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Exercise Intervention Regulates Fibroblast Growth Factor 21: A Systematic Review and Meta-analysis

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Abstract: To clarify the change of fibroblast growth factor 21 (FGF21) concentration in circulating blood induced by exercise intervention in adults, this meta-analysis was designed. PubMed, Medline, and Web of Science databases were searched until July 18, 2022. Two authors work independently, including literature screening, data extraction and quality assessment. RevMan 5.3 and StataSE 15 software were used to data analysis. Eleven studies were eventually included. Compared with the control group, after exercise intervention [SMD = -0.63, 95% CI: -1.17 to -0.08, P = 0.02], the concentration of plasma FGF21 in adults was increased significantly more than control group. Subgroup analysis showed that the effect size was significant in diseased populations [SMD = -1.51, 95% CI: -2.89 to -0.13, P = 0.03]. Regardless of the subjects' BMI, the results showed statistical differences. The effect size was larger in those with BMI ≥ 28 [SMD = -1.91, 95% CI: -2.91 to -0.91, P = 0.0002] and smaller in those with BMI < 28 [SMD = 0.32, 95% CI: -0.01 to -0.65, P = 0.05]. The promotion of FGF21 concentration by exercise was also correlated with age. When the age of the subjects was equal to and greater than 40 years old, the effect size was significant [SMD = -1.20, 95% CI: -2.13 to -0.26, P = 0.01]. When the duration of exercise intervention was equal to and greater than 40 min, the effect size was significant [SMD = -1.21, 95% CI: -2.18 to -0.25, P = 0.01]. Meta-regression analysis showed that the P value of the subjects' BMI (p = 0.009) was < 0.05, and the subjects' BMI was the main source of heterogeneity. Exercise intervention can increase the concentration of FGF21 in adult plasma, providing a clinical theoretical basis for exercise intervention to regulate FGF21. Currently, there is limited research on exercise intervention, and more research is needed to confirm this theoretical basis due to the complex mechanism of upregulation of FGF21.

1. Introduction

Sports activities and professional sports training have become the foundation of various chronic disease treatments, inducing various forms of exercise adaptations such as increased skeletal muscle blood flow, muscle endurance, and cardiovascular function [1]. Fibroblast growth factor 21 (FGF21), a group of liver-derived proteins, can directly or indirectly affect arterial function by regulating endothelial dysfunction and inflammatory cell vascular wall infiltration processes [2-4], and is closely related to insulin resistance and prevention of weight gain. Studies have shown that exercise intervention can upregulate FGF21, but there are few studies on the regulation of FGF21 by exercise, and the results are inconsistent [5-8]. FGF21 has potential clinical significance in the treatment of obesity-induced type 2 diabetes and metabolic syndrome. Therefore, whether the overall research results of exercise intervention on FGF21 can support its application in improving chronic diseases is of practical significance. In this study, by collecting articles related to exercise intervention regulating FGF21, we reviewed existing experimental studies and conducted quantitative analysis of the included study results according to the requirements of meta-analysis.

2. Methods

2.1. Source and Retrieval of Studies

Two individuals conducted document retrieval in a double-blind manner using a predetermined search strategy to search databases including PubMed, Web of Science, and Medline. A total of 978 relevant English articles were identified, including 566 from PubMed, 302 from Web of Science, and 110 from Medline. In addition, 2 articles were obtained through reference reading. These 978 articles were imported into Endnote literature management software, and after excluding duplicates, 430 remained. After excluding animal experiments, 132 were obtained. First, articles not relevant to the current meta-analysis were excluded by assessing the title and abstract. After that the text was screened and ultimately 11 articles (17 studies) were included.

2.2. Criteria for the Screening of Studies

2.2.1. Criteria for Inclusion

The inclusion criteria were developed based on the PICOS principle. To maximize the results obtained from the search, the population of interest included individuals of any nationality, gender, and age 18 years or older. And the intervention of interest included any form of physical activity. The study design of interest was randomized controlled trials (RCTs). The measurement of interest was the plasma concentration of FGF21.

2.2.2. Criteria for Exclusion

The exclusion process was conducted independently by researchers (PL and JL). In case of disagreement, a third reviewer determined whether a study met the inclusion criteria. In the process of literature selection, studies with repeated reporting, non-human experiments, non-adult subjects, non-randomized controlled trials, studies that did not measure plasma FGF21 concentrations, studies that used drugs or other means in combination with exercise as an intervention, or studies that did not report exercise regimens in detail were excluded from this meta-analysis.

2.3. Quality Evaluation of Studies

Two authors independently assessed the risk of bias (ROB) according to the Cochrane Collaboration's guidelines in RCT (Figure 1).

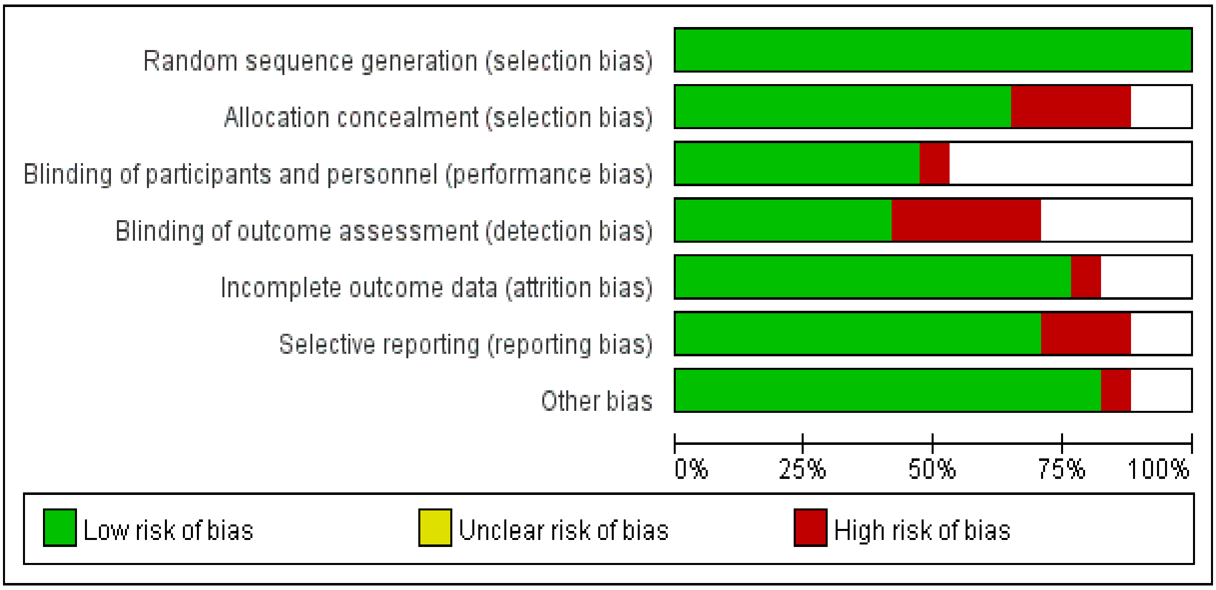

Figure 1: Quality evaluation of included literature.

3. Data Extraction and Statistical Analysis

RevMan 5.3 software was used for pooled effect size and subgroup analysis, and meta-regression analysis was performed on the data using Stata-SE15.1 software. The effect size indicators for continuous variable outcome measures were described as weighted mean differences (WMD) or standardized mean differences (SMD), and the corresponding 95% confidence intervals (CI) were calculated. According to the Cochrane Handbook, the choice between WMD and SMD depended on the similarity or difference of the outcome measure evaluation criteria. The heterogeneity was tested by Q-test and I2-test. When $P \geq 0.05$ and $I2 \leq 50\%$, a fixed-effect model was used for meta-analysis. While $P < 0.05$ and $I2 > 50\%$, a random effect model was used for meta-analysis. Subgroup analysis was performed for studies with significant heterogeneity, and if subgroup analysis failed to explain the source of heterogeneity, meta-regression was used. Getdata2.20 software was used to extract the mean values and standard deviations from the histogram for studies that only provided outcome measure data. The data extraction included basic information of the studies, research type and methodological characteristics, characteristics of the study population, intervention measures, sample size, and other relevant indicators (Table 1).

4. Results

4.1. Results of Meta-analysis

4.1.1. Regulation of FGF21 by Exercise Intervention

The 11 included studies (17 interventions) were combined, and as shown in Figure 2, the heterogeneity test was $I2 = 87\%$ and $P < 0.00001$. It indicates that there is significant heterogeneity across studies. Therefore, a random effects model was used in present meta-analysis. The pooled effect size was [SMD = -0.63, 95%CI: -1.17 to -0.08, P = 0.02], indicating a significant difference. Exercise intervention significantly increased FGF21 concentration in the plasma of adults compared with the control group. Therefore, exercise intervention can significantly improve plasma FGF21 concentration in adults.

Table 1: Baseline characteristics of participants.

Author and year	Sample size	Study population	Gender	BMI	Age	Intervention cycle	Intervention duration
Asghar 2021 [9]	10	Healthy	Female	31 ±2	30 ±3	8	47min
Saeidi 2019 [10]	12	Healthy	Female	28 ±2	56 ±5	8	48min
Banitalebi-A 2019 [11]	17	T2D	-	33 ±6	55 ±6	10	20min
Banitalebi-B 2019 [11]	17	T2D	-	34 ±5	54 ±5	10	40min
Ghanbari-A 2018 [12]	17	Healthy	Male	22 ±2	23 ±2	Acute	45-50
Ghanbari-B 2018 [12]	17	Healthy	Male	22 ±2	23 ±2	Acute	45-50
Ghanbari-C 2018 [12]	17	Healthy	Male	22 ±2	23 ±2	Acute	50
Kozlowska 2021 [13]	27	Healthy	-	32 ±3	42 ±13	2	25min
Sanayei 2022 [14]	11	Healthy	Female	-	25 ±3	8	25-30min
Scharhag 2018 [15]	10	Healthy	Male	-	-	Acute	1h
Farzanegi-A 2022 [16]	14	T2D	Female	32 ±3	51 ±7	8	40min
Farzanegi-B 2022 [16]	14	T2D	Female	30 ±4	53 ±1	8	40min
Scalzo 2014 [17]	19	Healthy	Male	28 ±1	24 ±1	3	-
Shabkhiz 2021 [18]	12	Healthy	Female	28 ±4	72 ±5	12	-
Shabani 2020 [19]	23	NAFLD	8 male/15 Female	28 ±4	56 ±12	12	20-30min
Kong-A 2016 [20]	10	Healthy	Male	34 ±6	20 ±1	5	20min
Kong-B 2016 [20]	8	Healthy	Male	34 ±4	20 ±2	5	40min

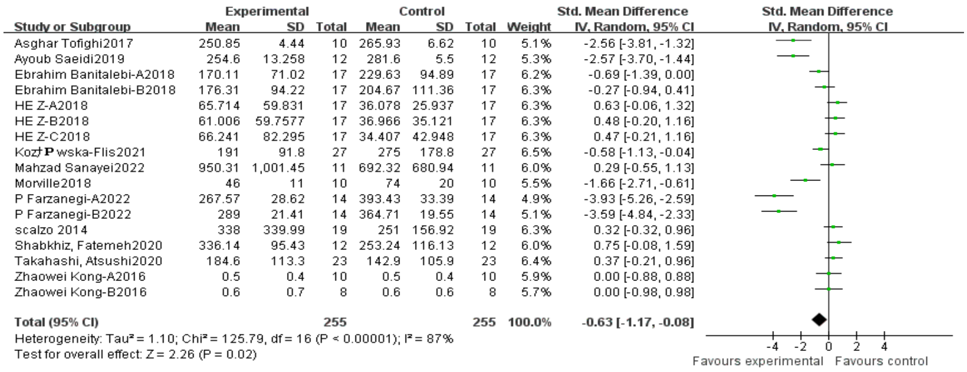

Figure 2: Meta-analysis forest map of plasma FGF21 concentration regulated by exercise.

Table 2: Results of meta-regression analysis.

	Corf.	Std. Err.	t	P	95% CI	
Study population	1.199	0.737	1.63	0.179	-0.846	3.244
BMI	3.139	0.659	-4.76	0.009	-4.967	-1.31
Age	-0.152	0.852	-0.02	0.987	-2.382	2.351
Intervention duration	-0.463	0.485	-0.96	0.394	-1.809	0.883

When the number of included studies exceeds 10 and the heterogeneity I2 is greater than 50%, regression analysis is needed to further explore the potential sources of heterogeneity. In this study, four covariates were set according to the extracted data from the literature, including age of the participants, BMI of the participants, population of the participants, and intervention duration for exercise intervention. Meta-regression analysis (see Table 2) showed that the P value of the subjects' BMI (p = 0.009) was less than 0.05, while the P values of the subjects' population (p = 0.179), age (p = 0.987), and intervention duration (p = 0.394) were greater than 0.05. Therefore, the subjects' BMI was the main source of heterogeneity, while the subjects' age, population, and intervention duration may also be sources of heterogeneity.

4.1.2. Subgroup Analysis of Regulation of Exercise on FGF21

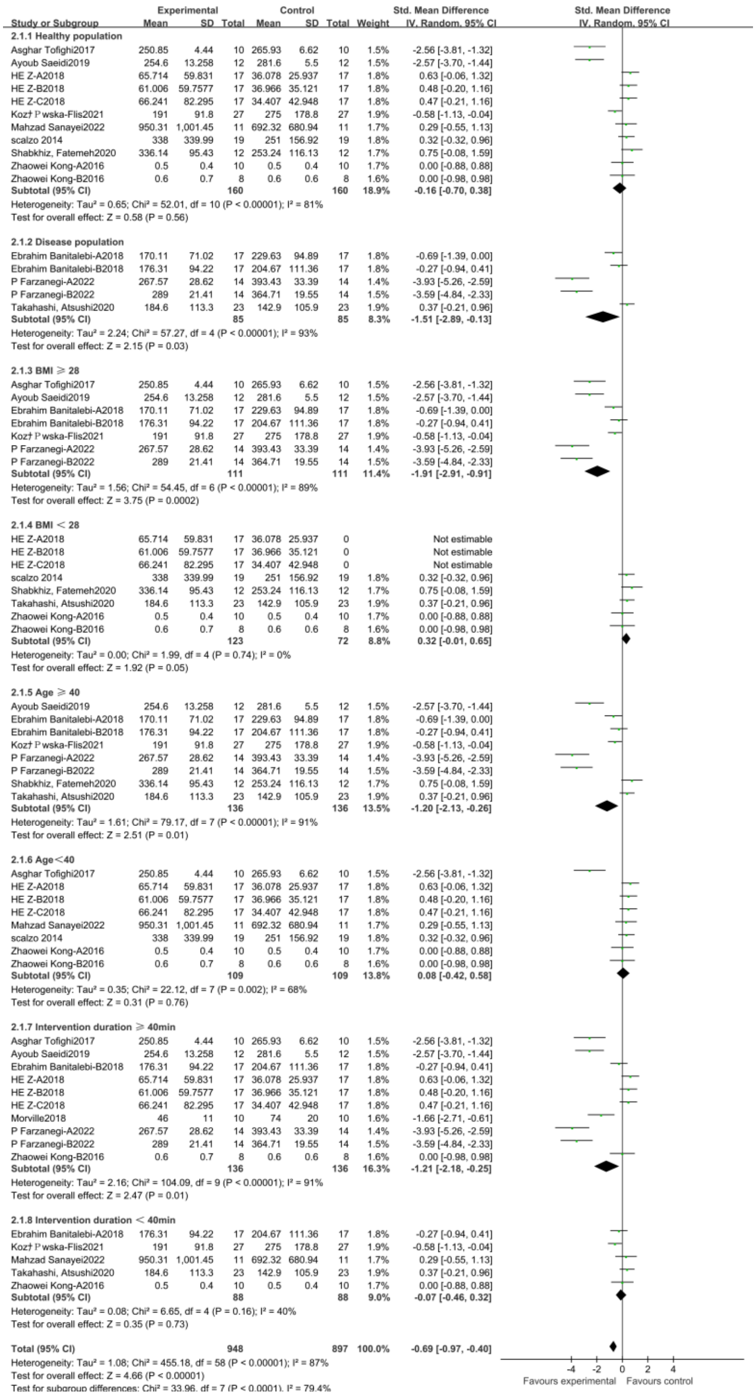

Figure 3: Forest map of subgroup analysis

Further the subgroup analysis was conducted according to the four covariates in Meta-regression to explore the regulation of exercise on FGF21. As shown in Figure. 3, the subgroup analysis indicate that the up-regulation of FGF21 by exercise was related to the subject population. Disease populations, such as type 2 diabetes patients, had a significant combined effect size [SMD = -1.51, 95%CI: -2.89 to -0.13, p = 0.03], indicating a significant difference. Regardless of the subject's BMI, the results were statistically different. The combined effect size for BMI ≥ 28 was [SMD = -1.91, 95%CI: -2.91 to -0.91, p = 0.0002], and for BMI < 28, it was [SMD = 0.32, 95%CI: -0.01 to -

0.65, p = 0.05]. The upregulation of FGF21 by exercise was also related to age, with a significant combined effect size [SMD = -1.20, 95%CI: -2.13 to -0.26, p = 0.01] when the subject's age was 40 years or older. When the exercise intervention duration was ≥ 40min, the combined effect size was [SMD = -1.21, 95%CI: -2.18 to -0.25, p = 0.01], indicating a significant difference.

4.2. Publication Bias Analysis

As shown in the funnel plot (Figure 4), the 17 included studies can be considered unbiased.

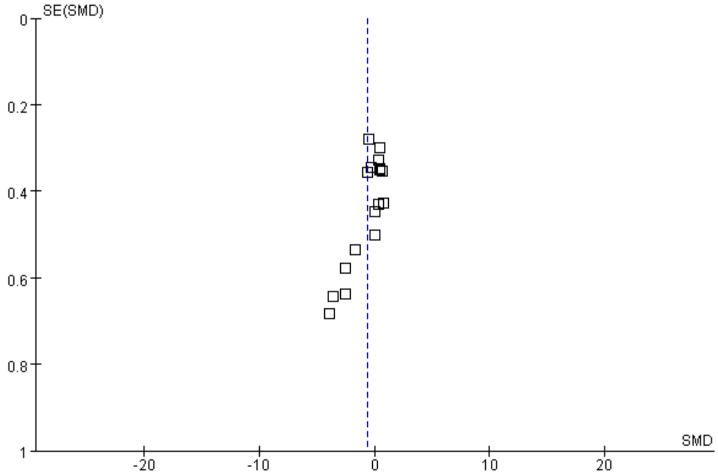

Figure 4: Funnel plot of publication bias

5. Discussion

FGF21 is a novel metabolic regulator whose expression in the liver is primarily regulated by peroxisome proliferator-activated receptor α (PPARα) [21-24]. Liver-specific knockout of the FGF21 gene in mice results in a significant decrease in circulating FGF21 levels, leading to varying degrees of metabolic syndrome in the mice. In mice models of diabetes, knockout of the FGF21 gene exacerbates insulin resistance caused by diabetes [12, 25-27]. These studies demonstrate the essential role of the liver factor FGF21 in maintaining and protecting the physiological health.

This study shows that exercise intervention can significantly and effectively enhance the levels of FGF21 in adults circulating blood, and this increase is related to exercise duration, and the presence of disease, as demonstrated by meta-analysis. Exercise interventions lasting longer than 40min improved circulating blood levels of FGF21. In healthy adults younger than 48, exercise interventions did not appear to lead to an increase in FGF21. In addition, BMI was also associated with exercise effects, and an increase in FGF21 levels in overweight and obese individuals as a result of exercise intervention was not observed in the general population. In summary, the effect of exercise on improving FGF21 is evident in patients with obesity or metabolic syndrome and appears to be due to the effect of exercise on fat or metabolism-related tissues, inducing tissues to indirectly promote the release of FGF.

Since FGF21 can play an effective role in regulating the body's metabolism, especially fat metabolism, it may play an important role in improving motor processes in people with metabolic disorders. The mechanism by which exercise intervention promotes the release of FGF21 is still unclear, but there is no doubt that exercise improves the metabolic status of target tissues and target cells by increasing FGF21 levels in circulating blood. A complete exercise regimen consists of exercise intensity, exercise load, exercise time, and exercise mode, and subtle variations in different exercise times or exercise intensities [28] can lead to different adaptations in the body. However, few studies have investigated whether different exercise types and exercise strategies have different effects on FGF21. When more research emerges in the future, meta-analysis can be used to find the most suitable exercise regimen for upregulating FGF21, providing a theoretical basis for future clinical treatment. The differences in FGF21 half-life or secretion duration among the studies included in this paper may have affected the results [14, 29].

Another consideration of the effect of exercise intervention on FGF21 is the change in the expression level of its cofactor β-Klotho. β-Klotho is an important part of the transmembrane protein Klotho group. Which is widely distributed in FGF21 target tissues. However, due to the complexity of the relationship between β-Klotho and FGF21, and the influence of various factors on exercise intervention [30-33], the mechanism needs further exploration.

6. Conclusions

Exercise interventions significantly and effectively enhance FGF21 levels in circulating blood in adults. Our meta-analysis provides a clinical theoretical basis for the regulation of FGF21 through exercise interventions. However, there is limited research on exercise intervention related to FGF21, and the mechanism of FGF21 upregulation is complex, which requires more studies to confirm this theoretical basis.

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