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María Mercedes Pardo-Tendero [1], Vannina G Marrachelli [2], Jose Manuel Morales [1], Ana Díaz [3], María Martín-Grau [4], Pilar Casanova [1], Daniel Monleón [1]

1. Universidad de Valencia - Departamento de Patología, Valencia, España
2. Universidad de Valencia - Departamento de Fisiología, Valencia, España
3. Universidad de Valencia - UCIM, Valencia, España
4. Centro de investigación Príncipe Felipe, Valencia, España

Correspondencia: María Mercedes Pardo-Tendero, Departamento de Patología – Facultad de Medicina (Universidad de Valencia)
email: m.mercedes.pardo@uv.es

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Abstract

The study of the metabolism involved in the development of obesity and the research of biomarkers for early detection could be essential in patients' management. Therefore, this work aims to identify early biomarkers of obesity, using metabolomics by nuclear magnetic resonance (NMR). Therefore, a study was conducted on 16-week-old male Wistar rats, in which animals were divided into four groups based on diet and housing environment. Weight measurements were taken, and a metabolomic analysis was performed on serum and fecal samples.

The results showed that the high-fat and high-sucrose diet increased body weight and/or abdominal circumference, compared to the group that had received a standard diet. The metabolomic profile showed differences in the metabolism of the high-fat diet groups that mainly affected co-metabolites involved in the host-microbiota co-metabolism. Thus, we conclude that co-metabolism of the gut microbiota appears to modulate the early stages of obesity development in the host organism, and NMR metabolomics could provide a non-invasive way for early detection of these changes.

Keywords: metabolomic, NMR, obesity

Introduction

Obesity is included in a pattern of metabolic disorders which can involve hypertension, dyslipidemia, type 2 diabetes and cardiovascular disease. It is considered a comorbidities-related disease, so these cardiometabolic risk factors can coexist simultaneously in the individual increasing the risk of developing the disorders associated, with a high risk of mortality in the world (1). Moreover, western diets have been related to the high prevalence and development of these cardiometabolic diseases (2).

Consequently, finding early biomarkers of the progression of the disease could be crucial for the early management of these metabolic diseases, evidencing the necessity to investigate the disease's development with new approaches (3). As a result, the study of metabolic pathways involved seems essential (4), so metabolomics could represent a good approach for the early detection of these pathological changes (5). This methodology could represent an innovative approach due to metabolomics is the quantitative measure of metabolic responses of organisms to pathophysiological stimulus or genetic alterations, and it can be performed in a non-invasive way by NMR.

The objective of this study is to identify early potential biomarkers for obesity development detection with an approach methodology based on metabolomics by high-resolution nuclear magnetic resonance spectroscopy (^{1}H-NMR) in non-invasive biological samples.

Materials and Methods

In this study, thirty-two male Wistar rats, sixteen-week-old weeks old were fed with a high-fat and sucrose diet (HFD) for twelve weeks to induce metabolic disorders, randomly divided into four study groups based on diet and housing conditions: male standard chow diet at conventional housing (M-CTL.C, n=8), male high-fat and sucrose diet at conventional housing (M-HFD.C, n=8), male standard chow diet at specific pathogen-free (SPF) housing (M-CTL.S, n=8), and male high-fat and sucrose diet at SPF housing (M-HFD.S, n=8). Animal experimentation was approved by the Ethics Committee of Animal Experimentation (CEBA) of the University of Valencia (A1405675789374).

The pathophysiological characterization of the disease in these animals was measured by several parameters including body weight, abdominal perimeter, BMI and diet intake. Furthermore, ^{1}H-NMR was used for the determination of the metabolomic profiling in blood and fecal samples. Metabolomics profiling of rat samples was carried out using a Bruker Advance 600 spectrometer. A total study of 64 samples with serum (n=32) and fecal samples (n=32) was conducted to identify metabolomic patterns in the spectra obtained from NMR. All spectra were processed to obtain the data and analysed by Matlab to explore the chemical shift regions.

Results

HFD produced alterations in the physiological parameters of male rats in twelve weeks. The alterations included an increase in body weight with significant differences in conventional housing conditions, followed by a significant increase in abdominal perimeter in both housing groups with a decrease in diet intake. These alterations showed the development of obesity in adult male rats (table 1).

	M-CTL.C (n=8)	**M-HFD.C (n=8)**	**M-CTL.S (n=8)**	**M-HFD.S (n=8)**
Body weight (g)	633,13 ± 56,56	**736,25 ± 93,37 ***	651,63 ± 54,74	707,63 ± 64,73
Diet intake (g)	3,80 ± 0,39	**2,80 ± 0,32 *** **	4,01 ± 0,37	**3,28 ± 0,29 ###**
Abdominal perimeter (cm)	23,44 ± 1,08	**26,19 ± 1,65 ****	24,25 ± 0,85	**26,00 ± 1,44 #**
BMI	8,16 ± 0,55	8,57 ± 0,49	9,22 ± 0,43	9,60 ± 0,51

Values are expressed as means ± standard deviations.
* pvalue<0.05 M-CTL.C vs M-HFD.C; ** pvalue<0.01 M-CTL.C vs M-HFD.C; *** pvalue<0.001 M-CTL.C vs M-HFD.C; # pvalue<0.05 M-CTL.S vs M-HFD.S; ## pvalue<0.01 M-CTL.S vs M-HFD.S; ### pvalue<0.001 M-CTL.S vs M-HFD.S; BMI: Body Mass Index
M-CTL.C (male standard chow diet at conventional housing), M-HFD.C (male high-fat and sucrose diet at conventional housing), M-CTL.S (male standard chow diet at SPF housing), M-HFD.S (male high-fat and sucrose diet at SPF housing).

Table 1. Clinical parameters in Wistar male rats under different diet and housing conditions

Also, a metabolomic study was performed through the analysis of NMR spectra. This analysis allowed us to observe metabolic differences between groups based on the metabolome in each individual, focusing on the groups' distribution by partial least squares discriminate analysis (PLS-DA). The metabolomic profile showed differences in the metabolism of HFD groups, that affected metabolites involved in different metabolic pathways including host-microbiota co-metabolites, with principal dysregulations in acetate levels, mainly in fecal samples (figure 1).

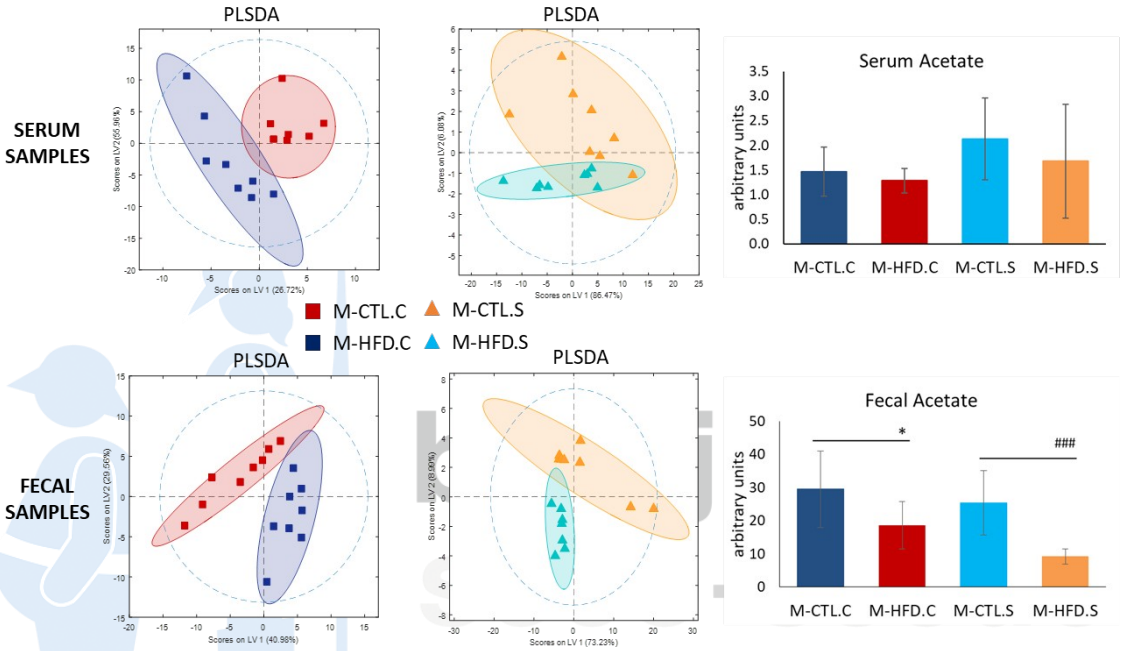

Figure 1: PLSDA of serum and fecal NMR spectra from male rats in the control group (blue square- M-CTL.C) and HFD group (red square- M-HFD.C) at conventional housing, and male rats in the control group (turquoise triangle- M-CTL.S) and HFD group (orange triangle- M-HFD.S) at SPF housing, both groups at 12 weeks of diet. Relative levels of acetate metabolite in serum and fecal samples in rats with control and high-fat and sucrose diet. Values are expressed as means ± standard deviations. * pvalue<0.05 M-CTL.C vs M-HFD.C; ### pvalue<0.001 M-CTL.S vs M-HFD.S

Discussion

As expected, our results indicate physiological alterations which were produced in male Wistar rats under a high-fat and sucrose diet. The significant increase in body weight and abdominal perimeter in HFD groups at both housing groups, even with a lower diet intake, highlights the effect of the diet on the rats' physiology (6). Moreover, some changes were observed in both animal maintenance conditions,

although SPF housing is designed to provide a controlled environment with a reduction in the exposure of rats to specific pathogens (7, 8).

In addition, the study of the metabolome of serum and fecal samples elucidated metabolic dysregulations from the high-fat diet groups mainly in fecal samples. In contrast to blood samples, the metabolomic shift in acetate levels revealed a decreasing tendency without statistical differences between diet groups after twelve weeks of high-fat and sucrose diet. This disruption in acetate levels was more evident in fecal samples, allowing us to identify this metabolic compound as a potential metabolomic biomarker of obesity development for further investigations.

The metabolic shifts detected in acetate as part of short-chain fatty acids (SCFA) are associated with host-microbiota co-metabolism when rats were subjected to a high-fat and sucrose diet. SCFAs are known to play a key role in preserving gut integrity, modulating immune responses, and influencing metabolic processes (9, 10). Therefore, a decrease in these metabolic compounds could probably lead to increased vulnerability to developing diseases and metabolic disorders.

The intricate complex of metabolic interactions underscores the importance of considering the influence of general metabolism and host-microbiota co-metabolism (11, 12) when interpreting the effects of dietary interventions in animal models. This metabolic influence provides valuable insights into the potential mechanisms underlying diet-induced physiological changes.

Conclusion

The study highlights variations in host-microbiota co-metabolism which may influence the development of metabolic disorders related to obesity, providing valuable insights by metabolomics. Further research could advance our understanding and make clear the need to fully understand the implications of these interactions for disease prevention and treatment strategies.

Finally, host-microbiota co-metabolism seems to be involved in the first stages of development of obesity in the host organism and metabolomics by NMR can provide early potential biomarkers in a non-invasive way for early detection.

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References

1. Shah NS, Lloyd-Jones D, Kandula NR, et al. Adverse Trends in Premature Cardiometabolic Mortality in the United States, 1999 to 2018. Journal of the American Heart Association. 2020; 9(23):e018213.

2. Stanhope KL, Goran MI, Bosy-Westphal A, et al. Pathways and mechanisms linking dietary components to cardiometabolic disease: thinking beyond calories. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2018; 19(9):1205-35.

3. Olivier M, Asmis R, Hawkins GA, et al. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. Int J Mol Sci. 2019 Sep 26; 20(19):4781.

4. Tahir UA, Gerszten RE. Omics and Cardiometabolic Disease Risk Prediction. Annu Rev Med. 2020 Jan 27; 71:163-75.

5. Ji Y, Luo K, Zhang JM, Ni P, Xiong W, Luo X, Xu G, Liu H, Zeng Z. Obese rats intervened with Rhizoma coptidis revealed differential gene expression and microbiota by serum metabolomics. BMC Complement Med Ther. 2021 Aug 11; 21(1):208

6. An Y, Li Y, Wang X, Chen Z, et al. Cordycepin reduces weight through regulating gut microbiota in high-fat diet-induced obese rats. Lipids in health and disease. 2018; 17(1):276.

7. Sbierski-Kind J, Kath J, Brachs S, et al. Distinct Housing Conditions Reveal a Major Impact of Adaptive Immunity on the Course of Obesity-Induced Type 2 Diabetes. Frontiers in immunology. 2018; 9:1069.

8. Kaiser T, Nalluri H, Zhu Z, Staley C. Donor Microbiota Composition and Housing Affect Recapitulation of Obese Phenotypes in a Human Microbiota-Associated Murine Model. Front Cell Infect Microbiol. 2021 Feb 22; 11:614218

9. Tan J, McKenzie C, Potamitis M, et al. Chapter Three - The Role of Short-Chain Fatty Acids in Health and Disease. Adv Immunol. 2014; 121:91-119.

10. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2016; 165(6):1332-45.

11. Hills-Ronald D.Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut Microbiome: Profound Implications for Diet and Disease. Nutrients. 2019; 11(7):1613.

12. Ussar S, Griffin NW, Bezy O, et al. Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome. Cell metabolism. 2015; 22(3):516-30.