METABOLIC DYSFUNCTION ASSOCIATED LIVER DISEASE (MAFLD)

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WHAT WE ALL KNOW??

NAFLD

- NAFL- Only Steatosis
- NASH – Steatosis with ballooning of hepatocytes and lobular inflammation
- CIRRHOSIS

- No history of significant alcohol intake
- No other liver disease

- NAFLD can lead to HCC
- NAFLD affects about a quarter of world population
- By 2030, number of cases likely to increase by 18%
- Presence of advanced liver disease likely to become double by 2030

WHY NAFLD TO MAFLD??

- Name like NAFLD trivializes a major problem

- History of Significant Alcohol Intake is not reliable always

- NAFLD is a diagnosis of exclusion

- A patient with AIH with fatty liver, will you call it NAFLD WITH AIH?? --------NO

- Though associations with Diabetes, Obesity etc. have been known but these have not been included in the diagnostic criteria of NAFLD

- A patient has chronic HCV with DM-2 with fatty liver-------
Is this patient having NAFLD?? ----No

* Eslam M et al. MAFLD: A Consensus Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020 May

MAFLD

- Not a disease of exclusion– There are well defined diagnostic criteria based on presence of metabolic dysfunction
- Can co-exist with other liver disease

- A patient has chronic HCV with DM-2 with fatty liver------- Is this patient having NAFLD?? ----No

BUT PATIENT CAN HAVE DIAGNOSIS OF MAFLD WITH HCV

- NHANES III Survey database, MAFLD was diagnosed in 31.24%

- Those with MAFLD compared to NAFLD:-

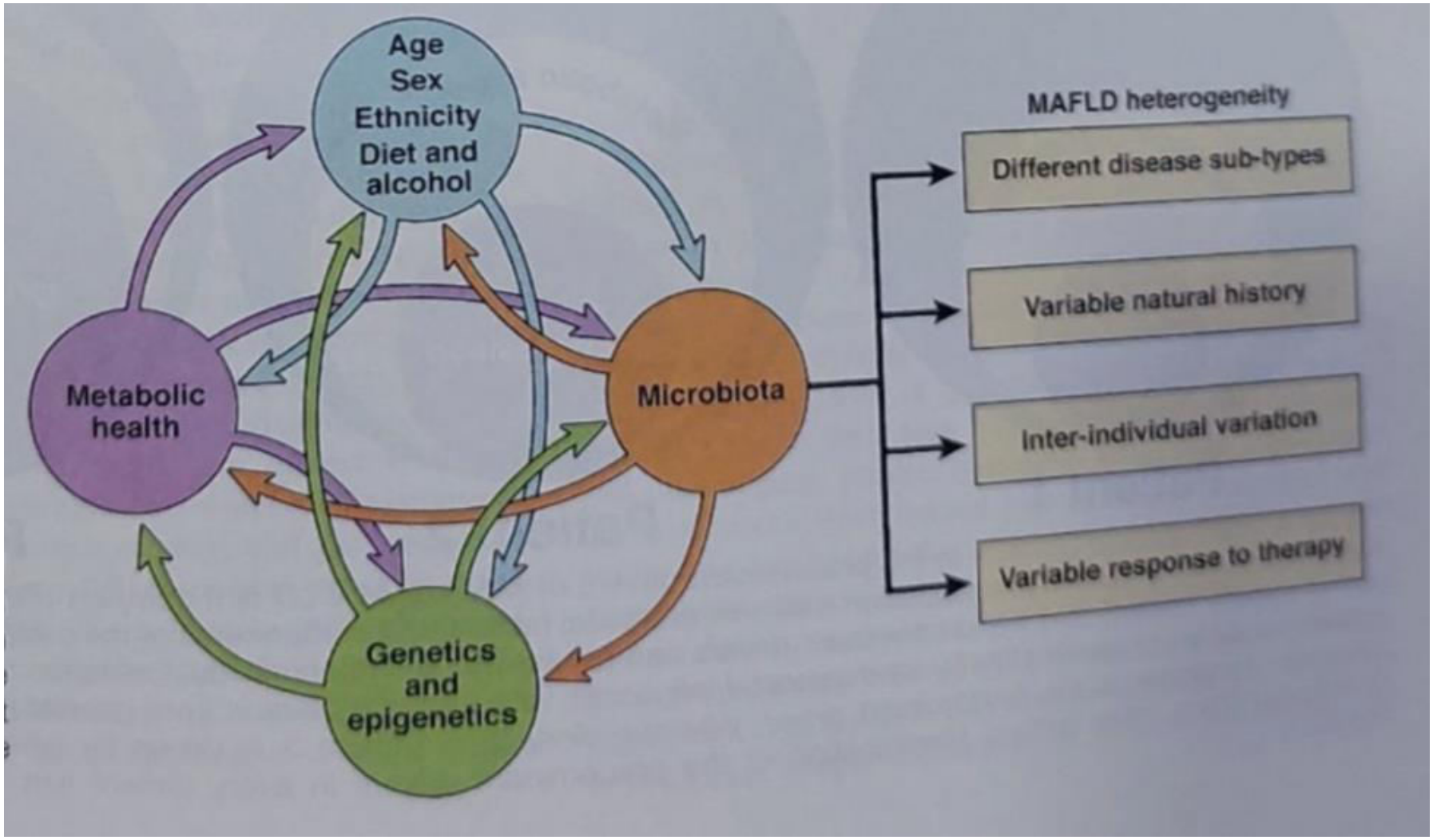
- Were older
- Had Higher BMI
- Had higher metabolic derangements (diabetes, hypertension, Higher HOMA-IR, higher lipids)
- Higher enzyme levels
- More had advanced fibrosis

*Lin S, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver International 2020

MAFLD has a Heterogenous Phenotype

- Asymptomatic
- Steatosis only
- Steatohepatitis
- Steatosis and Steatohepatitis can shift into one another
- Fibrosis leading to cirrhosis and decompensation
- HCC after fibrosis or even with steatohepatitis only

REASONS FOR THIS HETEROGENOUS PHENOTYPE



- Advancing age --- severe the phenotype
- Males and Post-menopausal females tend to have higher disease prevalence and complications
- Ethnicity

- Hispanics have highest steatohepatitis, fibrosis is same across all races
- Asian individuals accumulate liver fat at lower BMI; also have higher severity and fibrosis

- Low to Moderate Alcohol intake – Worsens the disease

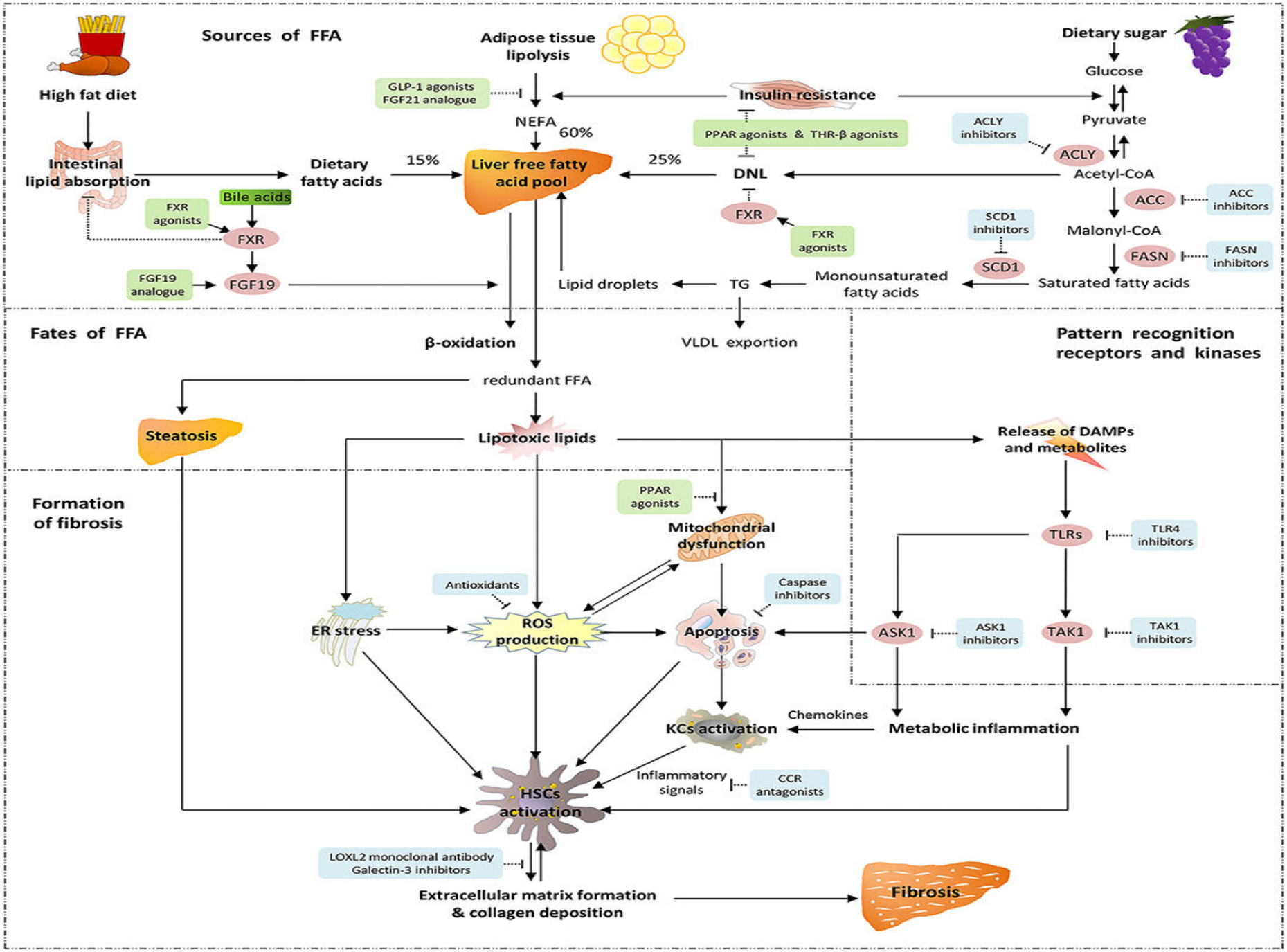
- Western Diet rich in sugars (fructose) and saturated fats
- Altered gut microbiome
- More Visceral Fat – More liver inflammation and fibrosis
- Lean Individuals – Contrasting study results
- Familial Risk --- Seen for steatosis, inflammation and fibrosis
- Genomic Variations –

- PNPLA 3, GCKR, MBOAT7, TM6SF2, HSD17B13 (all associated with NAFLD)

PATHOPHYSIOLOGY OF MAFLD

- Shares a lot of similarity with pathophysiology of NAFLD
- **“Multiple –hit” hypothesis**

- First hit is- Hepatic Triglyceride Accumulation
- De novo hepatic lipogenesis (DNL)
- Oxidative Stress by lipotoxic molecules and ROS
- Formation of Danger Associated Molecular Patterns (DAMP)
- Metabolic Inflammation (ASK-1, TAK-1 activation)
- Altered intestinal microbial signals
- Autophagy
- Activation of Hepatic Stellate Cells(Fibrosis Starts)
- Gene polymorphisms, such as PNPLA3, TM6SF2, and HSD17B13, may increase an individual's susceptibility to liver fibrosis during metabolic dysregulation


Sources of FFA
High fat diet
Adipose tissue lipolysis
Dietary sugar
Glucose
GLP-1 agonists
FGF21 analogue
Insulin resistance
NEFA
60%
PPAR agonists & THR-β agonists
ACLY inhibitors
Pyruvate
ACLY
Intestinal lipid absorption
Dietary fatty acids
15%
Liver free fatty acid pool
25%
DNL
Acetyl-CoA
Bile acids
FXR agonists
FXR
ACC
ACC inhibitors
SCD1 inhibitors
Malonyl-CoA
FGF19 analogue
FGF19
Lipid droplets
TG
Monounsaturated fatty acids
SCD1
FASN
FASN inhibitors
Saturated fatty acids
Fates of FFA
β-oxidation
VLDL exportion
Pattern recognition receptors and kinases
redundant FFA
Steatosis
Lipotoxic lipids
Release of DAMPs and metabolites
Formation of fibrosis
PPAR agonists
Mitochondrial dysfunction
TLRs
TLR4 inhibitors
Antioxidants
Caspase inhibitors
ER stress
ROS production
Apoptosis
ASK1
ASK1 inhibitors
TAK1
TAK1 inhibitors
Chemokines
KCs activation
Metabolic inflammation
Inflammatory signals
CCR antagonists
HSCs activation
LOXL2 monoclonal antibody
Galectin-3 inhibitors
Extracellular matrix formation & collagen deposition
Fibrosis

DIAGNOSIS

SCREENING FOR MAFLD

- PCOS
- Obesity
- Hypothyroidism
- OSA
- Psoriasis

Hepatic steatosis in adults

tected either by imaging techniques, blood biomarkers/scores or by liver histology)

ight or obesity
as BMI ≥25 kg/m² in
BMI ≥23 kg/m² in Asians)

Lean/normal weight
(defined as BMI <25 kg/m² in Caucasians
or BMI <23 kg/m² in Asians)

Type 2 diabetes me
(According to widely accept
international criteria)

***If* presence of <u>at least</u> two metabolic risk abnormalities:**

- Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women)
- Blood pressure ≥130/85 mmHg or specific drug treatment
- Plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or specific drug treatment
- Plasma HDL-cholesterol <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for women or specific drug treatment
- Prediabetes (*i.e.*, fasting glucose levels 100 to 125 mg/dl [5.6 to 6.9 mmol/L], or 2-hour post-load glucose levels 140 to 199 mg/dl [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol])
- Homeostasis model assessment of insulin resistance score ≥2.5
- Plasma high-sensitivity C-reactive protein level >2 mg/L

MAFLD

(Metabolic dysfunction-associated fatty liver disease)

EXAMINATION

- Weight, Height, BMI
- Waist Circumference
- Blood Pressure
- Abdominal System examination
- Other examination as deemed appropriate

APPROPRIATE INVESTIGATIONS

- LFT, PT WITH INR
- LIPID PROFILE
- TSH, FT3, FT4
- Blood Sugar (F, PP)
- HbA1c
- HOMA-IR
- Hs-CRP
- HBsAg, Anti-HCV
- Rule out other causes of Liver disease
- Rule out other causes of fat accumulation in liver
- Non-invasive assessing of liver inflammation and fibrosis
- Liver Biopsy (May be required)

Non-invasive methods to detect steatohepatitis

- Presence of Metabolic Syndrome in a patient of Fatty Liver
- Elevated liver enzymes in a patient of Fatty liver not explained by any other cause
- Cytokeratin 18
- CXCL 10, TNF-alpha, IL-8
- FGF-21
- NASH Test, NASH ClinLipMet Score
- Fibrotest-Actitest

Non-invasive Methods for Assessing Fibrosis

- Fibrosis Index Based on 4 factors (FIB-4) (>1.45)
- NAFLD FIBROSIS SCORE (NFS) (<-1.5)
- AST to Platelet ration Index (APRI) (>0.45)
- Enhanced Liver Fibrosis Panel (ELF) (>7.7)
- Liver Stiffness Measurement (LSM) by Vibration Controlled Transient elastography (VCTE) (>7.0 pKa)
- Magnetic Resonance Elastography (MRE)

TREATMENT

- Qu W, et al. Liver fibrosis and MAFLD: From Molecular Aspects to Novel Pharmacological Agents. Frontiers in Medicine 2021.
- Semler G et al. Diet and Exercise in NAFLD/NASH: Beyond the obvious. Liver International 2021.
- Takahashi Y et al. Current Pharmacological treatment for NAFLD/NASH. World Journal of Gastroenterology 2015.

DIET

- 7-10% weight reduction is the target (0.5-1 kg/week)
- Mediterranean Diet (EASL-EASD-EASO 2016), Hypocaloric diet (AASLD 2018)[500-1000 Kcal/day reduction].....also endorsed by APASL 2020 for MAFLD
- Avoid processed food and beverages rich in fructose
- No alcohol
- Coffee --???

PHYSICAL ACTIVITY

- Aerobic + Resistance Exercises
- 150-200 minutes/week
- Moderate Intensity (Brisk walking, Stationary cycling)

INSULIN SENSITIZERS:-

Pioglitazone-

- PPAR- gamma agonist
- 30-45 mg/day
- Reduces steatosis, inflammation, ballooning, AST-ALT levels
- Approved for biopsy proven NASH
- Watch for side effects

ANTIOXIDANTS:-

Vitamin E –

- 800 IU/day in non-diabetic adults
- Reduces steatosis, inflammation and ballooning
- No improvement in fibrosis
- Recommended for biopsy proven NASH
- Watch out for long term supplementation with Vitamin E (All cause mortality increases, diet supp can lead to prostate cancer)
- *Vitamin E (1000 IU/day) + Vitamin C (1000 mg/day) has also shown effect in biopsy proven NASH*

PPAR (Alpha + Gamma) Agonist:-

Saroglitazar:-

- 4 mg once a day
- Improves ALT levels, CAP, LSM, Lipid levels and IR
- Histology based large trials are lacking

HYPOLIPIDEMIC DRUGS:-

EZETIMIBE-

- 10 mg/day
- Improves inflammation, enzyme levels, ballooning but no improvement in fibrosis
- Larger trials required

STATINS-

- Atorvastatin
- Shown some effect
- Larger trials required

ANGIOTENSIN RECEPTOR BLOCKERS:-

- Losartan, Telmisartan
- Improve ALT levels, HOMA-IR, NAS in NASH in patients with metabolic syndrome
- ?? Use in normotensive individuals
- Large trials required

PENTOXYFYLLINE:-

- Phosphodiesterase inhibitor and reduces TNF-α
- 1200 mg/day
- Trials show mixed results
- Large trials required

PREBIOTICS, PROBIOTICS AND SYNBIOTICS:-

- Lactbacillus rhamnosus (12 billion CFU/day) for 2 months reduced enzyme levels in paediatric population
- Synbiotic (200 miliion CFU of 7 strains + Probiotic culture+ Fructooligosaccharide) for 28 weeks reduces enzyme levels and fibrosis (N=54)
- Larger Trials are required

GLP 1 Agonists:-

Liraglutide—

- Phase II trial
- Attenuated fibrosis progression and histological improvement
- Reduction in body weight
- Improvement in liver enzymes

Exenatide –

- Similar results to Liraglutide

<u>Semaglutide</u>

<u>Tirzepatide</u> (GLP-1 agonism + Insulinotropic Polypeptide)- Improvement in fibrosis biomarkers in NAFLD with diabetes

Acetyl Coenzyme A Carboxylase (ACC) Inhibitors:-

- Inhibit DNL

Firsocostat-

- 20mg, 12 weeks, reduces hepatic steatosis and fibrosis biomarkers in NASH
- Combination with 30 mg Cilofexor in F3-F4 patients led to improvement in Fibrosis to ≤ F2
- Asymptomatic hypertriglyceridemia is a side effect
- Combination with Cilofexor causes low HDL and increase Total Cholesterol

PF-05221304- Trials still going on

ATP Citrate Lyase Inhibitors:-

Bempedoic Acid-

- Improves lipid parameters
- Decrease inflammation as suggested by decrease in hs-CRP
- Studies in MAFLD awaited

Farsenoid X Receptor Agonists (FXR):-

- Reduces bile acid signalling in intestines
- Reduces intestinal fat absorption
- Increases fatty acid oxidation liver
- Reduce HSC actiavtion

<u>Obeticholic Acid (OCA)-</u>

- FLINT 2 Trial (Phase 2, 25 mg once a day, improved inflammation and histological features in NASH)
- REGENRATE TRIAL (Phase 3, 25 mg OD, improved liver fibrosis in 25% patients with NASH)
- Problem is Increase in LDL, Pruritus
- CONTROL 2 Trial (OCA + Statins) 16 weeks, increase in LDL mitigated by statins

Cilofexor- As discussed previously

Tropifexor – Under study

OTHER NOVEL AGENTS:-

- FGF-19 Analog--- Aldafermin
- FGF-21 Analog ---Pegbelfermin, Efruxifermin
- PPAR (Alpha + Delta)- Lanifibranor, Elafibranor
- Thyroid Hormone Receptor Beta Agonists – Resmetirom, VK2809
- Caspase Inhibitors – Emricasan
- ASK1 Inhibitors – Selonsertib
- TAK 1 Inhibitors
- TLR4 Inhibitors – JKB 122
- TGF Beta Monoclonal Antibody - Gelunisertib

NO ROLE

- Metformin
- Ursodeoxycholic acid

CONCLUDING REMARKS

- MAFLD is a new term over the backdrop of an already existing entity
- MAFLD must be looked into actively and treated to prevent long term liver disease related complications
- Newer agents are upcoming to offer treatment specific to MAFLD

THANK YOU