Review

Lower circulating IGF-1 levels in fibromyalgia: meta-analysis highlighting potential pathogenic role

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ABSTRACT

Objective. *To evaluate the relationship between circulating insulin-like growth factor (IGF-1) levels and fibromyalgia (FM).*

Methods. *Meta-analyses were performed to compare serum/plasma IGF-1 levels in patients with FM and healthy controls and in patients with FM according to subgroups based on region, sample size, data type, publication year, and matched variables (age, sex, and/or BMI).*

Results. *Twelve studies from eleven reports including 512 patients with FM and 308 controls were selected. IGF-1 levels were not found to be decreased in the FM group (standardised mean differences (SMD) =-0.347, 95% confidence interval [CI]: -0.747 to 0.053, p=0.089. However, sensitivity analysis showed that results of one study significantly affected the pooled SMD (SMD =-0.458, 95% CI: -0.822 to -0.093, p=0.014), indicating that the results of this meta-analysis were unstable. Additionally, the SMD changed to be significant after adjusting for publication bias (SMD =-0.513, 95% CI: -0.924 to -0.102). Stratification according to data type showed a significantly lower IGF-1 level in the FM group with original data (SMD =-0.458, 95% CI: -0.857 to -0.060, p=0.024). Stratification by publication year revealed a significantly lower IGF-1 level in the FM group by recent year (year ≥ 2012) (SMD =-0.679, 95% CI: -1.066 to -0.293, p=0.001).*

Conclusion. *Our meta-analysis demonstrated that IGF-1 levels were significantly lower in patients with FM, suggesting that IGF-1 might play an important role in the pathogenesis of FM.*

Introduction

Fibromyalgia (FM) is a chronic disorder characterised by widespread musculoskeletal pain, fatigue, and tender points (1, 2). Despite extensive research, the pathophysiology of FM remains poorly understood. Various hypotheses have been proposed, including abnormalities in the central nervous system, hormonal imbalances, and genetic predispositions (3-5). Among potential biomarkers investigated, insulin-like growth factor 1 (IGF-1) has garnered interest due to its role in muscle growth, repair, and overall metabolic regulation. IGF-1 is a peptide hormone structurally similar to insulin. It plays a pivotal role in growth and development, particularly in muscle repair and regeneration (6). Synthesised primarily in the liver, IGF-1 production is stimulated by growth hormone (GH) (7). It exerts systemic effects by promoting anabolic processes in various tissues (8, 9). Given its crucial role in muscle physiology, IGF-1 has been hypothesised to be involved in the pathogenesis of FM, a condition often marked by muscle pain and weakness. Understanding the role of IGF-1 in FM could have significant clinical implications. If a consistent relationship is found, IGF-1 could potentially serve as a biomarker for FM, aiding in the diagnosis and monitoring progression of this disease. Additionally, elucidating the involvement of IGF-1 in FM could inform the development of novel therapeutic strategies aimed at modulating IGF-1 levels to alleviate symptoms.

However, research findings on IGF-1 levels in FM patients have been inconsistent, with some studies reporting elevated levels while others finding no significant differences compared to

healthy controls (10-20). This disparity in findings is likely attributable to small sample sizes, low statistical power, and/or clinical heterogeneity. To address these discrepancies, a comprehensive meta-analysis is warranted to synthesise existing evidence and provide a clearer understanding of the relationship between IGF-1 and FM (21-23). This meta-analysis aimed to determine the relationship between circulating IGF-1 levels and FM. We also explored potential sources of heterogeneity by analysing subgroups based on region, sample size, data type, publication year. We also matched variables such as age, sex, and body mass index (BMI).

Materials and methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined IGF-1 levels in patients with FM and controls. Medline, Embase, Web of Science, and Cochrane library databases were searched to identify all available past articles up to May 2024. The following keywords and subject terms were used in the search: 'insulin-like growth factor-1', 'IGF-1', and 'fibromyalgia'. All references cited were also reviewed to identify additional studies not covered by the above-mentioned electronic databases. Studies were considered eligible if they were case-control, cross-sectional, or cohort studies and if they provided data on serum/plasma IGF-1 levels in case and control groups. Language and race restrictions were not applied. Studies were excluded if they contained overlapping or insufficient data, or they were reviews or case reports. The following information was extracted from each study: primary author, year of publication, country, region, number of participants, data type, and the mean and standard deviation (SD) of IGF-1 levels. Data on methods and results were extracted from original studies by two independent reviewers. Any discrepancies between the two reviewers were resolved by consensus. Meta-analysis was conducted in accordance with PRISMA guidelines. (24) When data were presented in terms of medians, interquartile ranges, or ranges, we computed the mean and SD using previously described formulae (25, 26). We also conducted a sensitivity test on imputed values. The quality of each component of the meta-analysis was scored using the Newcastle-Ottawa Scale (27).

Evaluation of statistical associations

We performed a meta-analysis examining the relationship between IGF-1 levels and FM. For continuity of data, results are presented as standardised mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between two groups by the pooled SD. They were used when different scales were integrated to measure the same concept. This measure can compare case and control arms in terms of standardised scores. The magnitude of SMD was considered as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect (28). We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics (29). The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When a significant Q-statistic ($p<0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis (30, 31). If not, the fixed effects model was used, which assumed that all studies estimated the same underlying effect and considered within-study variation only (29, 32). We quantified the effect of heterogeneity using $I^2=100\% \times (Q\text{-}df)/Q$(33), where I^2 measured the degree of inconsistency between studies and determined whether the percentage total variation across studies was due to heterogeneity rather than chance. I^2 ranged between 0% and 100%. I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively (33, 34). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer programme (Biostat Inc., Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity test, and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, meta-regression analyses were performed using the following variables: ethnicity, adjustment for variables, publication year, sample size, and data type. A sensitivity test was performed to assess the influence of each individual study on the pooled odds ratio by omitting each study individually. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes. In addition, their interpretation involves subjective judgment. Therefore, we evaluated publication bias using Egger's linear regression test (35), which measured funnel plot asymmetry using a natural logarithm scale of ORs. When asymmetry was indicated, we used the 'trim and fill' method to adjust summary estimates for observed bias (36). This method removes small studies until funnel plot symmetry is achieved by recalculating the centre of the funnel before removed studies are replaced with their missing mirror-image counterparts. A revised summary estimate was then calculated using all original studies and hypothetical 'filled' studies.

Results

Studies included in the meta-analysis

We identified 125 studies using electronic and manual search methods, 17 of which were selected for full-text review based on their titles and abstracts. Of them, six were excluded because they had no data on IGF-1, or they were review studies. A total of 11 articles met the inclusion criteria (Fig. 1) (10-20). One report contained data on two different groups. Thus, we analysed these studies independently (11). Ultimately, 12 separate studies were considered in the meta-analysis, which contained 512 patients with FM and 308 controls. Of these studies, seven were conducted in Europe and five were conducted in North America regions (Table I). Each study was evaluated on a scale of 1 to 10, resulting in quality ratings ranging from 6 to 7. Selected characteristics of these studies related to the association between IGF-1 levels and FM are summarised in Table I.

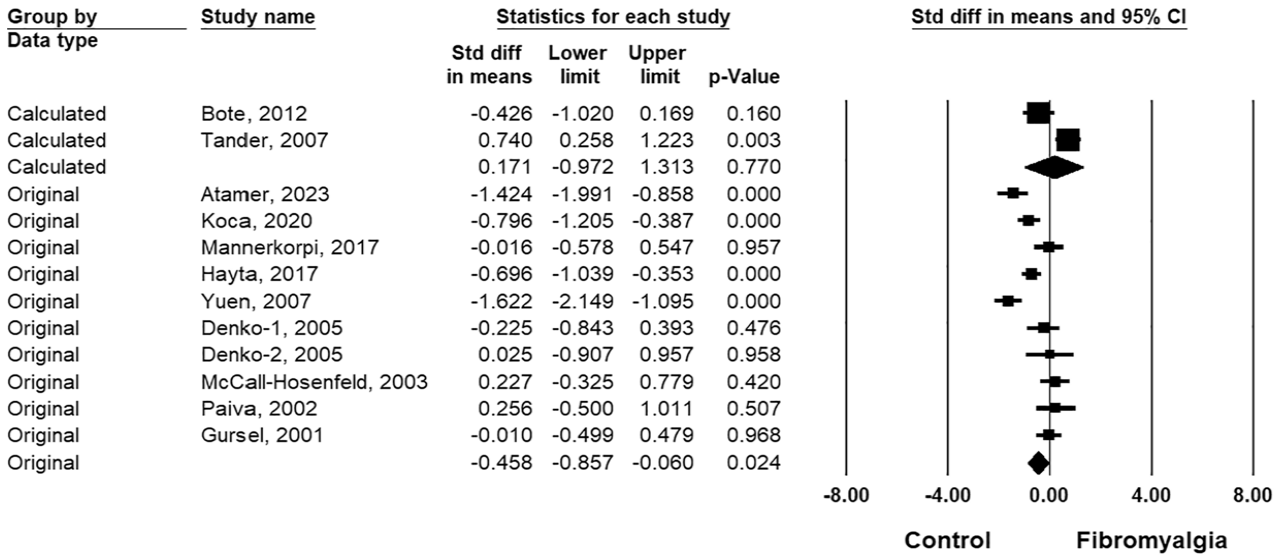

Fig. 1. Meta-analysis of the relationship between IGF-1 levels and fibromyalgia according to data type.

Meta-analysis of IGF-1 levels in patients with fibromyalgia compared to controls

The meta-analysis showed a trend of decreased IGF-1 levels in the FM group compared to that in the control (SMD=-0.347, 95% confidence interval [CI]: -0.747 to 0.053, p=0.089) (Table II). However, sensitivity analysis showed that Tander *et al*. study significantly affected the pooled SMD (SMD = -0.458, 95% CI: -0.822 to -0.093, p=0.014), indicating that results of this meta-analysis were unstable (10).

Additionally, the SMD changed to be significant after adjusting for publication bias (SMD = -0.513, 95% CI: -0.924 to -0.102).

Meta-analysis of IGF-1 levels in patients with fibromyalgia compared to controls in subgroup

Stratification by region showed no significantly elevated IGF-1 levels in the FM group in European or Latin American populations (Table II). Meta-analysis of studies adjusted for BMI revealed no association between IGF-1 levels and FM (Table II). Results of the group analysis by sample size showed no significantly elevated IGF-1 levels in the SLE group for studies with a large sample size (n≥50) or with a small sample size (Table II). Stratification according to data type showed a significantly lower IGF-1 level in the FM group for studies with original data (SMD=-0.458, 95% CI: -0.857 to -0.060, p=0.024), but not for studies with calculated data (SMD = 0.171, 95% CI: -0.972 to 1.313, p=0.770) (Table II, Fig. 2). Stratification by publication year revealed a significantly lower IGF-1 level in the FM group by recent year (year ≥2012) (SMD = -0.679, 95% CI: -1.066 to -0.293, p=0.001), but not by old year (year <2012) (SMD =-0.093, 95% CI: -0.713 to -0.528, p=0.770) (Table II, Fig. 2).

Heterogeneity, sensitivity test and publication bias

Between-study heterogeneity was identified during meta-analyses of IGF-1

Table I. Characteristics of the individual studies included in the meta-analysis.

Author	Country	Region	Number		Data type	Matched variables[a]	Statistical findings		
			Case	Control			SMD	Magnitude*	p-value
Atamer, 2023 (13)	Turkey	Europe	30	30	Original	Age, BMI	-1.424	Large	< 0.001
Koca, 2020 (16)	Turkey	Europe	60	42	Original	Age, sex, BMI	-0.796	Medium	< 0.001
Mannerkorpi, 2017 (17)	Sweden	Europe	22	27	Original	Age, sex	-0.016	Small	0.957
Hayta, 2017 (18)	Turkey	Europe	105	51	Original	Age, BMI	-0.696	Medium	0.000
Bote, 2012 (14)	Spain	Europe	25	20	Calculated	Age	-0.426	Medium	0.160
Tander, 2007 (10)	Turkey	Europe	47	28	Calculated	Age, sex, BMI	0.740	Medium	0.003
Yuen, 2007 (19)	USA	North America	64	24	Original	Age, BMI	-1.622	Large	< 0.001
Denko-1, 2005 (11)	USA	North America	25	17	Original	Age, sex	-0.225	Small	0.476
Denko-2, 2005 (11)	USA	North America	7	12	Original	Age, sex	0.025	Small	0.958
McCall-Hosenfeld, 2003 (12)	USA	North America	24	27	Original	Age, BMI	0.227	Small	0.420
Paiva, 2002 (20)	USA	North America	21	10	Original	Sex	0.256	Small	0.507
Gursel, 2001 (15)	Turkey	Europe	82	20	Original	Age, sex	-0.010	Small	0.968

SMD: standard mean difference; NA: not available; BMI: body mass index.
[a]Matched or no statistical difference in variables between fibromyalgia and control groups; *magnitude of Cohen's d effect size: 0.2 to 0.5: small effect; 0.5 to 0.8: medium effect; ≥ 0.8: large effect.

Table II. Meta-analysis of the IGF-1 levels in patients with fibromyalgia compared to healthy controls.

Group	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD[a]	95% CI	*p*-value	Model	*p*-value	I^2
All	Overall	12	-0.347	-0.747-0.053	0.089	R	< 0.001	85.1
Ethnicity	Europe	7	-0.347	-0.868-0.116	0.134	R	< 0.001	86.5
	North America	5	-0.290	-1.082-0.503	0.474	R	< 0.001	86.4
Matched variables*	Yes	6	-0.593	-1.236-0.077	0.083	R	< 0.001	91.9
	No	6	-0.090	-0.342-0.163	0.486	F	0.786	0
Sample size	N < 50	5	-0.119	-0.414-0.176	0.430	F	0.681	0
	N ≥ 50	7	-0.510	-1.100-0.081	0.091	R	< 0.001	91.2
Data type	Original	10	-0.458	-0.857- -0.060	0.024	R	< 0.001	81.9
	Calculated	2	0.171	-0.972-1.313	0.770	R	0.003	88.7
Publication year (yr)	Yr ≥ 2012	5	-0.679	-1.066- -0.293	0.001	R	0.011	69.1
	Yr < 2012	7	-0.093	-0.713-0.528	0.770	R	< 0.001	87.0

SMD: standard mean difference; R: random effects model.
*body mass index; [a]magnitude of the Cohen d effect size (SMD) (0.2–0.5, small effect; 0.5–0.8, medium effect; and ≥0.8, large effect); No.: number; CI: confidence interval.

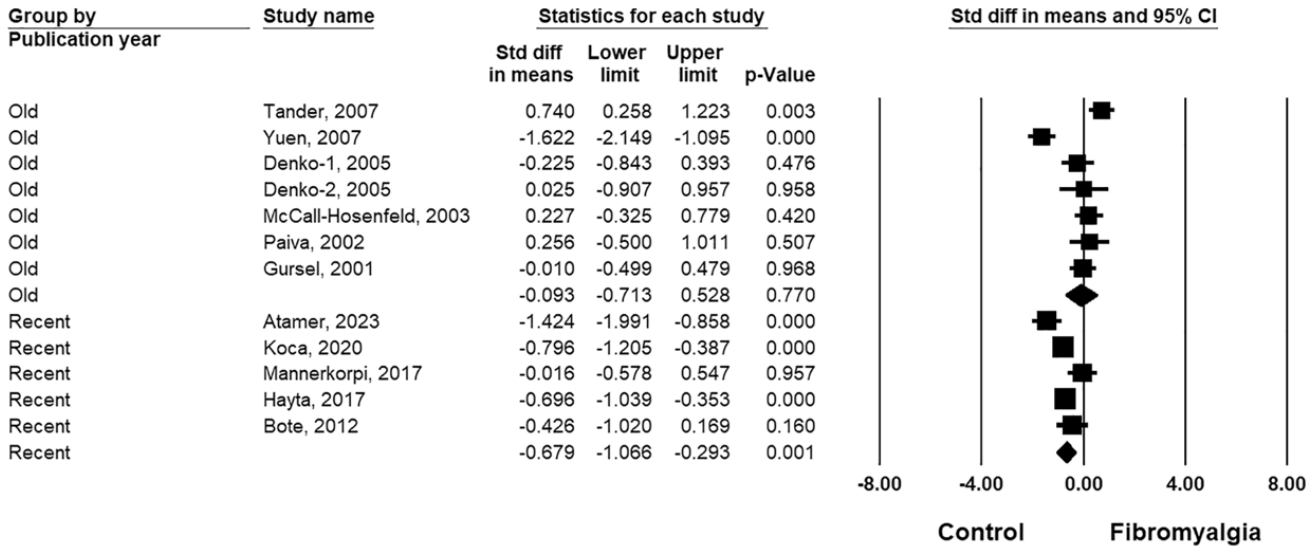

Fig. 2. Meta-analysis of the relationship between IGF-1 levels and fibromyalgia according to publication year.

levels in patients with FM (Table II). Meta-regression analysis showed that publication year and data type, but not sample size, region, study quality, or BMI adjustment, had significant impacts on the heterogeneity in the meta-analysis of IGF-1 levels in patients with FM. Sensitivity analysis showed that Tander *et al*. study significantly affected the pooled SMD (SMD=-0.458, 95% CI: -0.822 to -0.093, *p*=0.014), indicating that results of this meta-analysis were unstable (10). Although Egger's regression test showed no evidence of publication bias (Egger's regression test *p*-value=0.433), the funnel plot showed asymmetry. Therefore, the 'trim and fill' method was used to adjust for publication bias (Fig. 3). However, SMDs were significant after adjusting for publication bias (SMD=-0.513, 95% CI: -0.924 to -0.102).

Discussion

Our meta-analysis provides several key insights into the relationship between circulating IGF-1 levels and FM. Although the overall analysis indicated decreased IGF-1 levels in the FM group, the result did not reach statistical significance (SMD =-0.347, *p*=0.089). The sensitivity analysis demonstrated that results were unstable, as one study significantly affected the pooled SMD. Upon adjusting for publication bias, the SMD changed to a statistically significant value (SMD =-0.513, 95% CI=-0.924 to -0.102), indicating that publication bias might have influenced the initial results. This adjustment highlights the importance of considering potential biases in meta-analyses and suggests that IGF-1 levels might indeed be higher in FM patients.

Subgroup analysis by region revealed no significant elevation in IGF-1 levels in the FM group in European or Latin American populations. This lack of significance suggests that regional differences, possibly due to genetic, environmental, and/or lifestyle factors, might influence IGF-1 levels. The analysis of studies adjusted for BMI showed no association between IGF-1 levels and FM. This indicates that BMI, a common confounder, does not significantly impact IGF-1 levels in the context of FM. Given that BMI is a measure of body fat that could influence hormone levels, this finding suggests that the ob-

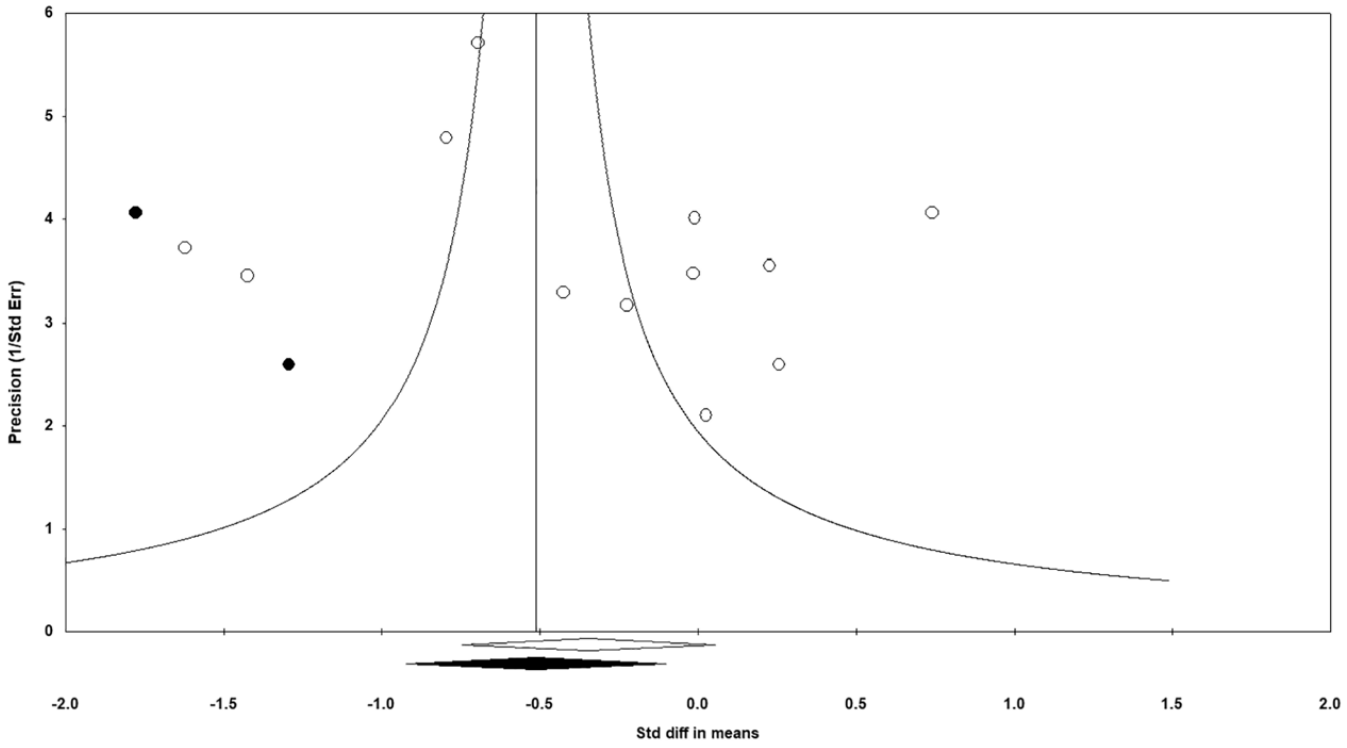

Fig. 3. Funnel plot of studies that have examined the association between IGF-1 levels and fibromyalgia (Egger's regression *p*-value = 0.493). Filled circles represent studies having publication bias. The diamonds at the bottom of the figure show summary effect estimates before (open) and after (filled) publication bias adjustment.

served differences in IGF-1 levels are not driven by variations in body compositions between FM patients and controls. The subgroup analysis by sample size found no significant differences in IGF-1 levels in studies with either small (n <50) or large (n >50) sample sizes. This consistency across different sample sizes suggests that the lack of significant findings is not due to the scale of studies but might be due to other factors such as methodological differences and/or heterogeneity among study populations.

Subgroup analyses provided further insights. Stratification by data type revealed that studies using original data showed a significant decrease in IGF-1 level in the FM group (SMD=-0.458, p=0.024). In contrast, studies with calculated data did not show such significant decrease (SMD=0.171, p=0.770). This discrepancy might be due to methodological differences, such as data handling and calculation methods, which might have impacted the results. Stratification by publication year revealed a significant difference in IGF-1 level in more recent studies (post-2012) (SMD=-0.679, p=0.001), but not in older studies (pre-2012) (SMD=-0.093, p=0.770). This finding could reflect advancements in research methods and diagnostic criteria over time, leading to more accurate assessments of IGF-1 levels in FM patients. It may also indicate that newer studies are better designed or that there has been a shift in the understanding of the role of IGF-1 in FM.

The observed decrease in IGF-1 levels among FM patients suggests a potential role for this hormone in the pathogenesis of FM. IGF-1 is known to have various biological functions, including promoting muscle growth, regeneration, and neuronal survival (6). Decreased levels of IGF-1 in FM patients could indicate a dysregulation in the IGF-1 axis contributing to FM symptoms (8, 37). However, the heterogeneity among studies and the instability of pooled results underscores the need for further research. Future studies should aim to standardise measurement techniques for IGF-1, control for potential confounding factors such as age, sex, and BMI, and explore the mechanisms by which IGF-1 may influence FM symptoms.

In conclusion, our meta-analysis suggests that IGF-1 levels are decreased in patients with FM, supporting the hypothesis that IGF-1 plays a role in the pathogenesis of FM. This finding provides a basis for further investigation into IGF-1 as a potential biomarker for FM and a target for therapeutic interventions. Continued research in this area is crucial for improving our understanding of FM and developing effective treatments.

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