Review Article

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Metabolic dysfunction-associated fatty liver disease from definition to complications

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a novel term to describe new diagnostic criteria for diagnosing fatty liver disease free of alcohol intake and associated viral hepatitis infection. These new diagnostic criteria, make it easier to diagnose than non-alcoholic fatty liver disease (NAFLD). Although we may not have a lot of studies about MAFLD yet, we have plenty of evidence about IR, metabolic syndrome and dysfunction, and NAFLD. In this review, we try to spotlight some important and updated knowledge about MAFLD and its related conditions, to help us better understand and deal with this global problem.

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new term and definition introduced in 2020 by expert consensus, describing primary fatty liver disease related to insulin resistance and associated metabolic dysfunction. The term MAFLD is superior in reflecting the pathogenesis of the majority of cases of what was called non-alcoholic fatty liver disease (NAFLD), and it is easier to diagnosis [1]. MAFLD has a better role in detecting steatosis-related fibrosis [2], and the ability to be applied in cases where multiple etiologies of steatosis are present [3, 4]. Additionally, MAFLD raises the awareness about the cause of this serious global medical issue and it is better accepted by general population and patients. MAFLD also focuses on the main cause of primary steatosis, making its management plan more obvious [5].

Definitions.

Steatosis.

Steatosis or fatty liver is defined as fat or lipid accumulation inside the hepatocytes in at least 5% of hepatocytes [6, 7]. The causes have been identified for steatosis, these causes can be classified into primary and secondary ones [8].

Primary steatosis or NAFLD.

Primary steatosis refers to steatosis not related to significant alcohol consumption, with the absence of identified causes of the name secondary steatosis [7-9]. Significant alcohol consumption is defined as alcohol intake which is greater than 30 grams of alcohol daily in men and 20 grams in women [9,10].

Secondary steatosis and AFLD.

Secondary steatosis includes alcoholic fatty liver disease (AFLD) which is fatty liver disease caused by significant alcohol intake. Many other conditions have been identified as causes for secondary accumulation of fat in hepatocytes, for example; starvation, hepatitis C virus (HCV) especially genotype 3, steatogenic drugs (glucocorticoids, valproate, amiodarone, tamoxifen, methotrexate, anti-retroviral agents for HIV), parenteral nutrition, acute fatty liver of pregnancy, HELLP (hemolytic anemia, elevated liver enzymes and low platelet count) syndrome, Reye's syndrome, lipodystrophies, a-beta-lipoproteinemia, Wilson's disease and inborn errors of metabolism [6,9,11,] **(Figure 1)**.

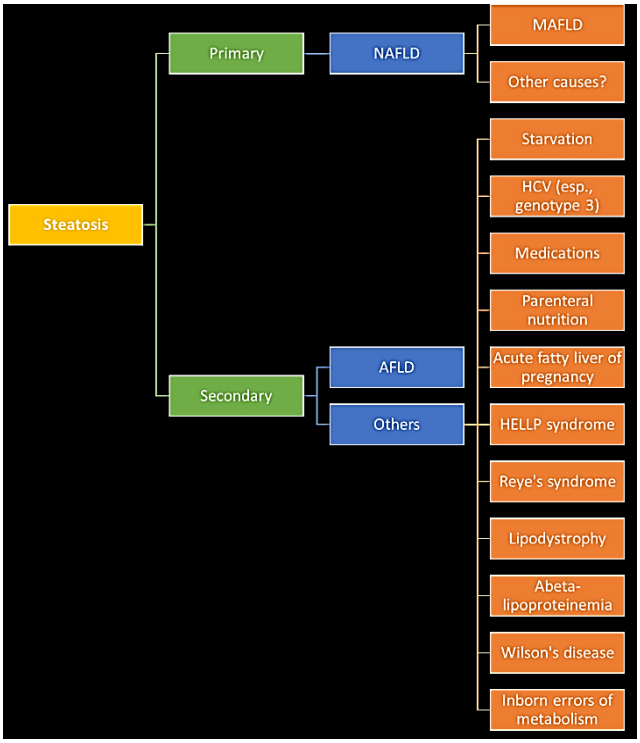

Figure 1: Causes of fatty liver; AFLD, alcoholic fatty liver disease; HELLP, hemolytic anemia, elevated liver enzymes and low platelet count; HCV, hepatitis C virus; MAFLD: metabolic dysfunction-associated fatty liver disease; NAFLD: non-alcoholic fatty liver disease[11].

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MAFLD. Extensive research has showed that insulin resistance (IR) and its related metabolic dysfunction are the main pathogenesis in most cases of primary steatosis or NAFLD, so metabolic dysfunction-associated fatty liver disease (MAFLD) has been introduced as a new term to describe this condition [1].

MAFLD versus NAFLD.

MAFLD and NAFLD are not exactly the same, as some cases of NAFLD have not been linked to IR, raising the possibility that they may have another undiscovered cause of steatosis, or they have not been evaluated properly for secondary causes of steatosis. In addition, some cases of MAFLD have another etiology for steatosis like significant alcohol consumption or any other secondary cause of steatosis, but for NAFLD to be diagnosed these causes must be excluded [3, 4], **(Figure 2)**.

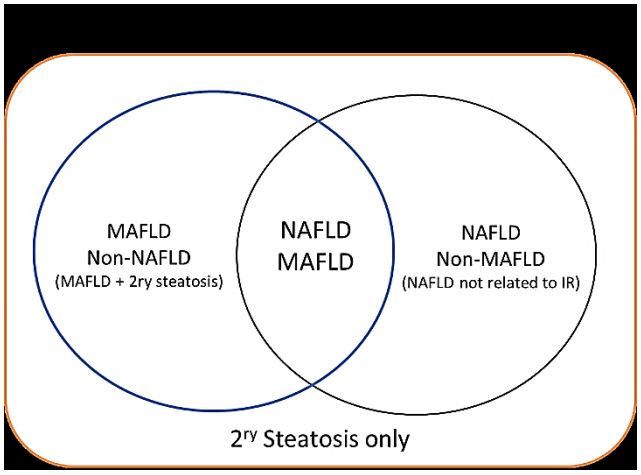

Figure 2. Diagrammatic presentation of the relationship between different types of steatoses (2ry: secondary, IR: insulin resistance, MAFLD: Metabolic dysfunction-associated fatty liver disease, NAFLD: non-alcoholic fatty liver disease [3, 4].

NAFL and MAFL.

In histopathological evaluation, cases of NAFLD may have no significant evidence of hepatitis related to the fat accumulation process, i.e., steatohepatitis, this condition is called non-alcoholic fatty liver NAFL [3, 7]. In the era of MAFLD, MAFLD cases without evidence of significant steatohepatitis may be named metabolic dysfunction-associated fatty liver MAFL.

NASH and MASH.

NAFLD cases have a significant steatohepatitis at histological level are named non-alcoholic steatohepatitis (NASH) cases [3, 7] while MAFLD cases with significant steatohepatitis in histopathology named metabolic dysfunction-associated steatohepatitis (MASH) cases.

Cryptogenic cirrhosis and NASH-cirrhosis.

several causes of cirrhosis have been identified, however; a portion of cirrhosis cases with unknown etiology have been always present, these cases were assumed the name 'cryptogenic cirrhosis', which is defined as cirrhosis without known etiology. NASH has been identified as a chief cause of cryptogenic cirrhosis, leading to the presentation of a new term 'NASH-cirrhosis'. However, NASH-cirrhosis does not describe all cases of cryptogenic cirrhosis, so new causes of cirrhosis must be examined [12, 13].

NASH-cirrhosis and MASH-cirrhosis.

As stated above, NASH-cirrhosis is the chief part of cryptogenic cirrhosis, so; MASH-cirrhosis is also a great contributor of both NASH-cirrhosis and cryptogenic cirrhosis (figure 3). MASH-cirrhosis, as any other cirrhosis, has two stages; compensation and decompensation [14].

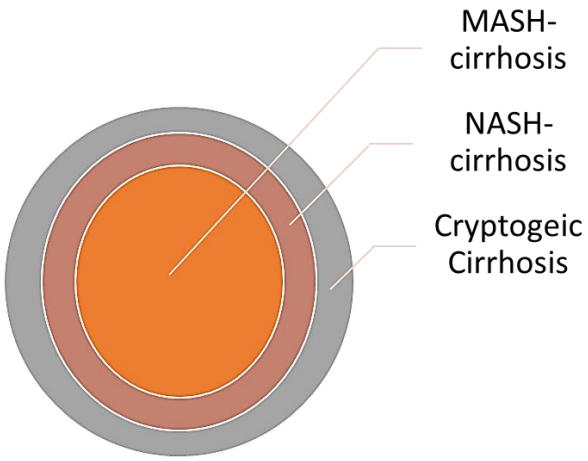

Figure 3. Diagrammatic presentation of the relationship between cryptogenic cirrhosis, NASH-cirrhosis and MASH cirrhosis [3, 13].

Spectrum of MAFLD.

As noticed before, MAFLD, like NAFLD, includes a spectrum of different diseases and conditions, ranging in severity [3, 7] **(Figure 4)**.

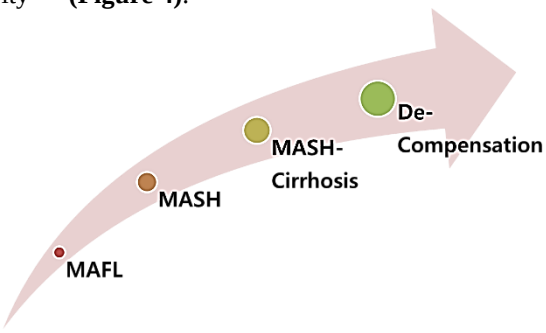

Figure 4. Spectrum of MAFLD is the same as NAFLD (MAFL: metabolic dysfunction-associated fatty liver disease, MASH: metabolic dysfunction steatohepatitis) [3, 7].

Prevalence.

Now, no sufficient data is existing about the exact extension of MAFLD around the globe, though NAFLD epidemiology has been studied well, giving an important idea about the widespread of both NAFLD and MAFLD. NAFLD is the most common cause of chronic liver disease

worldwide, affecting about 25% of all adults around the globe [15]. Studies demonstrated that, the prevalence of NAFLD in the United States, is up to 46% of the adults [16], 32% in the middle east, [17] and in Egypt, about 33% of the adult population [18].

Risk factors.

MAFLD is found exclusively in patients with IR-associated metabolic dysfunction, so it is found mostly in obese patients, diabetic patients, dyslipidemia patients, and patients with metabolic syndrome [17, 19].

Pathogenesis

Insulin resistance.

Numerous strong evidences suggesting that, the main pathogenesis in most NAFLD cases is the insulin resistance (IR) [20-22]. MAFLD, on the other hand, is based by definition on the presence of insulin resistance-related metabolic dysfunction [1]. IR means subnormal response by the tissues to insulin levels [23, 24], due to primary or secondary causes. Primary causes of IR include inherited disorders like mutations of the insulin receptors [24]. however, secondary causes of IR include obesity, inactivity with sedentary life style, pregnancy (due to placental lactogen), auto-immunity (anti-insulin antibodies, and anti-insulin receptors antibodies in type 2 syndrome of IR), medications (as steroids, combined oral contraceptives and antiretrovirals for HIV),[25]. IR has many sequences and complications, like; prediabetes, diabetes mellitus (DM), dyslipidemia, metabolic syndrome, hypertension (HTN), cardiovascular diseases (CVS), metabolic dysfunction-associated fatty liver diseases (MAFLD), polycystic ovary syndrome, acanthosis nigricans, skin tags, alopecia, and obesity-related cancers [23, 24]. IR leads to MAFLD by increasing lipolysis, synthesis of triglyceride, uptake of free fatty acids (FFA) by the liver, and accumulation of triglyceride in the liver, which results in steatosis, and may lead to steatohepatitis and related fibrosis and cirrhosis [3,7,26,27]. Several lipid-derived hormones have an significant role in pathogenesis of MAFLD including; adiponectin, leptin, and incretins as aprotective hormones from MAFLD. On the other hand, resistin plays an important role in insulin resistance, however, further researches are required to understand well these mechanisms [27, 28].

Metabolic Syndrome/Insulin-Resistance.

Metabolic syndrome is a group of diseases linked to IR, including; prediabetes, DM type2, HTN, obesity, and dyslipidemia. In most cases, NAFLD can be considered as a part of the metabolic syndrome [21], while MAFLD is linked to metabolic syndrome by name, definition and diagnostic criteria [1]. Metabolic syndrome has many definitions, for example; according to the American association of clinical endocrinologists (AACE) in 2003, its diagnosis requires presence of high risk of IR (presence of one or more complications of IR, sedentary lifestyle, history of gestational DM, non-white race, or family history of DM type 2, HTN or CVD) or presence of overweight or obesity (body mass index ≥25 kg/m^2, or waist circumference ≥ 102 cm in men and 88 cm in women), plus two or more conditions from the following; impaired glycemic status (fasting blood glucose ≥ 110 mg/dl, or 2 hours postprandial blood glucose ≥ 140 mg/dl), HTN (arterial blood pressure ≥ 130/85 mmHg), low level of high-density lipoprotein (HDL) cholesterol (<40 mg/dl in men and <50 mg/dl in women) or hypertriglyceridemia (≥150 mg/dl) [29], **(figure 5).**

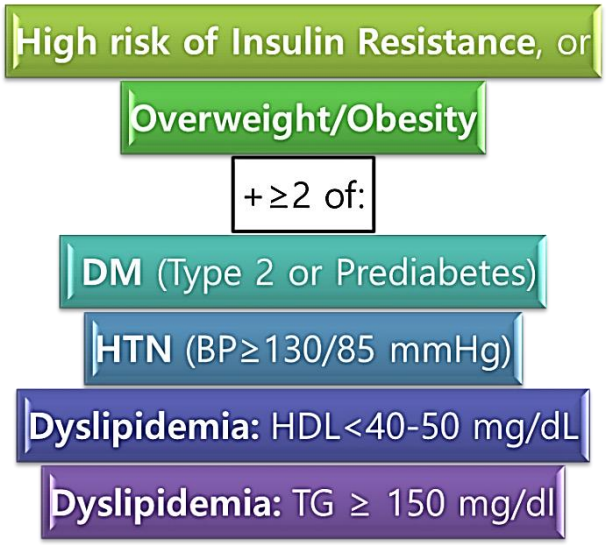

Figure 5. Diagnosis of metabolic syndrome according to AACE, 2003 AACE: American association of clinical endocrinologists, BP: blood pressure, DM: diabetes mellitus, HDL: high density lipoprotein, HTN: hypertension, TGs: triglycerides) [29]

Many components of metabolic syndrome have been studied independently with NAFLD, these components are considered risk factors for MAFLD [17], and MAFLD is a risk factor for them [30].

Diagnosis of MAFLD.

Diagnostic criteria.

For diagnosis of NAFLD, it is required to diagnose steatosis and exclude all causes of secondary steatosis, which is difficult. MAFLD diagnosis is much easier, it is enough to detect steatosis and metabolic dysfunction related to insulin resistance, for example; obesity, type 2 DM, or two of the following; prediabetes, increased WC, HTN, hyper-triglyceridemia, decreased HDL, increased homeostasis model assessment of insulin resistance (HOMA) score, and elevated level of C-reactive protein (CRP) [1] **(figure 6).**

1. Diagnosis of steatosis.

There is no specific clinical presentation or single laboratory test can diagnose steatosis. Some patients may have hepatomegaly with normal liver function tests or slightly elevated alanine transaminase (ALT) and aspartate transaminase may (AST) [31, 11]. On the other side, many markers and scores have been developed to detect fibrosis related to steatohepatitis [32].

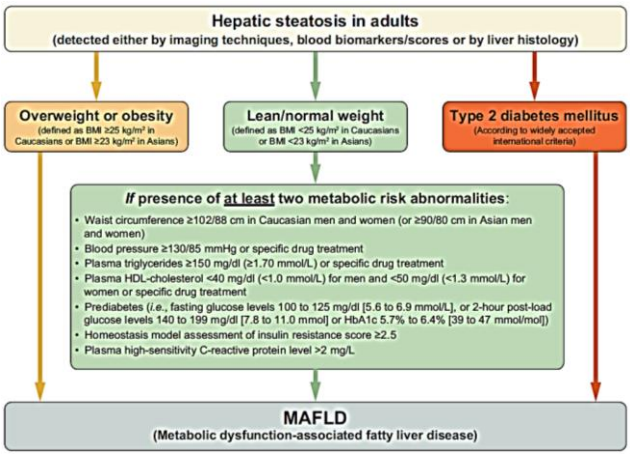

Figure 6. Diagnostic criteria of MAFLD (BMI: body mass index, HDL: high density lipoprotein) 1.

Radiological, ultrasound (US) is the most used modality and can diagnose grades steatosis by detection of increased echogenicity of the liver versus the kidneys and the spleen. If the diaphragm and portal vein wall can be detected easily, it is mild steatosis (score 1). Moderate steatosis (score 2) is diagnosed when there is slight impairment in detection of the diaphragm and portal vein wall, and severe steatosis (score 3) is diagnosed when both of them cannot be visualized or difficultly visualized [33] (figure 7). Computed tomography (CT) scan can identify steatosis by detection of decreased hepatic attenuation [34]. Magnetic resonance imaging (MRI) identify steatosis by detection of increased fat signal [32].

Liver biopsy is still the gold standard for diagnosis of steatosis, but it is rarely indicated, and can only be obtained if the diagnosis is unclear, or there is another indication for biopsy [35].

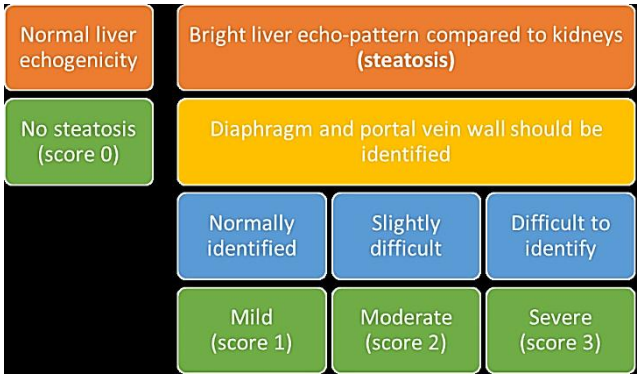

Figure 7. Diagnosis and grading of steatosis by ultrasound B mode [33]

2. Diagnosis of metabolic dysfunction.

Metabolic dysfunction associated with MAFLD can be detected by.

Clinical evaluation. including body mass index (BMI) ≥ 25 in Caucasians and 23 in Asians , waist circumference (WC) ≥ 102/88 in Caucasian men and women, or ≥ 90/80 in Asian men and women., HTN defined as chronic elevation of blood pressure (BP) ≥ 130/85, or being on specific BP lowering treatment [1, 36].

Laboratory criteria. including diagnosis of DM type 2 by hemoglobin A1c (HbA1c) ≥ 6.5, fasting blood glucose (FBG) level ≥ 126 mg/dl, 2-hour post-prandial blood glucose (PPBG) level ≥ 200 mg/dl, or random blood glucose (RBG) ≥ 200 mg/dl in patients with classic symptoms of hyperglycemia or hyperglycemic crisis [1, 36], triglyceride (TGs) level in plasma ≥ 150 mg/dl or patient is on lipid lowering agent, HDL-cholesterol < 40 mg/dl in men and 50 mg/dl in women or patient is on a lipid lowering agent, high-sensitivity C-reactive protein level (CRP) > 2mg/l, homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.5, prediabetes defined as FBG level ranging from 100 to 125 mg/dl, PPBG level ranging from 140 to 199 mg/dl, or hemoglobin A1c (HbA1c) ranging from 5.7 to 6.4% [1, 36].

Complications. IR has many serious complications like DM, HTN, CVD, and their complications like; neuropathy, nephropathy, retinopathy, diabetic foot, neurovascular events, coronary events, and other serious events. MAFLD increases the risk of HTN, DM and, as a result, may aggravate these complications [37, 38]. Mortality in MAFLD is linked mainly to these complications [30]. MAFLD also leads to MASH, then MASH-related fibrosis, ending in cirrhosis, decompensation, and complications of cirrhosis including hepatocellular carcinoma (HCC) [39, 40].

Conclusion

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a novel term which is more accurately reflects the pathogenesis of fatty liver disease related to insulin resistance and associated metabolic dysfunction and can help in patients stratification for management than term non-alcoholic fatty liver disease (NAFLD). Compared to NAFLD, MAFLD was suggested as a more appropriate central term.

References

1. Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., ... & George, J. (2020). A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of hepatology*, *73*(1), 202-209.
2. Yamamura, S., Eslam, M., Kawaguchi, T., Tsutsumi, T., Nakano, D., Yoshinaga, S., ... & Torimura, T. (2020). MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. *Liver International*, *40*(12), 3018-3030.
3. Kawaguchi, T., Tsutsumi, T., Nakano, D., & Torimura, T. (2021). MAFLD: Renovation of clinical practice and disease awareness of fatty liver. *Hepatology Research*.
4. Lin, S. U., Huang, J., Wang, M., Kumar, R., Liu, Y., Liu, S., ... & Zhu, Y. (2020). Comparison of

MAFLD and NAFLD diagnostic criteria in real world. *Liver international*, *40*(9), 2082-2089.

5. Shiha, G., Korenjak, M., Eskridge, W., Casanovas, T., Velez-Moller, P., Högström, S., ... & Eslam, M. (2021). Redefining fatty liver disease: an international patient perspective. *The lancet Gastroenterology & hepatology*, *6*(1), 73-79.
6. Idilman, I. S., Ozdeniz, I., & Karcaaltincaba, M. (2016, December). Hepatic steatosis: etiology, patterns, and quantification. In *Seminars in Ultrasound, CT and MRI* (Vol. 37, No. 6, pp. 501-510). WB Saunders.
7. Cobbina, E., & Akhlaghi, F. (2017). Non-alcoholic fatty liver disease (NAFLD)–pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug metabolism reviews*, *49*(2), 197-211.
8. Maurice, J., & Manousou, P. (2018). Non-alcoholic fatty liver disease. *Clinical medicine*, *18*(3), 245.
9. Chalasani, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., ... & Sanyal, A. J. (2018). The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*, *67*(1), 328-357.
10. Liangpunsakul, S., & Chalasani, N. (2012). What do we recommend our patients with NAFLD about alcohol use?. *The American journal of gastroenterology*, *107*(7), 976.
11. Sunil G Sheth, S.C., Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults. Uptodate, Post, TW (Ed), UpToDate, Waltham, MA., 2021.
12. Caldwell, S. H., & Crespo, D. M. (2004). The spectrum expanded: cryptogenic cirrhosis and the natural history of non-alcoholic fatty liver diseasePowell EE, Cooksley WGE, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years [Hepatology 1990; 11: 74–80]. *Journal of hepatology*, *40*(4), 578-584.
13. Thuluvath, P. J., Kantsevoy, S., Thuluvath, A. J., & Savva, Y. (2018). Is cryptogenic cirrhosis different from NASH cirrhosis?. *Journal of hepatology*, *68*(3), 519-525.
14. D'Amico, G., Morabito, A., D'Amico, M., Pasta, L., Malizia, G., Rebora, P., & Valsecchi, M. G. (2018). New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. *Hepatology international*, *12*(1), 34-43.
15. Younossi, Z., Anstee, Q. M., Marietti, M., Hardy, T., Henry, L., Eslam, M., ... & Bugianesi, E. (2018). Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nature reviews Gastroenterology & hepatology*, *15*(1), 11-20.
16. Williams, C. D., Stengel, J., Asike, M. I., Torres, D. M., Shaw, J., Contreras, M., ... & Harrison, S. A. (2011). Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*, *140*(1), 124-131.
17. Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*, *64*(1), 73-84.
18. Tomah, S., Hamdy, O., Abuelmagd, M. M., Hassan, A. H., Alkhouri, N., Al-Badri, M. R., ... & Eid, E. A. (2021). Prevalence of and risk factors for non-alcoholic fatty liver disease (NAFLD) and fibrosis among young adults in Egypt. *BMJ open gastroenterology*, *8*(1), e000780.
19. Younossi, Z. M., Stepanova, M., Afendy, M., Fang, Y., Younossi, Y., Mir, H., & Srishord, M. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clinical gastroenterology and hepatology*, *9*(6), 524-530.
20. Watt, M. J., Miotto, P. M., De Nardo, W., & Montgomery, M. K. (2019). The liver as an endocrine organ—linking NAFLD and insulin resistance. *Endocrine Reviews*, *40*(5), 1367-1393.
21. Lonardo, A., Leoni, S., Alswat, K. A., & Fouad, Y. (2020). History of nonalcoholic fatty liver disease. *International Journal of Molecular Sciences*, *21*(16), 5888.
22. Chitturi, S., Abeygunasekera, S., Farrell, G. C., Holmes-Walker, J., Hui, J. M., Fung, C., ... & George, J. (2002). NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology*, *35*(2), 373-379.
23. Venkatasamy, V. V., Pericherla, S., Manthuruthil, S., Mishra, S., & Hanno, R. (2013). Effect of physical activity on insulin resistance, inflammation and oxidative stress in diabetes mellitus. *Journal of clinical and diagnostic research: JCDR*, *7*(8), 1764.
24. Semple, R. K., Savage, D. B., Cochran, E. K., Gorden, P., & O'Rahilly, S. (2011). Genetic syndromes of severe insulin resistance. *Endocrine reviews*, *32*(4), 498-514.
25. Mantzoros, C. (2005). Insulin resistance: definition and clinical spectrum. *Up to Date Online*, *14*, 1-5.
26. Santoleri, D., & Titchenell, P. M. (2019). Resolving the paradox of hepatic insulin resistance. *Cellular and molecular gastroenterology and hepatology*, *7*(2), 447-456.
27. Tendler, D.A., Pathogenesis of nonalcoholic fatty liver disease. Uptodate, Post, TW (Ed), UpToDate, Waltham, MA., 2021.
28. Richardson, M. M., Jonsson, J. R., Powell, E. E., Brunt, E. M., Neuschwander–Tetri, B. A., Bhathal, P. S., ... & Clouston, A. D. (2007). Progressive fibrosis in nonalcoholic steatohepatitis: association with altered regeneration and a ductular reaction. *Gastroenterology*, *133*(1), 80-90.

29. Adediran, O., Akintunde, A. A., Edo, A. E., Opadijo, O. G., & Araoye, A. M. (2012). Impact of urbanization and gender on frequency of metabolic syndrome among native Abuja settlers in Nigeria. *Journal of cardiovascular disease research*, *3*(3), 191-196.

30. CD, B., & Targher, G. (2015). NAFLD: a multisystem disease. *J Hepatol*, *62*, S47-S64.

31. Mofrad, P., Contos, M. J., Haque, M., Sargeant, C., Fisher, R. A., Luketic, V. A., ... & Sanyal, A. J. (2003). Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*, *37*(6), 1286-1292.

32. Stern, C., & Castera, L. (2017). Non-invasive diagnosis of hepatic steatosis. *Hepatology international*, *11*(1), 70-78.

33. Ferraioli, G., & Monteiro, L. B. S. (2019). Ultrasound-based techniques for the diagnosis of liver steatosis. *World journal of gastroenterology*, *25*(40), 6053.

34. Taydas, O., & Koc, U. (2020). Evaluation of Hepatic Steatosis with CT and Correlation with Anthropometric Measurements. *Current medical imaging*, *16*(4), 452-458.

35. Papatheodoridi, M., & Cholongitas, E. (2018). Diagnosis of non-alcoholic fatty liver disease (NAFLD): current concepts. *Current pharmaceutical design*, *24*(38), 4574-4586.

36. Eslam, M., Sanyal, A. J., George, J., Sanyal, A., Neuschwander-Tetri, B., Tiribelli, C., ... & Younossi, Z. (2020). MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*, *158*(7), 1999-2014.

37. Cole, J. B., & Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature reviews nephrology*, *16*(7), 377-390.

38. MacFadyen, R. J., Tree, M., Lever, A. F., & Reid, J. L. (1992). Effects of the angiotensin II receptor antagonist losartan (DuP 753/MK 954) on arterial blood pressure, heart rate, plasma concentrations of angiotensin II and renin and the pressor response to infused angiotensin II in the salt-deplete dog. *Clinical Science*, *83*(5), 549-556.

39. Ekstedt, M., Nasr, P., & Kechagias, S. (2017). Natural history of NAFLD/NASH. *Current hepatology reports*, *16*(4), 391-397.

40. Tsochatzis, E. A., Bosch, J., & Burroughs, A. K. (2014). Liver cirrhosis. *The Lancet*, *383*(9930), 1749-1761.