Original Article

Peripheral IGF-1 in bipolar disorder and major depressive disorder: a systematic review and meta-analysis

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Background: In recent years, a number of studies have shown abnormal levels of peripheral insulin growth factor-1 (IGF-1) in patients with mood disorder, but the results are not uniform. Therefore, this paper focuses on such studies, conducts a systematic review and meta-analysis, and discusses the factors affecting peripheral IGF-1 in patients with mood disorder.

Methods: Cochrane database, PubMed database, Embase database, CNKI database, Wanfang Database and Weipu database were searched by computer. The retrieval time was from June 2020 to search for a controlled study of the relationship between bipolar disorder (BD) or major depressive disorder and normal control peripheral IGF-1. Review Manager (version 5.3) software was used for meta-analysis.

Results: A total of 14 articles in Chinese and English were included; 285 patients with BD and 503 patients with major depressive disorder. Meta-analysis showed that in comparison with the control group, IGF-1 levels in peripheral blood of patients with BD (MD =67.66, 95% CI: 7.01–128.31, P=0.03) and major depressive disorder (MD =8.01, 95% CI: 3.43–12.58, P=0.0006) were significantly increased. In the meta-analysis comparing the peripheral IGF-1 levels of patients before and after treatment, the results showed no significant change in the peripheral IGF-1 level before and after treatment (P=0.53).

Conclusions: High peripheral IGF-1 level is a related factor of BD and major depressive disorder, although this needs to be confirmed by further large sample studies.

Keywords: Meta-analysis; bipolar disorder (BD); major depressive disorder; IGF-1.

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Introduction

Insulin-like growth factor (IGF) is a type of broad-spectrum growth-promoting factor. Its chemical structure is similar to proinsulin and is homologous to a single chain polypeptide. IGF combines with insulin-like growth factor binding protein (IGFBP) in tissues or blood to play its physiological roles (1) which include major functions in the growth and development of human tissues and cells. The synthesis and secretion of IGF is controlled by the level of growth hormone (GH) in the blood and IGF has a negative feedback regulating effect on the secretion of GH in circulation, thus forming the GH/IGF axis. The most widely studied IGF is IGF-1. IGF-1 is a polypeptide chain consisting of 70 amino acids. Eighty percent of the IGF-1 in human peripheral blood is synthesized and secreted by the liver (2,3), but the expression of IGF-1 is distributed in almost all tissues (4). IGF-1 has a wide range of biological

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functions, which include the promotion of glucose metabolism and sugar transport, the acceleration of fat and glycogen synthesis, facilitating DNA, RNA and protein synthesis, motivating cell proliferation and differentiation, inhibiting cell apoptosis and regulating the immune process.

IGF-1 also plays an important role in the central nervous system. Studies have shown that IGF-1 can affect the structure and function of synapses (5,6), regulate the glucose metabolism of brain cells (7), inhibit the apoptosis of neurons and glial cells (8,9), regulate enzyme activity (6,10), reduce the damage caused by various pathological factors to the central nervous system (11,12), and play an important protective role in the growth, development and remodeling of nerve tissues. In recent years, there have been continuous studies on IGF-1 in psychiatric patients. In 2016, Tu *et al.* (13) conducted a meta-analysis of six studies on IGF-1 levels in the peripheral blood of patients with major depressive disorder (MDD) and three studies on IGF-1 levels in the peripheral blood of patients with bipolar disorder (BD). Similar studies in recent years have found something different. According to a case control study from Italy, there was no statistically significant difference in peripheral IGF-1 level between MDD patients and healthy controls [25], while a study from China in the same year showed that the peripheral IGF-1 level of MDD patients was significantly higher than that of healthy controls [27]. Therefore, we summarized 14 studies on peripheral blood IGF-1 levels of patients with mood disorders from 1988 to 2020, where five were related to BD (14-18) and nine were related to MDD (19-27). A literature review and meta-analysis were performed here. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1967).

Methods

Literature search

The following databases were queried; Cochrane database, PubMed database, Embase database, Chinese Journal Full-Text Database (CNKI), Wanfang Database and Weipu database. The retrieval time was set up until June 2020. The following English retrieval keywords and titles were used to search ("IGF-1" OR "insulin-like growth factor 1") AND ("depression" OR "bipolar disorder" OR "mood disorder" OR "mental disorder" OR "depressive disorder" OR "affective disorder" OR "mania").

Inclusion and exclusion criteria

Inclusion criteria: (I) published studies in English and Chinese on the relationship between BD, MDD and peripheral blood IGF-1; (II) the subjects were diagnosed as BD or MDD according to DSM or ICD standards; (III) complete data to carry out the original analysis; (IV) have at least one set of control study. Exclusion criteria: (I) review, case reports and other non-academic literature and non-clinical studies; (II) The samples were not from the peripheral blood; (III) the datasets were incomplete and the original IGF-1 values of peripheral blood could not be extracted; (IV) lack of normal control group. Data extraction and risk assessment of literature: literature search, data extraction and quality assessment were conducted independently by two doctors. If the two doctors disagreed, the third doctor would assess the results. The screening and search protocols are shown in *Figure 1*.

Statistical analysis

To control for confounding factors and to reduce heterogeneity, we extracted from the original literature the age, sex, race, sample source (peripheral blood or serum or plasma), sample extraction time, medication situation, detection mode (ELISA or RIA), and performed subgroup analysis based on the above factors. In order to exclude the possible confounding effects of drugs, we conducted an additional meta-analysis to explore the effect of treatment on peripheral IGF-1 levels in four of the studies that recorded both pre-treatment and post-treatment IGF-1 levels.

Meta-analysis of data was performed using Revman software (version 5.3). Mean difference (MD) and 95% confidence intervals (95% CI) were used for IGF-1 levels. The heterogeneity of the study was tested by the heterotopic coefficient I^2. Heterogeneity between studies was determined by P value and I^2 test where $P>0.05$ and $I^2<50\%$ indicated no statistical heterogeneity between studies. A fixed effect model was used for the meta-analysis. If $P\leq0.05$ or $I^2\geq50\%$, there was statistical heterogeneity among studies. A random effect model was used for meta-analysis. The source of heterogeneity and its influence on the stability of results were found by sensitivity analysis.

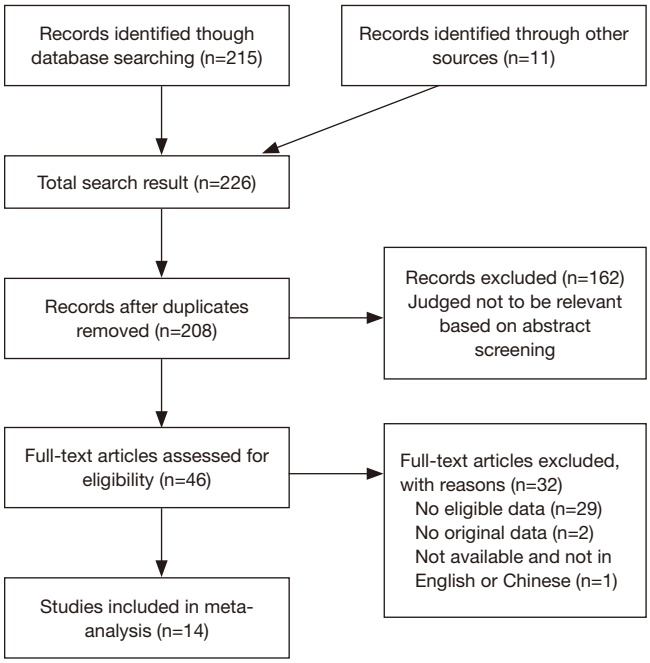

Figure 1 Study identification and literature review process.

P≤0.05 was considered statistically significant. Funnel plots were used to assess publication bias.

Results

Studies included in each meta-analysis

A total of 237 related studies were searched for in the included study against the English database and the Chinese database, among which 211 were in English and 26 were in Chinese. After reading the title and abstract, 187 were excluded and 36 were excluded after reading the full text. Finally 14 (14-27) were confirmed to be included in the meta-analysis which included 12 English studies (14-25) and two Chinese studies (26,27). The data of the selected studies are shown in *Table 1*.

The main results of the current meta-analysis

A total of 14 studies were included, nine of which focused on MDD (19-27). A total of 503 patients and 488 controls were included. Five studies on BD (14-18) included 285 patients and 274 controls. A random effect model was used for meta-analysis. The meta-analysis revealed that the peripheral IGF-1 level of BD and MDD patients was significantly higher than that of normal controls (MD =11.23, 95% CI: 6.29–16.18, P<0.00001). When BD (MD =67.66, 95% CI: 7.02–128.31, P=0.03) and MDD (MD =8.01, 95% CI: 3.43–12.58, P=0.0006) were compared separately the peripheral IGF-1 levels were significantly increased in both groups (*Figure 2*). The heterogeneity test indicated that there was heterogeneity in the included articles (I^2=95% in BD + MDD, I^2=91% in BD group, I^2=96% in MDD group), and that subgroup analysis was required to explore the source of heterogeneity.

Investigation of heterogeneity and bias

Funnel plots of the 14 studies included in this meta-analysis are shown in *Figure 3*. The scatter points of validity of each study are arranged symmetrically around the centerline in an inverted funnel shape which indicates that the literature in this meta-analysis had little publication bias.

Subgroup meta-analysis

The main results of subgroup meta-analysis of studies which included the medication situation

The studies can be divided according to whether patients are drug naive or drug free, which includes the Yes group (14-16,19,21-23,25,26) and the No group (17,18,20,24,27). This showed that the medication situation is a source of heterogeneity as peripheral levels of IGF-1 were higher in both subgroups compared to normal control groups.

The main results of subgroup meta-analysis of studies with sample source

According to the sample source, the included studies can be divided into three subgroups; plasma subgroup (15,19,21), serum subgroup (16-18,20,22-27) and peripheral blood subgroup (14). These results show that sample source is a source of heterogeneity as peripheral levels of IGF-1 were higher in the peripheral blood subgroups and serum subgroup than in the normal control group.

The main results of subgroup meta-analysis of studies with different methods of measuring

According to the different methods of measuring, the included studies can be divided into three subgroups; ELISA subgroup (14-16,18,24,25,27), RIA subgroup (19-21,23,26) and CL subgroup (17). The results reveal that different methods of measuring is a source of heterogeneity

Table 1 Summary of characteristics of studies in the current meta-analysis

Study	Time	Diagnostic criteria	Comparison	N	Mean age (years)	Gender (female %)	Drug naïve/ drug free	Sample source	Tools	IGF-1 levels	Time of blood drawn	Country
Kim	2013	DSM-IV	BD	116	35.9±11.8	63.8	Yes	Peripheral blood	ELISA	514.6±259.8 pg/mL	Early morning	Korea
			HC	123	35.5±10.4	54.5				316.8±270.0 pg/mL		
Palomino	2013	DSM-IV	BD	23	27.0±1.4	34.8	Yes	Plasma	ELISA	126.2±66.1 ng/mL	Early morning	Spain
			HC	23	25.7±1.0	30.2				155.4±67.0 ng/mL		
Liu	2014	DSM-IV	BD	70	37.9±14.5	58.6	Yes	Serum	ELISA	162.0±72.0 ng/mL	Early morning	China
			HC	50	36.8±11.2	60.0				138.9±80.1 ng/mL		
Emily	2017	DSM-IV	BD	31	41.7±11.8	80.6	No	Serum	CL	248.8±104.9 ng/mL	Early morning	Brazil
			HC	33	41.0±11.9	81.8				169.2±74.2 ng/mL		
Tuncel	2020	DSM-IV	BD	45	34.9±10.8	48.9	No	Serum	ELISA	279.3±139.5 ng/mL	Early morning	Turkey
			HC	45	34.9±10.8	48.9				190.7±56.6 ng/mL		
Lesch	1988	DSM-III	MDD	34	48.2±12.2	NA	Yes	Plasma	RIA	1.4±0.8 U/mL	Early morning	Germany
			HC	34	44.7±11.9	NA				0.8±0.3 U/mL		
Michelson	1996	DSM-III	MDD	10	41.0±8.0	100.0	No	Serum	RIA	189.0±86.0 ng/mL	NA	U.S.
			HC	10	41.0±7.0	100.0				189.0±37.0 ng/mL		
Deuschle	1997	DSM-III	MDD	24	47.2±16.4	45.8	Yes	Plasma	RIA	157.0±40.0 mg/L	Early morning	Germany
			HC	33	51.4±19.2	33.3				120.0±33.0 mg/L		
Franz	1999	DSM-III	MDD	19	34.7±8.8	100.0	Yes	Serum	na	289.0±108.0 ng/mL	Early morning	U.S.
			HC	16	36.1±6.6	100.0				228.0±58.0 ng/mL		
Li	2013	DSM-IV	MDD	15	32.3±7.7	0	Yes	Serum	RIA	167.3±6.6 pg/mL	Early morning	China
			HC	12	31.2±10.2	0				159.6±11.8 pg/mL		
Kopczak	2015	DSM-IV	MDD	78	48.6±13.9	44.9	No	Serum	ELISA	189.6±79.7 ng/mL	Early morning	Germany
			HC	92	48.1±13.7	45.7				155.6±60.0 ng/mL		
Rosso	2016	DSM-IV	MDD	37	42.4±11.9	78.4	Yes	Serum	ELISA	128.1±48.3 ng/mL	Early morning	Italy
			HC	43	42.3±11.3	65.1				121.2±51.6 ng/mL		
Quan	2016	ICD-10	MDD	30	41.7±14.9	56.7	Yes	Serum	RIA	22.5±7.0 ng/mL	Early morning	China
			HC	30	46.3±16.0	46.7				16.3±4.3 ng/mL		
Li	2017	ICD-10	MDD	256	47.3±8.8	45.7	No	Serum	ELISA	23.4±6.8 ng/mL	Early morning	China
			HC	218	47.7±9.0	46.3				16.4±4.1 ng/mL		

BD, bipolar disorder; MDD, major depressive disorder; HC, healthy control; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; CL, chemiluminescent immunoassay; NA, not available.

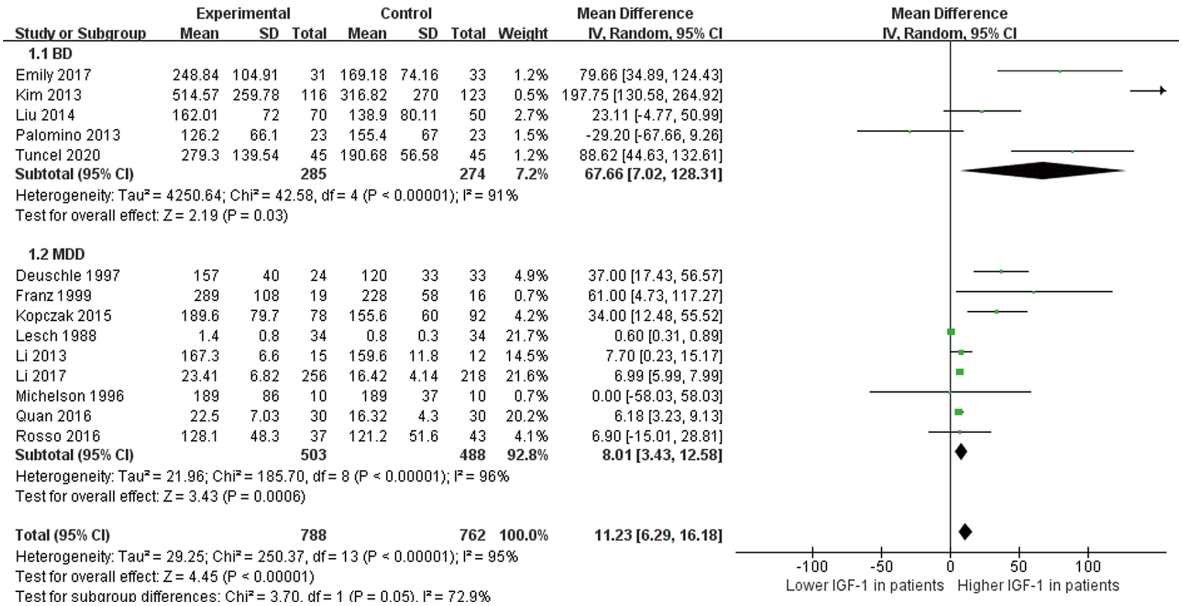

Figure 2 Meta-analysis of peripheral IGF-1 in bipolar disorder and major depressive disorder. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval; IGF-1, Insulin-like growth factor 1.

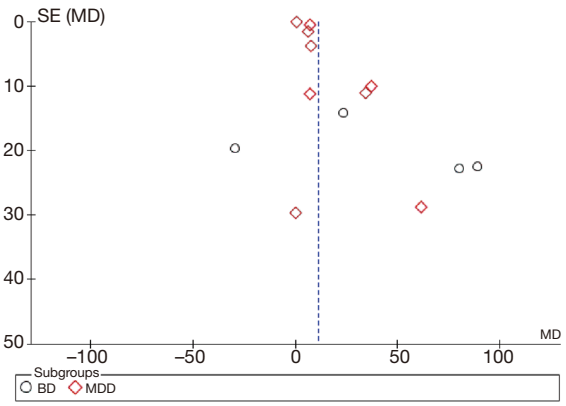

Figure 3 The funnel plot of meta-analysis. BD, bipolar disorder; MDD, major depressive disorder.

as peripheral level of IGF-1 was higher in all three subgroups compared to the normal control group.

The main results of subgroup meta-analysis of studies with the time of blood drawn

When considering that the level of peripheral blood IGF-1 is affected by food intake, the time of blood drawn may be a source of heterogeneity. According to the time of blood drawn, and excluding the study that did not specify the time of blood collection (20), the studies can be divided into two subgroups; early morning subgroup (14-19,21-22,24-27) and not early morning subgroup (23). The results showed that the time of blood drawn was not the source of heterogeneity. However, whether the time is in the morning or not, it was correlated with peripheral IGF-1 levels, and peripheral IGF-1 levels in both subgroups were higher than those in the normal control group.

The main results of subgroup meta-analysis of studies with the participants race

According to the participants race, the included studies can be divided into three subgroups; Asia subgroup (14,16,18,23,26,27), American subgroup (17,20,22) and Europe subgroup (15,19,21,24,25). These result shows that the participants race is a source of heterogeneity, and peripheral level of IGF-1 was higher in both Asia subgroup and American subgroup than in the normal control group.

All subgroup analysis results are shown in *Table 2*.

The main results of meta-analysis of before and after treatment

In the 14 included studies some could not exclude the influence of psychiatric drugs on peripheral blood IGF-

Table 2 Subgroup analysis of periphery IGF-1 level of BD and MDD patients

Subgroup		Heterogeneity test		MD	95% CI	Z	P
		P	I^2 (%)				
Drug naïve/drug free	Yes	<0.00001	87	9.08	2.04–16.12	2.53	0.01
	No	<0.00001	86	39.54	8.10–70.97	2.47	0.01
Sample source	Plasma	0.0004	87	6.10	–23.10 to 35.29	0.41	0.68
	Serum	<0.0001	74	11.85	6.20–17.51	4.11	<0.0001
	Peripheral blood	–	–	197.75	89.60–305.90	3.58	0.0003
Methods of measuring	ELISA	<0.00001	83	25.43	3.72–47.13	2.30	0.02
	RIA	<0.00001	87	6.71	0.79–12.63	2.22	0.03
	CI	–	–	79.66	34.89–124.43	3.49	0.0005
Time of blood drawn	Early morning	<0.00001	95	10.90	5.67–16.12	4.09	<0.0001
	No early morning	–	–	7.70	0.23–15.17	2.02	0.04
Participants race	Asian	0.0001	80	9.78	4.22–15.34	3.45	0.0006
	America	0.10	57	49.42	2.99–95.84	2.09	0.04
	Europe	<0.0001	84	12.24	–7.06 to 31.55	1.24	0.21

IGF-1, Insulin-like growth factor 1; BD, bipolar disorder; MDD, major depressive disorder; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; CI, chemiluminescent immunoassay.

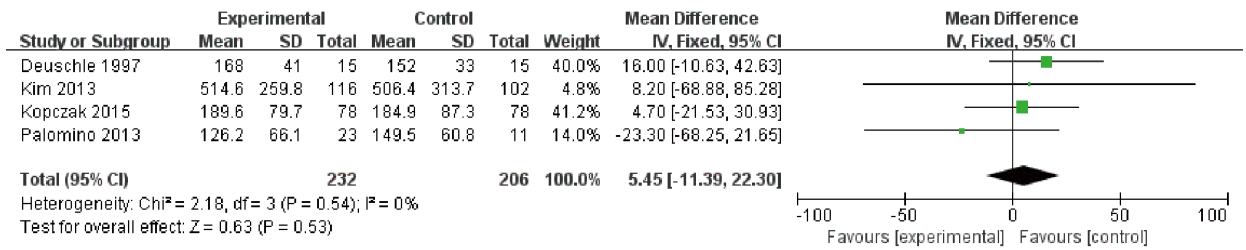

Figure 4 The meta-analysis of before and after treatment. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

1 levels. We then conducted another meta-analysis on the changes of peripheral blood IGF-1 levels before and after treatment. Five studies (14,15,21,23,24) mentioned related content, among of which Kim (14) and Palomino (15) used mood stabilizers combined with antipsychotic drugs and Deuschle (21) and Kopczak (24) used antidepressant drugs. The above studies involved treatment for more than 24 days, and so blood was collected in the morning on an empty stomach, and so meta-analysis of drug influence was included. Li (23) used enalapril and compared the changes of IGF-1 in peripheral blood within 24 hours before and after the use of enalapril. These results were affected by circadian rhythm and eating situation, so this meta-analysis was not included. A fixed effect model was used for this meta-analysis. The results show that there were no significant change in IGF-1 level before and after treatment (MD =5.45, 95% CI: –11.39 to 22.30, P=0.53, I^2=0%) (*Figure 4*).

Discussion

Previous studies have shown that the most important role of IGF-1 in the brain is to control cell growth, differentiation, tissue metabolism and promote DNA synthesis. However, a number of studies in recent years have shown that IGF-1, as a neurotrophic factor regulated by the immune system, can reduce the excitatory toxicity induced by aspartic acid (NMDA) and prevent neuronal autophagy (28). IGF-1 can

also enhance the effects of anti-inflammatory cytokines IL-4 and IL-10, thereby negatively regulating inflammatory response in the brain. As the inflammation hypothesis of the central nervous system plays an important role in the mechanism of depression and BD, we must consider special significance in the roles of IGF-1 in the field of mood disorders (29). Some researchers suggest that a decrease in IGF-1 expression in the brain disrupts neuroplasticity and promotes inflammatory pathways in the brain which leads to morphological deterioration in brain regions responsible for emotional and cognitive processes. From this perspective, the increased level of systemic IGF-1 observed in patients with mood disorder can be considered as a compensatory mechanism which enhances the activity of the hypothalamic-pituitary-growth promoting axis in response to insufficient cerebral IGF-1 concentration (30).

The results of this study show that peripheral IGF-1 levels of BD and MDD patients were significantly higher than that of the control group. These results were similar to a number of domestic and foreign studies (14,16-19,21-27), but inconsistent with the results of Palomino (15) and Michelson (20). This may be related to the sample size, disease course, patient age and other factors of the two studies. We found that peripheral IGF-1 levels were correlated with the sample source. The IGF-1 levels in the studies which used serum as the sample source were significantly higher than that in the control group, while IGF-1 levels in the study using plasma as the sample source were not significantly changed. According to the above 14 studies, most of the earlier studies used plasma as samples, but in the recent ten years, most studies chose serum as the sample source. Compared with plasma, serum can exclude the influence of fibrinogen and some coagulation factors, so it is more accurate.

Studies have shown that age, sex, body mass index (BMI), region, dietary structure and nutritional status are possible factors affecting the level of serum IGF-1. The level of serum IGF-1 in adults decreases with the increase of age, and the decline rate is first fast and then slow, and the decline rate of women is faster than that of men (31), such as the research results of Brabant *et al.* (32). There are gender differences in serum IGF-1 levels in adults, but the specific mechanism is not clear. The effect of gender on serum IGF-1 may be mainly through estrogen. Studies have confirmed that estrogen has a clear inhibitory effect on the process of IGF-1 synthesis regulated by growth hormone (33). In order to exclude the heterogeneous effects of age and sex on serum IGF-1 levels, it is best to distinguish between age and sex grouping studies, and exclude oral contraceptive and other factors that interfere with female growth hormone and hormone replacement therapy. Nutritional status and body composition affected the level of serum IGF-1, the level of growth hormone decreased and the level of serum IGF-1 increased in obese people (34), while in patients with malnutrition caused by cachexia or neurasthenia, the level of serum growth hormone increased and the level of IGF-1 decreased (35). In epidemiological studies, the relationship between serum IGF-1 level and BMI has not been determined. Physical exercise may also have an effect on serum IGF-1. In 1990, Kelly first reported in JCEM that the level of serum IGF-1 was related to fitness. People who exercise regularly have higher levels of serum IGF-1 (36). However, Porch *et al.* reported in 1997 that daily physical exercise could significantly reduce the content of body fat, but had no effect on the level of serum IGF-1 (37). This finding was especially confirmed in the elderly population (38,39). We found that peripheral IGF-1 levels were correlated with the race of participants as patients in Asia and American have higher peripheral IGF-1 level than the normal control group, while patients in Europe were not as obvious. This may be related to different geographical and cultural diet habits. To investigate this further we are looking towards future larger sample sizes, especially from Africa and Oceania. Subgroup analysis revealed that heterogeneity was influenced by whether patients were drug naive or drug free and the detection method of IGF-1. However, the results of different subgroups show that the peripheral IGF-1 levels of patients with mood disorders were higher than that of the normal control group. Subsequent meta-analysis on the effect of treatment showed that peripheral IGF-1 levels do not change significantly with treatment, which reflects the specificity of IGF-1 as a biomarker for patients with mood disorders.

This meta-analysis has the following limitations; This study only showed that there was no significant difference in the age of BD and MDD patients between the control group and the control group, that is, age had no effect on the heterogeneity of included articles (MD =0.02, 95% CI: −0.08 to 10.12, P=0.64, I^2=14%). However, all the literatures have not conducted a stratified study on patients of different ages. The average age among these studies were different, the probability of the metabolic syndrome was different in the different age subjects, and IGF-1 as a broad-spectrum growth-promoting factor widely participate in the body's metabolism of sugar and fat transfer process, so there are many confounding factors which can affect peripheral IGF-1 level in patients. Secondly, there were differences

in the degree of disease onset in each study group. By one-arm research and analysis, five studies (14-18) recorded the patient's Young Mania Rating Scale(YMRS) (ES =25.349, 95% CI: 7.441 to 43.257, P=0.006, I^2=99.8%), and in the terms of nine studies on MDD, the Hamilton Depression Rating Scale (HAMD) was recorded in six studies (17,19,21,22,25,26) (ES =23.196, 95% CI: 16.846 to 29.545, P<0.001, I^2=98.9%). In the terms of the five studies on BD, three were during a manic episode, one was in remission and one was not indicated. Thus it can be seen that there is a great heterogeneity among the evaluation results of the disease degree of each study. The lack of unified evaluation criteria and grouping of evaluation results are common problems. Studies have shown that the severity of mood disorders can affect serum IGF-1 levels (40), but in this meta-analysis, due to the lack of relevant information, we are unable to move from qualitative to quantitative data. Finally, there are potential confounding factors which influence the reliability of the results, such as the fact that diagnostic criteria for diseases have been updated several times over the years.

IGF-1, as a polypeptide widely existing in various tissues and organs of human body, is involved in and regulates multiple physiological activities, and its special significance in the field of psychiatry is being explored. In recent years, researchers have found abnormalities in IGF-1 levels in Alzheimer's disease, obsessive-compulsive disorder, alcohol dependence, eating disorders and other psychological diseases (25,41-43). Animal experiments show that IGF-1 gene knockouts reduce a mice's ability to adapt to the environment and the degree of task completion decreases obviously. A subsequent study found that exogenous IGF-1 can reverse these abnormal behavior and ability to adapt (44). According to the above study, researchers presented the hypothesis that IGF-1 gene knockout mice can function as animal model of depression, and that IGF-1 has potential antidepressant effect (45). Zhang *et al.* used chronic unpredictable mild stress (CUMS) to established depression rat model and injected 5 mL IGF-1 (5 mg/mL), the results suggest that IGF-1 may improve depression symptoms by mediating TDAG51 activation of PI3K/Akt/FoxO3a signal pathway in hippocampus of depression model rats (46). In the study of effective dose, Hiney *et al.* studied the effect of prepubertal IGF-1 on the release of luteinizing hormone-releasing hormone (LHRH) in the hypothalamus of female rats, and observed it with the minimum effective dose of 10 ng/mL and the maximum effective dose of 100 ng/mL. The results showed that IGF-1 played a role in the median eminence, and the density of IGF-1 receptor was the highest in the median eminence of the brain, resulting in an increase in dose-dependent release of LHRH (47). However, the study does not involve the side effects of IGF-1, indicating that IGF-1 involves many aspects of neuroendocrine and its mechanism and side effects are still not clear. At the same time, it also reflects that the pathogenesis of depression involves many factors, which can be explained by the existing antidepressant therapy after a period of time. In the field of BD, researchers found patients sensitive with lithium carbonate have high expression of IGF-1 related genes (48). Additionally, it was observed *in vitro* that exogenous IGF-1 may induce the up-regulation of lithium carbonate response-related microRNAs (49). Therefore, IGF-1 may be involved in the pharmacological processing of lithium salt, and its gene expression level could provide a predictive role for the therapeutic effect of lithium salt. What specific role IGF-1 plays in the field of mood disorders, and how can we use its physiological and pharmacological effects benefit clinical patients, remains to be answered by future researchers.

Conclusions

In summary, IGF-1 in peripheral blood of patients with BD and major depressive disorder is higher than that of the normal population. IGF-1 can be used as a potential laboratory indicator for mood disorders.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1967

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1967). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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