Significantly higher peripheral fibroblast growth factor-2 levels in patients with major depressive disorder

A preliminary meta-analysis under MOOSE guidelines

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Abstract

Background: In vivo and in vitro studies demonstrate the important roles of fibroblast growth factor (FGF) and FGF receptors (FGFRs) in neural survival, neurogenesis, oxidative stress, and emotional behavior. However, evidence on the role of FGF and FGFR in the pathophysiology of major depressive disorder (MDD) remains limited and inconclusive.

Objectives: This preliminary meta-analysis aimed to examine changes in peripheral or central FGF and FGFR levels in patients with MDD.

Data sources: Electronic research through platform of PubMed and ClinicalTrials.gov.

Study eligibility criteria, participants, and interventions: We used the inclusion criteria: articles discussing the comparisons of FGF levels, either in peripheral or central environment, in patients with MDD and in healthy controls (HC); articles on clinical trials in humans; and case–control trials. Case reports or series and nonclinical trials were excluded.

Study appraisal and synthesis methods: Using a thorough literature search, the FGF/FGFR levels in patients with MDD and HC were compared. Four studies on peripheral FGF-2 and 3 on central FGF-2 and FGFR1 levels were included.

Results: The findings reveal significantly higher peripheral FGF-2 protein and central FGFR1 RNA levels in patients with MDD than in HC ($P = 0.005$ and 0.006, separately), but no significant association with clinical variables. There was also no significant difference in the central FGF-2 levels in patients with MDD and in HC ($P = 0.180$).

Limitation: The study has limitations of a small number of included studies, lack of meta-analysis of the FGF changes along with treatment, and lack of direct evidence on correlation of peripheral FGF-2 with central FGF-2 levels.

Conclusions and implications of key findings: This preliminary meta-analysis points out a new direction for future studies investigating the relationship among MDD, oxidative stress, and the FGF family.

Abbreviations: AnCG = anterior cingulated gyrus, BBB = blood–brain barrier, CI = confidence interval, CNS = central nervous system, ES = effect size, FGF = fibroblast growth factor, FGFR = fibroblast growth factor receptor, HC = healthy controls, MA = meta-analysis, MDD = major depressive disorder, MOOSE = Meta-analysis Of Observational Studies in Epidemiology, VEGF = vascular endothelial growth factor.

Keywords: biomarker, disease marker, growth factor, neurotrophic factor, oxidative stress

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1. Introduction

Major depressive disorder (MDD) contributes to a significant socioeconomic burden across the world.[1–3] Little is known about the pathophysiology of major affective disorders. Evidence suggests neurodegeneration, dysfunction of neurotrophic factors, and oxidative stress are a part of the pathophysiology of MDD.[4–6] Nevertheless, there has been no definitive or conclusive mechanism found.

The fibroblast growth factor (FGF) family has been found for decades. However, the role of the FGF family in neural function has not been explored until the 1990s.[7–9] Some have presented benefits in neural proliferation (e.g., FGF-2),[10] maturation and maintenance of neuron cells (FGF-1),[11] and neuronal excitability (FGF-14),[12] among others.[13] FGF receptors (FGFRs) also play important roles in neural function. For example, FGFR1 helps with neural proliferation and long-term potentiation in the hippocampus.[14] FGFR2 has important functions in neurogenesis and learning in the hippocampus.[15]

However, most of these extensive investigations are animal studies. Furthermore, the roles of FGF and FGFR in the pathophysiology of MDD, one of the disorders with neurodegeneration, remain unclear. To date, few literatures have attempted to investigate the roles and changes in FGF or FGFR among patients with MDD, and the results are inconsistent. In the report by Lu et al,[16] there is significantly higher peripheral FGF-2 in patients with MDD than in healthy controls (HC). However, contradictory findings are reported by He et al,[17] with significantly lower FGF-2 in patients with MDD than in HC. In earlier reports, differences in FGF-2 between patients with MDD and HC are insignificant.[18,19]

Inconsistent findings exist in studies about not only peripheral FGF levels but also the central nervous system (CNS). In an earlier report, FGF-2 levels in the postmortem brain of patients with MDD are significantly lower than those in the postmortem brain of HC, but without significant difference in FGFR1 levels between the 2 groups.[20] In a newer study by Goswami et al,[21] there is only significant difference in the comparison of FGFR1 levels, not with FGF-2 levels, in the postmortem brains of patients with MDD and of HC. Such inconsistencies may be due to different sample sources (e.g., serum vs plasma and prefrontal cortex vs anterior cingulated gyrus [AnCG]), different ages, or different subject resources.

A recent review article by Turner et al[13] tries to summarize current evidence of FGF functions in the pathophysiology of MDD. However, most of the studies used in this review article are animal or in vitro studies rather than human ones. Fortunately, in recent years, there have been some newer clinical reports regarding FGF levels in MDD.[16,17,21]

The present study aimed to update current evidence on changes in the FGF and FGFR family in patients with MDD, and to investigate such changes before and after treatment.

2. Materials and methods

2.1. Literature search and screening

The current research strategy and protocol of meta-analysis (MA) followed Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[22] and was adapted from recent MA reports.[4,5] The target included literatures about any observational studies or related trials about the FGF levels in patients with MDD. In the initial stage, 2 independent psychiatrists performed a systematic literature search in the electronic databases of PubMed, ScienceDirect Online, and ClinicalTrials. gov. After the initial screening, these 2 authors cross-checked the screening results. In cases of inconsistent selection and lack of agreement, a final decision was attained through consensus. The keywords of "(FGF OR fibroblast growth factor) AND (depression OR mood disorder)" were used in the search process, which was limited to articles written in English and was conducted on April 8, 2016. Literatures published in languages other than English were excluded at this stage. Initially, 2 authors screened the titles and abstracts. Reports not related to FGF in patients with MDD were excluded. Furthermore, the 2 independent psychiatrists manually inspected the reference lists in the recruited literatures to expand the number of the included literatures.

The remaining studies were then examined using the inclusion criteria: articles discussing the comparisons of FGF levels, in the forms of either peripheral protein or messenger ribonucleic acid/ protein in CNS, in patients with MDD and in HC; articles on clinical trials in humans; and case–control trials. Case reports or series and nonclinical trials were excluded. Furthermore, to achieve high-quality recruited studies, the studies which did not fulfill the followed criteria would be excluded: providing information about the FGF levels in both patients and control subjects. To evaluate the quality of the clinical trials, Jadad scale were used in the MA.[23]

The primary outcome was FGF concentration in the peripheral environment or in the CNS. All primary outcomes and clinical variables in the studies were extracted. If data were unavailable, the authors were contacted for the original data. The entire screening process is shown in Fig. 1.

There was no need for ethical approval for this study because we did not use detailed personal data of any patient.

2.2. Methods of MA and data extraction

The effect size (ES) was defined as the difference in peripheral or CNS FGF levels between patients with MDD and HC. The ES was set as the standardized mean difference based on Hedges adjusted g, which was defined as ES > 0, signifying "higher FGF levels in patients with MDD than in HC." In case of absent actual FGF levels in the literature or no response from the authors, the ES was derived from other statistical parameters such as the t or P values, with the sample size. All of the ES were treated with a random-effects model in every MA.

All of the MA procedures were performed using the Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ). Statistical significance was set at a 2-tailed $P < 0.05$. Heterogeneity within the recruited studies was examined via Q statistics, related P values, and I^2 statistics. Publication bias was evaluated by visual examination of funnel plots and through Egger regression analysis.[24]

Subgroup MA and meta-regression were performed to evaluate the possible confounding effects of clinical variables. Meta-regression was performed through the unrestricted maximum likelihood method. The clinical variables for meta-regression were mean age, sex, body mass index, duration of illness, age at disease onset, disease severity, brain tissue pH, and postmortem interval.

3. Results

3.1. Studies included in each MA

A total of 18 articles were screened, including 2 that focused on genetic polymorphism rather than FGF concentration[25,26] and 6 that were review articles.[13,27–31] There was 1 article on the
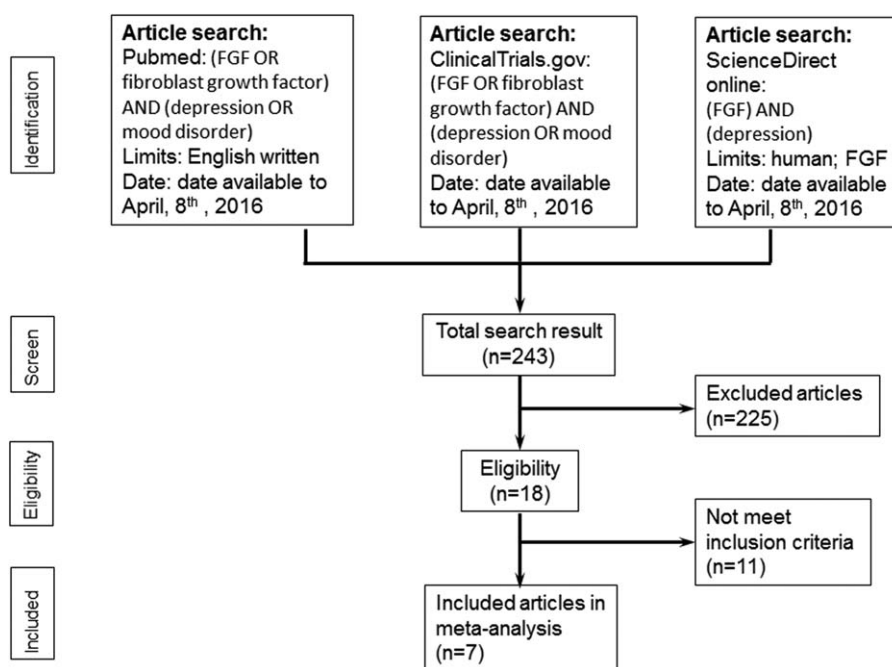
Figure 1. Flowchart of the selection strategy and inclusion/exclusion criteria for current meta-analysis.

concentration of FGF in patients with BD,[32] 1 article discussing the concentration of FGFR3 in postmortem brains,[33] and 1 discussing FGF-23 levels in acute depression.[34] Hence, MA could not be performed on such topics.

The 7 remaining studies were entered into the MA procedure (Table 1).[16–21,35] These included 4 articles providing peripheral FGF levels in patients with MDD and in HC,[16–19] and 3 articles on the FGF levels in the CNS of patients with MDD and HC.[20,21,35] For the quality of the clinical trials, the average Jadad score was 1.0 (Supplemental Table 1, http://links.lww.com/MD/B192). For information about the MOOSE guideline checklist, please refer to Supplemental Table 2, http://links.lww.com/MD/B192.

3.2. MA of peripheral FGF levels in patients with MDD

The 4 studies that compared different levels of peripheral FGF included 99 patients with MDD and 80 HC. The detected FGF samples were FGF-2 proteins. The peripheral FGF-2 proteins were significantly higher in patients with MDD than in HC (ES: 0.43; 95% confidence interval (CI): 0.13–0.73; $P = 0.005$) (Fig. 2A). There was no significant heterogeneity within these studies (Q = 2.42; df = 3; $I^2 = 0.00\%$; $P = 0.491$). There was no potential publication bias detected using visual examination of the funnel plot (Fig. 3). The Egger test could not be performed to detect possible publication bias because of the small number of recruited studies.[24,36] About the methods of determining peripheral FGF levels used in each included studies, 3 used method of enzyme-linked immunosorbent assay[17–19] and the other 1 used protein antibody array methodology.[16] However, there had not been consensus about which one provide better specific rate/sensitivity rate than the other one.

The meta-regression could only be performed in clinical variables of mean age and sex (female) proportion because of a lack of data. The results revealed no statistically significant associations between peripheral FGF-2 levels and mean age or sex (female) proportion ($P = 0.128$ and 0.587, respectively).

For subgroup MA, the studies were grouped according to the criteria of "drug-free or not," "different sample source," or "overnight fasting before sample collection." However, after subgrouping, there were <3 studies per subgroup, so subgroup MA was not performed.

Among the included studies, only 1 report discussed changes in peripheral FGF-2 proteins in patients with MDD before and after treatment.[17] In that report, the peripheral FGF-2 proteins in patients with MDD were significantly decreased after treatment. However, further MA of changes in the pre- and post-treatment peripheral FGF-2 protein levels was not performed.

3.3. MA of central FGF levels in patients with MDD

The 3 studies that compared different levels of FGF in the CNS included 31 patients with MDD and 33 HC. Our analysis found that there were significantly higher central FGFR1 RNA levels in patients with MDD than those in HC (ES: 0.68; 95% CI: 0.19–1.17; $P = 0.006$; Fig. 2C), but no significant difference in central FGF-2 RNA (ES: 0.59; 95% CI: −0.27 to 1.45; $P = 0.180$; Fig. 2B). About the methods of determining the central FGF levels used in each included studies, they were diversity in each studies, including NanoString assay[21] or Microarray Data Analysis.[20] Therefore, it was difficult to perform further subgroup MA to compare the difference of central FGF levels using different methods.

In the reports, the FGF-2 and FGFR1 were extracted from distinct parts of the cerebellum, including the prefrontal cortex,[21] dorsolateral prefrontal cortex,[20] hippocampus,[35] and AnCG.[20] Due to the small number of cases, subgroup MA of the different parts of the cerebrum was not performed.

4. Discussion

The main findings of the preliminary MA indicate that peripheral FGF-2 proteins and central FGFR1 RNA are significantly higher in patients with MDD than in HC. However, there is no

Table 1

Summary of characteristics of studies in current meta-analysis.

Study	Peripheral or central	Diagnostic criteria	Diagnosis	Comparison	N	Mean age, y	Gender, % female	Severity	Drug free	Overnight fast	Sample source	FGF	FGF levels	Country
He et al[17]	Peripheral	DSM-IV	MDD	MDD	28	46.3±12.4	64.3	28.1±8.07 (HAM-D)	Yes	Yes	Serum	FGF-2	200.5±134.5	China
				HC	30	42.8±9.2	56.7						246.6±163.2 (pg/mL)	
Lu et al[16]	Peripheral	DSM-IV	MDD	MDD	43	30.2±7.7	58.1	28.8±3.8 (HAM-D)	n/a	Yes	Plasma	FGF-2	n/a	China
				HC	22	27.7±4.8	50.0						75.8 (median)	
Takebayashi et al[18]	Peripheral	DSM-IV	MDD	MDD	16	53.2±13.0	50.0	n/a	n/a	No	Plasma	FGF-2	3.5±4.6	Japan
				HC	16	53.8±12.5	50.0						3.2±3.3 (pg/mL)	
Kahl et al[19]	Peripheral	DSM-IV	MDD	MDD	12	26.3±5.1	100.0	34.9±8.3 (BDI)	Yes	No	Serum	FGF-2	14.3±16.8	German
				HC	12	25.6±3.9	100.0						6.4±5.9 (pg/mL)	
Goswami et al[21]	Central	DSM-IV	MDD	MDD	16	49.6±3.8	25.0	n/a	n/a	n/a	Prefrontal cortex	FGF-2	n/a	USA
				HC	16	51.3±3.7	31.3					FGFR1	8.9±0.1	
													8.6±0.1	
Gaughran et al[35]	Central	DSM-IV	MDD	MDD	9	46.4	40.0	n/a	n/a	n/a	Hippocampus	FGF-2	116.0±28.7	UK
													125.6±40.9 (gray scale)	
				HC	12	48.1	40.0					FGFR1	108.6±38.7	
													136.4±39.5 (gray scale)	
Evans et al[20]	Central	DSM-IV	MDD	MDD	4	57.0±19.9	25.0	n/a	n/a	n/a	DLPFC	FGF-2	n/a	USA
				HC	6	57.0±15.8	16.7				AnCG	FGFR1	n/a	

Data presentation: mean±SD.

AnCG = anterior cingulated gyrus, BDI = Beck Depression Inventory, DLPFC = dorsolateral prefrontal cortex, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, FGF = fibroblast growth factor, FGFR = fibroblast growth factor receptor, HAM-D = Hamilton depression rating scales, HC = healthy controls, MDD = major depressive disorder, n/a = not available, SD = standard deviation, UK = United Kingdom, USA = United States.
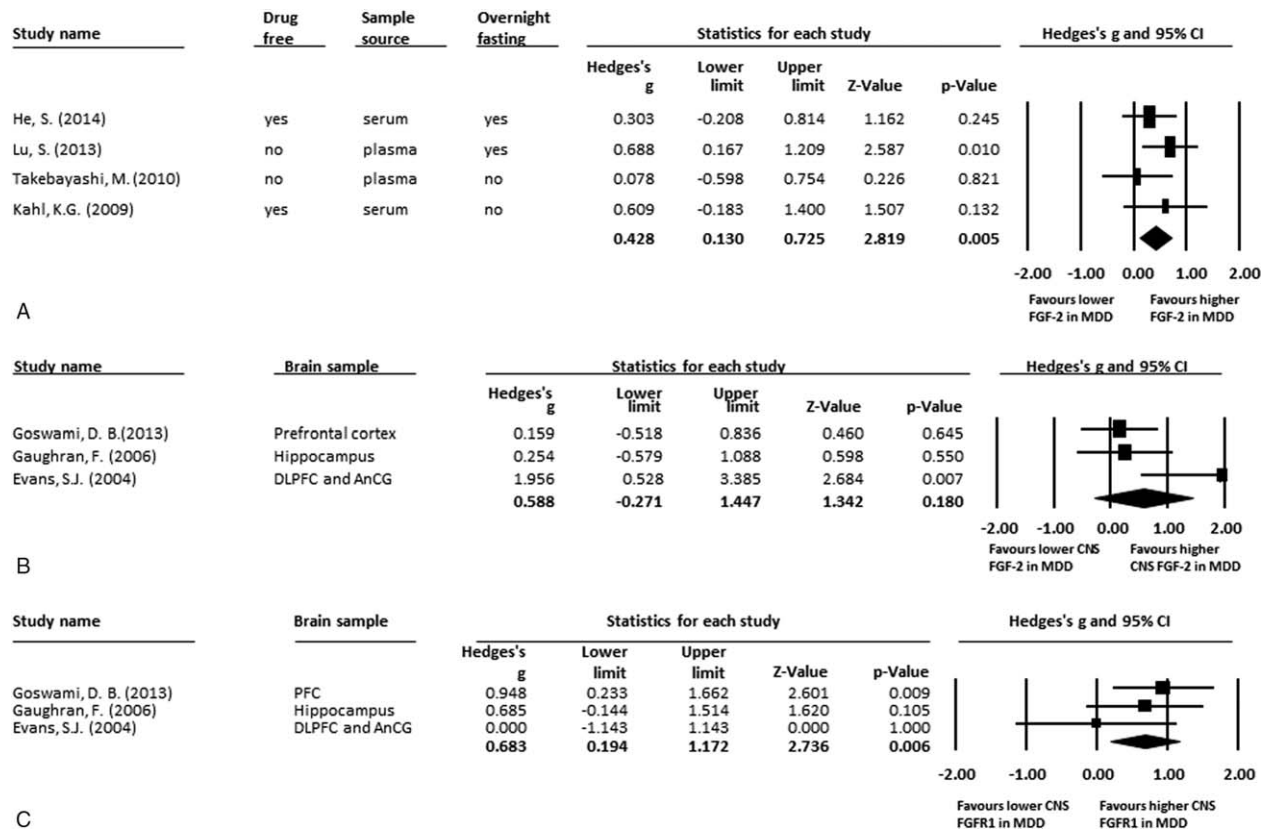
Figure 2. (A) MA of comparisons of peripheral FGF-2 in patients with MDD and HC; (B) MA of comparisons of CNS FGF-2 levels in patients with MDD and HC; (C) MA of comparisons of CNS FGFR1 levels in patients with MDD and HC. (A) The peripheral FGF-2 levels were significantly higher in patients group than HC group ($P = 0.005$). (B) There was no any significant difference in CNS FGF-2 levels in patients group and HC ($P = 0.180$). (C) There were significantly higher CNS FGFR1 levels in patients group than those in HC ($P = 0.006$). CNS = central nervous system, FGF = fibroblast growth factor, FGFR = fibroblast growth factor receptor, HC = healthy controls, MA = meta-analysis, MDD = major depressive disorder.

statistically significant difference in the FGF-2 RNA levels between patients with MDD and HC.

In reviews by van Scheltinga et al[28] and Turner et al,[31] the authors summarize current evidence of the FGF family in the pathophysiology of affective disorder. However, the evidence

Figure 3. Funnel plot of comparisons of peripheral FGF-2 in patients with MDD and HC in current meta-analysis by Hedges g. FGF-2 = fibroblast growth factor-2, HC = health controls, MDD = major depressive disorder.

recruited in these articles is mostly from animal studies rather than human studies. This may be due to the limited published literature on human studies.[18–20,35] In recent years, there have been some newer articles regarding FGF levels in human studies.[16,17,21] Based on the newer evidence, the present study performed further MA of the difference in FGF between patients with MDD and HC, either in the peripheral environment or in the CNS.

At first, without significant heterogeneity, there are significantly higher FGF-2 proteins and FGFR1 RNA levels in patients with MDD than in HC, without significant association with mean age and sex. This finding is surprising under the current hypothesis of the neurotrophic factor's role in the pathophysiology of MDD, such as nerve growth factor (NGF)[5] or glial cell line-derived neurotrophic factor (GDNF).[6] In theory, decreased neurotrophic factors or growth factors in patients with MDD are responsible for the pathophysiology of MDD. On the other hand, the roles of FGF-2 (also known as basic FGF), including those in angiogenesis[11] and neurogenesis,[7,31,37] may be similar to another angiogenesis factor, the vascular endothelial growth factor (VEGF). In fact, changes in VEGF among patients with MDD are similar to those of FGF-2, which is significantly increased in patients with MDD compared with HC.[4] Thus, changes in FGF-2 may share a similar pathophysiology to changes in VEGF among patients with MDD.

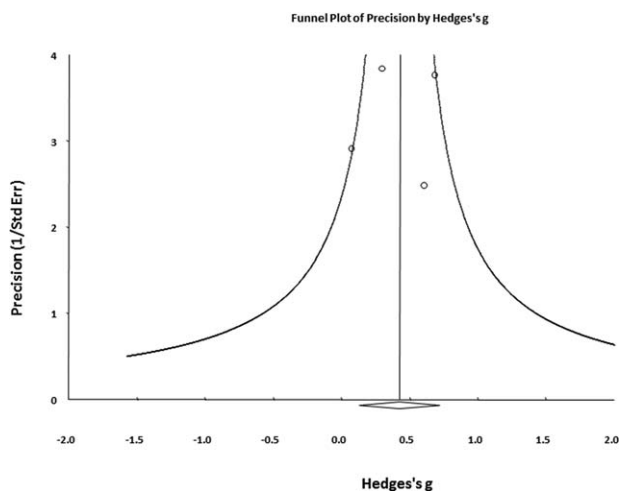There is evidence proving the benefit of FGF-2 in the blood–brain barrier (BBB) integrity[38,39] and in helping cell

survival under oxidative stress by attenuating endoplasmic reticulum stress and mitochondrial injury.[40,41] In addition, MDD is believed to be a neurodegenerative disease with a possible etiology of inflammation and increased oxidative stress,[4,42] which may induce BBB dysfunction and cell apoptosis.[43,44] Increased peripheral FGF-2 proteins may therefore be the consequence of the compensating effect of FGF-2, which increases to counter the increased oxidative stress and BBB dysfunction in MDD. This hypothesis can be indirectly explained by the phenomenon found in another study in which peripheral FGF-2 levels in patients with MDD are significantly decreased after treatment.[17] Although the aforementioned hypothesis cannot be proven by the current MA, this suggests a new direction for future studies.

The roles of FGFR1 have been found in aspects of neurogenesis,[45] memory consolidation,[14] and affective disorders.[13] However, in the current MA, the central FGFR1 RNA levels were significantly higher in patients with MDD. Although the expression of FGFR1 would alter with the sites of the brain samples, including the hippocampus, prefrontal cortex, and AnCG,[7] the altered FGFR1 in CNS environment might have some pathophysiologic meanings. In report by Gaughran et al,[35] the authors suggested that the increased central FGFR1 RNA levels might be derived from, at least partially, the prolonged decrease in FGF-2 secretion.

5. Limitations

The study has several limitations that must be considered. First, the total number of studies included in this analysis is small and only 3 databases were used, which may have undermined its clinical significance. This is especially apparent in the MA of the postmortem brain FGF/FGFR levels. Second, an MA of the FGF changes along with treatment could not be done because only 1 study provided such information. Furthermore, there is a lack of direct evidence on whether peripheral FGF-2 levels are correlated with FGF-2 levels in the CNS. There is also no evidence to prove the permeability of FGF-2 across the BBB, which affects the application of this study to the pathophysiology of MDD. In addition, we could not perform further subgroup MA to compare the difference of peripheral/central FGF levels between different methods. Lastly, specific MA of changes in other FGF families was not performed because of limited literature with such information.

6. Conclusions

This MA provides evidence of significantly higher peripheral FGF-2 proteins and central FGFR1 RNA levels in patients with MDD than in HC. The FGF-2 levels in the postmortem brains of patients with MDD do not significantly differ from those of HC. These findings point to new directions of future studies investigating the relationship among MDD, oxidative stress, and the FGF family.

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