

IEEE
BERKSHIRE SECTION
High School STEM Research Challenge – 2024

**The Manifestation of NAFLD in Lean Individuals: A Personal Journey into its
Biological Framework**

Written for:
The Institute of Electrical and Electronics Engineers, Inc.
Berkshire Section
STEM Research Contest

By
Emilie Coziol-Desy



02/04/2024

Miss Halls
GRADE 11
Donna Daigle

The Manifestation of NAFLD in Lean Individuals.

No one really knows the truth about Non-alcoholic Fatty Liver Disease. Its intricate framework and constant development have fascinated researchers and scientists for decades, but none has successfully cracked its code. Though one of the most common disorders in America (“Staying Healthy: The Mystery of NAFLD”, 2022), this mysterious disease seems to manifest itself in various shapes and forms making it extremely hard to fully comprehend. Some experiments have led to a better understanding of its impact and manifestation, but there are no definitive answers regarding treatments or its connection to slender individuals. Being a lean person affected by this disorder, NAFLD has always been of interest to me. I’ve always wondered why a disease most commonly related to obesity would find its way into my liver, and if its impact could potentially be of danger to me. For many years I sought answers from doctors and professionals, but their responses were always unsatisfactory and insubstantial. To find the answers I was looking for, I concluded that I needed to take matters into my own hands and dive into the biological mystery of NAFLD.

Fatty liver disease is a condition triggered by an accumulation of fat cells in the liver (Marks, 2023). Though its most common form manifests itself through an over-consumption of alcohol, otherwise called Alcoholic-fatty liver disease, another variant of the disorder called non-alcoholic fatty liver disease (NAFLD) is completely independent of such variables. NAFLD is most commonly caused by high triglyceride levels, obesity, and a poor diet (Marks, 2023). Lean individuals who have been diagnosed with NAFLD fall on the other side of the spectrum, as obesity and weight gain are usually not a potential explanation for its materialization. Research has concluded that it is seemingly due to a higher insulin resistance rate which inevitably fails to hinder the production of hepatic glucose, leading to hyperglycemia (Santolieri and Titchenell,

2018). This phenomenon completely disjoints the production of carbohydrates, lipids, and proteins which become the building blocks for increased visceral adipose tissue (“Visceral Fat”, n.d). Visceral fat is found surrounding many major organs within the abdomen, such as the liver. Most professionals previously believed that visceral fat’s dangerous effects only affected Body Mass Index (BMI) and obesity, but research found its metabolic movement to be highly harmful when found in larger quantities near the liver. The metabolic movement of the liver regulates cell division, more specifically glycolysis in the nucleus of a cell. Research has found that people who are observed with liver disease, have enhanced glycolysis activity which heightens their lactic acid level. Accordingly, high lactic acid levels are one of the most prominent causes of liver failure (Shenghao Li, 2023). Furthermore, metabolic movement is believed to be a big part of the inflammatory system of liver disease, combined with insulin resistance, because of its constant secretion of adipokines (Bansal, 2023). Adipokines, also known as adipocytokines, are cell-signaling molecules (cytokines) that work through the adipose tissue and play a role in the inflammatory and obesity regulations of the body specific to the regulation of the cell cycle (Kirichenko, 2022). Unfortunately, no one knows why particular individuals are observed with abnormal amounts of visceral fat surrounding their liver without its manifestation in other areas of the body. A lean individual who has increased visceral adipose tissue surrounding their liver is simply believed to be genetically unlucky.

NAFLD has several stages of progression, which can cause significant damage to the liver. However, the disease is typically asymptomatic, meaning there are often no visible symptoms. The four most well-known stages of NAFLD are steatosis, steatohepatitis, fibrosis, and cirrhosis (Pujitha and Savio, 2023). Though they are most commonly talked about as a group of 4, there are two subdivisions where they could be placed: harmless and at risk. Steatosis, also known as the most harmless manifestation of NAFLD, is recognized when the fat percentage of

the liver's weight increases past 5% ("Steatotic (Fatty) Liver Disease",2023). Steatosis weakens the liver due to its concentrated fat percentage but is typically harmless as it does not prevent it from functioning. Steatosis can be treated easily if related to alcohol consumption or obesity as patients are asked to stop drinking and lose weight if necessary. However, when steatosis is diagnosed in lean individuals, it will most likely progress toward more severe stages because it correlates with genetic predisposition. ("Steatotic (Fatty) Liver Disease", 2023).

The second stage of NAFLD is called steatohepatitis, and it is the one I am diagnosed with. This stage is caused by a buildup of fat in the liver that eventually starts to cause inflammation ("Non-alcoholic Steatohepatitis (NASH)", n,d). Someone affected by steatohepatitis will have damaged tissue and its inflammation will hinder the liver's ability to function properly. When I received my diagnosis, doctors immediately put me on all sorts of food restriction plans. I was closely monitored and had to undergo multiple procedures such as endoscopies and colonoscopies which sounded so terrifying for a little girl. Nonetheless, I had hoped that all those events would help my doctors figure out a solution or at least a plan of action. Unfortunately, due to the lack of knowledge surrounding NAFLD, my expectations were not met and I was left without any support system. Furthermore, the diet I followed for years did nothing for my liver as the root of the problem is not food but rather, a complicated genetic predisposition. I consider myself lucky to have accidentally discovered my fatty liver at such a young age, as I am now constantly being monitored to make sure it does not progress. However, even if the doctors did observe progress in my liver state, there are no specific cures that could help me and no physical symptoms would indicate the worsening of my condition.

The two most risky stages of NAFLD, fibrosis, and cirrhosis, are notorious for being especially hard to diagnose, as the physical symptoms do not match the aggressiveness of the disease. In many cases, serious cases of steatohepatitis lead to fibrosis, the third stage of

NAFLD. During fibrosis, damaged and swollen tissue will progress, eventually forming scar tissue and stiffening the liver. A liver consumed with scar tissue cannot repair itself and certainly can't function, leading to more and more scar tissue replacing healthy ones. ("Fibrosis Scarring", 2023). Unfortunately, fibrosis is primarily asymptomatic, meaning many individuals will be affected by it without ever knowing the danger. Left untreated, fibrosis can develop into cirrhosis, the fourth stage of NAFLD and one of the prerequisites for liver cancer ("Fibrosis Scarring", 2023). Cirrhosis is often called "end-stage liver disease" ("Overview Cirrhosis", n,d) because of its high risk of fatality and reputation as the most aggressive stage of Non-Alcoholic Fatty Liver Disease. Many serious conditions, such as cancer and liver failure, will be directly linked to cirrhosis and may require the need for a transplant. This stage of NAFLD is highly unpredictable and its impact cannot be reversed, only slowed. Scientists and doctors have always struggled with diagnosing NAFLD because of its mild and unpredictable symptoms. Someone affected by steatosis could experience intense nausea and vomiting while someone with cirrhosis could simply experience a bit of fatigue. NAFLD is a silent killer for lean individuals who cannot rely on physical evidence such as obesity and alcoholism to identify the possibility of having chronic liver disease.

Doctors and scientists are working in opposite directions when it comes to treating and solving the issue of NAFLD. Most doctors will recommend weight loss when asked how to treat NAFLD without considering those who are already underweight. The widespread idea that dieting and exercising is the ultimate solution to "cure" NAFLD is rooted in the simple truth that weight loss does lead to less visceral fat and adipose tissue which could reduce the inflammation and scarring process of the liver. However, just as debated before, NAFLD manifests itself through so many different mediums that there is no one-size-fits-all solution. For example,

someone who is already slim would not be able to lose the visceral fat surrounding their liver, no matter the diet because its presence isn't related to weight at all.

Scientists, on the other hand, have been focusing on finding a therapeutic cure using a gene called *PNPLA3*. This gene “provides instructions for making a protein called adiponutrin, which is found in fat cells (adipocytes) and liver cells (hepatocytes)” (Bethesda, 2020). The expression of the *PNPLA3* gene is known to decrease in periods of fasting and increase again when food is introduced into the system, which makes it a key component in regulating and processing the fats in one's diet (Bethesda, 2020). A specific mutation of this gene is known to increase and potentially be the genetic cause of NAFLD in lean individuals. To counterattack its effect on increased fat production, scientists experimented with silencing the *PNPLA3* 148M mutant protein in a mammalian model. During preclinical trials, mice were fed a fatty diet to determine if silencing the *PNPLA3* gene would reduce their fatty liver content (Lindén, 2019). The experiment showed promising results; the team observed that *PNPLA3* ASO therapy could help in reducing the overall effects of NAFLD as well as “[in] suppress[ing] the expression of a strong innate genetic risk factor” (Lindén, 2019). Though the idea of silencing the *PNPLA3* gene to counterattack its harmful mutation in individuals diagnosed with NAFLD is still in the early stage of development, its discovery and success rate in mice gives hope to those affected. Clinical trials using human test subjects would be required before it can be deemed safe and marketable.

Though there is hope in finding a cure for NAFLD, this paper still left me with many concerns regarding my future. This experience was very personal as I had to dive straight into the realm of introspection with the hope of finding all of the answers to the questions my 8-year-old self had been longing for. Even though I am still left with a thousand more questions about the never-ending mysteries of NAFLD, I came to terms with the prospect that some of my

questions just cannot be answered at the moment. Researching variants, treatments, liver tissue, and fat cells, managed to broaden my horizon on the intricacies of the human body while also providing several new pieces of information to better understand the full picture of this enigmatic puzzle. I remember feeling my own mortality for the first time the day I received my diagnosis. I was 8 years old, facing the unknown, and hoping for answers. Unfortunately, I was confronted with a poorly understood disease that lacked any conclusive research. Looking ahead, I plan on being a gastroenterologist in hopes of helping thousands of others like me who feel alone navigating this disease. I am determined to continue my journey in exploring NAFLD and its biomolecular and genetic components so that I can confidently diagnose, treat, and support the thousands of individuals who are also looking for answers.

References

- Albhaisi, S., Abhijit Chowdhury, A., & Sanyal, A. J. (2019, August 30). *Non-Alcoholic fatty liver disease in lean individuals*. JHEP report. <https://doi.org/10.1016/j.jhepr.2019.08.002>
- Bansal, S., Vachher, M., Arora, T., Kumar, B., & Burman, A. (2023). Visceral fat: A key mediator of NAFLD development and progression. *Human Nutrition & Metabolism*, *33*, 200210. <https://doi.org/10.1016/j.hnm.2023.200210>
- Bataller, R., & Brenner, D. A. (2005). Liver fibrosis. *Journal of Clinical Investigation*, *115*(2), 209-218. <https://doi.org/10.1172/jci24282>
- Dong, X. C. (2019). PNPLA3—A Potential Therapeutic Target for Personalized Treatment of Chronic Liver Disease. *Frontiers in Medicine*, *6*, 503801.
- Fibrosis (Scarring)*. (2023, September 6). American Liver Foundation. <https://liverfoundation.org/about-your-liver/how-liver-diseases-progress/fibrosis-scarring/#:~:text=Unlike%20healthy%20liver%20cells%2C%20scar,itself%20and%20restrict%20blood%20flow>
- Kirichenko, T. V., Markina, Y. V., Bogatyreva, A. I., Tolstik, T. V., Varaeva, Y. R., & Starodubova, A. V. (2022). The role of adipokines in inflammatory mechanisms of obesity. *International Journal of Molecular Sciences*, *23*(23), 14982. <https://doi.org/10.3390/ijms232314982>
- Kudaravalli P, John S. Nonalcoholic Fatty Liver. [Updated 2023 Apr 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK541033/>
- Li, S., Hao, L., & Hu, X. (2023). Natural products target glycolysis in liver disease. *Frontiers in Pharmacology*, *14*. <https://doi.org/10.3389/fphar.2023.1242955>

- Lindén, D., Ahnmark, A., Pingitore, P., Ciociola, E., Ahlstedt, I., Andréasson, A.-C., Sasidharan, K., Madeyski-Bengtson, K., Zurek, M., Mancina, R. M., Lindblom, A., Bjursell, M., Böttcher, G., Ståhlman, M., Bohlooly-Y, M., Haynes, W. G., Carlsson, B., Graham, M., Lee, R., . . . Romeo, S. (2019). Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in pnpla3 i148m knock-in mice. *Molecular Metabolism*, 22, 49-61. <https://doi.org/10.1016/j.molmet.2019.01.013>
- Marks, J. W. (2023, July 18). *Fatty Liver (Nonalcoholic Fatty Liver)* (B. Anand, Ed.). Retrieved February 8, 2024, from https://www.medicinenet.com/fatty_liver/article.htm
- MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. PNPLA3 Genre; Available from:
- Mohamed, J., H, N. N. A., H, Z. A., & B, B. S. (2016). Mechanisms of diabetes-induced liver damage: The role of oxidative stress and inflammation. *Sultan Qaboos University Medical Journal*, 16(2), e132-141. <https://doi.org/10.18295/squmj.2016.16.02.002>
- Nonalcoholic fatty liver disease - diagnosis and treatment*. (2023, October 6). MayoClinic. <https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/diagnosis-treatment/drc-20354573>
- Non-alcoholic Steatohepatitis (NASH)*. (2022). Ceders Sinai. [https://www.cedars-sinai.org/health-library/diseases-and-conditions/n/non-alcoholic-steatohepatitis-nash.html#:~:text=Non%2Dalcoholic%20steatohepatitis%20\(NASH\)%20is%20an%20advanced%20form%20of,to%20scarring%20of%20the%20liver](https://www.cedars-sinai.org/health-library/diseases-and-conditions/n/non-alcoholic-steatohepatitis-nash.html#:~:text=Non%2Dalcoholic%20steatohepatitis%20(NASH)%20is%20an%20advanced%20form%20of,to%20scarring%20of%20the%20liver)
- Overview -Cirrhosis*. (2020, June 29). NHS. Retrieved February 8, 2024, from [https://www.nhs.uk/conditions/cirrhosis/#:~:text=Cirrhosis%20is%20scarring%20\(fibrosis\)%20of,the%20liver%2C%20such%20as%20hepatitis](https://www.nhs.uk/conditions/cirrhosis/#:~:text=Cirrhosis%20is%20scarring%20(fibrosis)%20of,the%20liver%2C%20such%20as%20hepatitis)

Robinson, J. (2022). Remedies for Inflamed Liver. *WebMD*. <https://www.webmd.com/a-to-z-guides/remedies-inflamed-liver>

Rui, L. (2014). Energy Metabolism in the Liver. *Comprehensive Physiology*, 4(1), 177.

<https://doi.org/10.1002/cphy.c130024>

Santolero, D., & Titchenell, P. M. (2019). Resolving the paradox of hepatic insulin resistance.

Cellular and Molecular Gastroenterology and Hepatology, 7(2), 447-456.

<https://doi.org/10.1016/j.jcmgh.2018.10.016>

Sookoian, S., & Pirola, C. J. (2019). *Genetics of Nonalcoholic Fatty Liver Disease: From*

Pathogenesis to Therapeutics. Thieme Medical. <https://doi.org/10.1055/s-0039-1679920>

Staying Healthy: The Mystery of NAFLD. (2022, March 30).

<https://www.allcarehealth.com/articles-events/articles/staying-healthy-the-mystery-of-nafld?locale=es>

Trépo, E., & Valenti, L. (2020, June). *Update on NAFLD genetics: From new variants to the*

clinic. *Journal of Hepatology*. <https://doi.org/10.1016/j.jhep.2020.02.020>

p.1196-1209

Visceral Fat. (2022, September 12). Cleveland Clinic.

<https://my.clevelandclinic.org/health/diseases/24147-visceral-fat>