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Review

Physical Exercise-Induced FGF-21 to Fight Obesity: An Update Review

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Abstract: Fibroblast growth factor 21 (FGF-21) is a protein that is involved in the regulation of glucose, lipids, and energy metabolism. To act on target tissues, endocrine FGF-21 binds preferably to FGF receptor 1 (FGFR1) in the presence of the coreceptor named β-klotho (KLB). Some of the effects of FGF-21 include increased fatty acid oxidation, glucose uptake, insulin sensitivity, and thermogenesis, which can regulate body weight and glycemia control. By exerting such metabolic effects, the therapeutic potential of FGF-21 for the treatment of obesity and diabetes has been investigated. Physical exercise has been widely used for the prevention and treatment of obesity. Several mechanisms mediate the effects of physical exercise, including the FGF-21 pathway. Studies have shown that physical exercise increases the concentration of circulating and tissue FGF-21 in animals, while contradictory results are still observed in humans. Considering the metabolic role of FGF-21 and the chance of physical exercise to induce FGF-21 secretion, in this review we explore the potential of physical exercise-induced FGF-21 modulation as a strategy for prevention and treatment of obesity.

Keywords: FGF-21; physical exercise; obesity

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1. Introduction

Fibroblast growth factor 21 (FGF-21), a protein with a molecular weight of 23 kDa, is produced in the liver, heart, pancreas, white adipose tissue (WAT), brown adipose tissue (BAT), skeletal muscle, and brain [1], and its action is mediated by the interaction of the transmembrane protein β-Klotho (KLB) with the receptors FGFR1, FGFR2, FGFR3, and FGFR4 [2].

Among other endocrine functions, FGF-21 is known as a potent metabolic modulator, since it stimulates glucose uptake and increases fatty acid oxidation by activating coactivator 1 alpha of the peroxisome proliferator-activated receptor gamma (PGC-1α) [3]. Administration of FGF-21 to rats fed a high-fat diet reduces body weight and visceral fat gain, and increases insulin sensitivity [4]. Apparently, its effect is associated with increased energy expenditure [5], increased fatty acid oxidation, and reduced adiposity and body mass [6]. By exerting such metabolic effects, the therapeutic potential of FGF-21 for the treatment of obesity and diabetes has been the subject of human studies [7].

Obesity has become a significant public health issue worldwide, and strategies to combat the high prevalence are necessary because it causes damage to health and is a financial burden on people and society. Physical exercise has been widely used for the prevention and treatment of obesity. This is because it has the potential to increase lipid oxidation, reduce fat mass, increase insulin sensitivity, and lower blood glucose, as described by some research groups [8,9] and by our [10,11]. We also showed that physical exercise exerts a protective effect diminishing lipid deposition in the kidneys of mice with

insulin resistance [12] and by modifying the skeletal muscle proteins expression to a more oxidative phenotype [13] in an animal model of obesity.

It is known that physical exercise increases both serum concentrations and expression of FGF-21 in the liver [14], increases FGF-21 gene expression in skeletal muscle [15] and increases the gene expression of FGFR1 and KLB in WAT [16] in animals. In humans, the effect of physical exercise on FGF-21 is still contradictory and deserves further investigation. Considering the metabolic role of FGF-21 and the chance of physical exercise to induce FGF-21 secretion, this review aims to explore the potential of physical exercise-induced FGF-21 modulation as a strategy for prevention and treatment of obesity. Therefore, we provided a summary of the research supporting the benefits of physical exercise for the prevention and treatment of obesity and describe the FGF-21 as one of the physiological mechanisms underlying these benefits.

2. FGF-21 Metabolic Effects

FGF is a large protein family, with 22 members in mammals. Based on gene sequence homology and phylogeny, the FGF family can be divided into seven subfamilies, among which the endocrine FGF-19 subfamily consists of three FGFs, namely FGF-19 (FGF-15 in rodents), FGF-21, and FGF-23 [17]. In order to act on target tissues, FGF-21 binds to FGF receptor 1 (FGFR1) in the presence of the transmembrane protein named β-klotho [18,19]. FGF-21 can also act by other receptors, such as FGFR2, FGFR3, and FGFR4, however it prefers to bind to FGFR1 over these other receptors [20].

Kharitonenkov et al. (2005) were the first to describe FGF-21 as a possible metabolic regulator [5]. They observed that transgenic mice expressing human FGF-21 submitted to high-fat diet for 15 weeks were resistant to obesity, and presented lower levels of fasting glucose and leptin. They also showed that FGF-21 indirectly exerts hypoglycemic effects by inhibiting glucagon secretion. Other studies have reported beneficial effects of FGF-21, including reduction in body weight, liver and circulating triglycerides, fasting plasma insulin and glucose, and increase in energy expenditure [3,21]. Interestingly, obesity and type 2 diabetes have also been associated with increased circulating FGF-21 concentration in humans [22] and animals [23]. The paradoxical effect of FGF-21 was first explained by the FGF-21 resistance associated with lower expression of KLB and FGFR1 [24], but this was contradicted in a recent review by [25].

FGF-21 exerts metabolic effects on several tissues (Figure 1). In the liver, FGF21 stimulates fatty acid oxidation and reduces lipid flux by increasing peripheral lipoprotein catabolism and reducing adipocyte lipolysis [26]. In the white adipose tissue (WAT), it suppresses lipolysis and enhances insulin sensitivity and adiponectin secretion [26,27], thus ameliorating some harmful effects of obesity, such as hyperglycemia, glucose intolerance, insulin resistance, and dyslipidemia [28,29]. In the brown adipose tissue (BAT), FGF-21 increases glucose uptake, lipolysis, and thermogenesis [30]. Other tissue actions of the FGF-21 can be found in the review published by She et al. (2022) [17].

Since FGF-21 improves hyperglycemia, dyslipidemia, and obesity, the cardioprotective effects of FGF-21 have also been elucidated. In a recent review, it was discussed that FGF-21 prevent endothelial dysfunction and lipid accumulation, inhibiting cardiomyocyte apoptosis and regulating oxidative stress, inflammation, and autophagy [31]. Thus, FGF-21 could be a potential target to prevent and to treat cardiovascular disease.

FGF-21 plays an important role on the metabolism by activating different pathways, usually involving cell differentiation, proliferation, and energy metabolism proteins. One of these proteins is the AMP- activated protein kinase (AMPK), which is recognized as an energy metabolic sensor in cells. The FGF-21 binding to a serine threonine kinase protein called LKB1, which is considered to be a major regulator of AMPK activation [32]. The activation of AMPK pathway leads to rise of PGC1-α, a special regulator of mitochondrial biogenesis, which increases mitochondrial respiratory function and oxidative capacity in adipocytes and consequently higher energy expenditure [33]. Together, FGF-21 and AMPK improve free fatty acid oxidation and energy expenditure [34,35], which can inhibit the

accumulation of triglyceride in hepatocytes, and possibly prevent the development of non-alcoholic fatty liver disease [36,37].

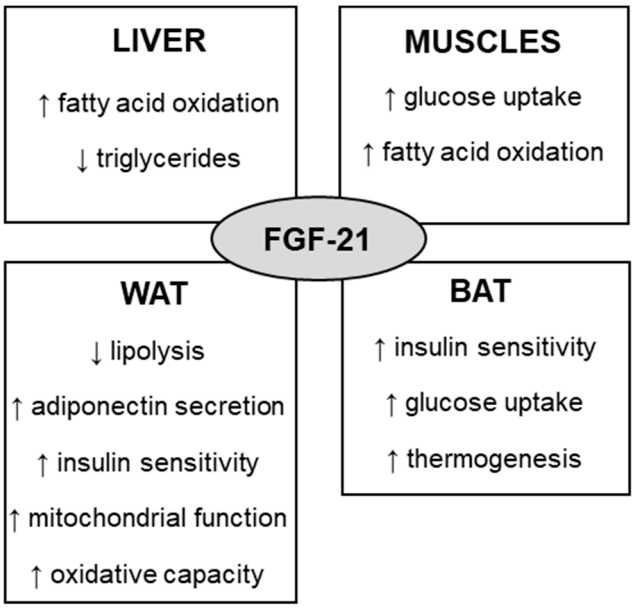

Figure 1. Metabolic effects of FGF-21 that may contribute to the body weight and glycemia control. Arrows indicate the following: upward, increase; downward, decrease. WAT = white adipose tissue; BAT = brown adipose tissue.

FGF-21 also can act through mitogen-activated protein kinases (MAPK) pathway. When the complex FGFR1 and B-klotho is auto phosphorylated, the cascade signaling for MAPK happens, and leads to the activation of ERK 1/2. Minard et al. (2016) submitted adipocytes cells to stable isotopes to see all the phosphorylation of FGF-21 in these cells [38]. About 15,687 phosphorylation sites occur in 4583 different proteins. FGF-21 signaling was initiated by tyrosine phosphorylation of FGFR1, followed by ERK1 and 2 phosphorylation. In the same study, the authors showed that when the cells were submitted to insulin, FGF-21 could stimulate the MAPK pathway 11-fold more and leads to the activation of mTORC1 resulting in glucose uptake, adiponectin secretion and UCP1 elevation.

Considering that FGF-21 significantly ameliorates metabolic diseases impacts, it has been investigated in pharmacological studies. In this context, six clinical trials in obese subjects have been conducted to test the therapeutic effects of FGF-21, specifically four drugs and one agonist receptor antibody [39]. As reviewed by the authors, the short half-life, the susceptibility to proteolytic inactivation and the obesity-mediated FGF21 resistance are the great challenges for therapies based on FGF-21. Therefore, regular physical exercise may be an alternative to induce the effects of FGF-21 that can contribute to combatting obesity and its damages. In addition, it is a strategy with lower cost and greater access for the population, which can promote more significant effects for individuals and for health systems.

3. Effect of Physical Exercise on FGF-21

Physical exercise acts in different ways in the body, as it can alter protein secretion, influencing circulating but also locally levels. A continuous aerobic exercise session increases the circulating FGF-21 in both lean and obese individuals immediately after exercise for up to one hour [40]. Interestingly, a high-intensity interval training (HIIT) session appears to prolong the increased levels of FGF-21 induced by the exercise up to 3 h after the end of the session in lean men, while this effect can last for up to 48 h when the resistance exercise with seven types of exercises targeting all the main muscle groups was performed [41]. In obese people submitted to acute moderate-intensity exercise (treadmill exercise, ∼60%

peak oxygen uptake), circulating concentrations of FGF21 were elevated after exercise for up to 6 h [42]. Based on research, it seems that resistance exercise session is the type of exercise that keeps the FGF-21 level higher for longer post-acute exercise.

It is important to point out that the acute exercise effect on FGF-21 is not a consensus in the literature. Cuevas-Ramos et al. (2012) [43] and Parmar et al. (2018) [44] observed no significant changes in serum FGF21 of lean individuals after a single session of aerobic exercise and resistance exercise, respectively. A summary of the effects of physical exercise on circulating FGF-21 in lean and obese individuals is demonstrated in the Figure 2. It appears that the intensity of the aerobic exercise affects the FGF-21 secretion response. In fact, He et al. (2019) [45] that showed a higher serum concentration of FGF-21 after performing exercise at 90% of maximum heart rate (HR max) in comparison to an exercise performed at 69% of HR max. Furthermore, the correlation between exercise volume and the levels of FGF-21 remains unclear and it is suggested that endogenous FGF-21 is associated with the magnitude of caloric expenditure and oxidative stress caused by acute strenuous physical exercise [46]. This gap remains, and further studies are needed to confirm this hypothesis.

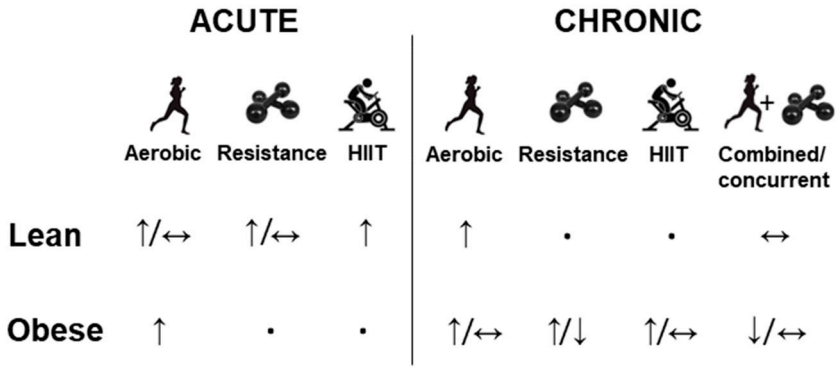

Figure 2. Effects of acute and chronic exercise in different modalities for circulating FGF-21 in lean and obese individuals. Arrows indicate the following: upward, increase in FGF-21; bidirectional, no change in FGF-21; downward, decrease in FGF-21. Dot = unknown.

The chronic physical exercise effect on FGF-21 has been extensively investigated. In lean individuals, a significant increase in FGF21 concentration was shown after two weeks of treadmill training [43]. On the other hand, Mendez-Gutierrez et al. (2022) [47] did not find difference in FGF-21 plasma concentration after a 24-week exercise program (continuous aerobic exercise + resistance). As discussed previously, differences in exercise protocols, age, and sex of participants can explain the results [48].

In obese people, both HIIT and resistance training increase FGF-21 levels [49] and the same can be observed in diabetic individuals who performed resistance training and continuous aerobic training [50]. On the other hand, some studies show a reduction in FGF-21 values after resistance training [51] and concurrent training [52], or no changes after continuous aerobic training in cycle ergometer [53] and HIIT [54]. A possible explanation for this phenomenon is the adaptation to subsequent sessions of physical exercise, lowering the production of FGF-21 by the liver.

The liver secretes most of FGF-21 in response to physical exercise. However, FGF-21 is also expressed in heart, adipose tissue, skeletal muscle, and pancreas. Physical exercise has the potential to induce greater tissue expression of FGF-21, as showed by studies with animals. For example, aerobic and resistance training promote greater expression of FGF-21 in the heart [55], while HIIT is able to increase the expression of FGF-21 in skeletal muscle [56]. In another study, continuous aerobic exercise was more effective in increasing FGF-21 in BAT, skeletal muscle, and liver than HIIT. Additionally in this study, there was a drop in the serum amount of trained animals, suggesting that chronic exercise reduces, in the long term, the synthesis of FGF-21 by the liver [57].

Considering that obesity and body adiposity have become a public health problem, FGF-21 has gained notoriety in last years. This attention came after a study that showed that FGF-21 administration promoted weight loss and reduced adiposity in animals fed a high caloric diet and that the effect was dose dependent. This effect was correlated to the higher oxygen consumption, resulting in increased caloric expenditure and proportionally oxidizing more fat at rest [6]. Thus, discovering whether the beneficial effects of physical exercise would be mediated by the action of FGF-21 could give support to understand which intensity and frequency are most appropriate to combat obesity and its damages.

In this context, exercise training reduces the body weight and adiposity of obese animals and restores the concentrations of FGF-21 and β-Klotho in WAT and BAT, ameliorating insulin sensitivity and glucose uptake impaired by obesity [58]. Considering that there are human studies showing that the reduction in fat mass through physical exercise is not necessarily accompanied by changes in FGF-21 levels, perhaps the FGF-21 anti-obesity effects are associated with better crosstalk between liver and BAT. In fact, part of the increase in caloric expenditure induced by FGF-21 has shown to be mediated through BAT and its thermogenic potential and adaptation to exercise training. Evidence shows that adipose tissue sensitivity to FGF-21 appears to be inversely correlated with lower BMI when indirect assessed by measuring the β-Klotho gene expression [59]. In addition, WAT is an endocrine organ, with great capacity to secrete adipokines and other proteins including FGF-21. Taken together, this evidence suggest that next studies should not focus on FGF-21 secreted by the liver through stimulation of exercise training, but by BAT and WAT, increasing their potential for energy expenditure [60].

As physical exercise is the focus of this topic, it is important to highlight its potential to alter the characteristics of adipose tissue, increasing adipokine secretion, heat production, and caloric expenditure. It is known that obese and elderly individuals have less activation of BAT [61], which makes BAT a target of studies in possible treatments. Studies have also already shown that physical exercise in humans has the potential to modify characteristics of BAT, increasing the expression of UCP1 and fatty acid transporters in people with obesity, but not overweight [62,63]. Other studies have already shown that the crosstalk of WAT to BAT is associated with greater tissue expression of FGF-21 [64]. However, more studies are needed to investigate the effect of physical exercise on the synthesis of FGF-21 in adipose tissue, and its potential to alter its characteristics enabling greater heat production and energy expenditure.

4. Conclusions

In this review, we showed that physical exercise has the potential to modulate circulating FGF21 levels in humans and animals, while tissue effects were primarily observed in animals. By acting in the reduction of blood glucose and lipid concentrations, which improves insulin sensitivity, FGF-21 deserves to be the target of studies that seek to discover ways to prevent and treat obesity. New studies are still needed involving the responses of FGF-21, FGF21 receptors, and co-receptor KLB to different types of physical exercise, which could be useful to support the prescription of physical exercise for the management of obesity.

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References

1. Staiger, H.; Keuper, M.; Berti, L.; de Angelis, M.H.; Häring, H.U. Fibroblast growth factor 21-metabolic role in mice and men. *Endocr. Rev.* **2017**, *38*, 468–488. [CrossRef] [PubMed]
2. Itoh, N.; Ohta, H.; Konishi, M. Endocrine FGFs: Evolution, Physiology, Pathophysiology, and Pharmacotherapy. *Front. Endocrinol.* **2015**, *6*, 154. [CrossRef] [PubMed]
3. Huang, Z.; Xu, A.; Cheung, B.M.Y. The Potential Role of Fibroblast Growth Factor 21 in Lipid Metabolism and Hypertension. *Curr. Hypertens. Rep.* **2017**, *19*, 17–22. [CrossRef] [PubMed]
4. Charoenphandhu, N.; Suntornsaratoon, P.; Krishnamra, N. Fibroblast growth factor—21 restores insulin sensitivity but induces aberrant bone microstructure in obese insulin—Resistant rats. *J. Bone Miner. Metab.* **2016**, *35*, 142–149. [CrossRef] [PubMed]
5. Kharitonenkov, A.; Shiyanova, T.L.; Koester, A.; Ford, A.M.; Micanovic, R.; Galbreath, E.J.; Sandusky, G.E.; Hammond, L.J.; Moyers, J.S.; Owens, R.A.; et al. FGF-21 as a novel metabolic regulator. *J. Clin. Investig.* **2005**, *115*, 1627–1635. [CrossRef] [PubMed]
6. Coskun, T.; Bina, H.A.; Schneider, M.A.; Dunbar, J.D.; Hu, C.C.; Chen, Y.; Moller, D.E.; Kharitonenkov, A. Fibroblast growth factor 21 corrects obesity in mice. *Endocrinology* **2008**, *149*, 6018–6027. [CrossRef]
7. Jimenez, V.; Jambrina, C.; Casana, E.; Sacristan, V.; Muñoz, S.; Darriba, S.; Rodó, J.; Mallol, C.; Garcia, M.; León, X.; et al. FGF21 gene therapy as treatment for obesity and insulin resistance. *EMBO Mol. Med.* **2018**, *10*, e8791. [CrossRef]
8. Venables, M.C.; Jeukendrup, A.E. Endurance training and obesity: Effect on substrate metabolism and insulin sensitivity. *Med. Sci. Sports Exerc.* **2008**, *40*, 495–502. [CrossRef]
9. Winding, K.M.; Munch, G.W.; Iepsen, U.W. The effect of low-volume high-intensity interval training versus endurance training on glycemic control in individuals with type 2 diabetes. *Diabetes Obes. Metab.* **2018**, *20*, 1131–1139. [CrossRef]
10. Higa, T.S.; Spinola, A.V.; Fonseca-Alaniz, M.H.; Evangelista, F.S. Remodeling of white adipose tissue metabolism by physical training prevents insulin resistance. *Life Sci.* **2014**, *103*, 41–48. [CrossRef]
11. Américo, A.L.V.; Muller, C.R.; Vecchiatto, B.; Martucci, L.F.; Fonseca-Alaniz, M.H.; Evangelista, F.S. Aerobic exercise training prevents obesity and insulin resistance independent of the renin angiotensin system modulation in the subcutaneous white adipose tissue. *PLoS ONE* **2019**, *14*, e0215896. [CrossRef] [PubMed]
12. Muller, C.R.; Américo, A.L.V.; Fiorino, P.; Evangelista, F.S. Aerobic exercise training prevents kidney lipid deposition in mice fed a cafeteria diet. *Life Sci.* **2018**, *211*, 140–146. [CrossRef]
13. Vecchiatto, B.; da Silva, R.C.; Higa, T.S.; Muller, C.R.; Américo, A.L.V.; Fortunato-Lima, V.C.; Ferreira, M.M.; Martucci, L.F.; Fonseca-Alaniz, M.H.; Evangelista, F.S. Oxidative phenotype induced by aerobic physical training prevents the obesity-linked insulin resistance without changes in gastrocnemius muscle ACE2-Angiotensin(1-7)-Mas axis. *Diabetol. Metab. Syndr.* **2021**, *13*, 74. [CrossRef]
14. Kim, J.; Hwang, H.; Yun, H.-Y.; Kim, B.; Lee, C.-H.; Suh, H.; Lim, K. Silk Peptide Intake Increases Fat Oxidation at Rest in Exercised Mice. *J. Nutr. Sci. Vitaminol.* **2013**, *59*, 250–255. [CrossRef]
15. Tanimura, Y.; Aoi, W.; Takanami, Y.; Kawai, Y.; Mizushima, K.; Naito, Y.; Yoshikawa, T. Acute exercise increases fibroblast growth factor 21 in metabolic organs and circulation. *Physiol. Rep.* **2016**, *4*, e12828. [CrossRef]
16. Yang, W.; Liu, L.; Wei, Y.; Fang, C.; Zhou, F.; Chen, J.; Han, Q.; Huang, M.; Tan, X.; Liu, Q.; et al. Exercise ameliorates the FGF21-adiponectin axis impairment in diet-induced obese mice. *Endocr. Connect.* **2019**, *8*, 596–604. [CrossRef]
17. She, Q.-Y.; Bao, J.; Wang, H.; Liang, H. Fibroblast growth factor 21: A "rheostat" for metabolic regulation? *Metabolism.* **2022**, *130*, 155166. [CrossRef]
18. Badman, M.K.; Pissios, P.; Kennedy, A.R.; Koukos, G.; Flier, J.S.; Maratos-Flier, E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab.* **2007**, *5*, 426–437. [CrossRef]
19. Inagaki, T.; Dutchak, P.; Zhao, G.; Ding, X.; Gautron, L.; Parameswara, V.; Li, Y.; Goetz, R.; Mohammadi, M.; Esser, V.; et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab.* **2007**, *5*, 415–425. [CrossRef]
20. Ding, X.; Boney-Montoya, J.; Owen, B.M.; Bookout, A.L.; Coate, K.C.; Mangelsdorf, D.J.; Kliewer, S.A. βKslotho is required for fibroblast growth factor 21 effects on growth and metabolism. *Cell Metab.* **2012**, *16*, 387–393. [CrossRef]
21. Geng, L.; Lam, K.S.L.; Xu, A. The therapeutic potential of FGF21 in metabolic diseases: From bench to clinic. *Nat. Rev. Endocrinol.* **2020**, *16*, 654–667. [CrossRef]
22. Zhang, X.; Yeung, D.C.Y.; Karpisek, M.; Stejskal, D.; Zhou, Z.-G.; Liu, F.; Wong, R.L.C.; Chow, W.-S.; Tso, A.W.K.; Lam, K.S.L.; et al. Serum FGF21 Levels Are Increased in Obesity and Are Independently Associated With the Metabolic Syndrome in Humans. *Diabetes* **2008**, *57*, 1246–1253. [CrossRef]
23. Hale, C.; Chen, M.M.; Stanislaus, S.; Chinookoswong, N.; Hager, T.; Wang, M.; Véniant, M.M.; Xu, J. Lack of Overt FGF21 Resistance in Two Mouse Models of Obesity and Insulin Resistance. *Endocrinology* **2012**, *153*, 69–80. [CrossRef] [PubMed]
24. Fisher, f.M.; Chui, P.C.; Antonellis, P.J.; Bina, H.A.; Kharitonenkov, A.; Flier, J.S.; Maratos-Flier, E. Obesity Is a Fibroblast Growth Factor 21 (FGF21)-Resistant State. *Diabetes* **2010**, *59*, 2781–2789. [CrossRef]
25. Spann, R.A.; Morrison, C.D.; den Hartigh, L.J. The Nuanced Metabolic Functions of Endogenous FGF21 Depend on the Nature of the Stimulus, Tissue Source, and Experimental Model. *Front. Endocrinol.* **2022**, *12*, 1–21. [CrossRef] [PubMed]
26. Kaufman, A.; Abuqayyas, L.; Denney, W.S.; Tillman, E.J.; Rolph, T. AKR-001, an Fc-FGF21 Analog, Showed Sustained Pharmacodynamic Effects on Insulin Sensitivity and Lipid Metabolism in Type 2 Diabetes Patients. *Cell Reports Med.* **2020**, *1*, 100057. [CrossRef] [PubMed]

27. Turer, A.T.; Scherer, P.E. Adiponectin: Mechanistic insights and clinical implications. *Diabetologia* **2012**, *55*, 2319–2326. [CrossRef] [PubMed]
28. Yamauchi, T.; Kamon, J.; Minokoshi, Y.; Ito, Y.; Waki, H.; Uchida, S.; Yamashita, S.; Noda, M.; Kita, S.; Ueki, K.; et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat. Med.* **2002**, *8*, 1288–1295. [CrossRef]
29. Xu, A.; Wang, Y.; Keshaw, H.; Xu, L.Y.; Lam, K.S.L.; Cooper, G.J.S. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J. Clin. Investig.* **2003**, *112*, 91–100. [CrossRef]
30. Babaknejad, N.; Nayeri, H.; Hemmati, R.; Bahrami, S.; Esmaillzadeh, A. An Overview of FGF19 and FGF21: The Therapeutic Role in the Treatment of the Metabolic Disorders and Obesity. *Horm. Metab. Res.* **2018**, *50*, 441–452. [CrossRef]
31. Zhang, Y.; Liu, D.; Long, X.X.; Fang, Q.C.; Jia, W.P.; Hua-Ting, L. The role of FGF21 in the pathogenesis of cardiovascular disease. *Chin Med. J.* **2021**, *134*, 2931–2943. [CrossRef]
32. Salminen, A.; Kauppinen, A.; Kaarniranta, K. FGF21 activates AMPK signaling: Impact on metabolic regulation and the aging process. *J. Mol. Med.* **2017**, *95*, 123–131. [CrossRef]
33. Chau, M.D.L.; Gao, J.; Yang, Q.; Wu, Z.; Gromada, J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 12553–12558. [CrossRef]
34. Planavila, A.; Redondo, I.; Hondares, E.; Vinciguerra, M.; Munts, C.; Iglesias, R.; Gabrielli, L.A.; Sitges, M.; Giralt, M.; van Bilsen, M.; et al. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. *Nat. Commun.* **2013**, *4*, 2019. [CrossRef]
35. Woo, Y.C.; Xu, A.; Wang, Y.; Lam, K.S.L. Fibroblast growth factor 21 as an emerging metabolic regulator: Clinical perspectives. *Clin. Endocrinol.* **2013**, *78*, 489–496. [CrossRef]
36. Zhang, Y.; Lei, T.; Huang, J.F.; Wang, S.B.; Zhou, L.L.; Yang, Z.Q.; Chen, X.D. The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes. *Mol. Cell Endocrinol.* **2011**, *342*, 41–47. [CrossRef]
37. Li, Y.; Xu, S.; Mihaylova, M.M.; Zheng, B.; Hou, X.; Jiang, B.; Park, O.; Luo, Z.; Lefai, E.; Shyy, J.Y.-J.; et al. AMPK phosphorylates and inhibits SREBP activity to attenuate hepatic steatosis and atherosclerosis in diet-induced insulin-resistant mice. *Cell Metab.* **2011**, *13*, 376–388. [CrossRef]
38. Minard, A.Y.; Tan, S.-X.; Yang, P.; Fazakerley, D.J.; Domanova, W.; Parker, B.L.; Humphrey, S.J.; Jothi, R.; Stöckli, J.; James, D.E. mTORC1 Is a Major Regulatory Node in the FGF21 Signaling Network in Adipocytes. *Cell Rep.* **2016**, *17*, 29–36. [CrossRef]
39. Shao, W.; Jin, T. Hepatic hormone FGF21 and its analogues in clinical trials. *Chronic Dis. Transl. Med.* **2022**, *8*, 19–25. [CrossRef]
40. Khalafi, M.; Alamdari, K.A.; Symonds, M.E.; Nobari, H.; Carlos-Vivas, J. Impact of acute exercise on immediate and following early post-exercise FGF-21 concentration in adults: Systematic review and meta-analysis. *Hormones* **2021**, *20*, 23–33. [CrossRef]
41. He, Z.; Tian, Y.; Valenzuela, P.L.; Huang, C.; Zhao, J.; Hong, P.; He, Z.; Yin, S.; Lucia, A. Myokine Response to High-Intensity Interval vs. Resistance Exercise: An Individual Approach. *Front. Physiol.* **2018**, *9*, 1735. [CrossRef]
42. Sargeant, J.A.; Aithal, G.P.; Takamura, T.; Misu, H.; Takayama, H.; Douglas, J.A.; Turner, M.C.; Stensel, D.J.; Nimmo, M.A.; Webb, D.R.; et al. The influence of adiposity and acute exercise on circulating hepatokines in normal-weight and overweight/obese men. *Appl. Physiol. Nutr. Metab.* **2018**, *43*, 482–490. [CrossRef]
43. Cuevas-Ramos, D.; Almeda-Valdés, P.; Meza-Arana, C.E.; Brito-Córdova, G.; Gómez-Pérez, F.J.; Mehta, R.; Oseguera-Moguel, J.; Aguilar-Salinas, C.A. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. *PLoS ONE* **2012**, *7*, e38022. [CrossRef]
44. Parmar, B.; Lewis, J.E.; Samms, R.J.; Ebling, F.J.P.; Cheng, C.C.; Adams, A.C.; Mallinson, J.; Cooper, S.; Taylor, T.; Ghasemi, R.; et al. Eccentric exercise increases circulating fibroblast activation protein α but not bioactive fibroblast growth factor 21 in healthy humans. *Exp. Physiol.* **2018**, *103*, 876–883. [CrossRef]
45. He, Z.; Tian, Y.; Valenzuela, P.L.; Huang, C.; Zhao, J.; Hong, P.; He, Z.; Yin, S.; Lucia, A. Myokine/adipokine response to "aerobic" exercise: Is it just a matter of exercise load? *Front. Physiol.* **2019**, *10*, 691. [CrossRef]
46. Ost, M.; Coleman, V.; Kasch, J.; Klaus, S. Regulation of myokine expression: Role of exercise and cellular stress. *Free Radic. Biol. Med.* **2016**, *98*, 78–89. [CrossRef]
47. Mendez-Gutierrez, A.; Aguilera, C.M.; Osuna-Prieto, F.J.; Martinez-Tellez, B.; Rico Prados, M.C.; Acosta, F.M.; Llamas-Elvira, J.M.; Ruiz, J.R.; Sanchez-Delgado, G. Exercise-induced changes on exerkines that might influence brown adipose tissue metabolism in young sedentary adults. *Eur. J. Sport Sci.* Online ahead of print. **2022**. [CrossRef]
48. Domin, R.; Dadej, D.; Pytka, M.; Zybek-Kocik, A.; Ruchała, M.; Guzik, P. Effect of Various Exercise Regimens on Selected Exercise-Induced Cytokines in Healthy People. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1261. [CrossRef]
49. Haghighi, A.; Hajinia, M.; Askari, R.; Abbasian, S.; Goldfield, G.S. Effect of high-intensity interval training and high-intensity resistance training on Irisin and fibroblast growth factor 21 in men with overweight and obesity. *Can. J. Physiol. Pharmacol.* **2022**, *100*, 937–944. [CrossRef]
50. Keihanian, A.; Arazi, H.; Kargarfard, M. Effects of aerobic versus resistance training on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 levels in male diabetic patients. *Physiol. Int.* **2019**, *106*, 70–80. [CrossRef]
51. Shabkhiz, F.; Khalafi, M.; Rosenkranz, S.; Karimi, P.; Moghadami, K. Resistance training attenuates circulating FGF-21 and myostatin and improves insulin resistance in elderly men with and without type 2 diabetes mellitus: A randomised controlled clinical trial. *Eur. J. Sport Sci.* **2021**, *21*, 636–645. [CrossRef] [PubMed]
52. Yang, S.J.; Hong, H.C.; Choi, H.Y.; Yoo, H.J.; Cho, G.J.; Hwang, T.G.; Baik, S.H.; Choi, D.S.; Kim, S.M.; Choi, K.M. Effects of a three-month combined exercise programme on fibroblast growth factor 21 and fetuin-A levels and arterial stiffness in obese women. *Clin. Endocrinol.* **2011**, *75*, 464–469. [CrossRef] [PubMed]

53. Garneau, L.; Parsons, S.A.; Smith, S.R.; Mulvihill, E.E.; Sparks, L.M.; Aguer, C. Plasma Myokine Concentrations After Acute Exercise in Non-obese and Obese Sedentary Women. *Front. Physiol.* **2020**, *11*, 18. [CrossRef] [PubMed]
54. Kong, Z.; Sun, S.; Liu, M.; Shi, Q. Short-Term High-Intensity Interval Training on Body Composition and Blood Glucose in Overweight and Obese Young Women. *J. Diabetes Res.* **2016**, *2016*, 4073618. [CrossRef]
55. Gonzalez-Gil, A.M.; Elizondo-Montemayor, L. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: A review. *Nutrients* **2020**, *12*, 1. [CrossRef]
56. Tanimura, R.; Kobayashi, L.; Shirai, T.; Takemasa, T. Effects of exercise intensity on white adipose tissue browning and its regulatory signals in mice. *Physiol. Rep.* **2022**, *10*, e15205. [CrossRef]
57. Xiong, Y.; Chen, Y.; Liu, Y.; Zhang, B. Moderate-Intensity Continuous Training Improves FGF21 and KLB Expression in Obese Mice. *Biochem.* **2020**, *85*, 938–946. [CrossRef]
58. Geng, L.; Liao, B.; Jin, L.; Huang, Z.; Triggle, C.R.; Ding, H.; Zhang, J.; Huang, Y.; Lin, Z.; Xu, A. Exercise Alleviates Obesity-Induced Metabolic Dysfunction via Enhancing FGF21 Sensitivity in Adipose Tissues. *Cell Rep.* **2019**, *26*, 2738–2752. [CrossRef]
59. Kruse, R.; Vienberg, S.G.; Vind, B.F.; Andersen, B.; Højlund, K. Effects of insulin and exercise training on FGF21, its receptors and target genes in obesity and type 2 diabetes. *Diabetologia* **2017**, *60*, 2042–2051. [CrossRef]
60. Horino, M.; Ikeda, K.; Yamada, T. The Role of Thermogenic Fat Tissue in Energy Consumption. *Curr. Issues Mol. Biol.* **2022**, *44*, 3166–3179. [CrossRef]
61. Worku, M.G.; Seretew, W.S.; Angaw, D.A.; Tesema, G.A. Prevalence and Associated Factor of Brown Adipose Tissue: Systematic Review and Meta-Analysis. *Biomed Res. Int.* **2020**, *2020*, 9106976. [CrossRef] [PubMed]
62. Otero-Díaz, B.; Rodríguez-Flores, M.; Sánchez-Muñoz, V.; Monraz-Preciado, F.; Ordoñez-Ortega, S.; Becerril-Elias, V.; Baay-Guzmán, G.; Obando-Monge, R.; García-García, E.; Palacios-González, B.; et al. Exercise Induces White Adipose Tissue Browning Across the Weight Spectrum in Humans. *Front. Physiol.* **2018**, *9*, 1781. [CrossRef] [PubMed]
63. Norheim, F.; Langleite, T.M.; Hjorth, M.; Holen, T.; Kielland, A.; Stadheim, H.K.; Gulseth, H.L.; Birkeland, K.I.; Jensen, J.; Drevon, C.A. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. *FEBS J.* **2014**, *281*, 739–749. [CrossRef] [PubMed]
64. Koh, Y.J.; Lee, J.H.; Park, S.Y. Moxibustion-simulating bipolar radiofrequency suppresses weight gain and induces adipose tissue browning via activation of UCP1 and FGF21 in a mouse model of diet-induced obesity. *Evid.-Based Complement. Altern. Med.* **2018**, *2018*, 4737515. [CrossRef]