Abstract

Aim The prevalence of non-alcoholic fatty liver disease (NAFLD) is rapidly increasing worldwide. A number of researchers have studied the relationship between Insulin-like growth factor-1(IGF-1) and NAFLD. However, the results are controversial. This meta-analysis, aimed to systemically evaluate the correlation between IGF-1 and NAFLD.

Methods We searched for four online databases: PubMed, Web of Science, Embase and CNKI up to Feb 2018. We then applied a random-effects model to evaluate the overall effect sizes by calculating Standard mean difference (SMD) and its 95% confidence intervals (CIs).

Results Twelve articles were included in this meta-analysis. The pooled analysis showed that the level of IGF-1 in the control group was significantly higher than that in the NAFLD group. (SMD: 1.00, 95% CI: 0.54–1.46, $P < 0.00001$). However, significant heterogeneity was discovered among the included studies ($P < 0.00001$, $I^2 = 96\%$). Then a series of subgroup analyses were performed. Compared to the nonalcoholic steatohepatitis (NASH) group, the level of IGF-1 was significantly higher in the Non- or probable-NASH group (SMD: 1.42, 95% CI: 0.25–2.58, $P = 0.02$). The level of IGF-1 in patients with increased insulin resistance (SMD: 0.49; 95% CI: 0.36–0.63; $P < 0.00001$) and high Body Mass Index (SMD: 0.50; 95% CI: 0.22–0.79; $P < 0.05$) were significantly lower than healthy control. In addition, the same conclusion were found in studies carried out in Asia and Europe (Asia: SMD: 0.69, 95% CI: −0.29–1.66, $P = 0.17$; Europe: SMD: 0.89, 95% CI: 0.41–1.38, $P < 0.05$).

Conclusion The level of IGF-1 is down-regulated in NAFLD patients compared to healthy controls, suggesting that IGF-1 might be used as a potential biomarker and therapeutic target for NAFLD.

Keywords IGF-1 · NAFLD · Meta-analysis · Insulin resistance · Heterogeneity

Introduction

In recent years, non-alcoholic fatty liver disease (NAFLD) has become a major cause of chronic liver disease worldwide [1]. It has a rapidly growing incidence and a dramatic increase in prevalence over the last few decades, with a morbidity rate of 25% [2]. The pathogenesis of NAFLD includes metabolic stress of liver, unfolded protein response, insulin resistance, activation of inflammatory and fibrotic pathways [3]. The decrese of Insulin-like growth factor-1 (IGF-1) expression induced by inflammatory cytokines is related to the development of NAFLD. IGF-1 is a member of the IGF family produced by the liver. It acts in response to growth hormone (GH) and affects hepatocyte differentiation, proliferation, and apoptosis [4]. Since growth factors have been widely involved in the pathogenesis of NAFLD and IGF-1 is an important member of these factors, a number of studies have investigated the

These authors contributed equally: Yang Yao, Xiangxia Miao

✉ Kaige Liu
kaigeliu007@163.com

[1] Department of Central Laboratory, the First Affiliated Hospital, Xi'an Medical University, Xi'an, Shaanxi 710077, PR China

[2] Clinical Medicine (three-year program) of Postgrade 2016, Xi'an Medical University, Xi'an, Shaanxi 710021, PR China

[3] Department of Hepatobiliary Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi 710032, PR China

[4] Department of Biochemistry and Molecular Biology, School of Basic Medical Science, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi 710061, PR China

[5] Clinical Medicine (three-year program) of Postgrade 2017, Xi'an Medical University, Xi'an, Shaanxi 710021, PR China

[6] Department of Gastroenterology, the First Affiliated Hospital, Xi'an Medical University, Xi'an, Shaanxi 710077, PR China

relationship between IGF-1 and NAFLD. Nishizawa et al. have reported that IGF-1 can ameliorate steatosis, inflammation, and fibrosis of the liver by inactivating Hepatic stellate cells (HSCs) in mouse models [5]. In vitro studies, IGF-1 has been shown to regulate multiple important cellular functions involved in the development of NAFLD. Takahashi et al. found that IGF-1 can directly modulate the expression of acute-phase reactants, such as decreasing C reaction protein (CRP) and fibrinogen levels and up-regulating albumin expression [6]. Some of the results also provide the experimental basisof the mechanisms of NAFLD. The present results raise that lower IGF-I level, resulting in an unbalance between pro-inflammatory and anti-inflammatory proteins, lowered protection against inflammation may have a role in the development of NAFLD [7]. However, the current results in the role of IGF-1 in NAFLD are controversial. A study with Asian patients by Sumida et al. demonstrated that serum IGF-1 level was inversely correlated with NAFLD patients [8]. Some studies showed different results. Dichtel et al. showed that steatosis in NAFLD was not significantly associated with serum IGF-1 level [9]. Therefore, we conducted this meta-analysis in order to clarify the relationship between IGF-1 expression and NAFLD, expanding our understanding of the role of IGF-1 in NAFLD and providing clues for developing novel treatments for NAFLD.

Materials and methods

Literature search and selection

We performed a comprehensive literature search for online databases, including PubMed, Web of Science, and Embase databases. The keywords for the search were as follows: 'Insulin-like growth factor-1', 'IGF-1', 'Fatty Liver Disease', 'Non-alcoholic Fatty Liver Disease', 'NAFLD' or 'NASH'. In addition, the references of eligible literature were manually screened to further retrieve relevant publications.

Inclusion and exclusion criteria

The initially retrieved publications were reviewed by two investigators independently. The discrepancy was resolved by discussion with all investigators. The inclusion criteria were as follows: (1) the study contained the case group and the control group, (2) the cases were NAFLD patients, and the controls were healthy persons, (3) We included only studies in which diagnosis of NAFLD was based on either biopsy or imaging techniques, and in the absence of excessive alcohol consumption (>20 g/day for women and >30 g/day for men) and other competing causes of chronic liver disease, (4) Among them, NASH diagnosis was based on NAS score, NAS scores of 0–2 was defined as simple steatosis, 3–4 as borderline NASH, and 5–8 was diagnosed as definitive NASH [10] (5) the study must provide mean ± standard deviation (SD) or mean ± standard error of the mean (SEM) of the IGF-1 levels in NAFLD patients and controls, Studies were excluded if they were (1) reviews, case reports, abstracts, or unpublished studies, (2) studies where NAFLD diagnosis was based exclusively on serum liver enzymes or other surrogate markers of NAFLD, (3) studies which did not exclude individuals with excessive alcohol consumption and other known causes of chronic liver disease, (4) studies in patients with end-stage renal disease, cancer, cirrhosis of any aetiology, or patients with end-stage liver disease awaiting liver transplantation. the reason for exclusion are shown in Table 2.

Dataextraction and quality assessment

Three authors independently extracted the following information from each included article: the title of the study, first author's name, year of publication, the location of the study, mean ± SD or mean ± SEM of the IGF-1 levels, clinical characteristics (including gender, ages, and body mass index (BMI)), and other relevant information. The quality assessment of retrieved articles was carried out by two investigators independently. Newcastle–Ottawa quality assessment scale was used for cohort study and the exposure for a case-control study. The scale is composed of three parts: selection, comparability,and exposure [11]. It is a semi-quantitative scale, and a score of 0–9 was assigned to each study. A total score of ≤3 was considered poor quality, 4 to 6 was considered moderate quality, and 7–9 was assigned for high quality.

Statistical analysis

This meta-analysis was performed by using RevMan 5.3 software (London, UK) and Stata SE12.0 (StataCorp LP, College Station, TX, USA). The standardized mean difference (SMD) with 95% confidence interval (CI) was calculated to assess the overall IGF-1 levels in the NAFLD and the control groups. Subgroup analysis was performed to investigatethe differences in IGF-1 level between NAFLD patients and healthy controls in different subgroups. Cochran's Q test and I^2statistic were used to determine the heterogeneity among studies. I^2 of 0–25% indicates insignificant heterogeneity, 26–50% means low heterogeneity, 51–75% indicates moderate heterogeneity, and 76–100% suggests high heterogeneity [12].

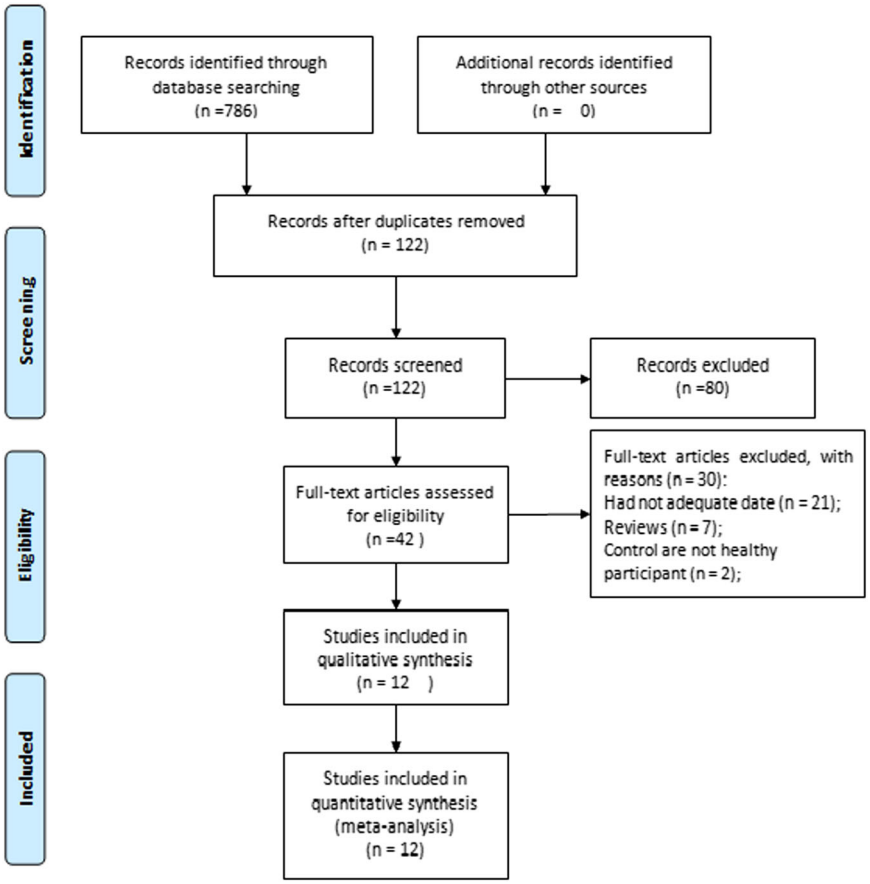

Fig. 1 Flow diagram of literature search and selection

Results

Literature search

Initially, 786 relevant articles were retrieved by the literature search. Among them, 122 studies were screened for the titles and abstracts, 80 articles were excluded, and 30 articles were excluded based on the exclusion criteria (21 articles had not adequate date, 7 articles were reviews and 2 articles in which the controls were not healthy participants). Finally, 12 articles with 5050 participants were included in this meta-analysis. The flow chart of the literature search and selection process was shown in Fig. 1.

Characteristics of the included studies

The general characteristics of the 12 included studies were summarized in Table 1. These studies were published from June 2007 to February 2018 and included 1211 NAFLD patients and 3839 healthy controls. All studies were based on blood samples. The IGF-1 level was measured using enzyme-linked immune sorbent assay (ELISA), chemiluminescent immunoassay (CLIA) or immune radiometric assay (IRMA). Ten studies reported a significant reduction in IGF-1 level in the NAFLD group, while the other two studies indicated that the IGF-1 level was up-regulated in the patient group. Regarding the location of the studies, six were carried out in Europe, four were conducted in Asia, one was in Egypt, and the other one was in the USA. In terms of study type, these studies included seven case-control studies and five cross-sectional studies. The diagnostic modalities of NAFLD has been revised and confirmed in each article. Five studies were diagnosis by Ultrasound and seven by liver biopsy. The NOS scoring system was used to assess the quality of included studies: one study scored 5 [13], three studies scored 6 [9, 14, 15], four studies scored 7 [8, 16–18] and four studies scored 8 [19–22], suggesting all studies had moderate or high quality, and therefore none of them was eliminated due to low quality (NOS score ≤ 2). Furthermore, the serum IGF-1 level, IGF-1 level in liver biopsy, BMI, and homeostatic model assessment (HOMA-IR) of theparticipants were summarized in Table 2.

The IGF-1 level betweenthe NAFLD and control groups

As shown in Fig. 2, the IGF-1 level in the control group was significantly higher than that in the NAFLD group (SMD: 1.00, 95% CI: 0.54–1.46, $P < 0.00001$). However,

Table 1 General characteristics of the included studies

Study	Year	Country	Design	Sample size (Control/NAFLD)	Sample	Method	Diagnosis of NAFLD	NOS
Arturi et al. [19]	2011	Italy	cross-sectional	503(195/308)	serum	Others	Risk factor: elevated blood pressure, overweight/obesity, diabetes or cardiovascular disease et al; US: presence of a bright hepatic echotexture (compared with the kidneys), deep attenuation, and vascular blurring either singly or in combination to diagnose hepatic steatosis	8
Colak et al. [14]	2012	Turkey	case-control	143(51/92)	serum	ELISA	ALT increased; did not consume alcohol more than 20 g/day; Exclude other liver diseases; US guided liver biopsy	6
Dichtel et al. [9]	2017	USA	case-control	62(21/41)	serum	CLIA	Exclude alcohol intake more than two drinks per day for men and more than one drink per day for women; Liver biopsy	6
Fusco et al. [17]	2012	Italy	case-control	115(50/65)	serum	IRMA	Exclusion: chronic liver disease and/or liver cirrhosis (alcoholic, viral, autoimmune or metabolic); alcohol intake (ethanol more than 30 g/day for men and 25 g/day for women); HBV and/or HCV infection;according to the standards of good clinical practice; US	7
García-Galiano et al. [20]	2007	Spain	cross-sectional	48(12/36)	serum	ELISA	morbid obesity, no history of alcohol intake, no treatment with metformin, vitamin E or thiazolidinedione; Liver biopsy	8
Hegazy et al. [16]	2017	Egypt	case-control	74(20/54)	serum	ELISA	overweight and obese; abdominal ultrasound +/− elevated liver enzymes, and confirmed by liver biopsy	7
Ichikawa et al. [13]	2007	Japan	case-control	52(34/18)	serum	Others	persistently raised ALT level (>1.5 times the upper normal limit for 6 months or more); no excessive alcohol intake (average daily consumption of more than 20 g of alcohol); no cirrhosis; Liver biopsy assisted by US	5
Liang et al. [21]	2018	China	case-control	84(36/48)	serum	CLIA	Excluded: subjects with hepatitis B or C, autoimmune hepatitis, other liver disease; chronic alcohol intake; US: diffusely increased echogenicity (bright) liver and stronger echoes in the hepatic parenchyma than those in the kidneys or spleen; 2) blurring visualization of intrahepatic structures; and 3) deep attenuation of ultrasound signals	8
Matsumoto et al. [18]	2018	Japan	cross-sectional	338(249/89)	serum	IRMA	Excluded: malignant disease, liver cirrhosis, hepatitis B or C, and autoimmune hepatitis;US: assessing hepato-renal contrast or impaired visualization of the hepatic vein borders or the diaphragm	7
Savastano et al. [15]	2011	Italy	cross-sectional	48(21/27)	serum	IRMA	Excluded: chronic liver diseases of viral, alcoholic et al; US analyses	6
Sesti et al. [22]	2013	Italy	cross-sectional	473(239/234)	serum	CLIA	Cardiometabolic risk factors; Excluded: known diabetes, history of any malignant disease, chronic gastrointestinal diseases or pancreatitis, self-reporting alcohol intake of 3 or more drinks per day, positivity for antibodies to hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg), and history of use of toxins or drugs known to induce liver damage; Liver biopsy	8
Sumida et al. [8]	2015	Japan	case-contrsol	3110(2911/199)	serum	IRMA	Liver biopsy showing steatosis in at least 5% of hepatocytes; appropriate exclusion of liver diseases of other etiology including viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, biliary obstruction, hemochromatosis, Wilson's disease and α1- antitrypsin-deficiency-associated liver disease. Patients consuming more than 20 g of alcohol per day and patients with evidence of HCC were excluded from the present study	7

NOS Newcastle-Ottawa quality assessment scale, *ELISA* enzyme-linked immune sorbent assay, *CLIA* chemiluminescent immunoassay, *IRMA* immunoradiometric assay, *US* ultrasonography, *US* ultrasound, *ALT* alanine aminotransferase

Table 2 IGF-1 level, BMI and HOMA-IR in the included studies

Study	IGF-1 concentration		BMI		HOMA-IR		Liver biopsy in NAFLD (IGF-1 concentration)		Liver biopsy in NAFLD (IGF-1concentration)	
	Control	NAFLD	Control	NAFLD	Control	NAFLD	Non- or probable-NASH	NASH	Mild fibrosis	Severe fibrosis
Arturi et al. [19]	168 ± 73	139 ± 57	27.7 ± 4.4	31.6 ± 5.8	2.6 ± 1.7	3.5 ± 2.1	NA	NA	NA	NA
Colak et al. [14]	126.8 ± 71.6	133.3 ± 76.7	24.6 ± 3.7	31.8 ± 5.3	1.35 ± 0.53	4.21 ± 4.1	142.6 ± 39.9	132.7 ± 85.5	NA	NA
Dichtel et al. [9]	133 ± 56	118 ± 54	42.7 ± 8.3	43.9 ± 6.8	NA	NA	NA	NA	125 ± 51	96 ± 40
Fusco et al. [17]	20.5 ± 6.9	17.1 ± 7.3	32.0 ± 1.7	33.7 ± 2.5	3.0 ± 1.8	4.8 ± 3.5	NA	NA	NA	NA
García-Galiano et al. [20]	200 ± 8.1	143 ± 10.5	24 ± 3.5	51 ± 7.0	2.1 ± 0.37	12 ± 2.7	157 ± 12.2	101 ± 14.3	NA	NA
Hegazy et al. [16]	130.00 ± 19.44	58.15 ± 20.26	NA	NA	1.87 ± 0.43	3.57 ± 1.57	66.81 ± 21.56	56.92 ± 19.8	NA	NA
Ichikawa et al. [13]	191.8 ± 128	129.2 ± 45.4	29.2 ± 4.4	28.7 ± 3.6	3.86 ± 2.18	3.86 ± 2.18	NA	NA	NA	NA
Liang et al. [21]	211 ± 55.8	172.50 ± 29.8	25.38 ± 0.98	29.17 ± 2.27	3.25 ± 0.6	5.16 ± 1.1	NA	NA	NA	NA
Matsumoto et al. [18]	161 ± 38.8	169 ± 42.2	22.4 ± 2.8	26.1 ± 3.0	1.1 ± 0.5	1.9 ± 0.9	NA	NA	NA	NA
Savastano et al. [15]	203.8 ± 94.8	138.0 ± 54.0	32.7 ± 5.8	37.4 ± 5.8	2.5 ± 1.5	4 ± 2.5	NA	NA	NA	NA
Sesti et al. [22]	172 ± 70	147 ± 57	27.9 ± 5.1	32.3 ± 5.7	2.6 ± 1.8	3.8 ± 2.6	NA	NA	NA	NA
Sumida et al. [8]	121 ± 5.7	112 ± 10.5	NA	NA	NA	NA	123 ± 17	104 ± 13.25	118 ± 15.25	80 ± 8

IGF-1 insulin-like growth factor-1, *BMI* body mass index, *HOMA-IR* homeostatic assay, *Non or probable-NASH* not nonalcoholic steatohepatitis or probable nonalcoholic steatohepatitis, *NASH* nonalcoholic steatohepatitis

significant heterogeneity was discovered ($P < 0.00001$, $I^2 = 96\%$). Then subgroup analysis and meta-regression were performed.

Subgroup analysis

The subgroup analysis was conducted to explore the sources of heterogeneity. We evaluated potential sources of heterogeneity between studies including NAFLD complications, insulin resistance, Diagnosis of NAFLD,BMI and the location of the studies were therefore performed (Table 3). Six studies conducted liver biopsies, among which four studies divided the NAFLD patients into nonalcoholic steatohepatitis (NASH) and not nonalcoholic steatohepatitis or probable nonalcoholic steatohepatitis (Non- or probable-NASH) groups, and the other two classified the patients into mild fibrosis and severe fibrosis groups. The IGF-1 level in the non- or probable-NASH group was found to be significantly higher than that in the NASH group (SMD: 1.42, 95% CI: 0.25–2.58, $P = 0.02$). However, the heterogeneity was still significant ($P < 0.00001$, $I^2 = 92\%$). (Table 3, Fig. 3). The analysis based on severity of fibrosis did not discover a significant difference in the IGF-1 level between patients with mild and severe fibrosis (SMD: 1.61, 95% CI: −0.39–3.61, $P = 0.12$). The heterogeneity was still significant ($P < 0.00001$, $I^2 = 97\%$) (Table 3, Fig. 4). It is known that the HOMA-IR is a method commonly used to quantify insulin resistance and beta-cell function. A HOMA-IR value of ≥2.0 or 2.5 indicates enhanced diagnostic value in differentiating NAFLD carriers and healthy individuals [23, 24]. Therefore we chose HOMA-IR ≥ 2.5 as an indicator of insulin resistance. The results showed that in the subgroup with HOMA-IR ≥2.5, IGF-1 level in NAFLD patients was lower than that in healthy controls (SMD:0.49, 95% CI: 0.36–0.63, $P < 0.00001$). And there was no obvious heterogeneity ($P = 0.32$, $I^2 = 15\%$) (Table 3, Fig. 5). The subgroup analysis based on BMI indicated that IGF-1 level in the NAFLD patients was lower than that in healthy controls (BMI ≥ 30, SMD: 0.50, 95% CI: 0.22–0.79, $P < 0.05$). but no difference was found between this two groups in low BMI (BMI < 30, SMD: 1.16, 95% CI: −0.11–2.43, $P = 0.07$) cohort. There was mild heterogeneity in the BMI ≥ 30 subgroup ($P = 0.33$, $I^2 = 9\%$), but the heterogeneity was still significant in the BMI < 30 subgroup ($P < 0.00001$, $I^2 = 97\%$) (Table 3, Fig. 6). In addition, we performed a subgroup analysis based on the region of studies. The results showed that the IGF-1 level in the NAFLD group was significantly lower than that in the control group for studies conducted in Asia and Europe (Asia: SMD: 0.69, 95% CI: −0.29–1.66, $P = 0.17$; Europe: SMD: 0.89, 95% CI: 0.41–1.38, $P < 0.05$). There was high heterogeneity among studies from both regions (Asia: $P <$

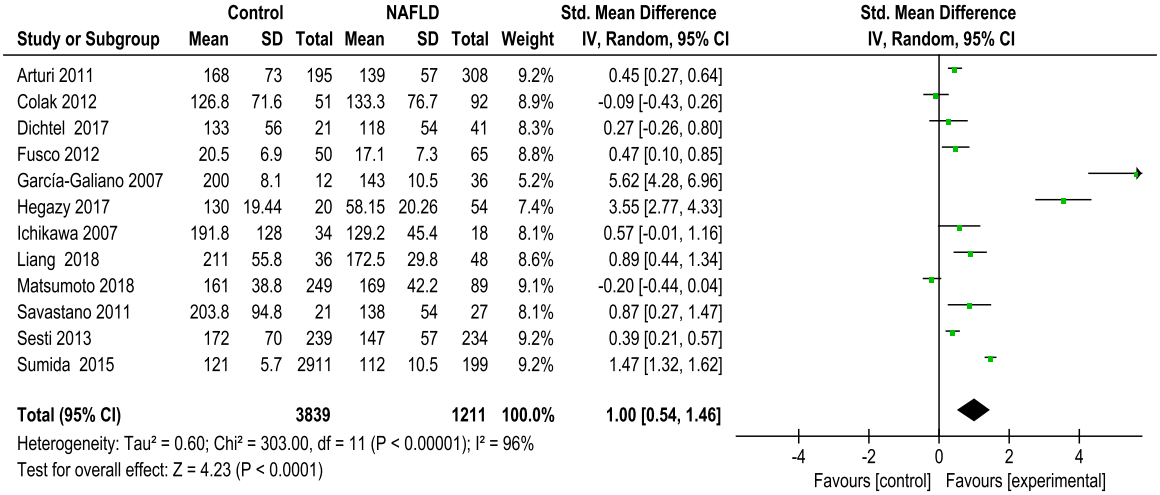

Fig. 2 SMD analysis of IGF-1 level in NAFLD patients and the controls

Table 3 Subgroup analysis of IGF-1 level in NAFLD patients and controls

Subgroups	SMD (95% CI)	Z	*P*	Test of Heterogeneity	
				I^2	*P*
Liver biopsy					
NASH	1.42 (0.25,2.58)	2.38	$P = 0.02$	92%	$P < 0.0001$
Fibrosis	1.61 (−0.39,3.61)	1.57	$P = 0.12$	97%	$P < 0.0001$
HOMA-IR					
HOMA-IR ≥ 2.5	0.49 (0.36,0.63)	7.32	$P < 0.0001$	15%	$P = 0.32$
BMI					
BMI < 30	1.16 (−0.11,2.43)	1.79	$P = 0.07$	97%	$P < 0.0001$
BMI ≥ 30	0.50 (0.22,0.79)	3.43	$P < 0.05$	9%	$P = 0.33$
Region					
Asia	0.69 (−0.29,1.66)	1.38	$P = 0.17$	97%	$P < 0.0001$
Europe	0.89 (0.41,1.38)	3.63	$P < 0.05$	92%	$P < 0.0001$
Diagnosis of NAFLD					
US	0.46 (0.06,0.85)	2.28	$P = 0.02$	87%	$P < 0.0001$
Liver biopsy	1.47 (0.73,2.22)	3.87	$P = 0.0001$	97%	$P < 0.0001$

NASH nonalcoholic steatohepatitis, *HOMA-IR* homeostatic assay, *BMI* body mass index, *SMD* standard mean difference, *CI* confidence intervals

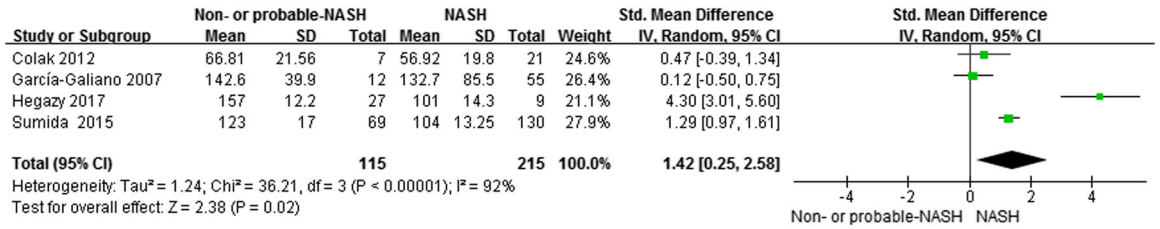

Fig. 3 Subgroup analysis for NASH and non-NASH in NAFLD patients

0.00001, $I^2 = 97\%$; Europe: $P < 0.00001$, $I^2 = 92\%$) (Table 3, Fig. 7). Finally, a subgroup analysis were performed based on the diagnosis way of NAFLD, which shows that both in US or Liver biopsy subgroups, the results showed that the difference of IGF-1 has statistical significance in both US and liver biopsy group (US: SMD: 0.46, 95% CI: 0.06–0.85, $P = 0.02$; Liver biopsy: SMD: 1.47, 95% CI: 0.73–2.22, $P = 0.0001$) (Table 3, Fig. 8).

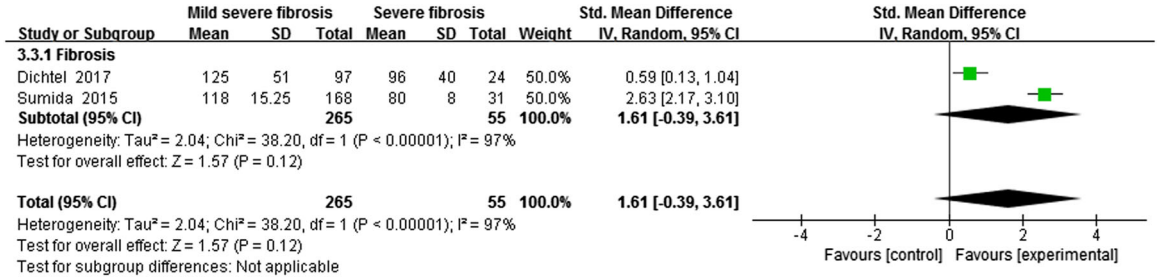

Fig. 4 Subgroup analysis for the severity of fibrosis in NAFLD patients

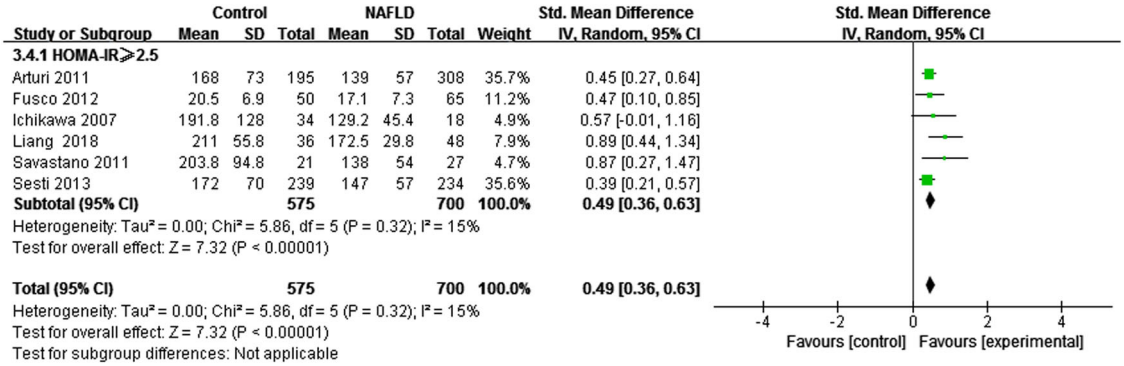

Fig. 5 Subgroup analysis for insulin resistance

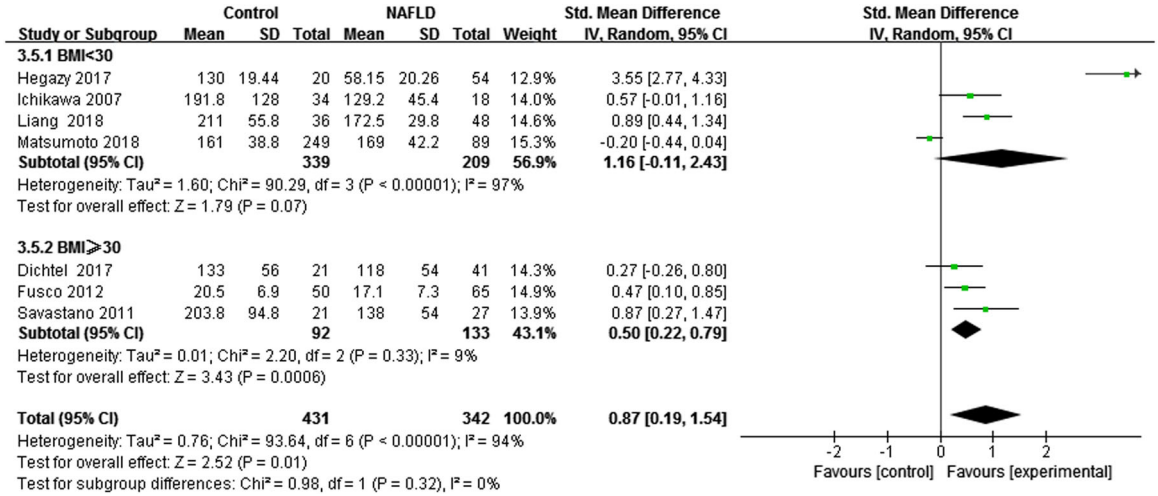

Fig. 6 Subgroup analysis for BMI

Sensitivity

Sensitivity analysis was then carried out to evaluate the influence of a single study on the results of this meta-analysis. The SMD, 95% CIs, and the I^2 values remained stable when the included studies were removed one at a time from this meta-analysis. These results indicated that removing any of the included studies had no significant influence on the final results, which suggested the robustness of the conclusions of this study (Table 4).

Meta-regression

To further investigate the impact of the above study characteristicson the study estimates of SMD in IGF-1, we

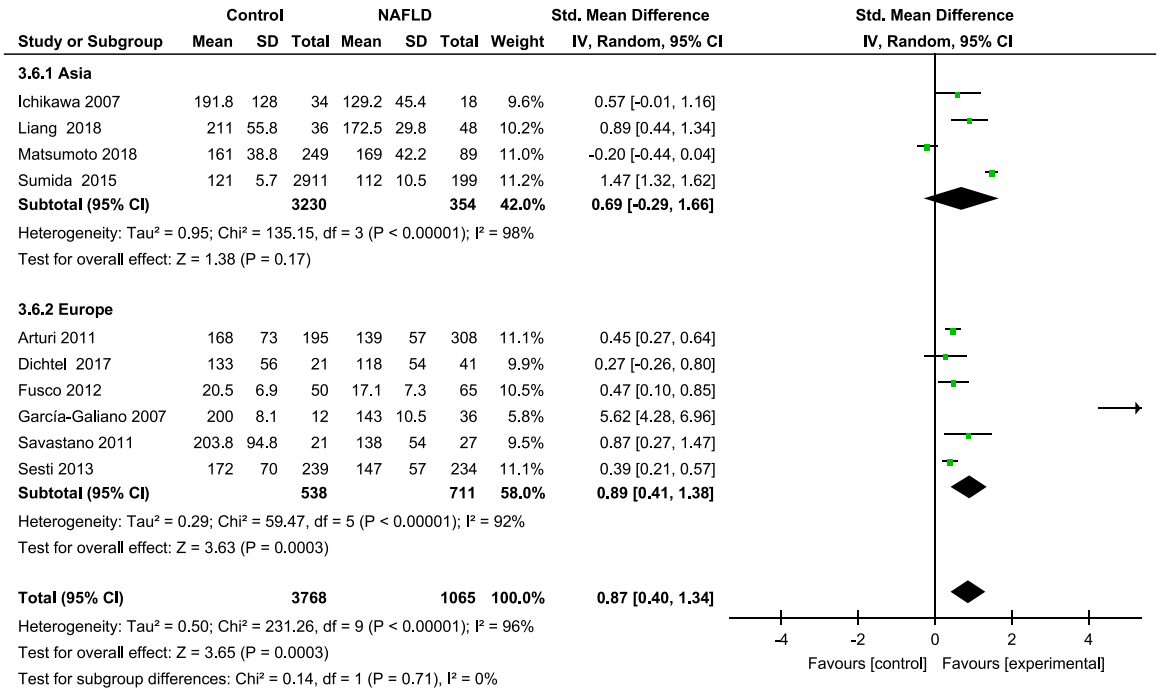

Fig. 7 Subgroup analysis for the locational origin of the included studies

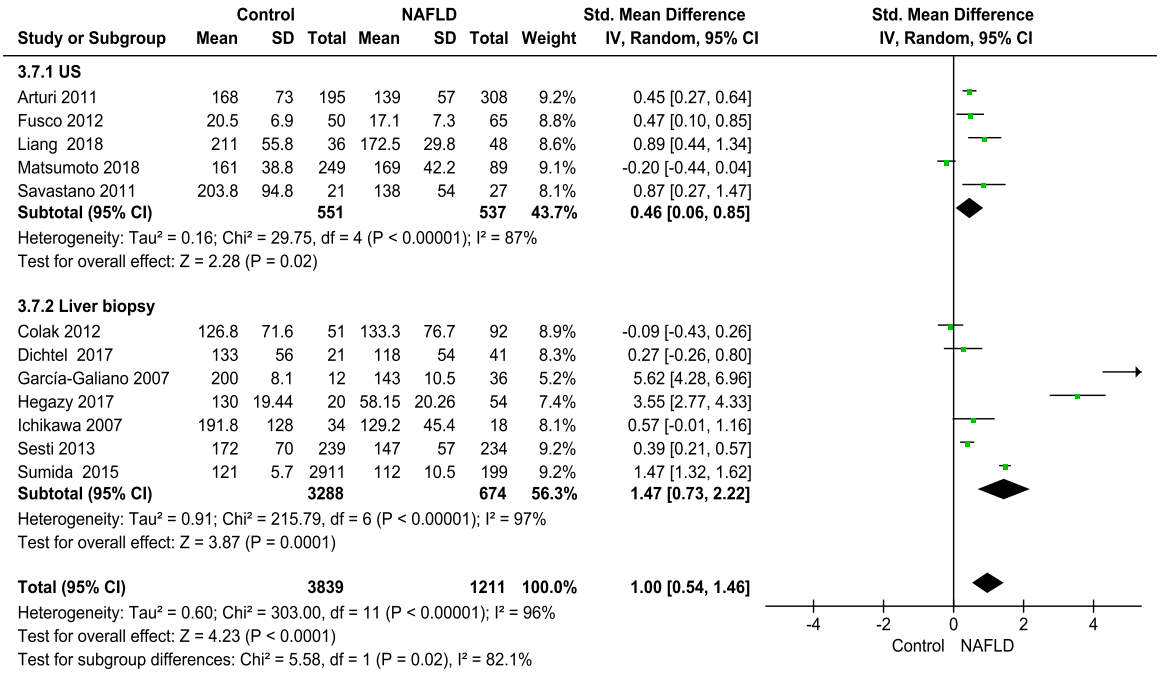

Fig. 8 Subgroup analysis for diagnosis way of DAFLD

conducted meta-regression analysis. SMD was used as thedependent variable, and BMI, Published year, Region, Design, Assay methods, NOS, and the Sample size were entered as explanatory covariates. Univariate meta-regression analysis was performed. In univariate meta-regression analysis, BMI (11 studies, $P = 0.134$), Year (12 studies, $P = 0.107$), Region (12 studies, $P = 0.503$), Design (12 studies, $P = 0.772$), Methods (12 studies, $P = 0.145$), NOS (12 studies, $P = 0.390$), and Sample size (12 studies, $P = 0.217$) were assessed in dependently. Results of the univariate analysis are presented (Table 5). The results of meta-regression suggested that all

the covariates failed to account for heterogeneity in the studies.

Publication bias

A funnel plot analysis was performed to investigate the potential publication bias of the 12 included articles. The Egger's ($t = -0.46$, $P = 0.657$) and Begg's ($z = 1.71$, $P = 0.086$) indicated that no significant publication bias existed in these studies (Fig. 9).

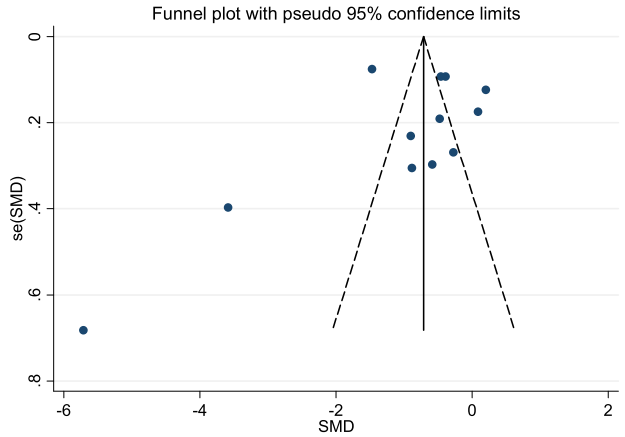

Fig. 9 A funnel plot analysis of publication bias

Table 4 Sensitivity analysis

Study	SMD (95% CI)	*P* heterogeneity	I^2
Arturi et al. [19]	1.08 (0.54–1.63)	$P < 0.0001$	97%
Colak et al. [14]	1.11 (0.62–1.59)	$P < 0.0001$	96%
Dichtel et al. [9]	1.07 (0.58–1.56)	$P < 0.0001$	97%
Fusco et al. [17]	1.06 (0.56–1.56)	$P < 0.0001$	97%
García-Galiano et al. [20]	0.74 (0.30–1.17)	$P < 0.0001$	96%
Hegazy et al. [16]	0.78 (0.33–1.41)	$P < 0.0001$	96%
Ichikawa et al. [13]	1.23 (0.73–1.22)	$P < 0.0001$	97%
Liang et al. [21]	1.02 (0.52–1.51)	$P < 0.0001$	97%
Matsumoto et al. [18]	1.11 (0.64–1.58)	$P < 0.0001$	96%
Savastano et al. [15]	1.01 (0.53–1.50)	$P < 0.0001$	97%
Sesti et al. [22]	1.09 (0.55–1.62)	$P < 0.0001$	97%
Sumida et al. [8]	0.91 (0.48–1.33)	$P < 0.0001$	94%

SMD standard mean difference, *CI* confidence intervals

Discussion

The rapidly increasing prevalence of NAFLD leads to an increasing number of patients with cirrhosis and end-stage liver diseases that require liver transplantation [25, 26]. However, the exact mechanisms for the formation and development of NAFLD remain unclear. Therefore, clarifying the pathogenesis and identifying valid predictive biomarkers of NAFLD are necessary. A large number of experimental and clinical researches have indicated that NAFLD is associated with low IGF-1 level [27–29]. IGF-1 is synthesized in the liver and belongs to the IGF system, which plays an important role in chronic liver diseases [30]. Insulin resistance may be involved in this mechanisms [31]. Insulin resistance is a key risk factor for NAFLD, which involves the development of oxidative stress and lipotoxicity [32]. The structure of IGF-1 is similar to that of insulin [33, 34], and IGF-1 deficiency has been shown independently associated with insulin resistance. IGF-I can lead to an increase in peripheral glucose uptake and a reduction in the production of hepatic glucose, thereby improving insulin sensitivity [35, 36]. Impairment of IGF-1 synthesis can result in worsening of insulin resistance [37]. Thus we hypothesized that IGF-1 deficiency promotes the development of NAFLD by increasing insulin resistance. Sumida et al. have pointed out that compared to NAFLD patients, patients with NASH had a significantly lower level of IGF-1 [8]. In Spanish patients, with the progression of NASH, IGF-1 level decreased, and the IGF-1 level was also decreased with the progression of liver steatosis in NAFLD patients [20]. Another study showed consistent results that IGF-1 level was negatively associated with hepatic steatosis [17]. However, some studies showed different results. Dichtel et al. showed that serum IGF-1 level was lower in patients in advanced fibrosis stage or with NASH than in

Table 5 Univariate meta-regression analysis for the potential variables between studies

Covariates	No. of studies	Coefficient	Standard error	*t*	*P*	95% Confidence interval	
BMI	11	1.728	0.847	2.04	0.134	−0.967	4.421
Year	12	0.402	0. 176	2.28	0.107	−0.158	0.963
Region	12	0.621	0.818	0.76	0.503	−1.981	3.223
Design	12	−0.364	1.147	−0.32	0.772	−4.013	3.285
Method	12	1.577	0.805	1.96	0.145	−0.984	4.139
NOS	12	−0.644	0.642	−1.00	0.390	−2.688	1.401
Sample size	12	−0.001	0.001	−1.56	0.217	−0.004	0.001

BMI body mass index, *NOS* Newcastle-Ottawa quality assessment scale

those without NASH, but steatosis was not significantly associated with serum IGF-1 level [9].

This is the first meta-analysis of the relationship between IGF-1 level and NAFLD. In the pooled analysis, we found that NAFLD patients had significant lower IGF-1 level than the healthy controls. As indicated by the results of the sensitivity analysis, this association was stable. However, there was significant heterogeneity among the included studies, which potentially compromise the validity of the above-mentioned conclusion. Due to the existence of significant heterogeneity, a subgroup analysis was carried out according to the liver biopsy in NAFLD patients. The pathological process of NAFLD includes NASH and fibrosis [38]. We thereby performed subgroup analyses based on these two pathological changes. In patients with NAFLD, IGF-1 level in the subgroup with NASH was significantly lower than that in the non-or probable NASH subgroup. However, There was no significant difference in the level of IGF-1 between fibrotic and non-fibrotic groups. These findings were inconsistent with the study of Alisi et al. who reported that IGF-1 and its receptor are upregulated in children with NAFLD [39]. Sampling error or the small number of included articles may contribute to this inconsistency. HOMA-IR is commonly used as an index to estimate insulin resistance [40] and HOMA-IR ≥ 2.5 is usually defined as having insulin resistance. therefore, we perform a subgroup based on HOMA-IR, in the HOMA-IR ≥ 2.5 subgroup, the level of IGF-1 was associated with insulin resistance. In the subgroup with BMI ≥ 30, The level of IGF-1 in NAFLD patients was higher than that in control group for the region of study, the low level of IGF-1 was observed in NAFLD patients compared to the controls for study conducted in Europe and Asia.

However, several limitations existed in this study, which may compromise the validity of the conclusions. Firstly, the sizes of the recruited cohorts in several studies were small, and some included studies didn't adjust for important potential confounders, such as age, sex, and obesity. Secondly, significant heterogeneity was present among the included studies, which might be caused by the differences in the enrolled population and measurement methods. Thirdly, selection bias was inevitable, because the included articles were limited to those published in English, leading to potential missing of high-quality studies published in other languages. Finally, the possibility of unidentified confounding bias cannot be excluded because of differences in the designs of included studies.

Conclusion

This study indicated that the level of IGF-1 in NAFLD patients was significantly lower than that in the healthy controls, suggesting that IGF-1 was a potential biomarker and therapeutic target for NAFLD. Furthermore, insulin resistance might be involved in the down-regulated expression of IGF-1 in NAFLD patients, although the exact mechanisms need to be further explored.

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Compliance with ethical standards

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

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