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FGF21 maybe have a Protective Role against Obesity in Cases of High-fat Diets, in Adult Mice, Malnourished during Their Embryonic Life

Athanasios Niarchos[1,2*]

[1]*Department of Medicine, University of Patras, GR 26504, Patras, Greece.*
[2]*Department of Pharmacy, University of Patras, GR 26504, Patras, Greece.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Short Communication

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ABSTRACT

Aims: To investigate if there is a possible protective role of FGF21 in malnourished adult mice which have been exposed to stress during their intrauterine life.
Place and Duration of Study: University of Patras, Department of Medicine, between September 2015 and August 2016.
Methodology: Five wild type and 5 FGF21 knockout mice, which have been subjected 50% caloric limitation during their embryonic life, were fed with high fat diet. As control 3 other sets of mice groups were used. One set was composed of 5 WT and 5 FGF21 KO mice, which had a normal embryonic life and fed with high fat diet, another set of 4 wild type and 4 knockout mice, with normal intrauterine life, were fed with chow diet, and another set of 4 wild type and 4 knockout mice which had subjected caloric limitation during their embryonic life, also fed with chow diet. All mice were male, 6-weeks old, when the diet (chow or high fat) was started and lasted for 12 weeks. Every week the mice were weighted, and the means of the weights and the weight gaining rates were calculated for each mice group.
Results: Although none of the differences was significant, the weight gaining rates of the high fat fed mice that had subjected 50% caloric limitation during their embryonic life presented higher than and the mice which had normal embryonic life. Furthermore, knockout mice appeared to have

**Corresponding author: E-mail: a.niarchos@gmail.com;*

higher weight gaining rates than the wild type. The mice which received chow diet for the same period of their lives (6-18 week) appeared very tiny weight gaining rates and no differences appeared.

Conclusion: FGF21 maybe plays a protective role against excessive weight gain in adult mice, in cases of high-fat diets, especially in mice malnourished during their embryonic life.

Keywords: FGF21; weight gain; high fat diet; malnourished; embryonic life.

ABBREVIATIONS

FGF21 : Fibroblast Growth Factor 21
WT : Wild Type
KO : Knock Out
HF : High Fat

1. INTRODUCTION

Fibroblast Growth Factor 21 (FGF21), the 21st discovered member of the superfamily of FGFs, first reported in 2000 [1], is widely recognized as an endocrine metabolic regulator and a stress hormone. The circulated levels of FGF21 under ideal conditions are conserved steadily by liver secretion [2]. However, under stressful conditions, the FGF21 is also secreted by several other tissue types such as adipose and muscle and its levels rise [3]. Malnutrition [4], exercise [5] and cold exposure [6] have been shown to increase the circulated levels of FGF21. Generally, FGF21 acts through stimulating ketogenesis [7], lipid catabolism, gluconeogenesis and glucose uptake [8].

In humans and animals, intrauterine life has been shown to have consequent affects on the adult life [9-11] In this study, in order to investigate if there is a possible protective role of FGF21 in malnourished adult mice which have been exposed to stress during their intrauterine life, wild type (WT) and FGF21 knock out (KO) adult mice that had been exposed to undernutrition during their embryonic life, were subjected to high fat diet and their weights were compared with those of other adult WT and FGF21 KO mice, which also fed with high fat diet but had a normal embryonic life.

2. MATERIALS AND METHODS

Female C57BL/6J FGF21 $^{(+/-)}$ mice, were mated with same strain and same genotype male mice and were subjected to 50% caloric limitation during gestation days: 8-15 (those gestation days, pregnant mice got the 50% of the calories that would be ate ad libitum). The offsprings where weaned at the 21th day and fed chow diet ad libitum until the sixth week, when 5 WT (Group I) and 5 FGF21 KO (Group II) male mice were exposed to ad libitum high fat (HF) diet (60% fat, Open Source Diets, #D12450J) for the next 12 weeks. Every week the mice were weighted along with 5 WT (Group III) and 5 FGF21 KO (Group IV) male mice which they got the same ad libitum HF diet, but they had had a normal intrauterine life. Along with the HF diet fed mice, another set of 4 WT (Group V) and 4 FGF21 KO (Group VI) mice which had been subjected, and also 4 WT (Group VII) and 4 FGF21 KO (Group VIII) mice which had not been subjected caloric limitation during their embryonic life, were getting ad libitum chow diet for the same period of their life (6-18 week of life). For every weekly measurement the means of the weights and the weight gaining rates were calculated for each mice group. The means of the weights and the weight gaining rates values were analyzed using Anova test for all the mice groups and t-test to compare the means of the 2 groups which presented the maximum differences.

3. RESULTS

The weights of the mice subjected the HF diet are presented at Fig. 1. At the beginning of the HF diet, WT and FGF21 KO mice that had a normal intrauterine life (Groups III & IV respectively) generally were appeared to be heavier than the mice, which they had been subjected the caloric limitation during their embryonic life (Groups I & II). Furthermore, the WT mice tended to be heavier than the FGF21 KO ones. At the end of the 12-weeks HF diet, the FGF21 KO mice seem to have similar weights with the WT ones and the differences between those mice suffered caloric limitation as embryos and the mice with normal intrauterine life tended to be minor. Although, no difference between the mice groups was determined to be significant.

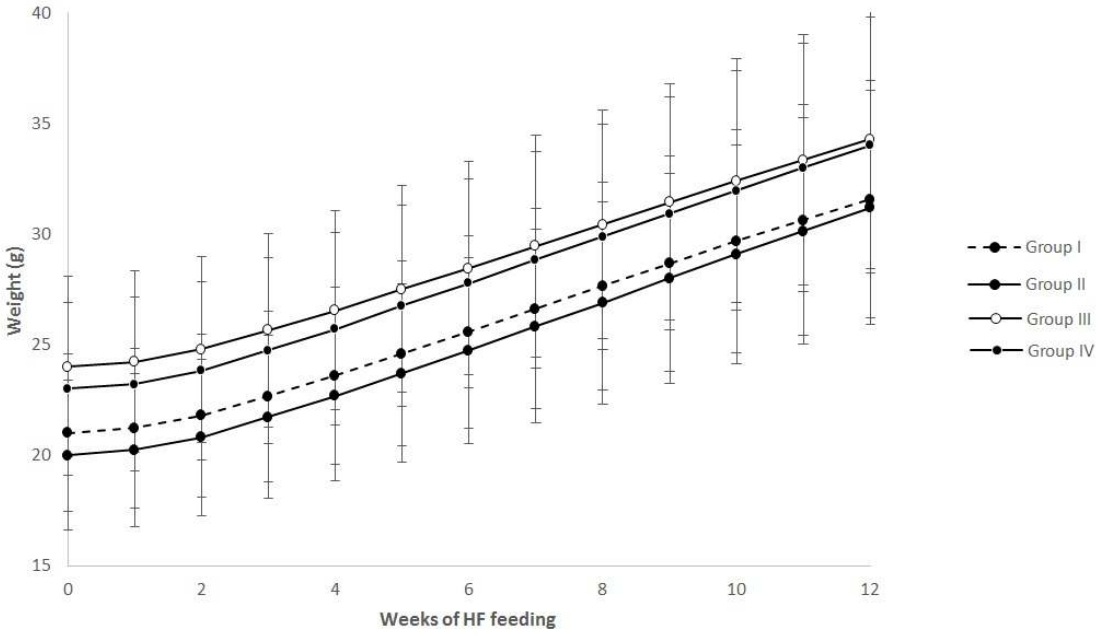

Fig. 1. The weights of the mice during the 12-weeks ad libido high fat diet

Groups I & II: WT and KO mice which they had been subjected the caloric limitation during their embryonic life.
Groups III & IV: WT and KO mice that had a normal intrauterine life
No difference was significant (P > 0.05)
Mean values ± Standard Deviation of 5 mice

The weight gaining rates of the mice subjected the ad libido high fat diet are presented at Fig. 2. The weight gaining rates of the WT and FGF21 KO mice which subjected the caloric limitation during their embryonic life (Groups I & II respectively) were presented generally higher than the WT and FGF21 KO mice that had a normal intrauterine life (Groups III & IV respectively). Furthermore, FGF21 KO mice tended to have higher weight gaining rates than the WT mice. The FGF21 KO mice which suffered caloric limitation as embryos appeared to have the highest weight gaining rate. Again, no difference between the mice groups was determined to be significant.

The weights of the mice subjected ad libido chow diet are presented at Fig. 3. WT and FGF21 KO mice that had a normal intrauterine life (Groups VII & VIII respectively) generally were appeared to be heavier than the respective mice, which they had been subjected the caloric limitation during their embryonic life (Groups V & VI). Furthermore, the WT mice tended to be heavier than the FGF21 KO ones. No difference between the mice groups was determined to be significant.

The weight gaining rates of the mice that have ad libido chow diet, presented at Fig. 4. Very low weight gaining rates were presented by the mice irrespective of the group, and no differences between the mice groups were presented.

4. DISCUSSION

The differences presented among the weight gaining rates of the different mice groups at Fig. 2 and in a smaller extend at the beginning and at the end of the 12-week HF diet presented at Fig. 1, although not statistically significant, implies a possible protective role of FGF21 against obesity in case of high fat diet, especially for mice exposed to malnutrition during their embryonic life. At Fig. 2, Group II (FGF21 KO mice that had suffered caloric restriction during intrauterine life) appeared to have the highest weight gaining rates among the 4 mice groups (Groups I to IV). Figs. 3 and 4 shows that mice irrespectively of their genotype (WT/KO) or their embryonic life (typical/caloric restricted) when fed with chow diet didn't appear differences in weight gaining or in weight gaining rates as those presented with the HF diet. Although in this study none of the recorded difference in weights or weight gaining rates was determined as

statistically significant (due to the limited available mice subjects and the weight variations inside the mice groups), a future study, free of these problems, could prove a protective role of FGF21 against obesity in the case of HF diet, especially in the case where a background of intrauterine malnutrition exists.

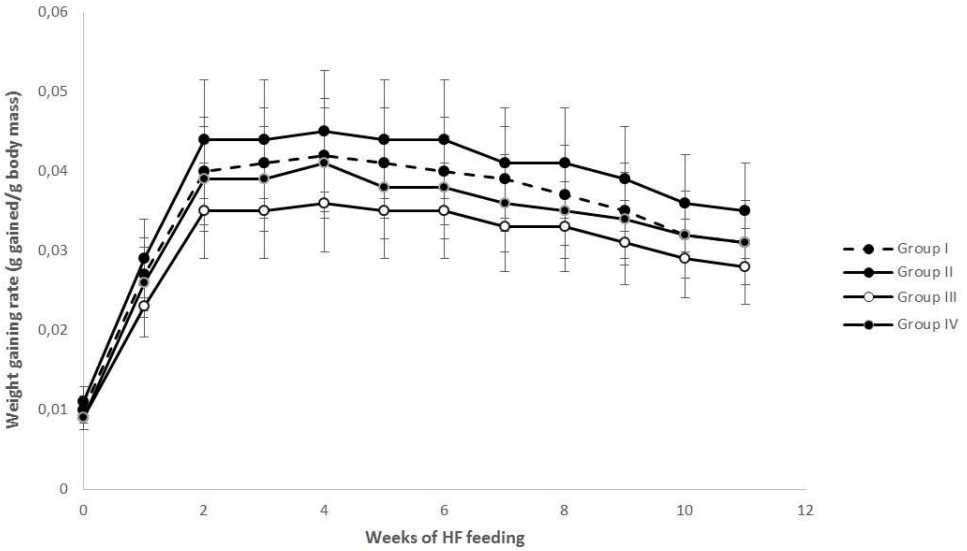

Fig. 2. The weight gaining rates of the mice during the 12-weeks ad libido high fat diet

Groups I & II: WT and KO mice which they had been subjected the caloric limitation during their embryonic life.
Groups III & IV: WT and KO mice that had a normal intrauterine life.
No difference was significant (P > 0.05)
Mean values ± Standard Deviation of 5 mice

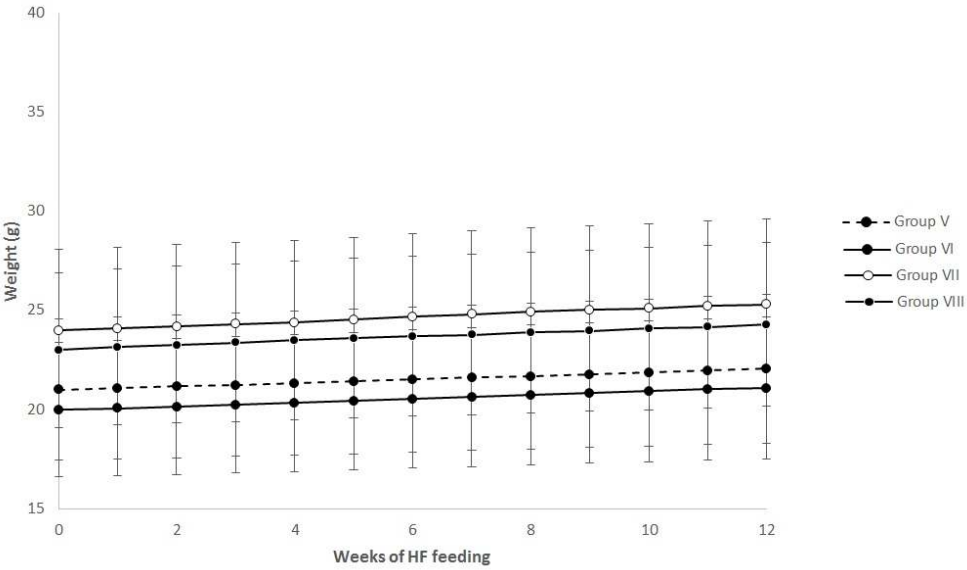

Fig. 3. The weights of the mice during 12-weeks ad libido chow diet

Groups V & VI: WT and KO mice which they had been subjected the caloric limitation during their embryonic life
Groups VII & VIII: WT and KO mice that had a normal intrauterine life
No difference was significant (P > 0.05)
Mean values ± Standard Deviation of 4 mice

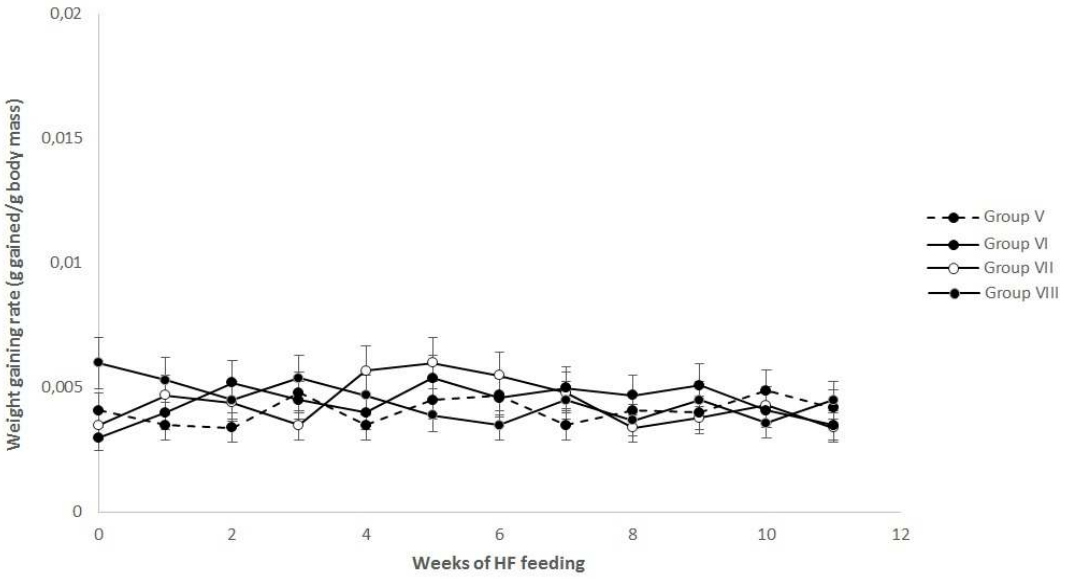

Fig. 4. The weight gaining rates of the mice during the 12-weeks ad libido chow diet
Groups V & VI: WT and KO mice which they had been subjected the caloric limitation during their embryonic life.
Groups VII & VIII: WT and KO mice that had a normal intrauterine life.
No difference was significant (P > 0.05)
Mean values ± Standard Deviation of 5 mice

5. CONCLUSION

FGF21 may play a protective role against excessive weight gain in adult mice, in cases of high-fat diets, in mice malnourished during their embryonic life.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Nishimura T, Nakatake Y, Konishi M, Itoh N, et al. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. Biochim Biophys Acta. 2000;1492(1): 203-6.
2. 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(12):4057-4063. Biochim Biophys Acta. 2000;1492(1):203-206.
3. 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(10): 2050-2064.
4. Kubicky RA, Wu S, Kharitonenkov A, De Luca F. Role of fibroblast growth factor 21 (FGF21) in undernutrition-related attenuation of growth in mice. Endocrinology. 2012;153(5):2287-2295.
5. Kim KH, Kim SH, Min YK, Yang HM, Lee JB, Lee MS. Acute exercise induces FGF21 expression in mice and in healthy humans. PLoS One. 2013;8(5):e63517.

6. Chartoumpekis DV, Habeos IG, Ziros PG, Psyrogiannis AI, Kyriazopoulou VE, Papavassiliou AG. Brown adipose tissue responds to cold and adrenergic stimulation by induction of FGF21. Mol Med. 2011;17(7-8):736-740.
7. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, 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(6):426-437.
8. Potthoff MJ, Inagaki T, Satapati S, Ding X, He T, Goetz R, et al. FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. Proc Natl Acad Sci USA. 2009;106(26):10853-10858.
9. Khandaker GM, Dibben CR, Jones PB. Does maternal body mass index during pregnancy influence risk of schizophrenia in the adult offspring? Obes Rev. 2012; 13(6):518-27.
10. Ojha S, Robinson L, Symonds ME, Budge H. Suboptimal maternal nutrition affects offspring health in adult life. Early Hum Dev. 2013;89(11):909-13.
11. Le Clair C, Abbi T, Sandhu H, Tappia PS. Impact of maternal undernutrition on diabetes and cardiovascular disease risk in adult offspring. Can J Physiol Pharmacol. 2009;87(3):161-79.

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