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Non- Alcoholic Fatty Liver Disease

Kalyani Dinkar Bankar, Sonali Kalam, Dr. Gajanan Sanap
Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Phulambri, Aurangabad, Maharashtra, India

Abstract: *The increase in Non-alcoholic Adipose Liver Disease(NAFLD) and the imminent exposure of habitual viral hepatitis thanks to new and effective curatives is motivating hepatologists to change their clinical approach to habitual liver complaint. NAFLD- cirrhosis or NAFLD- Hepatocellular Carcinoma(HCC) are now the alternate cause of liver transplantation in the USA. This short- review is concentrated to the epidemiology of NAFLD/ Non-alchoholic Steatohepatitis(NASH), including the description of this complaint which should be revised as well agitating the frequence, threat factors for progression, natural history and mortality. NAFLD is considered to be the hepatic incarnation of the metabolic pattern(MS). It affects 25- 30 of the general population and the threat factors are nearly identical to those of MS. The natural history involves either the development of cardiovascular conditions or cirrhosis and HCC. HCC can also develop in NASH in the absence of cirrhosis(45 of cases). We conclude that an transnational agreement conference on the description, natural history, programs of surveillance and new pharmacological treatments of NAFLD and NASH is urgently demanded.*

Keywords: Fatty liver, Insulin resistance, NAFLD, NASH, Non-alcoholic steatohepatitis, Pioglitazone, Prediabetes, Treatment, Type 2 diabetes

I. INTRODUCTION

Non-alcoholic adipose liver complaint(NAFLD) is a clinicopathological condition that comprises a wide diapason of liver damage, ranging from steatosis alone to steatohepatitis, advanced fibrosis and cirrhosis. The pathological picture resembles alcohol- convinced liver injury, but NAFLD occurs in cases who do not consume significant quantities of alcohol. Non-alcoholic steatohepatitis represents only a stage in the diapason of NAFLD and is defined pathologically by the presence of steatosis together with necro- seditious exertion, substantially of lobular distribution, with or without Mallory's hyaline or fibrosis(1,2)The clinical counteraccusations of NAFLD are deduced substantially from its implicit to progress to end- stage liver complaint, whereas simple uncomplicated steatosis follows a fairly benign course in utmost cases.(3,4)Adipose liver complaint is n't a new condition, and indeed, alcohol- convinced liver injury dates back thousands of times. The realityofnon-alcoholic adipose liver complaint(NAFLD) is also not a new condition, but was not appreciated in early reports. In the 1950s, livers harmonious withnon-alcoholic steatohepatitis(NASH) were described in fat individualities, but secret alcohol use was suspected.(5) In the now notorious report of Ludwig et al. in 1980, the term NASH was chased.(1) It was n't until the 1990s, still, that the frequence and adding prevalence of the condition brought it into the spotlight. It was n't coexistence that the recognition of NAFLD matched the intimidating increase in body mass indicator(BMI) in the American population(6)

Nonalcoholic adipose liver complaint(NAFLD) is a clinico- pathologically defined reality most generally associated with characteristics associated with increased cardiovascular threat, appertained to inclusively as metabolic pattern. Adipose liver itself is singly associated with increased cardiovascular threat(7) and biomarkers of cardiovascular complaint(8), and, in fat individualities, it's a marker of insulin resistance(9) and diabetes(10). Population studies have shown that NAFLD itself is presumably a cause of increased mortality(11). By description, NAFLD occurs in individualities whose alcohol consumption is insignificant(12)

PREVALENCE

The frequence of NAFLD is fleetly adding worldwide in resemblant with the increase in rotundity and type 2 diabetes(13). It's important to note that this frequence is incompletely dependent upon the system used to diagnose FL, the system used to assess alcohol input and the arrestment point used to count ' applicable' alcohol input, see table 2, with separate references(14,15). The frequence of NAFLD in the general population is estimated to be 20 – 30 in Western

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countries(16,17,18) and 15 in Asian countries(19,20). In Saudi Arabia, the frequence of NAFLD as estimated by reckoned tomography is about 10%.

Type of study	Country and type of population	Prevalence of NAFLD[%]	Prevalence of NASH[%]
Autopsy random series Hilden[20] Ground[21]	Sweden USA	24 16	n.r. n.r.
Autopsy hospitalized deaths Wanless[22]	Canada	7	3
Hospital series-liver biopsy 7 studies summarized by McCullough[23] Berasain[24]	USA,Japan,Europe Spain	15-84 n.r.	n.r. 16
Hospital series -surgical patients Living donors Macros and Hwang [25,26] Bariatric surgery Dixon ,Marceau, DelGaudio, Luyckx, Silverman and Kral [27-32]	USA USA, Europe	 20	 n.r. n.r.
General population study imaging ultrasound [33] Bellentani[34] Bedogi[35] Nomura[36] Omagari[38] Araujo[39] Radu[40]	 Italy Lean Obese Italy Italy Japan Italy Japan Brazil Romania	 58 16 76 24.5 25 14 20 9 33.5 20	 n.r. n.r. n.r. n.r. n.r. n.r. n.r. n.r. n.r. n.r.
Imaging CT scan E1-Hassan[41]	 Saudi Arabia	10 34	n.r. n.r.
Imaging PMRS Browning[42]	USA Hispanic White Black	45 33 24	n.r. n.r. n.r. n.r.
Eetrapolation based on alteration of ALT Patt[43] NHANES111[44]	 USA USA	 14-21 3-23	 n.r. n.r.
n.1=Not reported			

Table 1. Prevalence of NAFLD And NASH worldwide according to different types of study and population.

SIGNIFICANCE OF PATHOPHYSIOLOGY OF NAFLD/NASH:-

As NAFLD is frequently asymptomatic, it can be present for times before it's detected. This habitual, underpinning condition has the implicit to progress to serious, life- hanging ails. If not addressed. NAFLD has the implicit to progress to the ensuing conditions .

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Non-alcoholic Steatohepatitis:-

Nonalcoholicsteatohepatits(NASH) occurs when hepatocytes come injured by stored fats and seditious processes take over leading to the reclamation cells in the ingrain vulnerable system including Risk- suchlike receptors(TLRs), Kupffer cells(KCs), lymphocytes and neutrophils and conceivably inflammasome(21) The goods of NASH are destruction of liver cells with possible progression to fibrosis which leads to dropped liver function.

Cirrhosis :-

Cirrhosis still, damage in the liver can progress to cirrhosis, If the inflammation and fibrosis continue. Cirrhosis occurs when stringy towel replaces damaged hepatocytes, leading to farther drop in liver function. Cirrhosis is the twelfth leading cause of death in the United States and can lead to portal hypertension and hostility (22)

Liver Cancer:-

farther damage to the liver can affect in the conformation of nasty tumors or hepatocellular melanoma. Although cirrhosis is n't a direct cause for all cases of liver cancer, it's a significant and preventable threat factor that leads to a potentially-fatal condition. The American Cancer Society estimates individualities will be diagnosed with primary liver cancer in2018 and of those individualities, will die from this illness(American Cancer Society, 2018).(23).

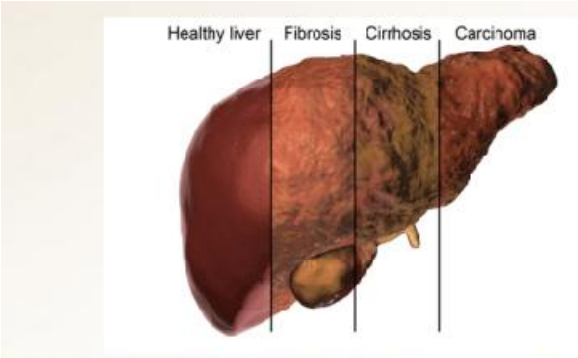
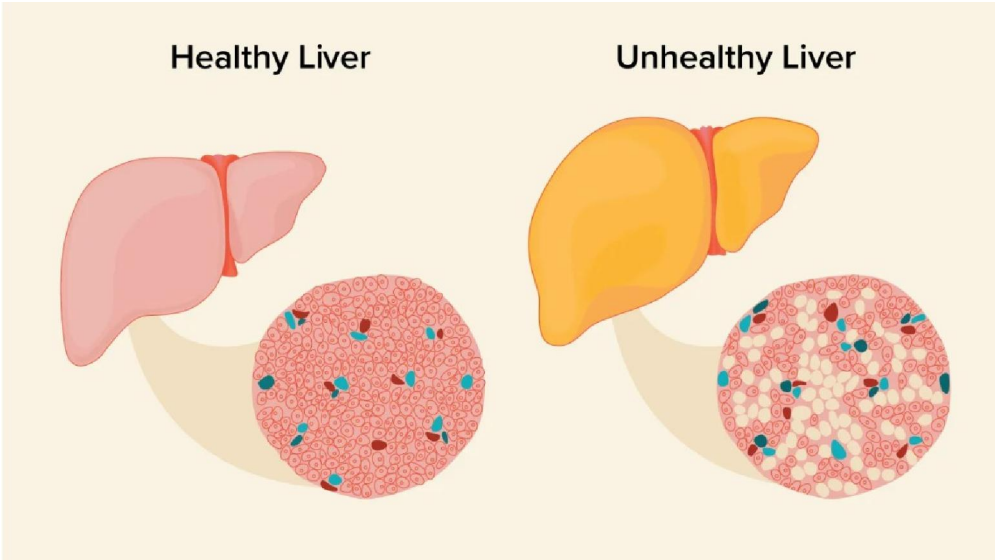


Figure 4. Progression of liver damage. From *Fatty liver disease* by Fact Dr., from https://factdr.com/health-conditions/fatty-liver-disease/

Damage to the liver may also result in disease processes in other body systems. Once the liver has become damaged, the affected individual is at risk for the following condition.



PATHOGENESIS:-

The pathogenesis of NAFLD is still unclear. Hepatic steatosis is due to lipid accumulation, substantially of triglycerides, within hepatocytes. The mechanisms leading to lipid accumulation are n't fully understood, but it could

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potentially affect from insulin resistance(24,25) and dropped disposal of adipose acids from disabled mitochondrial b-oxidation or deficient product of veritably low viscosity lipoprotein. Some lines of substantiation, albeit still inconclusive, and some deduced from studies in beast models of adipose liver, suggest that oxidative stress/ lipid peroxidation, bacterial poisons, overproduction of tumour necrosis factor- a, revision of hepatocyte adenosine triphosphate stores and cytochrome P450 Cyp2E1/ Cyp4A enzyme exertion may play a part in the birth and progression of NAFLD.

Lipid peroxidation seems to increase with the inflexibility of steatosis.(26) Malondialdehyde, an end- product of lipid peroxidation, activates hepatic stellate cells, stimulating collagen product and fibrogenesis. Malondialdehyde may also contribute to inflammation by cranking nuclear factor- jB(NF- jB), which regulates the expression ofpro-inflammatory cytokines, similar as tumour necrosis factor- a and interleukin- 8.30 Another end- product of lipid peroxidation, 4-hydroxynonenal, is a strong chemo- attractant for neutrophils. likewise, the threat factors for the development of NAFLD, videlicet rotundity with rapid-fire weight loss and type 2 diabetes mellitus, lead to increased circulating situations of free adipose acids with enhanced attention in the liver. Free adipose acids per se are potentially cytotoxic, 31 and may also increase cytochrome P450 Cyp2E1/ Cyp4A exertion, as shown in a rat model of NAFLD using a diet deficient in methionine – choline(27,28) This substantiation suggests that oxidative stress and lipid peroxidation may, in part, be critical factors involved in the birth and, presumably, progression of NAFLD.

Based on the fact that metronidazole and polymixin B may prevent the development of NAFLD in obese patients undergoing intestinal bypass,(29) and in rats receiving total parenteral nutrition,(30,31) a role of endotoxin/cytokine-mediated injury has been suggested as a contributing factor to the development of NAFLD. More recently, it has been shown that genetically obese mice are very sensitive to the effect of lipopolysaccharide in developing NAFLD.(32) The messenger RNA of interferon-c, which sensitizes hepatocytes to tumour necrosis factor-a toxicity, is over-expressed, whereas the messenger RNA of interleukin-10, which is inhibitory to tumour necrosis factor-a effects, is reduced. In this model, the phagocytic activity of Kupffer cells is reduced, presumably favouring the development of systemic endotoxaemia and the release of pro-inflammatory cytokines.

RISK FACTORS AND COMORBIDITIES :-

The frequence of NAFLD is adding in resemblant with the frequence of rotundity; both processes are nearly linked to insulin resistance. The worldwide epidemic of rotundity and the frequence of NAFLD are most clearly heavily told by, if not directly related to, the diet and relative lack of exercise of the Western life. The most recent reports from theCenters for Disease Control and Prevention(CDC) indicate that 66 of grown-ups in the United States are fat, and that of those, half are fat. It's projected that by 2025 up to 45 of Americans will be fat(33). As a reflection of the geographical and ethnical spread of rotundity, the projected percent increase in type 2 diabetes mellitus(T2DM) by 2030 is 32 in Europe, in the United States, and ≥ 150 in subSaharan Africa, India, and the Middle East(33). Children and adolescents, who are significantly less likely to have confounding processes similar as alcohol use and/ or viral hepatitis, are likewise affected by the adding frequence of fat, rotundity, and the features of metabolic pattern, and these factors are important associations with the comorbidity of NAFLD (34,35). As with other complex complaint processes, underpinning environmental, inheritable, and hormonal factors that affect in phenotypic complaint expression have to be considered in frequence estimates. Notable differences in partiality for NAFLD are set up related to age, gender, and race. To date, none of the varying styles for estimating frequence can distinguish steatosis and steatohepatitis performing from nonalcoholic sources from those performing from alcohol abuse. Although it's honored that at present the only unambiguous means of opinion for NAFLD is liver towel evaluation, this system easily can not be employed for population webbing, and outside the setting of a study, liver vivisection is only accepted for clinically detected abnormalities. Serologic assays grounded on liver tests are fraught with difficulties, not the least of which is agreeing on what constitutes the upper limits of " normal " for the common liver tests alanine amino transferase(ALT) and aspartate amino transferase(AST), as situations of these enzymes are constantly elevated in the fat population(36). Also, NAFLD and indeed NASH with fibrosis and/ or cirrhosis may be present histologically in the setting of normal ALT situations; 79 of subjects with> 5.5 steatosis by quantitative imaging had normal ALT in a large multiethnic population superstud(37).

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DIGNOSIS:-

The opinion of NAFLD is suspected in cases with elevated aminotransferases and, in numerous cases, substantiation of the metabolic pattern. The distinction between NASH and simple steatosiscan not reliably be made without liver vivisection. still, it's clear that vivisection as a webbing tool to distinguish these two conditions is impracticable as a population- grounded approach. also, definitive opinion of NAFLD and NASH requires rejection of the multiple other causes of hepatic steatosis(Table 2).

Biochemical Features/Laboratory Studies:-

Although 80 of cases with steatosis may have aminotransferases in the normal range, in some cases with NAFLD, the opinion is suspected in the presenceof mildly elevated aminotransferases.(38) Alanine aminotransferase(ALT) and aspartate aminotransferase AST) change, with two- thirds of cases with NASH having normal situations at any point in time.(39,40) Alkaline phosphatase may also be mildly elevated. Aminotransferases lesser than two times normal are prophetic of septal and bridging fibrosis across different populations.(41,42) Hyperbilirubinemia and a low albumin, still, indicate a state of advanced liver complaint and are n't else set up in NAFLD. The rate between AST and ALT has also been set up to have prophetic value. The rate increases in habitual liver complaint by dropped concurrence of AST as sinusoidal fibrosis increases.(43) Several other studies have set up an association between advanced fibrosis on vivisection and an AST ⁄ ALT rate of> 1(44,45).

Iron studies can be delicate to interpret as increased ferritin is seen in 20 – 50 and elevated transferrin achromatism in 5 – 10 of cases with NAFLD.(46) A complete laboratory evaluation to count other causes of liver complaint should also be performed. Clinical history to count significant alcohol ingestion is needed for the opinion. A diurnal consumption of 20 g ⁄ day of alcohol for women and 30 g ⁄ day or further for men are generally used as exclusionary criteria in studies; still, the validity of these cut- offs is unknown

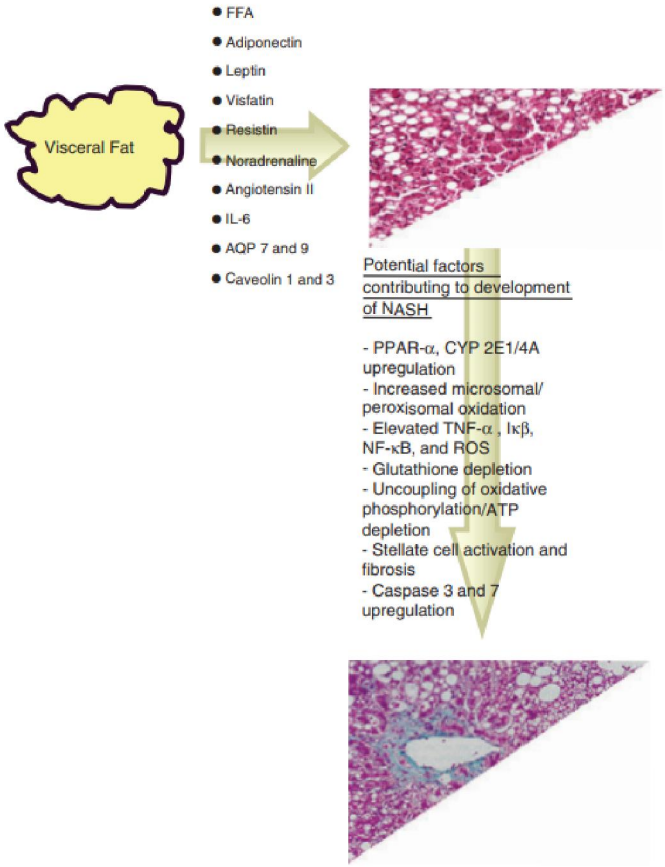

Figure 3. Steatosis to non-alcoholic steatohepatitis: potential mechanisms. FFA, free fatty acid; IL-6, interleukin-6; AQP, aquaporin; PPAR, peroxisome proliferator-activated receptor; TNF, tumour necrosis factor; IκB, inhibitor kappa-B; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; ATP, adenosine triphosphate.

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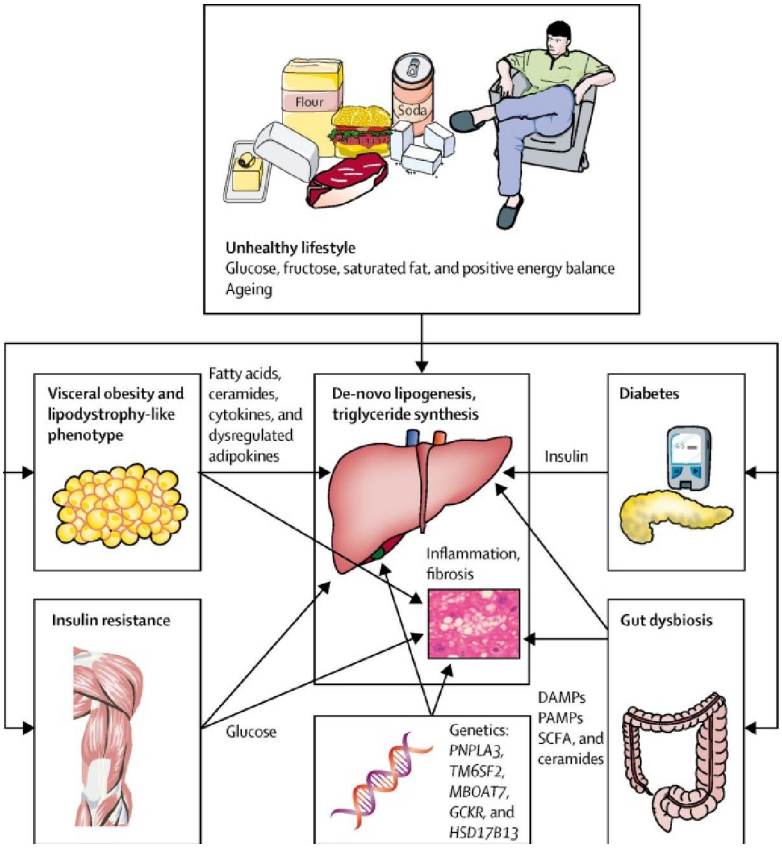
Treatment and Management:-

Hepatic steatosis without substantiation of NASH is not considered associated with increased liver- related morbidity or mortality.(47) still, the presence of hepatic cell necrosis and inflammation clearances more ferocious monitoring because NASH can progress to cirrhosis, end- stage liver complaint and hepatocellular melanoma. presently, there are no approved curatives for NAFLD. There are numerousproposed agents being estimated presently, each targeting a different step in the pathogenesis of development of hepatic steatosis or progression to steatohepatitis(Figure 6). The proper dosing, duration of treatment, safety, and tolerability of these treatments remain under disquisition.



Insulin Resistance:-

As described before, IR is believed to be a central medium involved in the development of hepatic steatosis. IR can be targeted through a multifaceted approach involving weight loss, surgical intervention, or pharmacological remedy. Weight loss. rotundity stimulates a down regulation of GLUT- 4 expression in adipose towel.(48) Muscle compression from exercise induces a flash increase in intracellular calcium content and AMP ⁄ adenosine triphosphate rates, which beget activation of downstream protein kinases. This triggers phosphorylation of substrates responsible for GLUT- 4 translocation.(48) Weight loss via diet and exercise together can significantly impact glucose homeostasis by adding insulin perceptivity. Multiple studies have demonstrated dropped hepatic steatosis and serum transaminases; (49,50) still, continuity of weight loss as well as its effect on steatohepatitis is uncertain(Table 3).

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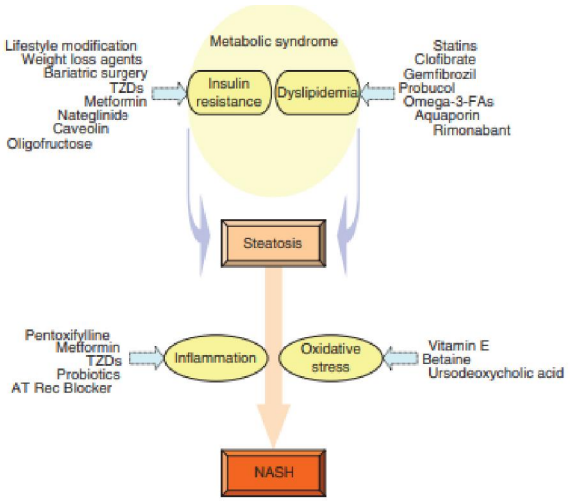

TZD, thiazolidinedione; FA, fatty acid; AT Rec Blocker, angiotensin II receptor blocker

Biopsy-proven NASH	Lifestyle intervention	Anthropometric change	Histology	ALT	Insulin resistance
Y[91]	50% CHO 30% fat 20% protein (Total kcal/day = 25 kcal/kg)	BMI +	+	+	+
Y[92]	Low CHO (<20 g/day), ketogenic diet plus exercise	Weight loss +	+	=	=
Y[93]	40–45% CHO 35–40% fat 15–20% protein plus exercise	Weight loss = BMI =	=	=	+
N[94]	500 kcal daily dietary reduction plus exercise	Weight loss + BMI +	n/a	+	=
N[95]	Aerobic exercise 30 min/day plus moderately-restricted diet (25 kcal/kg)	BMI +	n/a	+	=
N[96]	54% CHO 25% fat 21% protein	BMI +	n/a	+	n/a

+, statistically significant improvement; =, unchanged or improvement that did not reach statistical significance; n/a, not applicable; ALT, alanine aminotransferase; CHO, carbohydrate; BMI, body mass index; kcal, kilocaloric; NASH, non-alcoholic steatohepatitis.

Input as well as moderate diurnal exercise to promote weight loss and ameliorate insulin perceptivity. The part of pharmacological agents that induce weight loss is an area of interest that's presently being estimated.(51) Orlistat, an enteric lipase asset, and sibutramine, a serotonin and norepinephrine reuptake asset that increases malnutrition, have been associated with bettered aminotransferases, as well as possible dropped hepatic inflammation and fibrosis.(52,53) Orlistat use has been limited by gastrointestinal side goods, and neither of these composites is generally specified.

The weight loss approach with the most dramatic and durable effect on rotundity and NASH is bariatric surgery. In comparison with traditional diet and exercise, bariatric surgery more reliably goods substantial, long- term weight reduction for those with morbid rotundity(BMI> 35 kg ⁄ m2 . With advances in fashion, bariatric surgery results in significantly lower malabsorption and nutritive insufficiency.(54) Laparoscopic supported gastric banding is a minimally invasive procedure with veritably low perioperative morbidity and mortality.(55) In addition to weight loss, multiple studies have shown a significant enhancement in rotundity- related comorbidities similar as type- 2 diabetes mellitus, (56) hypertension, dyslipidemia, obstructive sleep apnoea, gravidity, depression and quality of life.(57)

With regard to its effect on the liver, bariatric surgery also produces a significant enhancement in liver histology and biochemistry, presumably because of the drop in cytokines and habitual inflammation associated with rotundity.

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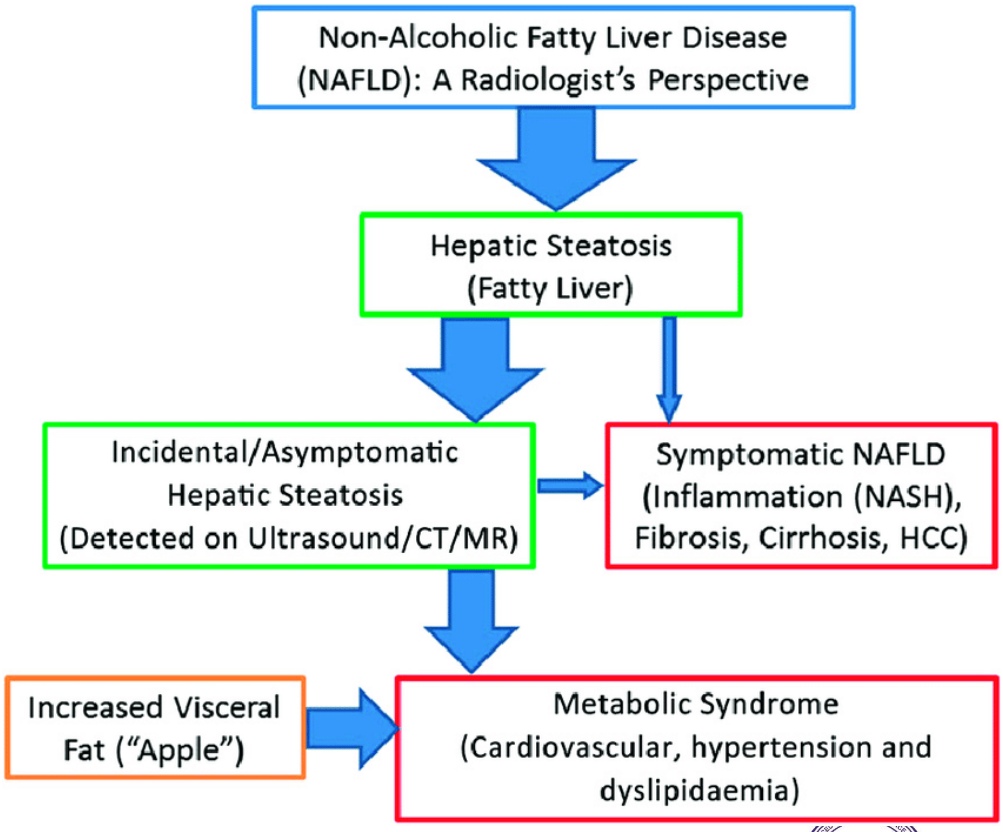
Histologically, surgical weight loss has been associated with significantly bettered steatosis, necroinflammation and fibrosis. Changes in anthropometrics, histology, biochemistries, and IR of studies probing the effect of bariatric surgery on vivisection- proven NASH are shown in Table 4.(58,59) In one study, necropsies performed 2 times postsurgery showed complete resolution of steatosis and fibrosis in 84% and 75% of cases independently.(60) also, other studies have demonstrated complete reversal of cirrhosis.(61).

Management of NASH:-

Although the liver related burden of NASH is substantial and adding , cardiovascular complaint and malice are the leading causes of death in people with , thus, operation of NASH(62,63,64,65) deserves a holistic approach that strives to minimise cardiovascular threat and to reduce motorists of steatosis and systemic inflammation. The balance between nutrients and energy is vital in the development of NAFLD and NASH. Central rotundity is an important motorist of complaint through the creation of insulin resistance and proinflammatory signalling. Although the macronutrient content of the diet is important, weight loss of further than 5 – 7 reduces hepatic fat content and steatohepatitis, and, for weight loss in excess of 10, indeed fibrosis is reduced in a large proportion of people, irrespective of system of weight loss.(66) Sustained weight loss is grueling because it requires a metamorphosis of hardwired geste
patterns. Indeed in the short term, success requires substantial particular commitment in addition to clear recommendations and support from the treatment platoon. walls to weight loss(eg, fiscal constraints, medical comorbidities, education, and little access to healthy food) should be considered when developing a treatment plan. Although not considered first- line remedy due to the surgical threat, bariatric surgery in cases with severe rotundity can lead to substantial(15 – 25) durable weight reduction and enhancement in liver histological features of NASH and fibrosis.(67) Weight loss improves NAFLD and all of its associated cardiometabolic comorbidities, which also favourably affects cardiovascular and malice related threat. There's an independent donation of NASH to cardiovascular and cancer threat but we do n't yet know if liver targeted treatment interventions will reduce them.



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Emerging Therapies of NASH:-

Multitudinous medicines with different mechanisms of action, targeting lipid metabolism, seditious, or fibrotic pathways, are in development as treatment for NASH.(68,69) To achieve full FDA blessing, a remedial intervention is needed to show a clinically meaningful benefit, definedas an improvement in how a patient feels, functions, or survives. Since most patients with NASH have few liverspecific symptoms, full approval of these drugs will require the drug to reduce the development of liver-related events or mortality. Given the course of the disease in NASH—it often takes decades to produce liver-related events or death, even in the context of advanced fibrosis— ongoing trials are mainly focused on surrogate endpoints, such as histology, that are reasonably likely to translate into clinically meaningful benefit. The FDA is considering two histological endpoints for conditional approval of NASH therapeutic agents. These endpoints are: NASH resolution without worsening of fibrosis; or an improvement in fibrosis of one stage or more without worsening of NASH. In comparison, EMA requires statistically significant improvement in both histological endpoints. Alternatively, if a therapeutic agent is primarily evaluated for its antifibrotic effects, it should show an efficacy in improving fibrosis by two or more stages. Previously, efficacy of NASH therapeutic agents has been moderate with statistical significance hedging on a somewhat unpredictable placebo response rate and variability in histological interpretation, which is beyond the scope of this Seminar.(70).

Future treatment for patients with NASH:-

It is clear from the preceding sections that NASH treatment requires the use of additional medications. Furthermore, no tested agent has been expressly authorized for this purpose. The fact that has caused a surge in the number of agents being investigated. Crucially, due to their increased likelihood of the condition developing, type 2 diabetics are now included in the majority of research.Numerous methods have been tried. Agents at more advanced phases of development (Phase 2a/2b or early Phase 3 trials) are included in Table 1. However, there is a significant obstacle in the way. For instance, efforts to regulate the synthesis of triacyl glycerol including with stearoyl coenzyme A desaturase (SCD)-1 pathways (71) or 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (72) have produced generally disappointing outcomes. Targeting PPARα/PPARδ using the dual agonist elafibranor (GFT505) (73), a partial PPARα agonist that has roughly 60% of the maximal response (Emax) of fenofibrate (74), has proven to be more effective. In vivo (75) and in individuals with insulin resistance (76), dual PPARα and PPARδ activation reduces inflammation and enhances hepatic insulin sensitivity. Conversely, fenofibrate, a PPARα agonist, has not been linked to a reduction in insulin resistance orDespite the compelling justification provided above, 276 patients with biopsy-proven NASH(77) (almost 40% of whom had type 2 diabetes) experienced disappointing outcomes following 52 weeks of elafibranor treatment because it could not meet the principal result of NASH resolution without fibrosis worsening (78). This was caused, at least in part, by the fact that many patients' liver histology showed border line NASH prior to therapy.However, in patients with more severe illness at baseline (NAFLD activity score [NAS] ≥4; n=234), the larger dose (120 mg/day) was associated with remission of NASH (20% vs. 11%, p=0.018) and improved scores of hepatocyte damage and fibrosis (79). An ongoing large multicenter RCT using elafibranor that solely enrolls patients with more advanced liver disease (NAS≥4) is based on these findings.(79).

II. CONCLUSION

Because of its rising incidence and prevalence in the general population, NAFLD is now a frequently diagnosed condition in clinical practice. We believe it is crucial to arrive at an operational definition of NAFLD that is "positive" and that researchers from all over the world may use. Given the facts, simple NAFL, which affects between 40 and 50 percent of the general population, must be regarded as benign. Being able to differentiate between NAFL and NAFLD is the primary challenge for the future. Long-term follow-up population cohort studies are crucial for defining the incidence and natural history of non-alcoholic fatty liver disease. To find out how much a person's genetic history predisposes them to developing significant liver disease and cardiometabolic disease, genetic investigations are also required.

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