Review

Tianru Jin*

Fibroblast growth factor 21 and dietary interventions: what we know and what we need to know next

https://doi.org/10.1515/mr-2022-0019
Received June 20, 2022; accepted August 10, 2022;
published online September 13, 2022

Abstract: Dietary interventions include the change of dietary styles, such as fasting and dietary or nutrient restrictions; or the addition of plant-derived compounds (such as polyphenols known as curcumin, resveratrol, or anthocyanin, or other nutraceuticals) into the diet. During the past a few decades, large number of studies have demonstrated therapeutic activities of these dietary interventions on metabolic and other diseases in human subjects or various animal models. Mechanisms underlying those versatile therapeutic activities, however, remain largely unclear. Interestingly, recent studies have shown that fibroblast growth factor 21 (FGF21), a liver-derived hormone or hepatokine, mediates metabolic beneficial effects of certain dietary polyphenols as well as protein restriction. Here I have briefly summarized functions of FGF21, highlighted related dietary interventions, and presented literature discussions on role of FGF21 in mediating function of dietary polyphenol intervention and protein restriction. This is followed by presenting my perspective view, with the involvement of gut microbiota. It is anticipated that further breakthroughs in this field in the near future will facilitate conceptual merge of classical medicine and modern medicine.

Keywords: dietary polyphenol intervention; fibroblast growth factor 21; gut microbiota; protein restriction.

Overview

To deal with the rapid increase on the prevalence of obesity, type 2 diabetes (T2D), fatty liver diseases, other metabolic disorders, as well as their devastating complications, great efforts have been made to identify novel therapeutic targets and develop novel therapeutic agents for those disorders. These, along with the vigorous promotion on changing sedentary lifestyles, are still not sufficient in preventing the elevation of the prevalence of those diseases globally. Other approaches to improve metabolic homeostasis are dietary interventions, either via changing dietary behaviors (fasting or nutrition restriction) or by adding chemical compounds, most of them are from edible plants, into the diet. Common ones include the polyphenol compounds known as curcumin, resveratrol, and anthocyanin. Without involving a drug prescription, dietary interventions have been adopted by more and more people in both developing and developed countries. Ill, sub-healthy, and healthy people, may pick up a type of dietary intervention, aiming to improve their health conditions. Although metabolic and other beneficial effects of dietary interventions have been reported in many clinical trials and pre-clinical investigations, mechanisms underlying their effects remain largely unclear.

Certain therapeutic agents are virtually metabolic hormones *per se*, such as insulin, amylin, and glucagon-like peptide-1 (GLP-1) [1, 2]. Other key metabolic hormones include leptin, adiponectin and glucose-dependent insulinotropic polypeptide (GIP). Due to various reasons, those hormones or their analogues may not be suitable for metabolic drug development yet. Recently, clinical trials have been conducted on a few analogues of a relatively novel hormone known as fibroblast growth factor 21 (FGF21). As a "fasting" hormone, FGF21 production and secretion can be triggered by fasting or other types of stresses. Interestingly, investigations have shown that various dietary interventions can regulate FGF21 production, or increase its sensitivity, or rely on FGF21 to achieve

***Corresponding author: Tianru Jin**, Division of Advanced Diagnostics, Toronto General Hospital Research Institute, University Health Network, 101 College St., Toronto M5G 1L7, Canada; Banting and Best Diabetes Centre, Temerty Faculty of Medicine, University of Toronto, Toronto, M5G 2C4, Canada; and Department of Physiology, Temerty Faculty of Medicine, University of Toronto, Toronto M5S 1A8, Canada, E-mail: tianru.jin@utoronto.ca. https://orcid.org/0000-0002-0307-7391

its metabolic and other beneficial effect [3–5]. Thus, FGF21 may serve as a linkage piece for mechanistic understanding of dietary intervention in general. Here I have presented a brief literature review on related studies and my personal view on one of the future directions.

A brief introduction on FGF21

Fibroblast growth factors (FGFs) are a protein family with 23 recognized members in humans and other mammals, which are able to act in paracrine, autocrine, or endocrine manners, serving as mitogens, androgen-induced growth factors, glia growth factors, or endocrine hormones [3]. FGFs can interact with a class of receptor tyrosine kinases known as FGF receptors (FGFRs), leading to complicated downstream signaling events. Among these 23 members, FGF21 was isolated in 2000 by Nishimura and colleagues as an FGF family member which is predominantly expressed in the liver [6]. Although FGF21 expression was then detected in pancreas, adipose tissues [7], testes [8], and hypothalamus [9, 10], it has been generally accepted that circulating FGF21 is hepatic driven [11]. Due to the lack of a heparin binding domain, FGF21, FGF19 (FGF15 in rodents) and FGF23 can be released into the bloodstream easily, making them fit the criterion as endocrine hormones [12]. In addition to FGFRs (mainly isoforms of FGFR1 and FGFR4), the obligatory co-receptor β-klotho (KLB) is also required for FGF21 to exert its metabolic and other functions. For cDNAs of *FGF21/Fgf21* genes and their transcriptional regulation, protein structure of the FGF21 hormone, as well as signaling pathways that mediate FGF21 function in various organs, please see our recent reviews [3, 13]. For additional information on FGF family member evolution and their role in embryonic development, metabolism, and disease development, as well as potential role of FGF21 and its analogues in metabolic disease treatment, please see review articles elsewhere [14–18].

Although metabolic beneficial effects of exogenous FGF21 (or its long-active analogue) administration have been demonstrated in various animal models; obesity, either due to genetic defects or induced by dietary challenges, is strongly associated with elevated plasma FGF21 level and increased hepatic FGF21 expression. Hence, it has been suggested that obesity represents FGF21 resistant status [4, 19].

As we have reviewed very recently [3], during the past decade, several clinical trials have been conducted at different scales utilizing the four designed FGF21 analogues (Figure 1A), known as LY2405319, PF-05231023, AKR-001, and Pegbelfermin (also known as BMS-986036), in testing their therapeutic potential in T2D, or in obese subjects with or without another defined metabolic disorder [20–25]. FGF19 (FGF15 in rodents) is a gut produced hormone. NGM282 (also known as Aldafermin), an analogue of human FGF19 [26, 27],

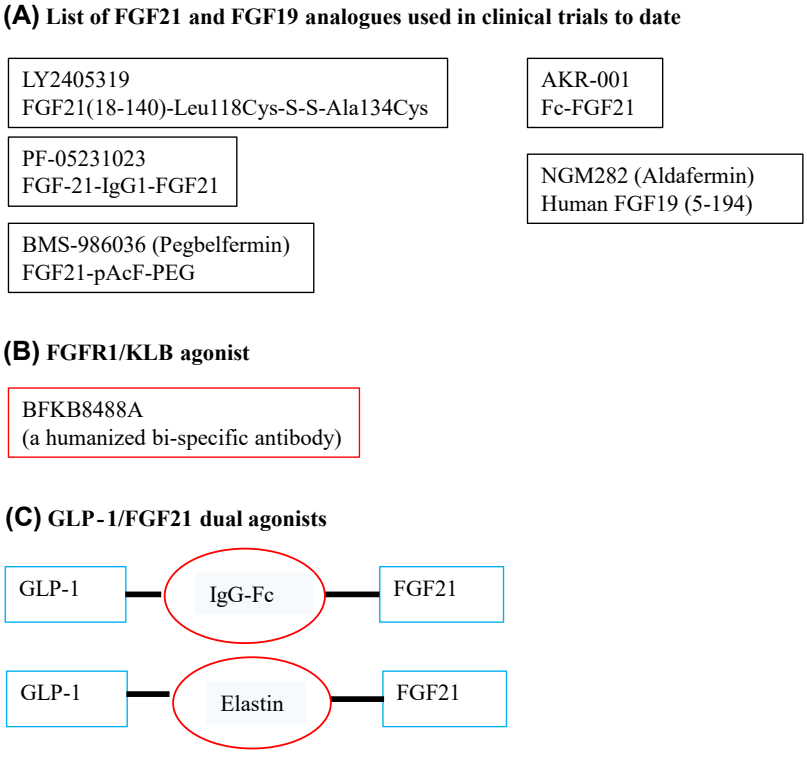

Figure 1: List of potential fibroblast growth factor based therapeutic agents that have been tested in clinical trials and pre-clinical investigations. (A) Names and structure of four fibroblast growth factor 21 analogues and an fibroblast growth factor 19 analogue. (B) A humanized bi-specific antibody as potential therapeutic agent to activate FGF21 receptor fibroblast growth factor receptor 1 and obligatory co-receptor β-klotho. (C) Structure of two glucagon-like peptide-1/FGF21 dual agonists. FGF21, fibroblast growth factor 21; FGF 19, fibroblast growth factor 19; FGFR1, fibroblast growth factor receptor 1; KLB, β-klotho; GLP-1, glucagon-like peptide-1.

is also included in Figure 1A. Although the body weight lowering effect of these FGF21 analogues was observed in pre-clinical studies, such effect was observed only in one trial with PF-05231023 [3]. The effects of these four FGF21 analogues on improving lipid homeostasis, including the reduction on LDL-c and fasting TG; and increase on HDL-c and adiponectin) are consistent for current clinical trials [3, 13]. Clinical trials have demonstrated the therapeutic effects of the FGF19 analogue NGM282 on nonalcoholic steatohepatitis (NASH) but not on diabetes [26–28].

Attempt has also been made to target FGF21 downstream signaling with humanized therapeutic antibody (Figure 1B) [29]. In addition, the additive effect of dual agonists that target both FGF21 and the incretin hormone GLP-1 have also been investigated by different groups (Figure 1C) [30, 31]. Together, studies conducted for the last two decades have clearly demonstrated that hepatic hormone FGF21 represents a promising pharmacological target for diabetes, fatty liver diseases, and other related metabolic disorders.

Protein restriction and dietary polyphenol intervention

Dietary intervention is defined as any types of alterations in an individual's diet with one or more designed goals, such as the management of body weight, the improvement on glucose or lipid homeostasis, cancer treatment or prevention, or even longevity. Among them, protein restriction (PR) is one category of dietary restriction. Epidemiological studies have suggested that lowering dietary protein content can support metabolic improvements [32–34]. In rodent models, studies have shown that PR can also extend lifespan [35, 36]. In addition to PR, pre-clinical investigations have been expanded into the restriction of selected amino acids, such as methionine, threonine, or tryptophan; or the branched-chain amino acids (leucine, isoleucine, and valine, BCAA) [37–39].

Many natural products, most of them are derived from edible plants, are available over the counter in many countries. They are commonly consumed by healthy, sub-healthy, and ill people to treat or to prevent metabolic and other diseases. This represents another category of dietary intervention, also known as dietary supplementation. Among those dietary compounds, three types of polyphenols, known as resveratrol, curcumin, and anthocyanin, have attracted most attentions. It is worth mentioning that resveratrol is also considered as a candidate of fasting mimetics. Approximately 50,000 PubMed publications have been generated on studying these three polyphenol compounds. A recent mega-data study has analyzed outcomes of 750 clinical trials that have been conducted over the past 20 years. A large amount of these registered clinical trials (139 per 750) have put lipid profile and blood pressure as their primary outcomes [40].

For decades, two common features of those dietary polyphenols have severely hampered our mechanistic exploration on their metabolic and other beneficial effects. Firstly, these compounds target multiple organs or cell signaling pathways, without a clearly defined membrane bound or nuclear receptor. Secondly, their bioavailability is extremely low. After taking 10 mg or even 100 mg of a defined phenolic compound, maximum plasma concentration of it can rarely exceed 1 μm [41]. A number of recent studies including our own published and unpublished observations suggest that gut microbiota is involved in mediating these dietary polyphenols [2, 42–44].

Hepatic FGF21 expression can be regulated by dietary polyphenol intervention

Dietary polyphenol interventions can improve insulin sensitivity. Early investigations have attributed this function to their effect on anti-inflammation, anti-oxidation and reducing body weight gain. Seven years ago, my lab asked whether insulin sensitizing effect of curcumin intervention could occur ahead of its anti-inflammation and anti-oxidation effect. For this purpose, we have generated insulin resistance in C57BL/6J mice with daily dexamethasone injection for five days, without or with daily curcumin intervention. In the absence of body weight lowering and the development of inflammation, we were still able to observe insulin signaling improvement effect of curcumin intervention [45]. Our follow up studies then indicated that the improvement involves the regulation of hepatic FGF21 [4, 45]. In mice fed with regular chow diet, short-term (5–7 days) curcumin gavage increased hepatic FGF21 expression level; while in high fat diet (HFD) challenged mice, curcumin intervention attenuated HFD induced FGF21 over-expression. Primary hepatocytes isolated from HFD-challenged mice with curcumin intervention showed increased sensitivity to *ex vivo* FGF21 treatment, associated with elevated expression of genes that encode FGFR1 and KLB [4]. We hence suggest that curcumin intervention attenuate HFD induced FGF21 resistance [4]. Other dietary polyphenols including anthocyanin and resveratrol, as well

as certain other nutraceuticals of plant origin were also shown to regulating hepatic FGF21 production, reported by our team and by others [42, 46–50].

Function of PR may also involve FGF21

In addition to clinical investigations, metabolic beneficial effects of PR have been demonstrated in organisms including rodent species, fruit flies and yeast. The restriction of protein but not carbohydrates was also shown to increase lifespan in fruit flies and certain rodent models. Mechanistic studies have then attributed the beneficial effect of PR and amino acid restriction to several signaling cascades including the mammalian target of rapamycin (mTOR), AMP activated protein kinase (AMPK), and general control nonderepessible 2 (GCN2), as well as autophagy. Several studies conducted by Morrison's team, however, suggested the involvement of FGF21 [51]. Back to 2014, Laeger et al. reported that hepatic FGF21 expression can be induced by PR but not by energy restriction. In human subjects, plasma FGF21 level was shown to be increased dramatically following 28 days on a low protein diet. Furthermore, effects of PR on food intake, energy expenditure, and body weight gain alterations, were observed in wild type mice but not in FGF21 deficient mice [52]. The team then demonstrated that FGF21 is required for both the metabolic and behavioral responses to PR and then made their effort in identifying upstream molecules including GCN2 and activating transcription factor 4 (ATF4) [53]. These molecules, however, are unlikely the direct trans-activators of FGF21. Utilizing the Geometric Framework, a nutritional modeling platform, Solon-Biet and colleagues have concluded that FGF21 is maximally increased under low protein and high carbohydrate intakes, and metabolic beneficial effect of FGF21 are dependent on nutrient context [54]. More recently, Hill et al. in Morrison's team reported that in male mice, PR increased lifespan, reduced frailty, body weight and adiposity, and improved physical performance. In FGF21 knockout mice, metabolic response to PR was virtually lost in early life [5]. In later life, FGF21 knockout mice showed early onset of age-related weight loss, increased frailty, reduced physical performance, associated with shortened life span [5].

What we need to know next?

Studies from several different disciplines are now all pointing to functions of the hepatic hormone FGF21 in mediating metabolic and other beneficial effects of PR as well as dietary polyphenol interventions. It is worth mentioning that we and several other teams have also reported the involvement of FGF21 in mediating functions of the diabetes drug liraglutide and other GLP-1 receptor agonists in T2D mouse models [55–59]. As a "fasting" hormone, we have already learned that FGF21 level rise during fasting for both humans and rodents species [3]. Thus, it is very likely that the hepatic hormone FGF21 also mediates functions of fasting as well as the use of fasting mimetics. These findings will further accelerate clinical investigations on FGF21 as well as FGF19 analogues, including further verifying clinical efficacy of each analogue as well as defining of the spectrum of disorders for each analogue. In the near future, explorations on mechanisms underlying *FGF21* transcription as well as FGF21 signaling sensitization in the liver and elsewhere will also be facilitated. Here, however, I would like to present an emerging view: it is gut microbiome that mediates effect of most dietary interventions, if not all, on FGF21 regulation. Rationales that support this view are as follows. Firstly, we are aware of that bioavailability of dietary polyphenols as well as other plant derived nutraceuticals are extremely low. It is unlikely that *in vivo* hepatic *FGF21* gene transcription is mediated by dietary polyphenols that are absorbed in the gut and then enter the circulation. Secondly, in HFD challenged mice, dietary curcumin or anthocyanin intervention was shown to attenuate HFD-induced FGF21 over-expression, associated with improved FGF21 signaling sensitivity. Such bi-directional effects of dietary polyphenols are likely mediated by mechanisms that involve multiple organs, including the brain or the central nerve system. Thirdly, as we have anticipated, PR was also shown to alter gut microbiome in animal models [60]. Indeed, a recent study by Martin and colleagues showed that hepatic FGF21 adaptive pathway can be triggered by dietary PR while in the absence of gut microbiome, FGF21 adaptive pathway is desensitized in response to dietary PR [61].

As presented in Figure 2, two typical types of dietary interventions, known as dietary polyphenol intervention and dietary PR, can alter gut microbiome, which send signals to the brain and elsewhere by gut-brain axis and yet to be defined gut-peripheral tissue axis that triggers the hepatic FGF21 adaptive pathway via brain-liver axis or other to be defined axis, which links a peripheral tissue (such as adipose tissue) and the liver. FGF21 as an endocrine hormone, exerts its metabolic beneficial effects via targeting multiple target tissues [3]. It is likely that fasting and the use of fasting mimetics may also trigger hepatic FGF21 adaptive pathway, involving alterations on gut microbiome. In addition to gut microbiome *per se*, various

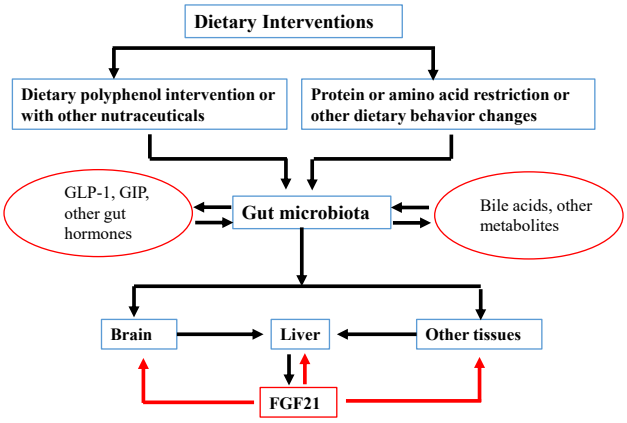

Figure 2: Gut microbiota mediates function of dietary interventions on triggering hepatic Fibroblast Growth Factor 21 adaptive pathway. Dietary interventions, either in the form of protein restriction or the form with dietary polyphenol supplementation will alter gut microbiome. This will trigger a gut/brain axis or gut/another peripheral tissue axis, with the participation of various gut hormones (*i.e.* glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, ghrelin, cholecystokinin and others), bile acids, bacterial products, and other metabolites. This will be followed by the activation of the hepatic fibroblast growth factor 21 adaptive pathway. Metabolic and other beneficial effects of various dietary interventions can be mediated, at least partially, via function of FGF21 on its target organs. FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

gut produced metabolic and other hormones, as well as farnesoid X receptor (FXR) mediated gut bile acid homeostasis, may also participate dietary intervention triggered hepatic FGF21 adaptive pathway for improving metabolic homeostasis. We anticipate seeing more and more breakthroughs in this field in next a few years, which will further facilitate conceptual merge of classical medicine and modern medicine.

Acknowledgement: The author thanks Miss Jia Nuo Feng for proofreading the manuscript.
Research funding: The author would like thank funding support from Canadian Institutes of Health Research (CIHR) and Banting and Best Diabetes Centre (BBDC) in the past decade on conducting our dietary polyphenol intervention and FGF21 related bench work research. Jin's lab is current supported by CIHR on FGF21 studies (PJT159735). Financial support from CIHR, BBDC, University of Toronto and elsewhere for trainees in my lab is also highly appreciated.
Author contributions: The author has accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The author declares the existence of no competing interest.

References

1. Jin T, Weng J. Hepatic functions of GLP-1 and its based drugs: current disputes and perspectives. Am J Physiol Endocrinol Metab 2016;311:E620–7.
2. Tian L, Jin T. The incretin hormone GLP-1 and mechanisms underlying its secretion. J Diabetes 2016;8:753–65.
3. Badakhshi Y, Jin T. Current understanding and controversies on the clinical implications of fibroblast growth factor 21. Crit Rev Clin Lab Sci 2021;58:311–28.
4. Zeng K, Tian L, Patel R, Shao W, Song Z, Liu L, et al. Diet polyphenol curcumin stimulates hepatic Fgf21 production and restores its sensitivity in high-fat-diet-fed male mice. Endocrinology 2017;158:277–92.
5. Hill CM, Albarado DC, Coco LG, Spann RA, Khan MS, Qualls-Creekmore E, et al. FGF21 is required for protein restriction to extend lifespan and improve metabolic health in male mice. Nat Commun 2022;13:1897.
6. Nishimura T, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta 2000;1492:203–6.
7. Hondares E, Iglesias R, Giralt A, Gonzalez FJ, Giralt M, Mampel T, et al. Thermogenic activation induces FGF21 expression and release in brown adipose tissue. J Biol Chem 2011;286:12983–90.
8. Fon Tacer K, Bookout AL, Ding X, Kurosu H, John GB, Wang L, et al. Research resource: comprehensive expression atlas of the fibroblast growth factor system in adult mouse. Mol Endocrinol 2010;24:2050–64.
9. Geller S, Arribat Y, Netzahualcoyotzi C, Lagarrigue S, Carneiro L, Zhang L, et al. Tanycytes regulate lipid homeostasis by sensing free fatty acids and signaling to key hypothalamic neuronal populations via FGF21 secretion. Cell Metabol 2019;30:833–44.e7.
10. Owen BM, Ding X, Morgan DA, Coate KC, Bookout AL, Rahmouni K, et al. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. Cell Metabol 2014;20:670–7.
11. Markan KR, Naber MC, Ameka MK, Anderegg MD, Mangelsdorf DJ, Kliewer SA, et al. Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. Diabetes 2014;63:4057–63.
12. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. J Clin Invest 2005;115:1627–35.
13. Shao W, Jin T. Hepatic hormone FGF21 and its analogues in clinical trials. Chronic Dis Transl Med 2022;8:19–25.
14. Itoh N, Ornitz DM. Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. J Biochem 2011;149:121–30.
15. Oulion S, Bertrand S, Escriva H. Evolution of the FGF gene family. Int J Evol Biol 2012;2012:298147.
16. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov 2009;8:235–53.

17. Kyrou I, Weickert MO, Gharanei S, Randeva HS, Tan BK. Fibroblast growth factors: new insights, new targets in the management of diabetes. Minerva Endocrinol 2017;42:248–70.
18. Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. Nat Rev Endocrinol 2020;16:654–67.
19. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, Flier JS, et al. Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes 2010;59:2781–9.
20. Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metabol 2013;18:333–40.
21. Talukdar S, Zhou Y, Li D, Rossulek M, Dong J, Somayaji V, et al. A long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. Cell Metabol 2016;23:427–40.
22. Kim AM, Somayaji VR, Dong JQ, Rolph TP, Weng Y, Chabot JR, et al. Once-weekly administration of a long-acting fibroblast growth factor 21 analogue modulates lipids, bone turnover markers, blood pressure and body weight differently in obese people with hypertriglyceridaemia and in non-human primates. Diabetes Obes Metabol 2017;19:1762–72.
23. Sanyal A, Charles ED, Neuschwander-Tetri BA, Loomba R, Harrison SA, Abdelmalek MF, et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. Lancet 2019;392:2705–17.
24. Charles ED, Neuschwander-Tetri BA, Pablo Frias J, Kundu S, Luo Y, Tirucherai GS, et al. Pegbelfermin (BMS-986036), PEGylated FGF21, in patients with obesity and type 2 diabetes: results from a randomized phase 2 study. Obesity 2019;27:41–9.
25. Kaufman A, Abuqayyas L, Denney WS, Tillman EJ, Rolph T. AKR-001, an Fc-FGF21 analog, showed sustained pharmacodynamic effects on insulin sensitivity and lipid metabolism in type 2 diabetes patients. Cell Rep Med 2020;1: 100057.
26. DePaoli AM, Zhou M, Kaplan DD, Hunt SC, Adams TD, Learned RM, et al. FGF19 analog as a surgical factor mimetic that contributes to metabolic effects beyond glucose homeostasis. Diabetes 2019; 68:1315–28.
27. Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391:1174–85.
28. Roberts SK, Majeed A. A short report on NGM282/aldafermin for the treatment of nonalcoholic steatohepatitis (NASH). Expert Opin Ther Targets 2021;25:889–95.
29. Baruch A, Wong C, Chinn LW, Vaze A, Sonoda J, Gelzleichter T, et al. Antibody-mediated activation of the FGFR1/Klothobeta complex corrects metabolic dysfunction and alters food preference in obese humans. Proc Natl Acad Sci U S A 2020;117: 28992–9000.
30. Gilroy CA, Capozzi ME, Varanko AK, Tong J, D'Alessio DA, Campbell JE, et al. Sustained release of a GLP-1 and FGF21 dual agonist from an injectable depot protects mice from obesity and hyperglycemia. Sci Adv 2020;6:eaaz9890.
31. Pan Q, Lin S, Li Y, Liu L, Li X, Gao X, et al. A novel GLP-1 and FGF21 dual agonist has therapeutic potential for diabetes and non-alcoholic steatohepatitis. EBioMedicine 2021;63:103202.
32. Fontana L, Cummings NE, Arriola Apelo SI, Neuman JC, Kasza I, Schmidt BA, et al. Decreased consumption of branched-chain amino acids improves metabolic health. Cell Rep 2016;16: 520–30.
33. Treviño-Villarreal JH, Reynolds JS, Bartelt A, Langston PK, MacArthur MR, Arduini A, et al. Dietary protein restriction reduces circulating VLDL triglyceride levels via CREBH-APOA5-dependent and -independent mechanisms. JCI Insight 2018;3:e99470.
34. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metabol 2014;19: 407–17.
35. Solon-Biet SM, McMahon AC, Ballard JWO, Ruohonen K, Wu LE, Cogger VC, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. Cell Metabol 2014;19:418–30.
36. Solon-Biet SM, Walters KA, Simanainen UK, McMahon AC, Ruohonen K, Ballard JW, et al. Macronutrient balance, reproductive function, and lifespan in aging mice. Proc Natl Acad Sci U S A 2015;112:3481–6.
37. Brown-Borg HM, Buffenstein R. Cutting back on the essentials: can manipulating intake of specific amino acids modulate health and lifespan? Ageing Res Rev 2017;39:87–95.
38. Solon-Biet SM, Cogger VC, Pulpitel T, Wahl D, Clark X, Bagley E, et al. Branched chain amino acids impact health and lifespan indirectly via amino acid balance and appetite control. Nat Metab 2019;1:532–45.
39. Yap YW, Rusu PM, Chan AY, Fam BC, Jungmann A, Solon-Biet SM, et al. Restriction of essential amino acids dictates the systemic metabolic response to dietary protein dilution. Nat Commun 2020;11:2894.
40. Marino M, Bo CD, Martini D, Porrini M, Riso P. A review of registered clinical trials on dietary (Poly)Phenols: past efforts and possible future directions. Foods 2020;9:1606.
41. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000;130:2073S–85.
42. Tian L, Ning H, Shao W, Song Z, Badakhshi Y, Ling W, et al. Dietary cyanidin-3-Glucoside attenuates high-fat-diet-induced body-weight gain and impairment of glucose tolerance in mice via effects on the hepatic hormone FGF21. J Nutr 2020;150: 2101–11.
43. Morissette A, Kropp C, Songpadith JP, Junges Moreira R, Costa J, Mariné-Casadó R, et al. Blueberry proanthocyanidins and anthocyanins improve metabolic health through a gut microbiota-dependent mechanism in diet-induced obese mice. Am J Physiol Endocrinol Metab 2020;318:E965–80.
44. Anhê FF, Choi BSY, Dyck JRB, Schertzer JD, Marette A. Host-microbe interplay in the cardiometabolic benefits of dietary polyphenols. Trends Endocrinol Metab 2019;30:384–95.
45. Tian L, Zeng K, Shao W, Yang BB, Fantus IG, Weng J, et al. Short-term curcumin gavage sensitizes insulin signaling in dexamethasone-treated C57BL/6 mice. J Nutr 2015;145: 2300–7.
46. Li Y, Wong K, Giles A, Jiang J, Lee JW, Adams AC, et al. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. Gastroenterology 2014;146:539–49.e7.
47. Cunningham RP, Moore MP, Moore AN, Healy JC, Roberts MD, Rector RS, et al. Curcumin supplementation mitigates NASH

development and progression in female Wistar rats. Physiol Rep 2018;6:e13789.
48. Jin T. Curcumin and dietary polyphenol research: beyond drug discovery. Acta Pharmacol Sin 2018;39:779–86.
49. Ejaz A, Martinez-Guino L, Goldfine AB, Ribas-Aulinas F, De Nigris V, Ribó S, et al. Dietary betaine supplementation increases Fgf21 levels to improve glucose homeostasis and reduce hepatic lipid accumulation in mice. Diabetes 2016;65: 902–12.
50. Zhang Y, Yin R, Lang J, Fu Y, Yang L, Zhao D. Epigallocatechin-3-gallate ameliorates hepatic damages by relieve FGF21 resistance and promotion of FGF21-AMPK pathway in mice fed a high fat diet. Diabetol Metab Syndrome 2022;14:53.
51. Hill CM, Berthoud HR, Münzberg H, Morrison CD. Homeostatic sensing of dietary protein restriction: a case for FGF21. Front Neuroendocrinol 2018;51:125–31.
52. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest 2014;124:3913–22.
53. Laeger T, Albarado DC, Burke SJ, Trosclair L, Hedgepeth JW, Berthoud HR, et al. Metabolic responses to dietary protein restriction require an increase in FGF21 that is delayed by the absence of GCN2. Cell Rep 2016;16:707–16.
54. Solon-Biet SM, Cogger VC, Pulpitel T, Heblinski M, Wahl D, McMahon AC, et al. Defining the nutritional and metabolic context of FGF21 using the Geometric Framework. Cell Metabol 2016;24:555–65.
55. Nonogaki K, Hazama M, Satoh N. Liraglutide suppresses obesity and hyperglycemia associated with increases in hepatic fibroblast growth factor 21 production in KKAy mice. BioMed Res Int 2014;2014:751930.
56. Liu J, Yang K, Yang J, Xiao W, Le Y, Yu F, et al. Liver-derived fibroblast growth factor 21 mediates effects of glucagon-like peptide-1 in attenuating hepatic glucose output. EBioMedicine 2019;41:73–84.
57. Yang M, Zhang L, Wang C, Liu H, Boden G, Yang G, et al. Liraglutide increases FGF-21 activity and insulin sensitivity in high fat diet and adiponectin knockdown induced insulin resistance. PLoS One 2012;7:e48392.
58. Lee J, Hong SW, Park SE, Rhee EJ, Park CY, Oh KW, et al. Exendin-4 regulates lipid metabolism and fibroblast growth factor 21 in hepatic steatosis. Metabolism 2014;63:1041–8.
59. Liu D, Pang J, Shao W, Gu J, Zeng Y, He HH, et al. Hepatic fibroblast growth factor 21 is involved in mediating functions of liraglutide in mice with dietary challenge. Hepatology 2021;74: 2154–69.
60. Fan P, Liu P, Song P, Chen X, Ma X. Moderate dietary protein restriction alters the composition of gut microbiota and improves ileal barrier function in adult pig model. Sci Rep 2017; 7:43412.
61. Martin A, Ecklu-Mensah G, Ha CWY, Hendrick G, Layman DK, Gilbert J, et al. Gut microbiota mediate the FGF21 adaptive stress response to chronic dietary protein-restriction in mice. Nat Commun 2021;12:3838.