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Non-alcoholic Fatty Liver Disease: Not Time for the Obituary Just Yet!

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Non-alcoholic fatty liver disease (NAFLD) affects about a quarter of the world's population and poses a major health and economic burden globally. Recently, there have been hasty attempts to rename NAFLD to Metabolic dysfunction-associated fatty liver disease (MAFLD) despite the fact that there is no scientific rationale for this. Quest for a "positive criteria" to diagnose the disease, and destigmatizing the disease have been the reasons put forth for the name change. A close scrutiny of the pathogenesis of NAFLD would make it clear that NAFLD is a heterogeneous disorder involving different pathogenic mechanisms of which metabolic dysfunction driven hepatic steatosis is only one. Replacing NAFLD with MAFLD would neither enhance the legitimacy of clinical practice orclinical trials, nor improve clinical care or move NAFLD research forward. In view of the heterogeneity of NAFLD and presence of multiple pathophysiological pathways, we have proposed a novel classification of NAFLD, wherein NAFLD remains an umbrella term for different subgroups with differing pathophysiological mechanisms. While the term ‘NAFLD’ would represent the common final point in the disease process, itsdifferent subgroups would represent the separate predominant pathological pathways culminating in hepatic steatosis. Rather than changing the nomenclature without a strong scientific backing to support such a change, collaborative efforts should be launched worldwide to improve our understanding of the vast heterogeneity in NAFLD across populations and ethnicities and explore the different pathophysiologic mechanisms with the sole purpose of reigning in this epidemic, modifying disease progression and strengthening the treatment armamentarium.

Keywords: Heterogeneity; MAFLD; Metabolic; NAFLD; NASH; Nomenclature; Steatohepatitis.

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1. Introduction:

There has been a concerted campaign recently for changing the nomenclature of Non-alcoholic Fatty Liver Disease (NAFLD) to MetabolicAssociated Fatty Liver Disease(MAFLD), and itmay seem to manythat the time to bid adieu to the good old term is fast approaching.Numerous reasons have been put forth for this change as outlined in a recentlypublished consensus statement proposing the definition of MAFLD.[1]However, there are considerable inaccuracies in the proposed name, raising the obvious question of how changing NAFLD to MAFLD might or might not, move the field forward.[1] Of critical importance is the understanding of how a change in nomenclature impactsdisease perception for both medical professionals and the lay public.[2–4] In this review, we have tried to critically analyse the historical perspective of NAFLD, the origin of the term, the pathophysiological mechanisms involved and highlight whether a change in nomenclature is warranted.

2. The History of Non-alcoholic Fatty Liver Disease (NAFLD):

NAFLD was first histologically described in the late 1950s by Wastewater and Fainer in persons who had no history of alcohol intake but had hepatic steatosis.[5]In 1979, Klatskin, Miller and Ishimaru presented their landmark study at the plenary session of American Association for the Study of Liver Diseases (AASLD) Annual Meeting where they described the hepatic histological findings in 27 patientswith typical features of alcoholic liver disease but with no history of alcohol intakeand labelled it as 'Non-Alcoholic Liver Disease'.[6] Perhaps, this was the point in time when the term 'NAFLD' had its humble beginnings. Similar findings were reported almost simultaneously by Adler and Schaffner whocategorized the patients on the basis of histopathological findings into 'fatty liver, fatty hepatitis, fatty fibrosis and fatty cirrhosis'.[7] Eight months later, Ludwig and his colleaguesat Mayo clinic reported similar findings in a cohort of patients which they named 'Non-alcoholic steatohepatitis'.[8]Surprisingly, the MAFLD consensus group make no mention of these facts and statethat the "….term non-alcoholic fatty liver disease(NAFLD) was coined by Ludwig and colleagues in1980..."[1] Ludwig et al coined

the term Non-alcoholic Steatohepatitis (NASH) in their 1980 article and never used the term NAFLD.

In the course of time, it became evidentthat NAFLD encompasses a spectrum of disorders ranging from simple steatosis to cirrhosis of the liver[9]anda strong association between obesity, metabolic syndrome (MS) and NAFLD was established.[10] However, it soon became obvious that this was an oversimplification and multiple factors were involved in NAFLD pathogenesis.[11] Despite all the advances in our understanding of the causes of hepatic steatosis, the exact pathophysiologic mechanisms driving NAFLD have not been clearly defined and the search for the Holy Grail continues. With each passing day, a new player emerges and the adjective 'key' is thrust upon it!

3. Pathophysiology of NAFLD- The Six Blind Men of Indostan:

"And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!"

-***The Blind Men and The Elephant.***
John Godfrey Saxe

The pathophysiology of NAFLD is similar to the story of the six blind men and the elephant**(Figure 1).** There have been numerous attempts to ascribe hepatic steatosis to a multitude of factors. It is generally accepted thatNAFLD/NASH is commonly associated with insulin resistance (IR) or metabolic diseases such as diabetes, obesity and dyslipidemia and has even been termed as the hepatic manifestation of the MS.[12]However, the complexity of the entity precludes any single hypothesis to explain the pathogenesis of NAFLD and the range of its manifestations.This attempt to change the nomenclature betrays a lack of complete understanding of the processes that go into the pathogenesis of NAFLD. Changing the name may neither reflect nor improve our understanding of 'what causes' or 'what leads to' or 'what happens to' this entity.

3.1 Is NAFLD merely an extension of the Metabolic Syndrome?

Two questions are of paramount importance while analysing the multiple factors involved in NAFLD pathogenesis.Firstly, is MS ubiquitous in NAFLD and secondly, is the pathogenesis of NAFLD/NASH so linear? A careful look at the various factors causing NAFLD and the complex interplay therein raisecrucial points to ponder upon.

3.1.1 Fatty Liver Disease- Different Avatars:

Lipid deposition in the liver is not exclusively hyperinsulinemia-mediated and can be caused by a range of conditions like lipodystrophies, Hepatitis C virus infection, adverse effects of drugs like tetracyclines, defects in metabolism like Reye's syndrome, chronic inflammation and in states of malnutrition.[13–18]**(Figure 2)** This lends credence to the hypothesis that NAFLD can exist in the absence of metabolic syndrome and insulin resistance and involve hitherto unexplored pathophysiological mechanisms.

3.1.2 NAFLD without metabolic syndrome: Peculiarities

Studies have revealed that underweight individualsand those with normal BMI also develop NAFLD.[19]In a study by Singh et al, nearly half of the NAFLD subjectsdid not have IR and a significantly higher proportion of patients in non-IR group were non-obese.[20]Similar findings were also observed in a study on NAFLD subjects in Bangladesh.[21]Although NAFLD with MS has been shown to have considerable risk for cardiovascular diseases, diabetes and increase of left ventricular mass index in comparison to NAFLD without MS,[22]other studieshave also shown that NAFLD patients without MS displayed preclinical cardiologic abnormalities which were independent of diabetes mellitus and hypertension.[23] Thus, two things are clear: neither is MS ubiquitous in NAFLD,nor does the association of MS and NAFLD follow the cause-effect equation, clearly indicating that there is much more to NAFLD pathogenesis than IR and MS.

3.1.3 CanHepatic steatosis give rise to IR?

The chicken-egg conundrum concerning the primacy of MS over NAFLD has persisted for long. NAFLD has essentially been considered to be a manifestation of MS.[24]While IR leading to hepatic steatosis has always held centre stage, hepatic TG accumulation is also recognizedfor causingIR in the liver.[25] This contributes to the postprandial hyperglycemia and hyperlipidemia, major components of the MS. In fact IR is deemed an adaptive mechanism of the body to preserve glucose for various cellular processes in conditions of stress.[26]IR is associated with release of inflammatory mediators at the cellular level;[27]

itacts at two levels- hepatic and peripheral sites. Hepatic IR can occur independent of changes in circulating adipokines.[28] Hepatic steatosis and hepatic IR have also been found to occur in experimental models prior to the development of obesity and increases in adipokine levels implying that hepatic steatosis may have an independent genesis..[29]

The diacylglycerol (DAG)- protein kinase C(PKC) hypothesis might possibly partly explain this conundrum. Increased hepatic DAG activates PKC-ϵ isoform which causes phosphorylation of insulin receptor and drives hepatic IR.[29] Knockdown of PKC-ϵ has been shown to protect rats from high fat diet induced hepatic IR.[30] The DAG-PKC-ϵ pathway successfully explains howNAFLD can act as a precursor to MS.

3.1.4 Do all patients with hepatic steatosis develop MS?

This hypothesis however, contradicts the findings of Monetti et al who have reported that mice overexpressing acylCoA:diacylglycerol acyltransferase 2 (DGAT2)-which converts DAG to TAG- in the liver do not demonstrate hepatic insulin resistance even with elevated hepatic TAG and DAG content.[31] This has brought to the fore the idea of compartmentalisation of DAG in the hepatocyte.[32] Cytoplasmic compartmentalisation of DAG in the hepatocyte in the form of lipid droplet strongly correlateswith PKC-ϵ activation and IR whereas other lipid metabolites had no correlation with IR.[33] The dissociation of hepatic steatosis from IR has also been seen in murine models.[32] The idea that PKCs might have different affinities for different species of DAGs has also gained prominence.[34]This might partly explain the dissociation of hepatic steatosis from IR in a subset of individuals.[35]

3.2 NAFLD Multifactorial Pathogenesis:

In addition to genetic and environmental factors as well as bile acid metabolism, gut microbiota and a host of other players work in tandem and play important roles in the pathophysiological processes. The various mediators of hepatocyte injury and the pathophysiological processes involved in the development of NAFLD/NASH are discussed below.

3.2.1 Genetic Factors:

Epidemiological, familial and studies on twins have provided ample evidence regarding heritability in NAFLD.[36,37] Genetic modifications occur at multiple steps of NAFLD

pathogenesis including insulin sensitivity, fatty acid influx, oxidative stress, cytokine activity and fibrogenesis.[38] Genome-wide association studies (GWAS) have identified single nucleotide polymorphism(SNP) inPatatin-like phospholipase domain-containing 3 (PNPLA3) gene- rs738409 C>G SNP- which conferred a more than twofold risk for higher hepatic fat content.[39] Importantly, steatosis has beenfound to be independent of insulin resistance and serum lipids concentration in subjects with PNPLA3 polymorphism.[39] In addition, several other SNPs have been identified in other genes- neurocan (NCAN, SNP rs2228603), protein phosphatase 1, regulatory (inhibitor) subunit 3B (PPP1R3B, SNP rs4240624), glucokinase regulator (GCKR, SNP rs780094), lysophospholipase-like 1 (LYPLAL1, SNP rs12137855),Peroxisome Proliferator Activator- alpha (PPAR-α SNP Val227Ala), Lipin1 (LPIN1, SNP rs13412852 T) and Transmembrane 6 Superfamily member 2 (TM6SF2, SNP rs58542926 c.449 C>T).[40–43]

3.2.2 Bile Acid Metabolism:

Increased serum levels of glychochendeoxycholate, glycholate, and taurocholate have been observed in patients with NASH compared to healthy controls.[44] Bile acids regulate multiple pathways through activation of nuclear receptors like farnesoid X receptor (FXR), Takeda G protein coupled receptor 5 (TGR 5),pregnane X receptor (PXR), and vitamin D receptor (VDR).[45,46] FXR functions to protect hepatocytes from the harmful effects of increased bile acid levels by FGF-19 mediated inhibition of endogenous bile acid synthesis, upregulation of bile acid biotransformation and ameliorating hepatic inflammation through [47,4847,4847,4847,48]nuclear factor kappa B (NFK-B) pathway.[47–49]Recent studies seem to suggest that increased serum bile acid levels are independently associated with non-alcoholic steatohepatitis in non-diabetes population.[50]

3.2.3 Gut Microbiota:

Increased intestinal permeability subsequent to small intestinal bacterial overgrowth with consequent inflammation has been observed in NASH patients.[51]Intestinal absorption of monosaccharides is promoted by gut microbiota thereby increasing DNL and suppressing fasting-induced adipocyte factor (FIAF) which causes adipocyte TG accumulation.[52]Conversion of choline to trimethylamine and trimethylamine oxide (TMAO) by gut microflora has been linked to hepatic inflammation and damage.[53]Gut dysbiosis leads to decreased synthesis of secondary bile acids, which in turn decreases activation of nuclear receptors.[54] Ethanol production by gut microbiota has also been

implicated in NAFLD pathogenesis..[55] Further, NAFLD patients have been found to have lower abundance of Ruminococcus, F.prausnitzii and Coprococcus independent of BMI and IR, implying that NAFLD is associated with dysbiosis independent of body mass index(BMI) and insulin resistance(IR).[56]

3.2.4 Epigenetic Modifications:

Epigeneticstudies have shed new light on NAFLD pathogenesis by explaining the effect of environmental factors like over nutrition and physical inactivity upon gene expression.[57] 5-Hydroxymethylcytosine (5-hmC), an epigenetic modification, is likely to be involved in the pathogenesis of NAFLD by regulating liver mitochondrial biogenesis and peroxisome proliferator activated receptor γ coactivator 1 α (PPARGC1A) expression.[58]DNA methylation at certain CpG islands in genes mediating fibrogenesis has been found to differentiate between patients with mild and severe fibrosis in NAFLD.[59]Significant hypermethylation in PNPLA3 promoter region has been observed in patients with severe (F3–4) fibrosis.[60]Histone deacetylase 3 (Hdac3) has also been implicated in the diversion of metabolites from hepatic gluconeogenesis to lipogenesis and storage.[61]Thus a growing body of evidence is accumulatingin favour of the role of epigenetics in NAFLD pathogenesis.

3.2.5 Role of Circadian Rhythm:

Pathways of energy homeostasis in the liver have been found to be governed bycomplex mechanisms of transcriptional and post-translational regulation of circadian clock gene expression.[62] Evidence suggests that transcription factors-PARbZIP and Nfil3- which regulate the process of hepatic xenobiotic transformation are under the control of circadian clock proteins-Per1, Per2, Rev-erbα, Rev-erbβ, Rorα, Rorβ, Rorγ.[63]One particular SNP 3111T>C in Clock (rs1801260) has been found to be associated with overweight and an increased risk of hepatic steatosis in women.[64]An intricate network operates between circadian rhythm, epigenetic changes, gene expression and nuclear receptor(NR) working.[65] Normal hepatic lipid homoeostasis requires recruitment of HDAC3 by Rev-erbα, a circadian NR.[66]Besides bile acid homoeostasis too works under circadian control, evidenced by disturbed bile acid metabolism in mice with Per1 and Per 2 knockouts.[67] Therefore, it is amply clear that circadian misalignment can cause dysregulation of cellular metabolism leading to hepatic steatosis.[65]

3.2.6 Dietary and Environmental Factors:

Dietary habits and intake of certain food products have been implicated in the pathogenesis of NAFLD.[68]*Consumption of soft drinks has been associated with development of fatty liver independent of obesity, diabetes and hyperlipidemia*.[69,70] In a large cohort study of 199,468 young and middle aged persons who did not have NAFLD at baseline and were followed up for 1,070,991 person-years, 45,409 persons developed NAFLD.[71]*Cigarette smoking and pack-years of cigarettes smoked were found to be positively associated with NAFLD incidence and smoking was found to be an independent risk factor for NAFLD progression.*[71] Therefore, the 'exclusive'view that dietary factors lead to obesity, diabetes, metabolic syndrome and thereby impact NAFLD pathogenesis[72]isbeingincreasingly questioned, and emerging evidence suggests that *environmental stressors can cause liver injury independent of traditional risk factors.*

The spectrum of the pathophysiological pathways in NAFLD, a maze in themselves, is illustrated in **Figure 3.**

4. The Philosophy behind Medical Nomenclature:

What's in a name? That which we call a rose
By any other name would smell as sweet.
-Romeo** and **Juliet
William Shakespeare

In medical science, there have been several attempts to systematise the nomenclature of diseases.[73] Best practice recommendations have also been issued by WHO in this regard for infectious diseases.[4] The term 'Nonalcoholic Fatty Liver Disease(acronym-NAFLD)' was aptly coined as it described all those individuals who had fatty liver but did not have any significant history of alcohol intake and had no other reason for fatty liver disease. Importantly, not all patients in Ludwig's study were overweight/obese. Further research has only consolidated the point that NAFLD is a disease of multifactorial and competing etiologies and can't be ascribed to any one single factor.

Research in NAFLD to date has failed to pinpoint any particular factor as the sole cause for hepatic steatosis and the unitary treatment targeting has not yielded successful treatment options. The general idea is that NAFLD is a spectrum of disorders, with metabolic syndrome being a part - may be a major part of that spectrum. The treatment armamentarium in NAFLD remains relatively barren, despite years of research. Will changing the nomenclature address these concerns? It may in fact paradoxically direct or misdirect the therapeutics in the direction of metabolic syndrome which ultimately may not turn out to be the correct target. When the pathophysiology is still a puzzle, how would a mere change in name help?

5. MAFLD: Is the new terminology justified?

The consensus group finds multiple faults with the term NAFLD-the most important of these being: i) NAFLD is a disease of exclusion and a disease should be defined by inclusion, ii) NAFLD is a vastly heterogeneous entity and cannot be managed as one single condition and iii) NAFLD patients do consume alcohol and the impact of alcohol, albeit in non-significant amounts, on hepatic steatosis is under scrutiny.[74]The diagnosis of MAFLD requires radiological evidence of hepatic steatosis and the presence ofany one of the following three conditions-overweight/obesity, presence of diabetesmellitus (DM), or evidence of metabolic dysregulation.[74]In fact in their algorithm, the diagnosis of MAFLD is essentially identical to the diagnosis of NAFLD

There are several problems with this approach. Firstly, putting ‘non’ in the nomenclature of a disease and approaching it through exclusion has been a time-tested, simple and very effective approach in medical science. Non-Hodgkin Lymphoma, for example, encompasses a diverse variety of malignancies with very different oncological signatures and yet the terminology is very effective in delineating those disorders from Hodgkin lymphoma.[75]It is perplexingthe way the change in name is sought to be justified. The proponents of MAFLD have surprisingly split “nonalcoholic” into two words: ‘non’ and ‘alcoholic’, followed by the assertion that the word “non” trivializes their problem, while the word alcoholic demeans the patient and blames the patient for the disease. This rationale for change in terminology,however, trivializes the seriousness of changing a term which has stood the test of time for almost half a century. In fact, contrary to what has been asserted, the term ‘nonalcoholic’, goes a long way in destigmatizing the patient.

To put things in perspective,the Rome Foundation has been changing the names of functional bowel disorders many of which are not so functional after all. For example, in a validation study of 1452 patients with GI symptoms, the Rome III criteria performed only modestly in identifying those with functional dyspepsia, and were not significantly superior to previous definitions.[76] Despite one of the rationales for the revision being to allow separation of FD (functional dyspepsia) and GERD**(**Gastroesophageal reflux disease) more clearly, almost identical proportions of patients meeting criteria for each of the different definitions of FD were found to have erosive esophagitis.[76]

Secondly, merely replacing the term NAFLD withMAFLD would not make the entity any less heterogeneous.At the moment, their exists considerable uncertainty regarding the pathogenesis of NAFLD,and a change in name cannot be justified.

Thirdly, the impact of non-significant intake of alcohol on hepatic metabolism is itself very unclearas acknowledged in the consensus paper.Moreover,lipid metabolism abnormalities[77], disturbances in sirtuin[78] and PPAR-γ[79] pathways have been shown to occur in alcoholic liver disease.So, should we start calling alcoholic liver disease MAFLD from now onwards? Can the change in terminology to MAFLD provide adequate answers to these perplexing questions?Thus, it is clear that the reasons stated for such a sudden change are very flimsy and have no rational basis.

In a review concerning the challenges concerning the diagnosis and classification of NAFLD, it was argued that recommendations to change the nomenclature of NAFLD to metabolic fatty liver or metabolicsteatohepatitis would be of little help and since patientswith NAFLD/NASH were also being treated by cardiologists and diabetologists in addition to hepatologists, such changes in nomenclaturewould create confusion and should be avoided.[80]

It will be worthwhile to mention here that as regards the change in nomenclature, European Liver Patients Association (ELPA) is supposed to have expressed displeasure with the term NAFLD to the European Commission in 2018, suggesting that a change in nomenclature of NAFLD was required.[1] We tried to elicit an answer from ELPA in this regard if this was true and if so, the reasons for such a suggestion. We also sought to know how this was decided, the percentage of patients who feel uncomfortable with such terminology and finally whether the diverse pathogenesis of NAFLD - especially in non-

Caucasians - was considered in the decision. However, despite repeated queries, unfortunately we did not receive any reply from ELPA yet.

6. NAFLD: Towards a more inclusiveclassification?

The heterogeneity of NAFLD and the presence of multiple pathophysiological pathways inherent to its progression means that the time is ripe to classify NAFLD in a novel way taking into account the individual components of the pathophysiological processes. In such an approach, NAFLD can remain as an umbrella term for different subgroups with differing pathophysiological mechanisms. While the term 'NAFLD' could well represent the common final point in the disease process, the different subgroups included under it would represent the multiple separate predominant pathological pathways culminating in hepatic steatosis. We propose such a new classification for NAFLD and we believe it will help in better understanding of this seemingly elusive entity. We have tried to summarise such an approach in **Figure 4.**

7. From NAFLD to MAFLD: A Misguided Purpose?

A recent paper highlighting the 'need' to change the terminology emphasizes upon NAFLD being the "hepatic manifestation of a systemic metabolic disorder".[81]Evidence clearly suggests that hepatic steatosis, far from being a manifestation of a systemic metabolic disorder can be a major driver of insulin resistance. In addition, while the consensus group[1] acknowledges the 'heterogeneity' of NAFLD, the reasons provided for this change in nomenclature- "non" in NAFLD apparently trivializing the severity of the problem, "alcoholic" apparently putting the blame on the patient- seem too puerile. If the term "metabolic" in MAFLD is meant as a reference to metabolic syndrome, it would be an abject denial of all the available scientific evidence gathered in NAFLD research.

Conclusion:

NAFLD cannot be kept confined to the precincts of metabolic syndrome, nor is NAFLD just another 'manifestation' of metabolic syndrome. It is clear that rather than changing the nomenclaturewithout a strong scientific backing to support such a change, collaborative efforts should be launched worldwide to better understand the vast heterogeneity in NAFLD across populations and ethnicities and explore the different

pathophysiologic mechanisms with the sole purpose of modifying disease progression, bolstering the treatment arsenal and curbing this epidemic. We hope in the near future, there would be sufficient advances in our understanding of NAFLD pathogenesis to enable translation into clinical practice.

Abbreviations:

5-hmC: 5-Hydroxymethylcytosine

AASLD: American Association for the Study of Liver Diseases

DAG: Diacylglycerol

DGAT2: Diacylglycerol acyltransferase 2

DNL: De novo Lipogenesis

ELPA: European Liver Patients Association

FD: Functional Dyspepsia

FGF-19: Fibroblast Growth Factor-19

FIAF: Fasting-induced adipocyte factor

FXR: Farnesoid X Receptor

GCKR: Glucokinase Regulator

GWAS: Genome Wide Association Studies

Hdac3: Histone deacetylase 3

IR: Insulin Resistance

LPIN1: Lipin1

LYPLAL1: Lysophospholipase-like 1

MAFLD: Metabolic Associated Fatty Liver Disease

MS: Metabolic Syndrome

NASH: Non-alcoholic Steatohepatitis

NCAN: Neurocan

Nfil3: Nuclear Factor, Interleukin 3 Regulated

NFK-B: Nuclear factor kappa B pathway.

NR: Nuclear Receptor

PARbZIP: Proline and acidic amino acid-rich basic leucine zipper

Per: Periodic Circadian Regulator

PKC: Protein Kinase C

PKC-ϵ: Protein Kinase C- epsilon isoform

PNPLA3: Patatin-like phospholipase domain-containing 3

POPARGC1A: Peroxisome proliferator activated receptor γ coactivator 1 α

PPAR-α: Peroxisome Proliferator Activator- alpha

PPP1R3B: Protein phosphatase 1, regulatory (inhibitor) subunit 3B

PXR: Pregnane X receptor

Ror: Retinoic acid receptor-related orphan receptors

SNP: Single Nucleotide Polymorphism

TAG: Triacylglycerol

TG: Triglyceride

TGR 5: Takeda G protein coupled receptor 5

TM6SF2: Transmembrane 6 Superfamily member 2

TMAO: Trimethylamine oxide

VDR: Vitamin D receptor

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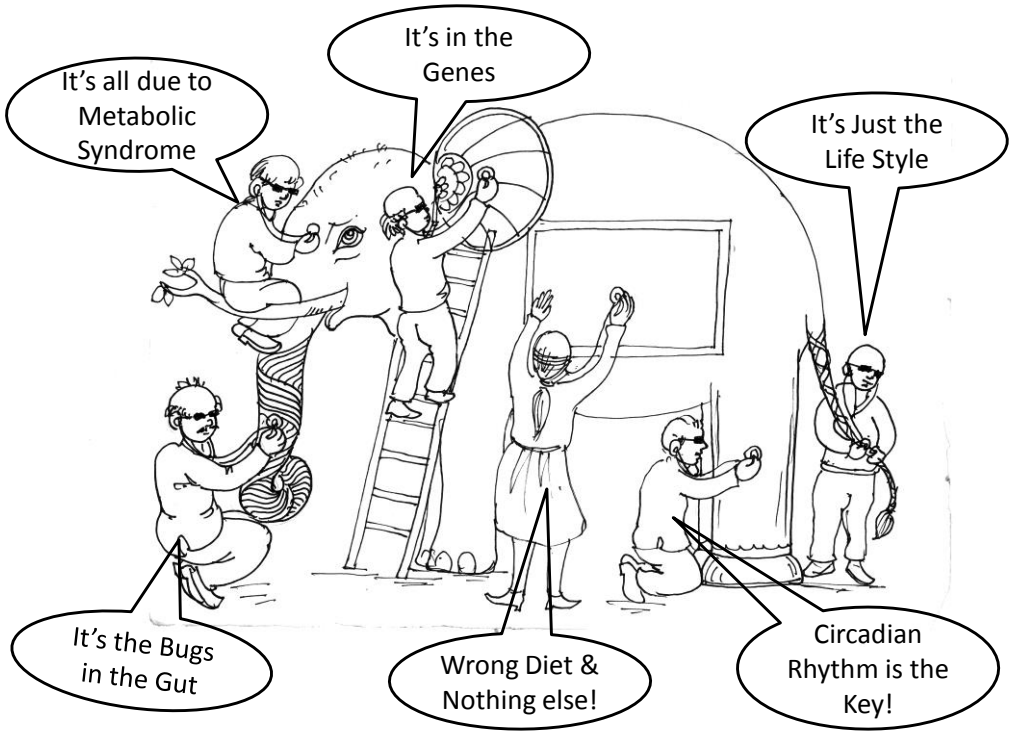

Figure 1. The different etiologies of NAFLD-described by different experts: No single factor can explain the whole spectrum of disease.

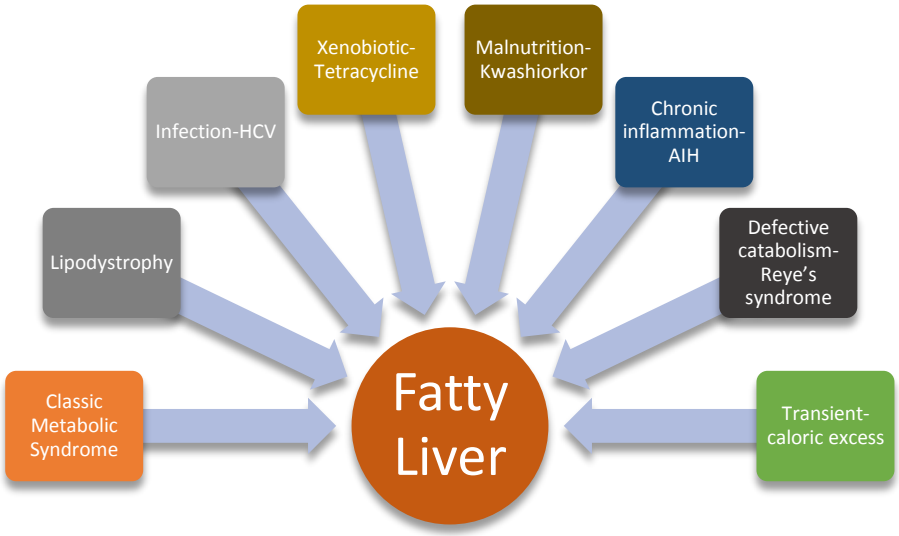

Figure 2: Different conditions that can cause hepatic steatosis

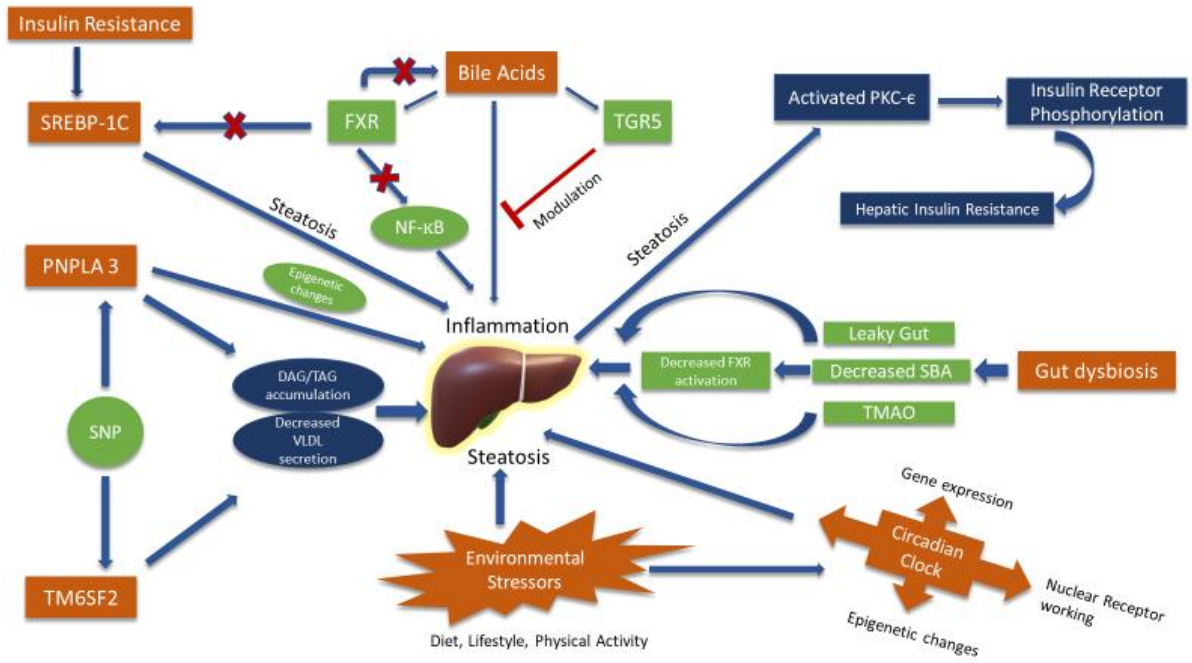

Figure 3. The Maze of NAFLD- Interactions and cross-talk among multiple factors leading to hepatic steatosis. Hepatic steatosis itself can give rise to insulin resistance.

Abbreviations: SREBP 1C- Sterol Regulatory Element Binding Protein 1C, PNPLA 3- Patatin Like PhospholipaseDomain Containing Protein-3, TM6SF2- Transmembrane 6 Superfamily Member 2, SNP- Single Nucleotide Polymorphism, DAG- Diacyl Glycerol, TAG- Triacyl Glycerol, VLDL- Very Low Density Lipoprotein, FXR- Farnesoid X Receptor, TGR5- Takeda G-Protein Receptor 5, NF-κB- Nuclear Factor Kappa B, SBA- Secondary Bile Acids, TMAO- Trimethylamine Oxide, PKCϵ- Protein Kinase C-epsilon isoform

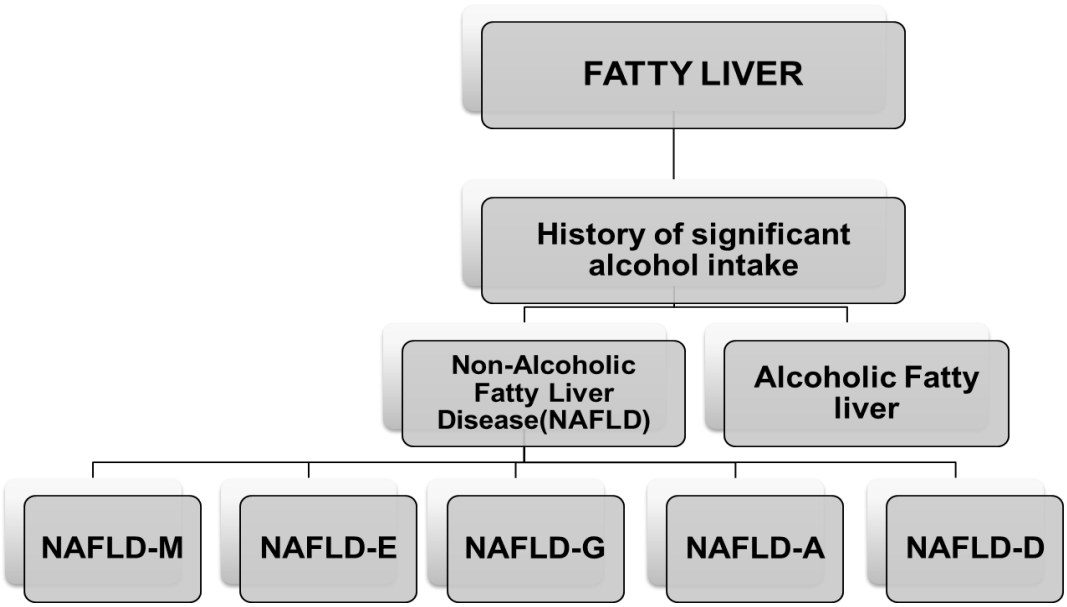

Figure 4:The MEGADiversity in NAFLD(MEGA-D): An approach to classifying NAFLD based on the predominant pathological pathway.

NAFLD-M:Metabolic syndrome associated NAFLD, **NAFLD-E:E**nvironmental Stressor Related NAFLD, **NAFLD-G:G**enetic Factor Associated NAFLD, **NAFLD-A:** Bile **A**cid Dysregulation Related NAFLD, **NAFLD-D:** Gut **D**ysbiosis Related NAFLD