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A LONG PERSPECTIVE ON A DIFFICULT PROBLEM: METABOLIC DYSFUNCTION AND STATOTIC LIVER DISEASE: A CORRELATIONAL STUDY

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ABSTRACT

An growing number of people at high risk are being affected by nonalcoholic fatty liver disease (NAFLD), which is becoming a bigger issue. The prevalence of nonalcoholic fatty liver disease exceeds 25% globally. Metabolic syndrome, a set of symptoms impacting the cardiovascular system and liver, is more likely to manifest. A comprehensive strategy is necessary for the treatment of NAFLD due to its complexity and the many comorbidities and challenges it often presents. When NAFLD is identified, many clinicians are unsure of how to proceed, the severity of the disorder, or the potential complications that may develop. Conditions like as cirrhosis, hepatocellular cancer, inflexible simple steatosis, and cardiovascular disease may lead to actively metabolising non-alcoholic steatosis (NASH). Due to differing views on the optimal methods of diagnosis and treatment, this might prove to be challenging. A study of NAFLD's history, diagnostic options, and treatment options is conducted by the researcher before any discussion of future possibilities for the development of multidisciplinary care routes is undertaken.

Keywords: Liver, Plasma Metabolomics, Fatty liver disease, Non-Alcoholic liver.

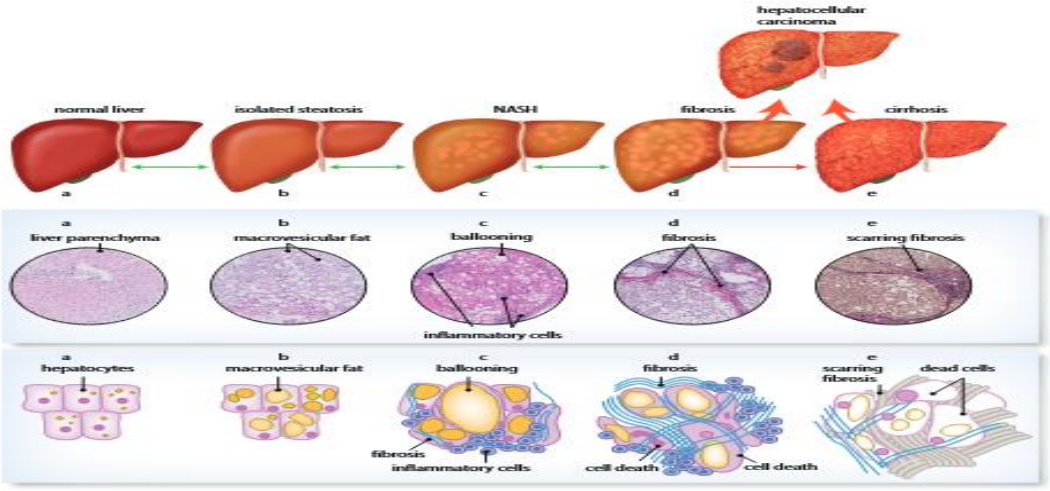
INTRODUCTION

An unhealthy fixation on food and insufficient physical activity, sometimes referred to as the "Western lifestyle," has seen a meteoric rise in its followers. According to Cariou (2022), the conventional Western way of life is linked to metabolic syndrome and obesity, which are marked by abnormal lipid profiles, abnormally high blood pressure, abnormally high blood sugar, and an accumulation of fat around the middle. As a group of liver issues linked to metabolic syndrome, "nonalcoholic fatty liver disease (NAFLD)"

describes a situation well. When alternative causes of hepatic steatosis, such as excessive alcohol use, particular metabolic abnormalities, or medication use cannot be identified, "Non-alcoholic fatty liver disease (NAFLD)" is defined as imaging or histological evidence demonstrating intracellular fat accumulation in more than 5% of hepatocytes. The obesity and metabolic disorder epidemics have increased the incidence of non-alcoholic fatty liver disease (NAFLD), a condition that affects more than 25% of the world's population. Type 2 diabetes mellitus (T2DM) is expected to be more common than 60% among communities at high risk. Healthcare systems are facing a number of challenges, including shorter life expectancy and higher death rates, as well as the increasing cost of treating "Non-alcoholic fatty liver disease (NAFLD)" and its related illnesses, including type 2 diabetes and cardiovascular disease. The development of NAFLD may occur along a continuum. Fibrosis, cirrhosis, "Nonalcoholic fatty liver (NAFL)", and "Hepatocellular carcinoma (HCC)" are only a few of the stages that Reed and Abunnaja (2023) note as possible outcomes of liver diseases. Though "Nonalcoholic fatty liver disease (NAFLD)" impacts a sizable portion of the population, hepatic steatosis has a much more severe impact on a small fraction of people.

Hepatic encephalopathy, oesophageal varices, ascites, HCC, and liver failure are among the consequences that might develop when NAFLD progresses to a more advanced stage of liver disease. In patients at high risk for cardiovascular events, liver disease, and colorectal cancer, it is more important to diagnose metabolically active NASH than to diagnose non-progressive uncomplicated steatosis in patients at low risk. Although these people may be difficult to recognise, the best way to diagnose and treat them is still up for debate. Because of this, many doctors and nurses are confused when they get a new diagnosis of NAFLD or suspect that their patients may have the illness. A big problem is that there isn't a single approach to treating NAFLD that takes the disease and all of its potential effects into account (Samanta & Sarma, 2024).

Figure 1: The range of symptoms associated with NAFLD is wide.

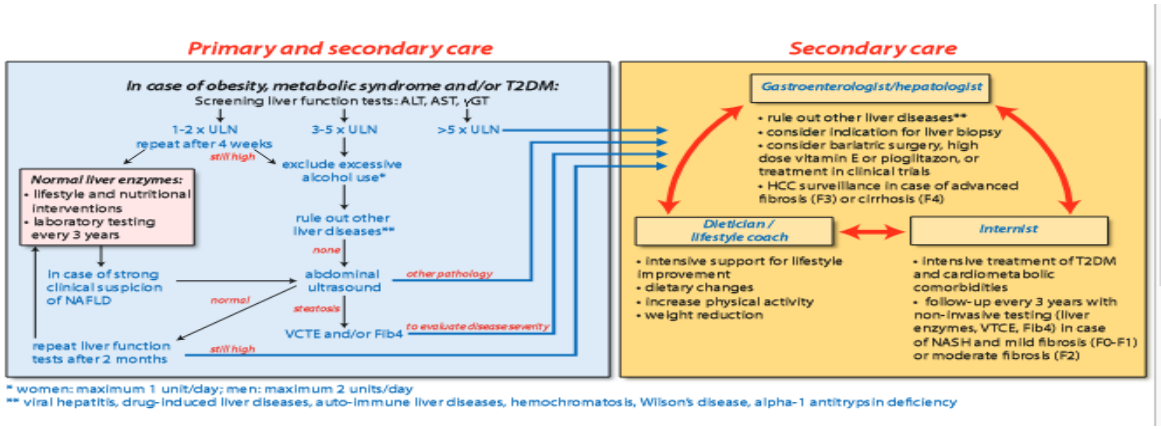


All parties involved aim to provide a comprehensive treatment plan that includes a detailed presentation of diagnostic choices, clinical care methods, and recommendations. This page covers the symptoms, causes, and therapies for NAFLD .

BACKGROUND OF THE STUDY

A significant public health issue is the increasing frequency of metabolic and cardiovascular disorders among people with non-alcoholic fatty liver disease (NAFLD). Patients at high risk for developing nonalcoholic steatohepatitis (NASH) may be identified by a multidisciplinary team including the patient's primary care physician, vascular specialist, hepatologist, internist-endocrinologist, and nursing assistant. To help with this kind of collaboration, a number of foreign medical centres have tried to form a NASH workgroup. It is common practice to identify a patient with non-alcoholic fatty liver disease (NAFLD) when distinguishing metabolically active NASH, cirrhosis, hepatocellular carcinoma, non-progressive simple steatosis, or cirrhosis becomes challenging. The fourth category is linked to a plethora of major health issues, such as a higher chance of cardiovascular disease. Researchers are seeking more accurate and non-invasive diagnostic methods to enhance screening, distinguish between stages of liver disease, and evaluate the risk of developing and worsening cirrhotic consequences such as HCC. Due to the absence of a widely available, accurate, and non-invasive diagnostic tool, Fig. 2 proposes a screening, diagnosis, and monitoring program for (possible) NAFLD patients.Ultrasonography or blood liver enzyme testing should be performed every three years to detect the presence of nonalcoholic fatty liver disease (NAFLD) in people at high risk for the condition. It is recommended to monitor HCC every six months in cases when there is extensive fibrosis or cirrhosis. Esophageal varices should be sought for in cases of suspected portal hypertension (Russo et al., 2021).

Figure 2: Approaching non-alcoholic fats liver disease (NAFLD) from several perspectives.



PURPOSE OF THE STUDY

Finding out how faecal microbiota transplantation (FMT) affected metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) patients was the main objective of this study. Find out how FMT influences NAFLD-related variables like gut microbiota composition, plasma metabolomics, and liver DNA methylation patterns. To further our understanding of the gut-liver axis in NAFLD and its therapeutic potential, we may utilise these biological markers to develop a machine learning model that can identify between patients getting autologous and heterologous FMT. This will assist in growing our knowledge within a 24-week timeframe. Look into the potential of using multi-omics data to predict and tailor how patients with NAFLD may respond to FMT. Describe the process by which FMT works to treat NAFLD and provide the framework for further research into its effectiveness. This study aimed to address that information vacuum by exploring the gut microbiota's possible therapeutic role in NAFLD. It also cleared the way for more effective and tailored treatments for a growing disease.

LITERATURE REVIEW

Even those who do not engage in excessive drinking may develop cirrhosis of the liver, a disease that is comparable to alcoholic hepatitis. Two of the most prevalent health issues among the patients were moderate obesity and diabetes mellitus. On the medical front, this condition is referred to as chronic non-alcoholic steatohepatitis. Ultrasound data may be used to identify non-alcoholic fatty liver disease (NAFLD), according to the Asian-Pacific Sitting Party for NAFLD. This can be done after other potential causes of chronic liver disease, including drugs that promote hepatic stenosis or extensive alcohol use, have been eliminated. In a policy statement acknowledging the earlier discovery of NAFLD, the European Association for the Study of Liver (EASL) acknowledged that all potential causes of chronic liver disease had been exhausted. Rebranding was warranted due to substantial evidence linking it to metabolic syndrome and other chronic liver illnesses. While NAFLD was still used by major international guidelines 4-6, a nomenclature change was imminent. It should be mentioned that while discussing "primary NAFLD," the 2016 EASL guidelines referred to NAFLD as being "associated with metabolic risk factors." "The Asian-Pacific Research Party's 2017 recommendations offered a "positive" definition of NAFLD (Kim et al., 2023) Fatal liver disease linked with metabolic processes dysfunction is increasingly used to describe adults with a history of metabolic risk factors such type 2 diabetes (T2DM), obesity, imaging-detected steatosis of the liver, biomarkers in the blood, or a liver biopsy. Multiple global organisations have voiced their support for this (Rinella et al., 2023). Asian Pacific Association for the Statistical Investigation of the Liver and the Malaysian Society of Gastro and Hepatology are two such instances. The term NAFLD was essentially dropped in a multi-society Delphi compromise statement on the new terminology for fatty liver disease in June 2022, and the term mitochondrial dysfunction-associated steatosis

hepatitis illness was created in its place. According to (Tzanaki et al., 2022), MAFLD and MASLD are superior choices since they cover more territory when describing the same subject.

Table 1

Characteristic	MAFLD
Positive diagnostic criteria	Yes
Attributes the condition to its etiology	Yes
Criteria	Hepatic steatosis detected either by imaging techniqu
Presence of other concomitant liver diseases	Other concomitant liver diseases retain their own terr

*MetALD, i.e., weekly intake 140–350 g for female, 210–420 g for male (average daily 20–50 g for female, 30–60 g for male).

Abbreviations:
MAFLD: metabolic dysfunction-associated fatty liver disease
MASLD: metabolic dysfunction-associated steatotic liver disease
HDL: high-density lipoprotein
HbA1c: glycosylated hemoglobin
HOMA-IR: homeostatic model for assessment of insulin resistance
hs-CRP: high sensitivity C-reactive protein
BMI: body mass index
MetALD: MASLD and increased alcohol intake

RESEARCH QUESTION

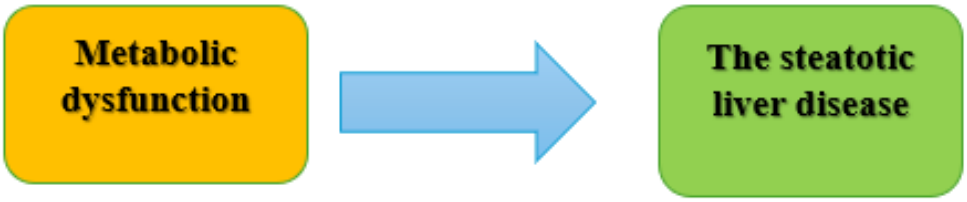
1. How does MASLD vary from other types of liver disease in terms of its long-term cardiovascular and metabolic consequences?

METHODOLOGY

In order to identify NASH and NAFLD-related fibrosis, this research is a component of the LITMUS project, an international multi-center effort. The whole systematic review procedure is accessible to the average person. This report was compiled in accordance with the PRISMA-DTA statement. Researchers used a sophisticated search methodology to examine the literature for studies assessing the diagnostic accuracy of Pro-C3 in persons with NAFLD. The search methodology used terms from the Medical Theme Headings, including not just the whole record but also its title and abstract. Databases such as MEDLINE (via OVID), EMBASE (through OVID and OVID as well), PubMed, Academic Citations Index, and CENTRAL (the Cochrane Library) were culled in 2022.

The supplement could provide researchers all the information they need for their quest. They contacted their LITMUS colleagues and manually reviewed the bibliographies of eligible research publications to uncover any other studies that the search approach could have missed. The search was revised in 2022. Prior to that point, it had checked all of the records that met researcher's requirements.

Conceptual Framework



RESULT

Among 21 treatment-naïve patients, hepatic steatosis and metabolic syndrome were treated with heterologous (n = 10) and autologous (n = 11) faecal microbiota transplantation (FMT). Individuals with a history of cholecystectomy, diabetes—especially type 2—cardiovascular disease, problems with the kidneys, or compromised immune systems were excluded from the study. No individuals in the group administered medication. The whole list of criteria for inclusion or exclusion is available elsewhere. Table 2 presents the beginning locations of the study participants.Importantly, there was no significant difference in food intake or age at starting across the therapy groups (Suppl. Table 2). The groups exhibited no differences in baseline steatosis percentage, fibrosis stage, or NAFLD action score (NAS). Table 2: Essential data about 21 individuals with biopsy-confirmed NAFLD. Data may be expressed as the mean with standard deviation, the median with interquartile range, or as percentage frequency. Various statistical tests, such as Fisher's exact test for binary data, the t-test for regularly distributed data, and the Mann-Whitney U test for independent data, provide results in the form of p-values. The acronyms "ALP," "ALT," and "AST" denote alkaline phosphatase, alanine transaminase, and aspartate transaminase, respectively. Hdl-C signifies high-density lipoprotein cholesterol, whereas LDL-C indicates low-density lipoprotein cholesterol. Alpha-lactamase, C-reactive protein, and faecal microbiota transplantation. The NAFLD Activity Score is referred to as the NAS score. The abbreviation for type 2 diabetes mellitus.

Table 2

Characteristic	Autologous FMT (n=11)	Allogenic FMT (n=10)	p-value
Age, years	48.5 ± 10.2	51.2 ± 6.6	0.48
Sex, male/female	10/1	7/3	0.31
BMI, kg/m²	31.5 ± 4.8	31.7 ± 3.5	0.91
HbA1c, mmol/mol	37.6 ± 3.8	38.2 ± 3.7	0.70
Glucose, mmol/L	5.7 ± 0.5	5.8 ± 0.7	0.79
AST, IU/L	29.0 [26.5-33.0]	39.5 [37.0-49.5]	0.001
ALT, IU/L	48.1 ± 16.5	70.8 ± 23.4	0.02
ALP, IU/L	83.0 [54.0-120.5]	71.0 [58.8-76.8]	0.67
GGT, IU/L	41.1 ± 21.4	45.1 ± 19.3	0.66
Cholesterol, mmol/L	5.8 ± 1.6	6.0 ± 0.8	0.75
HDL-C, mmol/L	1.2 [1.0-1.4]	1.2 [1.0-1.4]	0.80
LDL-C, mmol/L	4.0 ± 1.3	4.2 ± 0.7	0.71
Triglycerides, mmol/L	1.2 ± 0.6	1.4 ± 0.5	0.41
CRP, mg/mL	2.2 [0.8-4.3]	1.5 [0.9-3.2]	0.50
Steatosis, %	35.0 ± 20.7	34.1 ± 20.4	0.92
NAS score			0.38
1	1 (9%)	0 (0.0%)	
2	5 (46%)	4 (40%)	
3	4 (36%)	2 (20%)	
4	1 (9%)	4 (40%)	
Necro-inflammation score			0.06
0	1 (9%)	0 (0%)	
1	10 (91%)	6 (60%)	
2	0 (0%)	4 (40%)	
Fibrosis stage			1.00
F0	3 (30%)	2 (20%)	
F1	6 (60%)	5 (50%)	
F2	2 (20%)	2 (20%)	
F3	0 (0%)	1 (10%)	

The predictive machine learning model effectively differentiated between allogenic and allogeneic FMT patients between 0 and 24 weeks by examining changes to the intestinal microbiota (AUC 0.78), plasma metabolomics (AUC 0.74), the liver methylation of DNA patterns (AUC 0.75). The permutation study's findings showed that the likelihood that the obtained accuracy was the product of chance was very low (0.88; $p< 0.001$). The key distinguishing characteristics amongst all the groups in each research are described below.

DISCUSSION

New evidence suggests that intestinal microbiota transplantation may be a viable option for treating metabolic syndrome and non-alcoholic fatty liver disease. Researchers analysed the efficacy of allogeneic and autologous FMT in 21 individuals without prior training who had NAFLD verified by biopsy. Differentiating between autologous and non-autologous patients is one significant consequence of the ML algorithm. In order to differentiate, we looked at plasma metabolomics (AUC0.74), liver DNA methylation patterns (AUC0.75), and alterations to the gut microbiota over 24 weeks (AUC0.78). Permutations testing findings (0.88; $p< 0.001$) indicate that FMT reliably and substantially impacts NAFLD-related biological systems, indicating a suitable model. Such indicators have the potential to distinguish between allogeneic and autologous FMT recipients, indicating that the source of the transplanted microbiota greatly influences the host's physiological response. Recent studies have shown that allogeneic or autologous FMT may have a greater impact on patients with NAFLD. Because there were only 21 participants, the research did not include those who had NAFLD in addition to other conditions, such as type 2 diabetes or cardiovascular disease.

(Radu et al., 2023) While this does assist keep the study under control, it may restrict its applicability to NAFLD alone. The impact of FMT on the microbes in the gut, plasma metabolomics, and liver DNA methylation in NAFLD patients is examined comprehensively in this work. The multi-omics method is assisting researchers in learning more about NAFLD as a complex, multi-faceted illness with metabolic, genetic, and environmental factors to consider. The fact that there were no discernible improvements at the beginning of the study supports the findings that the two groups showed different levels of NAFLD severity, ages, and dietary habits after treatment (Loomba & Wong, 2024). These shifts may not have resulted from fundamental group differences but rather from the FMT intervention. This study shows potential for the use of FMT as a therapy for NAFLD, but additional research is needed. In order to further understand the clinical importance of the alterations seen for NAFLD development and outcomes, and how long they remain, ongoing follow-up studies are necessary. This study shows potential for the use of FMT as a therapy for NAFLD, but additional research is needed. Continuous, long-term research is necessary to determine the duration and clinical significance of the identified alterations in relation to NAFLD development and outcomes.

CONCLUSION

These findings indicate that by integrating machine learning with data from various omics datasets, a novel approach to medication efficacy prediction has been achieved. Suggestions for further studies on FMT as a medicinal therapy for NAFLD. The finding adds to the increasing amount of data on the gut-liver relationship in NAFLD (Lee et al., 2021), and it also introduces new options for medication modification for this common illness.

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