Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
2024; Vol 13: Issue 3 Open Access

# The Function Of The Epigenome And Microbiome In Controlling The Progression Of Endocrine-Mediated Inflammatory In Obesity Due To Diets

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Cite this paper as: Zhang Jiawei, Nurul Azmir Bin Amir Hashim (2024), The Function Of The Epigenome And Microbiome In Controlling The Progression Of Endocrine-Mediated Inflammatory In Obesity Due To Diets. *Frontiers in Health Informatics*, *13(8) 4937-4949*

**ABSTRACT**

The role of microbiomes, also known as epigenomes, in metabolic health and inflammation in diet-induced obesity (DIO) has recently been shown by new research. This work explores the interaction between DIO, the epigenomic landscape, and the makeup of the microorganisms in the digestive tract within the setting of endocannabinoid-mediated inflammatory control in a mouse model. Researchers were able to examine the effects of a high-fat diet (HFD) by making C57BL/6J mice gain weight and then monitoring their progress. Determining if there were alterations in metabolic parameters or inflammatory indicators was the primary objective. Epigenetic profiling and genome sequencing allowed researchers to find obesity-related changes in DNA methylation patterns. The mutations were more pronounced in genes involved in inflammation and lipid metabolism. At the same time, researchers found that the HFD was associated with substantial changes in the diversity and composition of gut microbiota when they used 16S rRNA sequencing. Specifically, researchers found more microbial taxa that promote inflammation, which is linked to higher amounts of endogenous cannabinoids. To identify the pathways, scientists used pharmacological treatment to alter endocannabinoid signaling and then studied the resulting metabolic and inflammatory effects. Inflammation in DIO is influenced by both the microbiota and the epigenome, as previously shown. Then, this influences the signaling of endogenous cannabinoids. While further study is required to clarify the precise processes at play and their relevance to obesity prevention and treatment, the present study does draw attention to the intricate relationship between the microbiome, nutrition, and epigenetic pathways as they pertain to metabolic health, as well as the possibility of using these pathways as therapeutic targets for the inflammation that accompanies obesity.

**Keywords:** *Environmental factors, changes in the microbiome and epigenome, the endocannabinoid system, and inflammation all have a role in the development of obesity.*

## 1. INTRODUCTION

One of the main reasons for the increasing prevalence of chronic diseases and metabolic disorders is diet-induced obesity (Zhang & Choudhury, 2021). When people eat more calories than they burn, a condition known as obesity develops. Poor dietary choices can make this condition worse. The microbiome and the epigenome are two major biological

systems that have recently been shown to impact diet-induced obesity. These systems are essential for regulating inflammation by altering the endocannabinoid system. Although the

genetic code remains unchanged, the epigenome may regulate gene expression by modifying DNA and histone proteins chemically. Possible environmental factors that contribute to these changes include people's dietary habits. Obesity-related disorders may be worsened by dietary changes that influence inflammatory pathways. An example would be how a high-fat diet alters the methylation landscape, which in turn impacts genes linked to metabolism and inflammation. The gut microbiome is the complex microbial population that lives in the intestines and plays a key role in metabolic wellness. Making changes to one's diet may have repercussions on one's microbiome's composition and function by influencing energy balance and chronic inflammation. The endocannabinoid system is known to regulate inflammation, metabolism, and hunger, among several other physiological activities. Potentially impacted by the microbiota is this process. Extending the current knowledge of obesity and its associated illnesses might be achieved by investigating the impact of diet-induced obesity on the microbiome, particularly the epigenome, and how these elements impact the regulation of inflammation by endocannabinoids. Novel approaches to reducing obesity-related inflammation and improving metabolic health may emerge from this multimodal strategy (Squillaro et al., 2020).

## 2. BACKGROUND OF THE STUDY

The way scientists study diet-induced obesity and its mechanisms has changed dramatically during the last several decades (Sadashiv et al., 2021). A long time ago, the conventional wisdom held that the primary cause of obesity was consuming more calories than the body burned. A complex interaction of biochemical, environmental, and genetic factors contributes to obesity, according to recent studies. When scientists began to question if factors other than DNA may affect gene expression, such as food, in the early 2000s, the area of epigenetics was born. Epigenetic research has demonstrated that environmental factors, such as food, may modify genes via processes including DNA methylation and histone modification. According to (Meruvu et al., 2021), these changes may affect inflammatory pathways, which in turn may worsen metabolic illnesses associated with obesity. Meanwhile, new data from microbiome investigations has shown that gut bacteria play a vital role in determining health. Digestive health, metabolic rate, and immune system function are all profoundly affected by the billions of microorganisms that make up the human microbiome. It was generally established in the 2010s that changes in food may affect the microbiome's makeup and function, which in turn affects obesity and systemic inflammation. Studies have shown that metabolic dysregulation, inflammation, and an imbalanced microbiome may all contribute to the development of obesity. The anandamide receptor-mediated endogenous cannabinoid system (ENdocannabinoid system) controls several physiological functions, including inflammation and metabolism. Dietary and microbial alterations may alter endocannabinoid profiles, which affects inflammatory responses, energy homeostasis, and hunger control, according to the research. The intersection of epigenetics, microbiome research, and endocannabinoid regulation holds great promise. New ways to prevent and cure obesity and related disorders may emerge from research into the ways these systems are affected by diet-induced obesity and how they collaborate to control inflammation (Ma & Kang, 2019).

## 3. PURPOSE OF THE RESEARCH

To understand diet-induced obesity and the role of the microbiome in regulating inflammation via endocannabinoids, it is crucial to investigate the complex interaction between the endocannabinoid system, the gut microbiota, and the epigenome. This study aims to investigate the mechanisms by which these systems influence inflammation, a critical aspect of obesity-related metabolic issues. The intricate network of relationships between nutrition, genes, microorganisms, and endocannabinoid signaling is a mystery to researchers, but understanding it might lead to new treatments for diet-induced obesity, such as improved metabolic health and inflammation management. The fundamental motivation for this study is the need to address knowledge gaps on the role of endocannabinoid signaling in inflammatory management, the effects of diet-induced obesity on microbiota composition changes, and epigenetic modifications. This data could pave the path for the development of personalized treatments for inflammatory illnesses linked to obesity.

## 4. LITERATURE REVIEW:

The relationship between diet-induced obesity (DIO), metabolic diseases, and inflammation makes it one of the biggest issues in public health today (Landrier et al., 2019). Studies into the functions of the microbiome, epigenome, and endocannabinoid signaling have been stimulated by the complex interplay between inflammation, obesity, and food. Endogenous cannabinoids are a class of lipid-based neurotransmitters that modulate inflammation and metabolic activity; they are thus crucial in the obesity setting. The complex relationship between the endocannabinoid system (ECS), microbiota, and the epigenome is becoming more and more linked to diet-induced obesity (DIO), a prominent public health concern. Components of the diet and inflammation linked to obesity may alter the epigenome, a set of changes in gene expression that are passed down through generations but do not change the DNA sequences themselves. Circuits connected to inflammation and metabolic imbalance may be exacerbated by these changes. The gut microbiota is a powerful regulator of host immune responses and metabolism. Dysbiosis, a prevalent complication of DIO, may influence the ECS, a network of lipid signaling molecules that controls inflammation, appetite, and overall energy balance. Through their interactions with immune cells and cytokine signaling, the bioactive lipids found within this system known as endocannabinoids regulate inflammatory processes. New evidence reveals that changes in the microbiome and epigenome brought about by dietary changes might impact the ECS, which in turn can increase inflammation and metabolic diseases. Dietary therapies and microbiota modification are two potential therapeutic targets for reducing the inflammatory effects of obesity, and a better understanding of this complex interaction may provide light on these issues (Gammone & D'Orazio, 2021).

## 5. RESEARCH QUESTIONS

- What is the impact of lack of sleep on the regulation of inflammation?

## 6. RESEARCH METHODOLOGY:

This study's research was carried out using laboratory procedures. The experiment was conducted using a model animal known as a mouse.

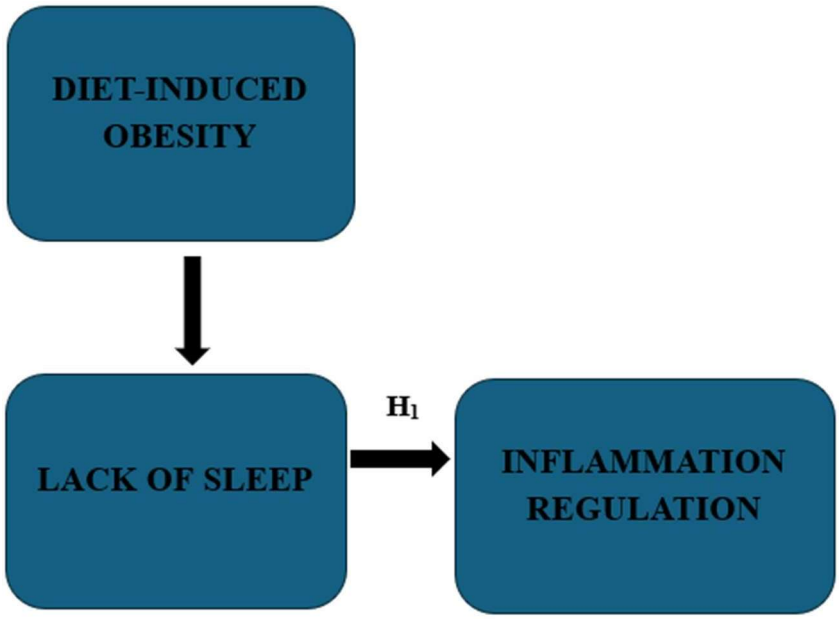
### 6.1 Research design:

It is unclear if the endocannabinoid system experiences changes in fat-fed obese mice, even though this system is critical for the processing of pain signals and emotions. Using fat mice as a model, this study will examine their nociceptive response to learn about the effects of dietary modifications on the endocannabinoid system. The purpose of this project is to explore the effects of genetic and pharmacological alteration of the gut microbiota and cannabinoid receptors CB1 and CB2 on inflammation and metabolic control in a diet-induced obesity mice model. To further evaluate the CB1 antagonist, obese mice were also used. Researchers gained a better understanding of how HFD affects leukocyte infiltration in the cecal-colonic lamina propria by investigating CB1 and CB2. It is plausible to infer that alterations in the gut microbiota mediated by the ECS contribute to the obesity phenotype, given that inhibiting cannabinoid 1 (CB1) reduces intestinal inflammation. Researchers were employing 16S rRNA gene sequencing to look at microbiota profiles to find out whether CB1-/- or CB2-/-mice were resistant to developing intestinal dysbiosis caused by a high-fat diet.

### 6.2 Mice Model

The University Laboratory provided the male C57Bl/6J mice used in this investigation. The results show that adult mice were solely fed a 10% low-fat diet for 12 weeks or a 60% kcal HFD for 12 weeks. Different diets were introduced to the mice between the ages of six and eight weeks. Animal facilities at the medical school at the University of South Carolina produced CB1-/- and CB2-/-mice. According to the treatment group, every single experiment employed cages with three to five mice each, except for the co-housing study. The study's mice were sourced from a wide range of litters and environments. It was common practice to keep mice in cages because of their hostile behavior. For the DIO intervention experiments, obese mice were split according to their average DEXA fat mass after 12 weeks of an unhealthy diet. Administered orally in a 0.1% Tween 80 solution, the treatment group received 10 mg/kg of AM251. Each of the other experimental groups received valves marked "Veh" from them. Researchers in the PA feeding program keep tabs on the Pair-fed group to make sure they're getting the same amount of HFD every day. The experiment concluded with the mice being induced to sleep by inhaling an excessive amount of isoflurane.

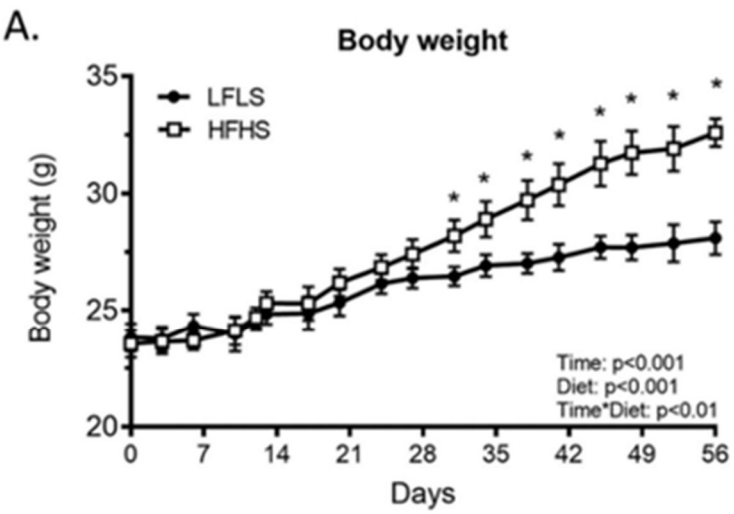
## 7. CONCEPTUAL FRAMEWORK

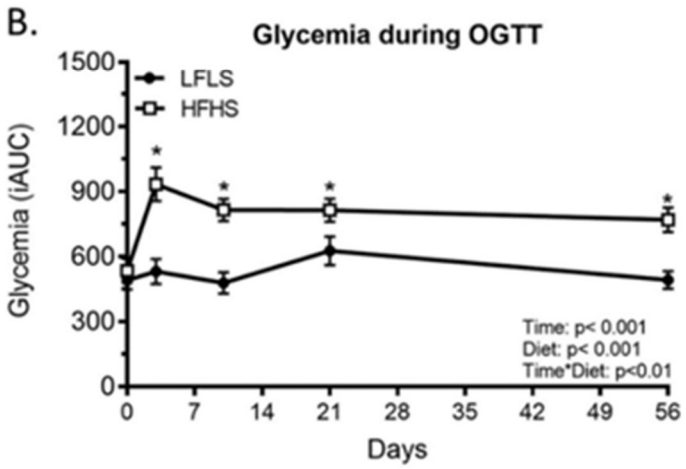


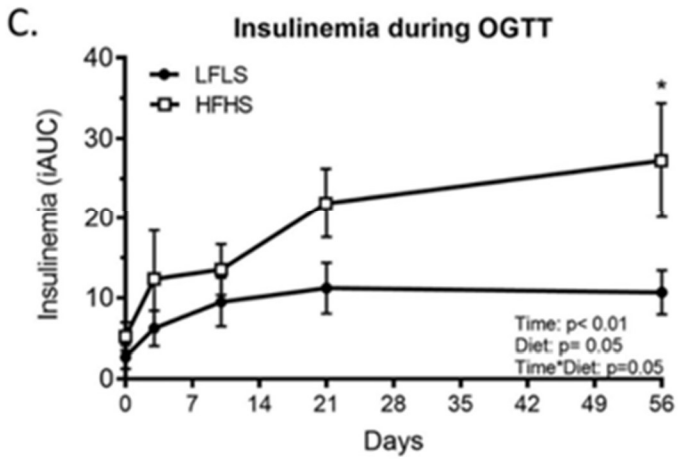

## 8. RESULTS

When fed diverse diets, the HFHS mice gained more weight than the LFLS animals. Figure 1A shows that a significant difference between the two groups became apparent on day 31. Weight increase was 32.6 ± 1.8 g for the HFHS group and 28.1 ± 1.6 g for the LFLS group. An increase in the glucose area under the curve (Fig. 1B) indicates a decrease in glucose tolerance, as revealed by the oral glucose tolerance test (OGTT). Day three of HFHS feeding was the beginning of these decreases. A lower tolerance threshold was linked to a higher percentage of body fat. Figure 1C shows that insulin sensitivity decreases throughout treatment as body weight increases; this observation is supported by the fact that the insulin area beneath the OGTT curves only showed a substantial improvement on day 56 of HFHS feeding.

**Fig 1:** Following 56 days of a low-fat diet high in sugar and fat, the rat's phenotypic is examined. For 56 days, eleven mice were sequentially administered either LFLS or HFHS. A person's weight increase, their oral glucose tolerance test (OGTT) curve, and their insulin area under the plasma OGTT curve (iAUC) are the three variables at play here. To ascertain the temporal and dietary impacts and connections, researchers used mixed linear regression and extended linear regression models. The mean ± SEM is shown for the data set consisting of 9 to 12 subjects. Using a Tukey HSD post hoc test (*, $P < 0.05$), a significant result was found when comparing the LFLS and HFHS groups.


A.
Body weight
LFLS
HFHS
Body weight (g)
35
30
25
20
0
7
14
21
28
35
42
49
56
Days
Time: p<0.001
Diet: p<0.001
Time*Diet: p<0.01


B.
Glycemia during OGTT
LFLS
HFHS
Glycemia (iAUC)
1500
1200
900
600
300
0
0
7
14
21
28
35
42
49
56
Days
Time: p< 0.001
Diet: p< 0.001
Time*Diet: p<0.01




**Segment-specific gut microbiome community reshaping during HFHS diet feeding**

The cecum and small intestine were segmented in a principal component analysis (PCA) of the gut flora that was conducted before the HFHS diet started (Fig. 2A). Predictions for populations of gut flora agreed with these. Bacillales, Erysipelotrichales, and Lactobacillales fare well in the small intestine segments, in contrast to obligatory anaerobes (Clostridiales, Bacteroidales, and Verrucomicrobiales), which do poorly in the cecum (Figure 3). Also, the number of genera and relative abundance of bacterial taxa at each location are shown in Figure 4. A greater diversity of bacteria (3.2 [3.0-3.3]) (indicated as median [Q1-Q3]) was found in the cecum, in contrast to the jejunum (2.1 [1.8-2.8]) and ileum (2.2 [1.9-2.5], $P < 0.01$), indicating that different parts of the small intestine exhibited different relative abundances of genera. However, in the cecum, the number of Bacteroidetes was 1.46 [1.31-1.65] and in the ileum and jejunum, it was 1.44 [1.40-1.64]; the p-value was less than 0.01. Research into the effects of the HFHS diet on specific intestinal regions continued after these results.

**Fig 2:** Gut microbiota composition due to HFHS diet. Scientists examined the microbiota composition in each area of the intestines (A) using "principal component analysis (PCA)" prior to beginning the HFHS diet. Effects of HFHS on the composition of the jejunum, ileum, and cecum microbiota (n= 6–12 each time point) between A and D.

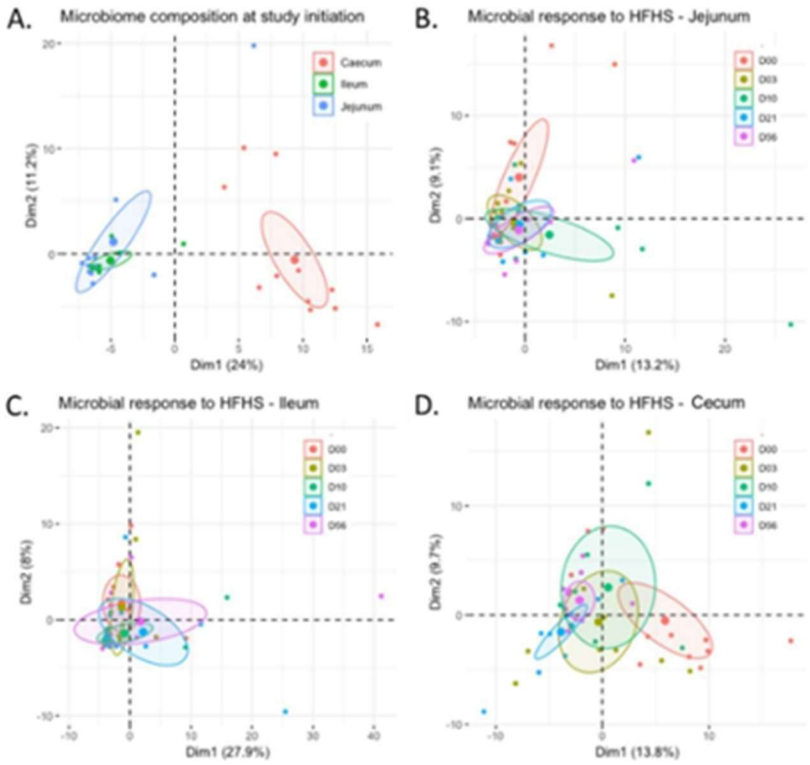
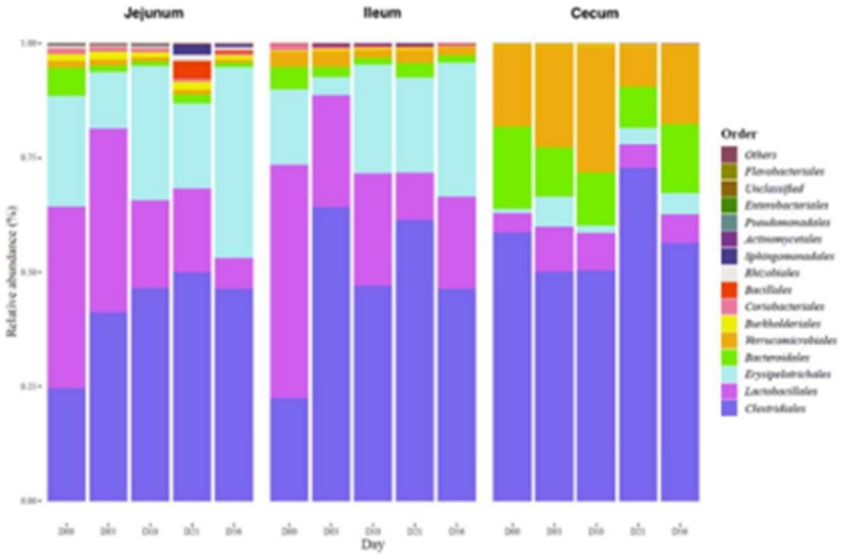



**Fig 3:** Impact of HFHS on microbial relative abundances at the order level. Even though they only accounted for 1% of the total, the orders that comprised the bacteria were mixed up in several sections.




**Become mediators are modified in response to the HFHS diet**

Researchers have found that changes in certain molecules can have a big effect on metabolic processes. These molecules include CB1 (AEA and 2-AG), PPARα (N-oleoyl ethanol amine [OEA] or N-palmitoyl ethanol, which are amines [PEA]), TRPV1 (all long-chain non-both

saturated N-acylethanolamines as well as 2-monoacylglycerols), the GPR technique119 (OEA, N-linoleoyl ethanol amine [LEA], 2-oleoyl-glycerol [2-OG], and 2-linoleoyl-glycerol [2-LG]), or GPR55 (PEA). These changes have been linked to the development of metabolic syndrome, obesity, and type 2 diabetes. They may also have a direct effect on gut microbiota. In order to determine the mediating impact of the HFHS diet, researchers looked at ileal or plasma eCBome levels. After 10 days of starting the HFHS diet, researchers found a significant increase in ileum AEA (+109 percent after 10 days, $P < 0.05$) when evaluating it using analysis of variance (ANOVA) linear comparability post hoc analysis. Two AEA congeners, OEA and PEA, tended to decrease after 10 days of HFHS feeding, even though PEA levels had recovered to baseline by day 56 of HFHS feeding. Avoiding HFHS had no effect on the concentrations of the anti-inflammatory AEA congener N-docosa hexa enoyleth anolamine (DHEA). Even though it had been dropping throughout the period, 2-AG, the second primary ECB, showed a non-significant reduction on day 56. Figure 4A shows a distinct decreasing trend for GPR119 and TRPV1 activators, as well as 2-OG and 2-LG, two 2-AG congeners.

**Fig 4:** The endocannabinoidome is activated by a high-fat and sugary diet. Each of A and B Each time HFHS feeding begins, the endocannabinoidome mediator is shown in the ileum (A) and plasma (B) in this line chart. The N-acylethanolamines (NAEs) are seen in the first row. 2-Monoacylglycerols (2-MAGs) could be located a few rows below on the page. The act approach was used to establish the FC of the ileum mRNA expression of the endocannabinoidome-related gene. The statistics were shown as percentages as of day 0 after being adjusted to Tbp. The data is presented as the mean plus or minus the average error of the mean, and there are 9-12 observations at each time point. In the bottom right corner, the student can see the P values from the post hoc nonlinear contrast analysis when the findings are statistically significant. For each time point, the Tukey HSD post hoc test is performed with a significance threshold of $P < 0.05$. Here, "not determined" (ND) is the descriptive phrase.

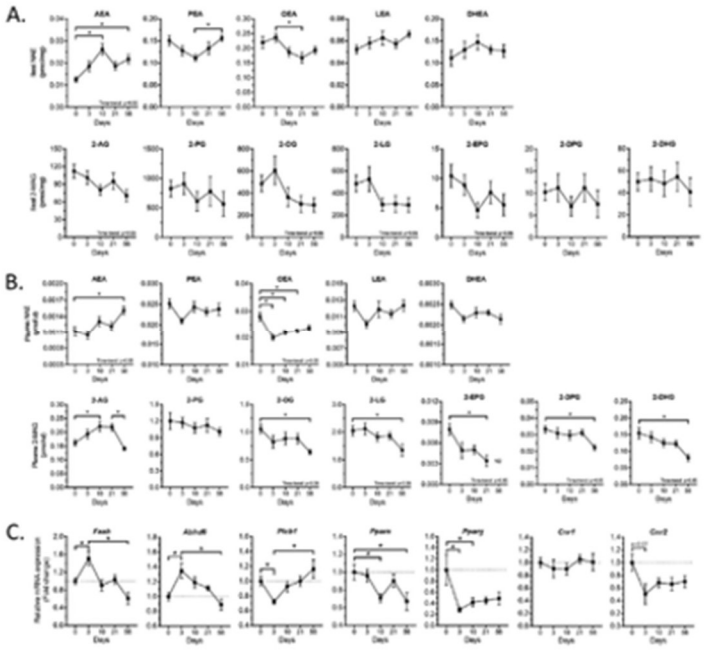
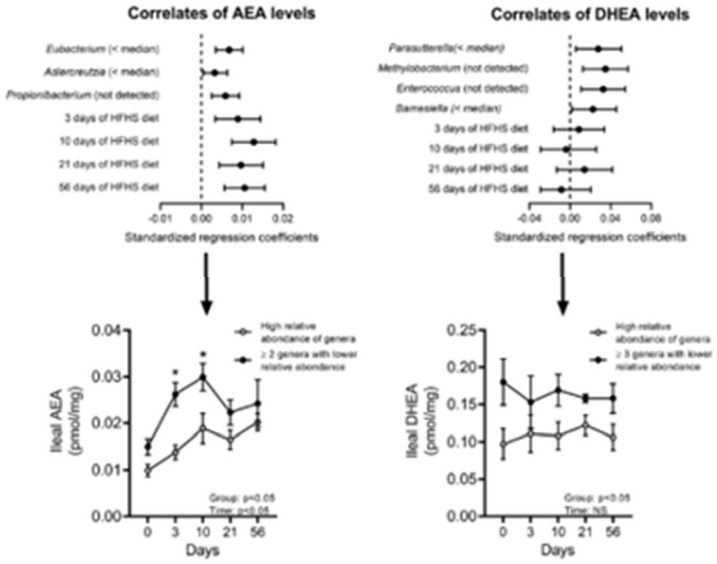



Figure 4B shows that the eCBome mediators in the plasma also underwent notable changes.

Arachidonic acid-containing ECBs showed a 31% increase while 2-AG (+31%; $P < 0.05$) showed a 50% increase. Levels of 2-AG in the plasma peaked on days 10 and 21, and by day 56, they had dropped considerably. Most eCBome mediators, including oleoyl "(OEA and 2-OG)-, linoleoyl (2-LG)-, and omega-3 [2-EPG, 2-DPG and 2-DHG]" were decreased when HFHS was administered, as shown in Figure 4B. Although the two diets were nutritionally identical, the HFHS diet purposefully consumed 4.5 times more total lipids than the LFLS diet. This made it possible to execute these changes in a controlled manner. They were able to detect changes in the intestinal microbiome-eCBome axis by identifying the smallest collection of ileal microbiome taxa that adequately reflects the levels of each ileal eCBome mediator following HFHS consumption (Fig. 5). Some bacterial species were either undetectable or had low levels, regardless of the increased weight, according to the regression models that were built in response to changes in the ileal levels for the eCB AEA and the PPARα/γ agonist DHEA. Eubacterium, Adlercreutzia, and Pro bacterium relative quantities in the ileum were either not detectable or very low. Consequently, a strong and clear association was seen between longer intervals between HFHS feedings and elevated AEA levels (Fig. 5). Results from this model-based study showed that on days 3 and 10, when glucose intolerance first manifested, AEA levels were much greater in mice whose ileum microbiota had reduced the relative abundance of two of these species (Fig. 5). Fig. 5 shows that there was a substantial and independent correlation between undetectable levels of Parasutterella, Methylobacterium, Enterococcus, or Barnesiella and elevated ileal DHEA. In most cases, the ileal DHEA level was greatest at 0 hours and lowest at the onset of glucose intolerance. Other eCBome mediators, such as 2-AG, could not be sufficiently mimicked either.

**Fig 5:** In reaction to HFHS, the ileum endocannabinoid me mediator interacts with the gut flora. There is a correlation between the ileum AEA and DHEA levels and the standardized regression coefficients of the intestinal flora (top). The ileum microbiota profile was used to filter the AEA and DHEA levels at each time point. Excluded from the analysis were species with undetectable relative abundance levels and those with established strong links to the eCBome as intermediates. All species that may be impacted by HFHS feeding and all species closely associated with the mediator were examined in this research. All models account for the amount of time spent HFHS feeding. A stepwise selection strategy was used to generate the final models. The data are shown as the average plus or minus the standard error of the mean, with n varying from 3 to 8 per group at each point. *, A Tukey HSD post hoc test was conducted at every time point with a significance threshold of $P < 0.05$.




## 9. DISCUSSION

The host's metabolic response to diet and environmental stimuli may be influenced by alterations in the gut microbiota and eCBome signaling (Dutta et al., 2020). In this stage of development, there are both endogenous and exogenous/symbiotic "omes" that engage in mutualistic interactions. The major goal of this study was to establish a causal association between diet-induced obesity and the metabolic consequences of this condition. In the early phases of glucose intolerance, obesity, and hyperinsulinemia produced by the HFHS diet, there is a correlation between changes in the relative abundance of specific genera in the gut microbiota and certain levels of eCBome mediators in the ileum or plasma. Previous study suggests that meals that promote obesity may change the composition of the gut microbiome by affecting the levels of eCBome mediators in both the blood and the gut. Depending on the time of day and the segmentation, certain variances emerge. In addition, regardless of changes in body weight, researchers found a link between certain bacterial species in the cecum and small intestine and eCBome mediator levels in blood and tissues. Here the students find the Adlercreutzia, Barnesiella, Parasutterella, Propionibacterium, Enterococcus, and Methylobacterium genera. Even after just three days on the HFHS diet, there were noticeable changes to the gut microbiota and eCBome, indicating that the gut microbiome-eCBome axis plays a role in the first host adaptation to the diet.

Modifications to 2-monoacylglycerol and N-acylethanolamine levels, together with alterations in the number of certain commensal bacteria, have been associated with dietary-induced obesity. As an example, previous research has shown that some species' stool abundance decreases because of obesity, which is in turn caused by a high-fat diet. So, it is consistent with this because the researchers have recently shown that HFHS causes a drop in Barnesiella populations throughout the intestines. The ileum and jejunum of overweight people also exhibit lower Parasutterella levels. Inflammation, obesity, Acinetobacter baumannii, and the subsequent metabolic mayhem are negatively correlated with the declining Akkermansia numbers in this area after HFHS feeding. Finally, studies on obese

pigs have shown that the ileum harbors more Intestinimonas and Sphingomonas than the jejunum. These two bacteria have been linked to obesity and impaired leptin signaling in previous studies. This and other variations in gut flora might be explained by reactions to different types of food. To isolate the effects of increased sugar and fatty acid consumption on weight gain, dysmetabolism, and gut microbiota, this research used HFHS and LFLS diets that were very similar in terms of fatty acid composition, fiber sources, and quantities.

After consuming HFHS, researchers discovered elevated plasma AEA and 2-AG levels, which are consistent with the large body of literature demonstrating that these intermediates are amplified in obese individuals and animal models of obesity. There was a negative connection between body mass index and other 2-monoacylglycerol levels, which is in line with the reduction in plasma 2-OG and 2-LG levels. Potentially connected to the existence of eCBome mediators is the makeup of the gut microbiome. This could be because the two systems react similarly to changes in dietary weight. Researchers still discovered several connections after controlling for changes in body mass index, suggesting this could be accurate in certain contexts. Changes in the same tissue may allow commensal bacteria and eCBome mediators to start interacting long before obesity develops. A significant change in ileal AEA levels over time disproved the expected protective benefits of the ileal genera Parasutterella, Coprobacillus, Akkermansia, and Barnesiella against diet-induced dysmetabolism in rats. These results lend credence to the idea that the two effects are causally related. Reintroducing this beneficial species by probiotic use immediately lowers AEA levels, and additional research has connected situations creating elevated AEA levels to a drop in A. muciniphila prevalence. The ileum's n-3 polyunsaturated fatty acid eCBome mediators have weight-independent interactions with certain genera. To some extent, these mediators may be able to reduce inflammation. In addition, plasma concentrations of eCBome mediators were shown to be correlated with the relative abundance of bacterial species in all three sections of the intestines. Researchers need more investigations to ascertain the importance of these associations, given the origins of plasma eCBome mediators remain unknown. There seems to be little evidence linking the genera found in the ileal microbiome to plasma mediators or eCBomes, which raises the possibility that the small intestine is not a primary source for these substances.

Scientists found that greater levels of AEA and DHEA were related to the lack of many metabolically beneficial genera in the ileum of mice fed the HFHS diet. The activation of CB1 and PPARα/γ might so be indicated by this. Glucose intolerance and local inflammation are linked to these outcomes. These results indicate that it would be more beneficial to study possible connections between gut microbiota and eCBome as a community rather than focusing on specific genera, as these interactions are likely to be metabolically relevant. Further investigation into the link between eCBome alterations and the impact of gut colonization on eCBome targets and mediators should be possible because of these results. Weirdly, results suggest that the HFHS diet elicits time- and segment-specific bacterial reactions. The need to investigate different parts of the intestines, preferably in animal models where it is easier to do so, is emphasized by this (Cortese, 2021).

## 10. CONCLUSION

This investigation documents the microbiome, or eCBome, in various sections of the intestines across time to map out the HFHS-related disorders, such as hyperinsulinemia, glucose intolerance, obesity, and others. Metabolic problems brought on by the HFHS diet and host-microbiota dysbiosis may have their origins in an endogenous signaling system, according to the study's authors. Interactions between the online community's biome and the gut microbiome occur throughout this process. Finally, the present findings should pave the way for future research into the molecular underpinnings of the gut microbiome-eCBome axis (Ahmed & Ansari, 2020).

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