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Effect of Weight-Loss Diet Combined with Taurine Supplementation on Fasting Levels of Fibroblast Growth Factors19, 21, and β-klothoCo-Receptor in Obese Women: A Randomized Clinical Trial

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ABSTRACT

Background: Taurine (Tau) is naturally synthesized in the body from cysteine. It plays a crucial role in lipid and carbohydrate metabolism, increasing energy consumption, reducing inflammation, and controlling appetite. Some research suggests that obesity may be associated with decreased serum Tau levels. This study is the first randomized controlled trial to assess the effectiveness of a Tau supplement in combination with a weight loss intervention on fibroblast growth factors (FGF) 19, 21, and β-Klotho co-receptor in obese women. **Methods:** Participants were randomly assigned to two groups: a standard weight-loss group receiving 3 g/day of Tau capsules for 8 weeks (n=20) and a standard weight-loss group receiving placebo capsules for 8 weeks (n=18). The weight loss intervention aimed to reduce 30% of the total energy consumed by the participants.A paired t-test and an independent sample t-test were employed to assess parametric continuous data within and between the groups. Analysis of covariance was utilized to control for confounding variables. **Results**: At post-intervention, there was a significant reduction in mean changes of β-Klotho (P=0.01) in Tau group, compared to the control group. However, there were no significant differences in mean changes of FGF 19 and FGF 21 between the two groups (P>0.05). **Conclusion:**This study suggests that Tau supplementation alongside a weight loss diet may lead to a reduction in serum levels ofβ-Klothoco-receptor, which could serve as an alternative marker of obesity.

Introduction

Obesity, classified as a metabolic disorder, is closely linked to inflammation, hyperlipidemia, and diabetes due to insulin resistance (Murakami, 2015).It ranks as the fifth

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leading cause of death globally, with a high prevalence rate. In the United States, the prevalence of obesity among individuals aged 20-74 is 34% for females and 31.7% for males. On a global scale, obesity affects 18% of men and 21% of women (Murakami, 2015, Rahmani *et al.*, 2015).Moreover, obesity is a significant contributor to various diseases, including diabetes, ischemic heart disease, and certain types of cancer. Consequently, it reduces lifespan and elevates the cost of treatment for affected individuals (Rahmani *et al.*, 2015).

Fibroblast growth factors (FGFs) play diverse roles in biology, including cellular differentiation, angiogenesis, wound healing, and regulation of metabolism. Two specific FGFs, FGF19 and FGF21, function as endocrine hormones (Degirolamo *et al.*, 2016).These hormones interact with β-klotho co-receptor to activate fibroblast growth factor receptors (FGFRs) (Degirolamo *et al.*, 2016).β-klotho co-receptors are abundantly present in the liver, white adipose tissue (WAT), brown adipose tissue (BAT), and the central nervous system (Lan *et al.*, 2017, Nie *et al.*, 2017). Some evidence suggests the involvement of FGF19 and FGF21 dysfunction in obesity (Babaknejad *et al.*, 2018, Gallego-Escuredo *et al.*, 2015). A clinical trial has revealed that obese individuals have higher serum levels of FGF21 and lower levels of FGF19 compared to individuals with normal metabolism and body mass index (BMI). This indicates a resistance to FGF21 in obese individuals (Gallego-Escuredo *et al.*, 2015). Furthermore, the expression of β-Klotho co-receptor gene significantly reduced in obese patients compared to healthy controls. Obesity-related pro-inflammatory factors may contribute to down regulation of β-Klotho expression. Given that the proper functioning of FGF19 and FGF21 relies on β-Klotho co-receptor, decreased expression of β-Klotho can lead to metabolic disorders (Gallego-Escuredo *et al.*, 2015).Studies have highlighted serum levels of β-Klotho co-receptor as a promising new marker for metabolic diseases (Tayyar *et al.*, 2018, Toloza *et al.*, 2018).Evidence suggests that inflammatory factors derived from adipocytes can diminish the expression of β-Klotho gene (Díaz-Delfín *et al.*, 2012). Therefore, weight loss can be an effective approach in reducing resistance to FGF21 and promoting the up regulation of β-Klotho co-receptor. Conversely, low serum levels of FGF19 have been observed in obese individuals, indicating an overlap in metabolic functions of FGF19 and FGF21 (Gallego-Escuredo *et al.*, 2015).Taking into consideration the potential impact of weight loss on FGFs and β-Klotho co-receptors, (Díaz-Delfín *et al.*, 2012, Gallego-Escuredo *et al.*, 2015, Tayyar *et al.*, 2018, Toloza *et al.*, 2018, Zhang *et al.*, 2015), it is plausible to suggest that weight loss, coupled with the use of nutritional supplements,(Sáez-Lara *et al.*, 2016, Talenezhad *et al.*, 2020)can be an effective approach to combat obesity.

Taurine (2-aminoethylsulfonic acid, Tau) is synthesized through endogenous processes from methionine or cysteine in the human body. Seafood also provides Tau. However, Tau derived from food is carried in small quantities to the body tissues (Haidari *et al.*, 2019). In a clinical study, lower serum levels of Tau were found in obese individuals compared to those who were of normal weight (58 μmol/lvs serum normal range of 65-179 μmol/l) (Rosa *et al.*, 2014). Tau plays an important role in regulating glucose metabolism, lipid metabolism, increasing energy expenditure, reducing inflammation, and controlling appetite. Thus, Tau affects several target tissues, including adipose tissue, liver, muscles, and the nervous system. However, the main effect of Tau in obesity results from its direct effects on adipocytes (Murakami, 2015, Rosa *et al.*, 2014).

A few human studies have investigated the effects of oral Tau supplementation on obesity, but the results have been controversial (Batitucci *et al.*, 2019, De Carvalho *et al.*, 2021, Rosa *et al.*, 2014, Zhang *et al.*, 2004). Furthermore, while Tau is known to play a role in improving energy metabolism and reducing inflammation, its impact on serum levels of FGFs and β-Klotho co-receptor has not yet been investigated. Therefore, for the first time, this randomized clinical study aimed to

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assess the effect of Tau supplementation in conjunction with a weight-loss intervention on FGF19, FGF21, and β-Klotho co-receptor in obese women.

Materials and Methods

Design and participants

This study was a double-blinded controlled clinical trial conducted at Clinics of Ahvaz Nutrition Therapy. A total of 50 obese women were participated in the study. Inclusion criteria were women aged 18-49 years with a BMI between 30 and 40 kg/m², and their consent to participate. Exclusion criteria included the use of herbal and nutritional supplements, as well as any weight-loss programs involving drugs or surgical procedures in the past six months.

The sample size was determined based on a previous study, considering a 95% confidence interval (CI) and 80% power (α=0.05, β=0.2). Taking into account a 20% attrition rate, 25 obese women were assigned to each group (Rosa *et al.*, 2014).

Participants were randomly allocated to two groups: the standard weight-loss group receiving capsule of Tau (3 g/day) for 8 weeks (n=20), and the standard weight-loss group receiving placebo capsule for 8 weeks (n=18). The allocation of Tau or placebo bottles to each group (A or B) was determined by a third party using random numbers. To maintain blinding, unique codes were used instead of the letters A or B, and the bottles were sealed to ensure similarity in appearance and weight. Both the researcher and participants were unaware of the treatment allocation. The randomization codes were revealed only after the completion of the study protocol by all individuals involved.

Tau capsules (1g, Nutricost Company, Midvale, UT, USA) and placebo capsules (prepared by the Pharmacy Faculty of Ahvaz Jundishapur University of Medical Sciences) were consumed three times daily by Tau + weight loss group and placebo + weight loss group, respectively. To facilitate weight loss, the total energy requirements of participants were reduced by 30%. The macronutrient distribution consisted of 50% carbohydrates, 30% fats, and 20% proteins. A nutritionist specialized in dietetics monitored participants' adherence to the prescribed regimen on a weekly basis.

Measurements

Participants completed a questionnaire that included demographic data, medical records, and information on nutritional supplements. Dietary information was obtained through a 24-hour recall of diet at the beginning and after the intervention. The dietary data was analyzedusing Nut IV software (The Hearst Corporation, San Bruno, CA, USA). Participants were instructed not to make any changes to their dietary habits or physical activities during the study.

The participants' physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) at baseline and the end of the intervention.Body weight and height measurements were taken with a precision of 0.5 kg and 0.1 cm, respectively. BMI was calculated by dividing the weight in kilograms by the square of height in meters. Blood samples (5 ml) were collected after a 10 to 12-hour fasting period before and after the intervention. The separated serum was stored at a temperature of -80°C. Enzyme-linked immunosorbent assay (ELISA) kits from Laboratory Bioassay Technology, China, were used to measure FGF-19 (ng/l), FGF-21 (pg/ml), and β-Klotho co-receptor (nmol/l).

Ethical considerations

This clinical trial was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Iran, in accordance with the Declaration of Helsinki (Registration Number: IR,AJUMS.REC.1397.590). The trial was also registered in the Iranian Registry of Clinical Trials with the registration number IRCT20131125015542N2.Prior to the intervention, all participants were required to sign a consent form.

Data analysis

The collected data were analysedusing IBM SPSS Statistics version 22 (Armonk, USA). A

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significance level of P-value<0.05 was considered statistically significant. The normality of the data was assessed using the Kolmogorov-Smirnov test. Categorical variables were analysedusing the chi-square test at baseline. Parametric data within the two groups were analysedusing the paired t-test and independent samples t-test. The Analysis of Covariance test (ANCOVA) was utilized to adjust for confounding variables. Numeric variables were reported as means ± standard deviation (SD), while categorical variables were reported as numbers (percentage).

Results

Figure 1 shows flow diagram of the study. Twelve participants were excluded from the Tau (n=5) and placebo group (n=7) because of their travels and personal circumstances. **Table 1** summarizes demographic and anthropometric characteristics of the participants before and after the intervention

There was no difference in baseline characteristics between the two groups. Furthermore, according to **Table 2**, there was no significant difference in the intake of macro and micro nutrients, as well as physical activity, between the two groups, before and after the intervention.

At baseline, there was no significant difference between the groups on serum FGF19, FGF21, and β-Klotho (P>0.05). The results of the comparisons between the groups and within the study did not show significant differences between the groups in serum FGF21, FGF19 or β-Klotho (P>0.05). However, the mean change of β-Klotho serum level (adjusted for age, dietary intake of energy, macronutrients, micronutrients, BMI, and physical activity) was significantly lower in Tau+weight loss group than placebo+weight loss group after adjustment of the confounding variables (P<0.01) (**Table 3**).

Discussion

The results of the study demonstrated that supplementation with 3g of Tau combined with a weight loss diet in obese women for eight weeks led to a significant reduction in the serum concentration of β-Klotho co-receptor, which serves as a new indicator of obesity. This reduction remained significant even after adjusting for confounding factors such as age, dietary intake of energy, macronutrients, antioxidant vitamins (such as vitamins A, C, and E), BMI, and physical activity, compared to the control group. However, there were no significant differences observed in serum levels of FGF19 and FGF21 in Tau + weight loss group.

Several uncontrolled studies have explored the relationship between serum concentrations of FGFs and weight loss through diet or surgical methods, yielding conflicting results(Bednarska *et al.*, 2020, Haluzikova *et al.*, 2013, Mai *et al.*, 2011, Mraz *et al.*, 2009, Mráz *et al.*, 2011, Watanabe *et al.*, 2020). In a clinical trial conducted by Mai *et al.*, the effects of a low-calorie diet and physical activity on weight loss were assessed in 30 obese individuals (24 women and 6 men) over a 6-month period. They did not observe any significant change in serum levels of FGF21, and the average weight loss was below 5%(Mai *et al.*, 2011). These findings align with the present study; however, the study designs differed. It appears that a more substantial degree of weight loss may be necessary to achieve a significant change in serum FGF levels.

A cross-sectional study comparing serum levels of FGF21, FGF19, and β-Klotho in 67 overweight women and 18 normal weight women revealed higher levels of these factors in overweight individuals (Bednarska *et al.*, 2020). However, to date, no studies have specifically investigated the effect of diet on serum levels of β-Klotho. In the present study, a significant decrease in serum β-Klotho levels was observed in the intervention group. It is possible that the increased cell resistance to FGF19 and FGF21 in obesity leads to an up regulation of β-Klotho(Babaknejad *et al.*, 2018). Therefore, weight loss combined with Tau supplementation may down regulate β-Klotho in response to reduced inflammation levels.

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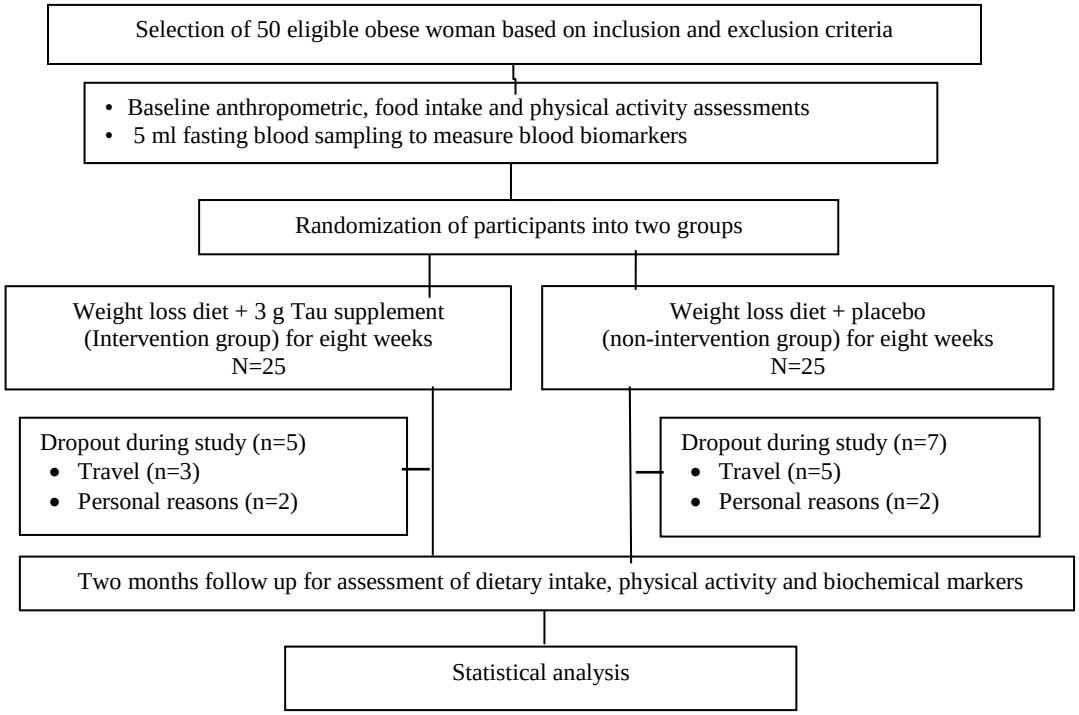

Figure 1. Flow chart of the study

Table 1. Demographic and anthropometric characteristics of subjects before and after the intervention

Variables	Tau + weight loss(n=20)	Placebo + weight loss(n=18)	P-value
Age (year)	38.75±9.54[d]	33.05±7.09	0.47[a]
Race			
Arab	4(20.0)[e]	2(11.1)	0.75[b]
Fars	9 (45.0)	9 (50.0)	
Bakhtiari	7 (35.0)	7 (38.9)	
Weight (kg)			
Before	81.94±12.64	80.17±14.49	0.69[a]
After	79.43 ±13.14	77.92±13.17	0.65[a]
P-value[c]	0.01	0.01	
Body mass index (kg/m^2)			
Before	33.28±3.12	32.38±1.94	0.64[a]
After	31.92±2.51	30.89±1.90	0.92[a]
P-value[c]	0.01	0.01	

[a]:Independent t-test;[b]: Chi-square test;[c]: Paired t- test;[d]: Means ± SD; [e]:n (%).

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Table 2. Comparing mean of macronutrients, micronutrients, and physical activity in participants before and after the study.

Variables	Tau + weight loss(n=20)	Placebo + weight loss(n=18)	*P-value* [a]
Energy (kcal/day)			
Baseline	1839.70 ± 418.96[c]	1872.74 ± 401.17	0.80
End	1394.41 ± 368.52	1341.60 ± 250.51	0.61
P-value [b]	<0.001	<0.001	
Carbohydrate(g/day)			
Baseline	211.93 ± 62.52	203.67± 48.98	0.65
End	142.03 ± 38.99	139.63 ± 30.08	0.83
P-value	<0.001	<0.001	
Protein (g/day)			
Baseline	64.23 ± 16.19	61.20 ± 11.61	0.51
End	49.21 ± 13.56	47.25 ± 15.25	0.67
P-value	< 0.005	0.002	
Fat (g/day)			
Baseline	83.80 ± 22.46	93.55 ± 32.65	0.28
End	71.38 ± 25.24	75.04 ± 26.23	0.66
P-value[b]	0.05	0.01	
Dietary fibre (g/day)			
Baseline	41.79 ± 20.38	38.39 ± 22.69	0.62
End	34.72 ± 18.38	28.83 ± 13.87	0.27
P-value	0.06	0.07	
Poly unsaturated Fatty acids (g/day)			
Baseline	27.01 ± 13.00	31.09 ± 14.45	0.36
End	25.22 ± 15.24	24.53 ± 12.63	0.88
P-value	0.62	0.12	
Mono unsaturated fatty acids (g/day)			
Baseline	28.41 ± 6.77	32.78 ± 12.31	0.17
End	24.88 ± 6.89	27.82 ± 7.81	0.22
P-value	0.06	0.09	
Saturated fatty acids (g/day)			
Baseline	18.36 ± 4.12	21.67 ± 7.33	0.09
End	17.49 ± 6.42	17.67 ± 6.80	0.93
P-value	0.55	0.11	
Vitamin A (iu/day)			
Baseline	120.77± 40.55	153.71 ± 38.40	0.23
End	122.73 ± 57.06	138.23 ± 84.00	0.50
P-value[b]	0.88	0.56	
Vitamin C (mg/day)			
Baseline	23.09 ± 21.25	29.78 ± 29.16	0.18
End	18.12 ± 15.48	19.62 ± 14.35	0.75
P-value[b]	0.36	0.08	
Vitamin E (mg/day)			
Baseline	25.35 ± 8.99	28.55 ± 11.47	0.30
End	22.76 ± 8.26	26.04 ± 6.14	0.17
P-value[b]	0.27	0.33	
Physical activity (MET-min/week)			
Baseline	1258.00± 859.19	1361.00± 1294.09	0.43
End	1303.21± 659.13	1424.00± 1082.18	0.36
P-value	0.52	0.63	

[a]*:Independent t-test;* [b] *: Paired t- test;* [c]*: Means ± SD.*

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Table 3. Comparing mean ± SD of FGF21, FGF19, and β-Klothoin participants before and after the study.

Variables	Tau + weight loss(n=20)	Placebo + weight loss (n=18)	P-value [a]	P-value [b]
FGF21 (pg/ml)				
Baseline	322.23 ± 480.40[c]	345.30 ±421.84	0.63	
End	329.18 ± 468.34	357.01 ±492.69	0.57	
P-value[c]	0.94	0.95		
Difference	6.95.00 ± 445.32	11.71 ± 432.14		0.51
FGF19 (ng/l)				
Baseline	119.76± 193.17	197.34 ± 210.58	0.24	
End	93.53± 131.90	168.12 ± 159.94	0.11	
P-value[c]	0.48	0.24		
Difference	-26.22 ± 163.58	-29.21 ± 102.91		0.83
β-Klotho(nmol/l)				
Baseline	66.52 ± 83.84	90.75 ± 101.79	0.42	
End	47.98 ± 71.22	102.63 ± 103.47	0.07	
P-value[c]	0.36	0.21		
Difference	-18.54± 89.41	11.88 ± 38.87		0.01

[a]: Independent t-test; [b]: Covariance (ANCOVA) (adjusted for age, dietary intake of energy, macronutrients, antioxidant vitamins such as vitamins A, C, and E, Body mass index and physical activity); [c]: Means ± SD; FGF: fibroblast growth factor.

In an uncontrolled pilot study conducted by Watanabe *et al*., serum levels of FGF21 were evaluated in 65 obese patients with non-alcoholic fatty liver disease (NAFLD) who followed a low-calorie diet for 90 days. The study found a decrease in serum FGF21 levels following the weight loss program (Watanabe *et al*., 2020). This finding contrasts with the results of the present research. Differences in study design, sample size, and duration of follow-up may account for this inconsistency.

In another clinical study conducted by Haluzikova*et al*., serum levels of FGF19 and FGF21 were measured in 17 obese women who underwent bariatric sleeve surgery and compared with a healthy control group of normal-weight individuals. Prior to the surgery, obese patients had lower serum levels of FGF19 and higher levels of FGF21 compared to the control group. However, after two years post-surgery, there was a significant increase in serum FGF19 levels and a significant decrease in serum FGF21 levels (Haluzikova *et al.*, 2013). In the current study, no significant differences were found in serum levels of FGF21 and FGF19. These discrepancies may be attributed to differences in the choice of control group, duration of the study, and the BMI of the participants. It is worth noting that the participants in the study by Haluzikova*et al.* were morbidly obese. Furthermore, achieving significant changes in FGFs, particularly FGF19, may require an intervention duration longer than 8 weeks, as the alteration of the intestinal tract micro biome plays a critical role in regulating FGF19 gene expression (Gadaleta *et al.*, 2020).

In another clinical trial, the serum levels of FGF21 and FGF19 were investigated in 12 obese patients with type 2 diabetes who underwent a very low-calorie diet for three weeks, compared to a control group of 30 normal-weight individuals. All diabetic patients were treated with fentanyl and exhibited hyperinsulinemia. After the dietary intervention, serum FGF21 levels showed a significant increase, while the increase in serum FGF19 levels was not statistically significant (Mraz *et al.*, 2009, Mráz *et al.*, 2011). These findings differ from the results of the current research. The disparity could be attributed to differences in study design and variations in the metabolic conditions of the participants.

FGF19 and FGF21 are hormones that have the ability to increase energy intake while reducing body weight, insulin levels, blood glucose, and hepatic lipid accumulation (Tomlinson *et al.*, 2002, Xu *et al.*, 2009).These hormones exert their metabolic effects by binding to FGFRs through

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tyrosine kinase activity. FGF19 and FGF21 form a complex with β-Klotho single-pass transmembrane protein, which leads to decreased gluconeogenesis and increased fatty acid beta-oxidation, insulin sensitivity, adiponectin levels, and thermogenesis. Moreover, they are known to reduce appetite and body weight(Lan *et al.*, 2017, Lin *et al.*, 2017, Owen *et al.*, 2014). However, in obesity, the function of these factors becomes impaired, and the expression of β-Klotho co-receptor gene is reduced due to adipose-derived inflammatory factors. As the function of FGF19 and FGF21 relies on the β-Klotho co-receptor, reduced expression of this protein can contribute to metabolic disorders (Gallego-Escuredo *et al.*, 2015).

Tau has been found to potentially regulate the expression of FGF21 gene in adipocytes and hepatocytes by up regulating energy-related genes such as PPARα, PPARγ, and SIRT1 (Zhang *et al.*, 2015).Additionally, Tau may regulate the expression of FXR gene in intestinal cells through the increase in tauroursodeoxycholic acid (TUDCA) and other Tau-containing bile acid metabolites, as well as through alterations in the intestinal micro biome, thereby affecting the expression of FGF19 gene(Li *et al.*, 2013, Qi *et al.*, 2015, Sayin *et al.*, 2013). Moreover, due to its anti-inflammatory properties, Tau could potentially regulate the expression of FGF19, FGF21, and β-Klotho co-receptor genes by reducing inflammation in the metabolic process (Díaz-Delfín *et al.*, 2012, Gallego-Escuredo *et al.*, 2015).

To the best of our knowledge, this study was the first trial investigating the effect of Tau supplementation along with a weight loss diet on serum levels of FGF19, FGF21, and β-Klotho in obese women. The design of the study was randomized-controlled double-blind clinical trial. To achieve more precise results, main confounding variables were controlled. However, the present study had some limitations. The gene expression of FGFs and β-Klotho was not examined. The study did not accurately adjust for variables such as sleep and wake-up patterns, which could potentially influence the expression of genes affected by FGFs due to the circadian clock (Yu *et al.*, 2020).The participants in this study were advised to maintain regular and timely sleep patterns. Additionally, physical activity, which is known to affect FGF levels, (Xiong *et al.*, 2020)was measured and analysedin the study.Future studies should consider investigating the genetic polymorphisms of the β-Klotho co-receptor, as the function of FGFs is dependent on this co-receptor (Dongiovanni *et al.*, 2020). While all trials, including our study, examined serum FGF levels in a fasting state, it is recommended to measure serum levels after meals to gain a better understanding of the metabolic behaviour of FGF19, which is secreted in response to bile acids.It was not possible in the present research to assess the serum level of Tau, which hinders a precise understanding of the cellular and molecular mechanisms underlying the effects of Tau on FGFs, which are suggested for the future research.

Conclusion

This studyexamined the impact of Tau supplementation (3g/day) for 8 weeks in non-menopausal obese women undergoing a weight loss diet. The results revealed a significant reduction in serum levels of β-Klotho co-receptor compared to Weight loss+placebo group. However, there were no significant differences observed in the levels of FGF19 or FGF21 between the two groups. For the first time, this study investigated the effect of Tau supplementation combined with a weight loss diet on FGF19, FGF21, and β-Klothoco-receptor as a new indicator of obesity.

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Authors' contributions

The authors' contributions are as follows: M Asadi and F Haidari conceived the topic; M Asadi collected data. M Asadi, J Mohammadi-asl, K Ahmadi-Angali and MJ Chitsazi analysed the data; M Asadi, F Haidari, and H BaviBehbahani drafted the manuscript. MJ Chitsazi edited the manuscript.

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All authors approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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