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REVIEW

The blind men 'see' the elephant-the many faces of fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a group of diseases with excess fat in liver in the absence of a poorly defined limit of alcohol consumption. Most common variety, a universal public health problem, is associated with insulin resistance caused by a host of genetic and epigenetic defects modulated by life style and environmental factors. In fact the term NAFLD is loose to incorporate so many etiologies except alcoholism and few other etiologies, presenting as fat in liver. However as a sign fatty liver is very important in predicting the risk of diabetes, cardiovascular disease, stroke, cirrhosis and cancer. Abnormal fat accumulation can result from several defects in nuclear receptors associated with lipid sensing, synthesis and oxidation like LXR, FXR, SREBP, ChREBP and PPAR; defects in the lipid influx-efflux channels, insulin signaling, proteins involved in fatty acid catabolism, defects in adipose tissue development and function, inappropriate nutrition and finally defects in neural regulatory mechanisms. The progress of the disease is determined by the basic defects which results in fat accumulation, an individual's immunological response to the accumulated fat and its derivatives and the oxidant stress response. Congregation of unrelated genetic defects under same diagnosis 'NAFLD' can result in inefficient patient management. Further studies are required to understand the molecular basis of fatty liver to enable a personalized management of diseases presenting as fatty liver in the absence of alcohol abuse.

Key words: Nonalcoholic fatty liver disease; Insulin resistance; Lipid homeostasis; Primate evolution; Lipid channels; Lipoprotein; Adipokines; Nuclear receptors; Bile acid metabolism; Personalized medicine

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INTRODUCTION

"It was six men of Hindustan, To learning much inclined, Who went to see the Elephant, (Though all of them were blind), That each by observation, Might satisfy his mind. "God bless me! but the Elephant: Is very like a wall! Is very like a spear! Is very like a snake! Is very like a tree! Is very like a fan! Is very like a rope!" 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!"

-John Godfrey Saxe (1816-1887).

Although alcohol-induced liver steatosis was already described by Thomas Addison in 1845, it is appreciated only since 1962 that steatosis can also occur without the use of alcohol, so-called non-alcoholic steatosis[1]. The term nonalcoholic steatohepatitis (NASH) was coined in 1980 to describe "the pathological and clinical features of non-alcoholic disease of the liver associated with the pathological features most commonly seen in alcoholic liver disease itself"[2]. In fact, the finding that some obese individuals had a liver disease histologically indistinguishable from alcoholic liver disease itself had long been recognized.

The etiopathogenesis of nonalcoholic fatty liver disease (NAFLD) has been disputed loud and long (Figure 1). NAFLD is a vague term for a spectrum of diseases which differ not only in the presentation but also in the etiologies which warrants a personalized approach in the diagnosis and treatment of this condition. All possible etiologies and pathogenesis models have been assigned to it from mitochondrial, oxidant stress, hormonocentric to adipocentric models[3,4]. On the other hand the term NAFLD is loose to incorporate so many etiologies except alcoholism and few other etiologies, presenting as fat in liver. Interestingly despite the diversity in root cause and irrespective of the fact they fall inside or out side the conventional inclusion or exclusion criteria many of them share common pathways of disease progression evolution and termination. Here in this review, we once again review the 'elephant' and attempt to classify and generalize the disorder based on the etiology.

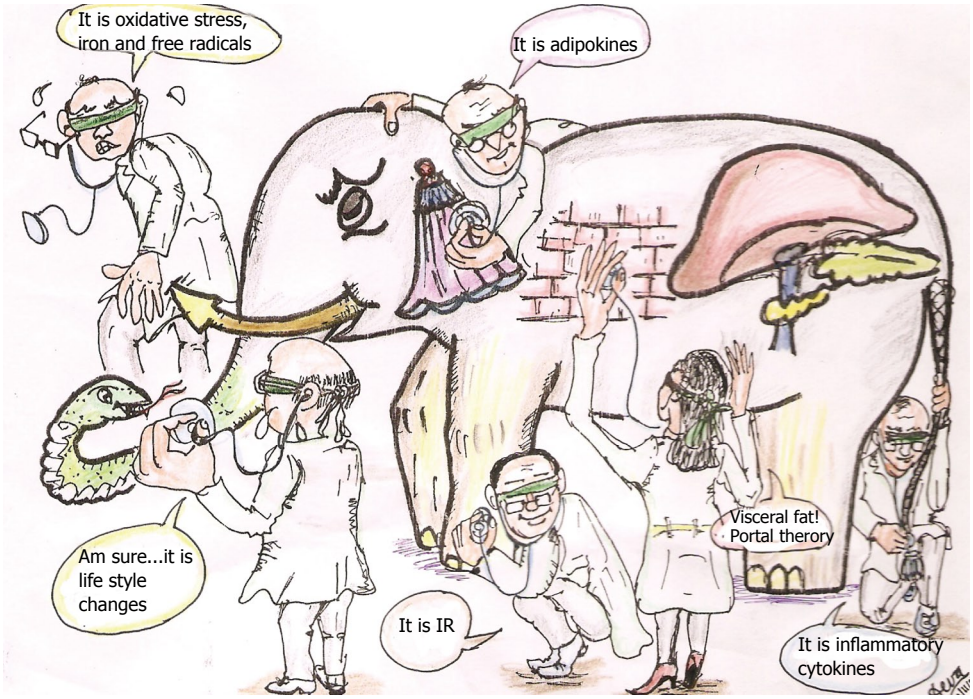

Figure 1 The pathogenesis of NAFLD has been disputed by many loud and long. The term "nonalcoholic fatty liver disease" is imprecisely defined; there is uncertainty regarding its pathogenesis. The elephant (NAFLD) has been interpreted by many and several possible etiologies and pathogenesis models have been assigned to it like 'insulin resistance', mitochondrial defects, adipokine imbalance, visceral fat, inflammatory cytokines and oxidant stress.

NAFLD: A nonspecific diagnosis and a misnomer?

A variety of genetic defects and pathogenic pathways can result in NAFLD. Fatty liver is a sign rather than a proper diagnosis. As a sign it is very important in predicting the possibility of diabetes, cardiovascular risk, stroke, cirrhosis and cancer. Symptoms, severity and prognosis for same amount of fat in liver differ very much from person to person and fat may be totally absent in late stages of the disease. In addition, there is no genetic or clinical marker specific for NAFLD. Opinion regarding the histopathological diagnosis and staging differ even among experts and there is a lack of reproducibility[5,6]. Furthermore, authors have differed on the level of alcohol consumption that can reliably distinguish between alcoholic steatohepatitis and NASH.

"Nothing makes sense in biology without the concept of evolution"

'Nothing in Biology Makes Sense Except in the Light of Evolution' is a 1973 essay by the evolutionary biologist Theodosius Dobzhansky, criticizing Young Earth creationism and espousing evolutionary creationism makes sense with 'NAFLD' as well.

The ability to obtain food and manage periods of starvation and the ability to fight infectious diseases were most critical in survival of primates and indeed their survival was threatened by starvation and infectious diseases than obesity and autoimmunity or cancer. So, primate evolution always favored "thrifty genotypes"[7] which were efficient in fat storage and burning. Similarly 'infection resistant' genotypes were favored by evolution. The cultural evolution was faster so that the 'genetic-evolution' lagged behind or became static. As we 'evolved' from hunter-gatherer life style to computer savvy-chair bound, calorie rich-fast food friendly and 'hygienic' life style our past started haunting and our 'vestigial genes' started their manifestation in the form of the pandemic called Metabolic Syndrome with associated insulin resistance (IR), NAFLD, chronic inflammatory disorders and cancer.

Evolutionary history of adipose tissue, liver and immunocytes adds more sense to this picture. It is interesting to note that all the above has same ancestor-the "fat body" which is the mammalian homologue of all the three tissues in insects[8,9]! Over expressing peroxisome proliferator-activated receptor gamma (PPAR-γ) a gene that is vital for differentiation and maturation of adipocyte genes in hepatocytes can induce adipocyte like features in hepatocytes. Similarly gene expression profile of macrophage is very similar to adipocyte[10-13]. Hence all the three systems are simultaneously affected in disorders like NAFLD (Figure 2). Indeed in fatty liver disease, hepatocytes become lipid-loaded and resemble adipocytes with the formation of large lipid droplets, expression of adipogenic and lipogenic genes such as adipose differentiation-related protein (ADRP), PPAR-γ and sterol regulatory element binding protein (SREBP)[3,9-13]. The interactions and involvement of the trio in development of fatty liver is discussed further in this article.

NAFLD AS THE LIVER MANIFESTATION OF A GENERALISED FAT STORAGE DISORDER

Logically if fat has to get accumulated there are four ways (Figure 3): (1) increased inflow (increased availability of lipids and lipid precursors); (2) decreased outflow/secretion; (3) increased synthesis; and (4) decreased oxidation.

Increased inflow

It has been observed that nearly 80% of people who undergo liver transplantation following cirrhosis from NASH get back the disease in few years[14]. This point

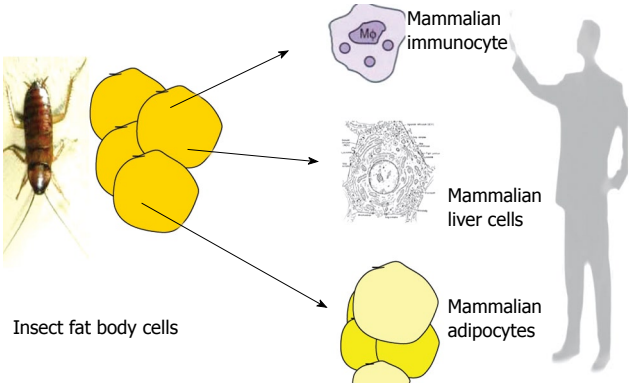

Figure 2 It is interesting to note that adipose tissue, liver and immunocytes has same ancestor-the "fat body" which is the mammalian homologue of all the three tissues in insects. Over expressing PPAR-γ in hepatocytes can induce adipocyte like features in hepatocytes. Similarly gene expression profile of macrophage is very similar to adipocytes. All the three cell systems are affected in disorders like NAFLD and obesity.

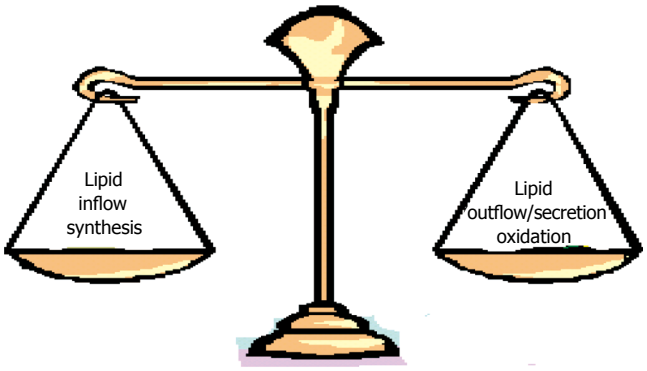

Figure 3 Fat gets accumulated in liver when there an imbalance between inflow (increased availability of lipids and lipid precursors) and outflow/secretion, synthesis and oxidation.

to the fact that at least in majority of the patients the cause lays outside the liver. Adipose tissue functions as an energy reserve; where energy can be stored in the most concentrated form viz. lipids safely unlike other tissues where it could cause 'lipid toxicity'[15]. This way it also acts as an energy sink in times of plenty. Soon after feeding the blood would be over loaded with energy rich compounds and the adipose tissue has an important role in clearing these compounds, especially lipids which are potentially harmful. However in chronic over nutrition adipocytes may become overloaded and may no longer be able to take up circulating lipids and glucose. Insulin is a stimulator of lipoprotein lipase the enzyme which mediates extraction of fatty acids from circulating lipoproteins which are the carriers of lipids as triglycerides (TG). Through the tissue-specific action of lipoprotein lipase, the TG-derived free fatty acids (FFA) are taken-up by peripheral tissues. Similarly the type-4 glucose transporters on adipocyte surface are also insulin dependent[16]. Probably the over loaded adipocytes may adopt insulin resistance (IR) as a strategy to save them selves from further overloading, damage and cell death (apoptosis?). As soon as the energy sinking capacity of the adipose tissue is exceeded the energy rich substrates starts 'over flowing' to other tissues like liver and muscle. This could be only one but the commonest mechanism of fatty liver. Nearly 60% of TGs deposited in liver in NAFLD comes from circulating nonesterified fatty acids[17]. The TGs contained within adipose tissue are continuously being hydrolyzed into fatty acids and glycerol by the enzyme hormone-sensitive lipase (HSL). Insulin resistance impairs uptake of glucose from blood into skeletal muscle and adipose tissue; serum non-esterified fatty acid (NEFA) levels may also be elevated due to the failure of insulin to suppress HSL mediated lipolysis[16].

However (1) other mechanisms which induces IR in adipose tissue or defects in the transporters of lipids into adipose tissue which limits influx of lipids, (2) defects in the control mechanisms involved in the release of lipids from adipocytes, (3) defects in normal growth and proliferation of adipose tissue, could result in plasma lipid pooling and ectopic fat deposition such as fatty liver. As in the case of adipocytes hepatic fat over load may lead to hepatic insulin resistance (HIR)[18]. Therefore it should be possible to reverse fatty liver by 'unloading' the extra fat. This is indeed true. For example surgical obesity management techniques like gastric banding based on restriction of the gastric reservoir produces early satiety and reducing oral intake induces significant weight loss by unloading of fat reserves reverses fatty liver. Exercise and diet restriction and consequent fat reduction still remains the mainstream therapy in NAFLD[19,20]. Interestingly removal of excess fat by liposuction doesnot improve insulin sensitivity[21]. This is possibly because as adipocytes are removed the buffering action provided by them on circulating energy rich substrates is decreased.

A small part of the fatty acids released by HSL as described before are re-esterified within adipocytes while most overflow into the blood which exceeds the normal oxidative needs of the body. Liver is another immediate buffer that has been shown to have a high capacity for accumulating fat and redirecting or oxidizing it later depending on the energy homeostatic signals. Within the liver, these fatty acids are either oxidized or re-esterified into TGs and secreted into the blood bound to VLDL[16,18]. The fatty acids re-esterified by the liver into TG are almost exclusively from adipose tissue lypolysis[22].

Gluconeogenesis in liver needs supply of fatty acids and glycerol released from adipocytes. Glycerol contributes 90% of the substrate for hepatic gluconeogenesis in prolonged fasting mice. In man about 20% of hepatic gluconeogenesis is mediated by glycerol. Gluconeogenesis needs a coordinated efflux of glycerol from adipocytes and influx into hepatocytes through adipocyte specific glycerol channel, designated aquaporin adipose (AQPap/7) and a liver-specific aquaglyceroporin was also identified and named AQP9[23]. Discord between efflux and influx channels possibly play an important role in the pathogenesis of NAFLD and diabetes mellitus.

Over flow of fat to liver could be due to increased dietary intake. Even after a short term fat feeding liver fat increases three fold without increase in visceral or skeletal muscle fat[18]. Indeed the adipose tissue fat is an indicator of liver fat. The intrahepatic lipids increase by 22% for

any 1% increase in total adipose tissue, by 21% for any 1% increase in subcutaneous adipose tissue and by 104% for 1% increase in intra-abdominal adipose tissue[24]. Thus liver bears the brunt as soon as adipose tissue buffering reaches its limit.

Zucker rats (*fa/fa*) have inactivating mutation in the leptin receptor and hence obese and develops fatty liver. Liver specific correction of leptin receptor deficiency results in reduced TG accumulation in the liver but not in other non-adipose tissues. This could be an example of adipokine mediated communication between adipose tissue and liver. Leptin in conditions of 'calorie excess' signals liver to increase lipid oxidation and to down regulate lipid synthesis and thus protect it and other organs from steatosis[25]. Ob/ob mice with mutations in Scd1 had histologically normal livers with significantly reduced triglyceride storage and VLDL production. Down regulation of SCD1 is an important component of leptin's metabolic actions[26].

As the buffering capacity of liver also exceeds its limit lipid starts getting accumulated in cardiovascular system and other organs. The macrophages associated with blood vessels, the evolutionary kin of adipocytes and hepatocytes, will try to "buffer" the excess lipids by phagocytosis and later oxidize them partly to form toxic free radicals and immunogenic compounds. They become 'foamy cells' as their capacity to accumulate fat reaches the limit[27]. This eventually leads to "fibrosis" of vessel wall (atherosclerosis is homologous to cirrhosis of liver) and an increase in CVS related mortality. Indeed some studies published recently find the seeds of CVS mortality in NAFLD[28-30] (Figure 4).

Defects in fatty acid transporters in adipocytes also could result in hypertriglyceridemia and subsequent increased inflow of FA to liver. For example

CD36-/-mice lacking the fatty acid transporter that is normally present in muscle and adipose tissue showed increased hepatic TG content and a decreased sensitivity of hepatic glucose production to insulin[31].

There are multiple genetic defects which culminate in adipose tissue deficiency and adipose tissue deficiency invariably results in fatty liver. Lean transgenic mice that express ZIP/F-1 protein in adipose tissue, which blocks the function of several classes of transcription factors, are insulin resistant and developed fatty liver. Interestingly in these mice upon transplantation of fat tissue insulin resistance as well as the fatty liver disappeared[32]. PPAR-γ mutant mice develop IR and fatty liver in conjunction with the terminal atrophy of adipose tissue[33]. Sterol regulatory element-binding proteins (SREBPs) are a family of transcription factors that activate the entire program of cholesterol and fatty acid synthesis. The transgenic mice that overexpress nuclear SREBP-1c (aP2-SREBP-1c) exclusively in adipose tissue have very little adipose tissue, apparently as a result of disturbed adipocyte differentiation. They develop severe hyperglycemia, hyperinsulinemia, and lipid accumulation in liver[34,35]. The fatty liver dystrophy (*fld*) mutant (lipin-deficient) mice are characterized by neonatal fatty liver and hypertriglyceridemia that resolve at weaning, glucose intolerance and increased susceptibility to atherosclerosis and neuropathy. Adult *fld/fld* mice exhibits 80% reduction in mass both white and brown fat pads compared with wild-type controls, and consist of immature adipocytes[36]. Human examples of adipose tissue deficiency and consequent fatty liver is described else where in this paper.

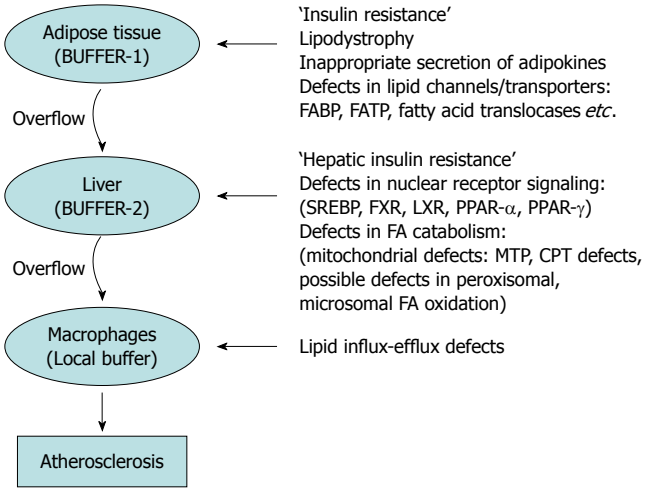

Figure 4 Adipose tissue functions as an energy reserve; where energy can be stored in the most concentrated form viz. lipids safely. In other tissues lipid accumulation could cause 'lipid toxicity'. Adipose tissue 'buffers' the lipids and energy rich compounds which are pumped into the blood stream soon after meals. However when excess calories overload adipose tissue the buffering action ceases, resulting in overflow of lipids to liver which is the next buffer. But as soon as liver also is overloaded, lipids overflow and gets accumulated in various other organs. In blood vessel walls macrophages takes up the excess lipids to form foam cells initiating a cascade which results in fibrosis of vessel walls.

Increased intake

The lipid intake is determined by lipoproteins which are carriers of lipids to liver predominantly from adipose tissue and digestive tract through the circulatory system. The lipids are further transported into hepatocytes by various 'lipid transporters' which are membrane bound channels and cellular lipid binding proteins like fatty acid transport proteins (FATP), fatty acid translocase (FAT/CD36), fatty acid binding proteins (FABP), caveolin-1 *etc*. Tissue accumulation of FA requires intracellular trapping involving association between many membrane' intracellular FA binding proteins.

FATP is highly expressed in hepatocytes and adipocytes that reveal high-level FA uptake for both metabolism and storage. FATP1 is found in adipose tissue and in the heart. FATP2 and FATP5 are expressed in the liver, while FATP4 is expressed in the intestine[37]. Overexpression of FATP5 in cultured cells has been shown to increase FFA uptake while knock out of FATP-5, results in decreased accumulation of fat in liver and decreased production of conjugated bile acids[38-40]. A recent study found an upregulation of FABP4 and FABP5 in NAFLD independent of obesity[13]. Thus FATP5 is an important membrane protein involved in fatty acid accumulation by the liver. In mice, which are FAT/CD36-deficient, the flux of fatty acids toward the liver is increased, precipitating steatosis, but there without any evidence of an increase in hepatic VLDL production[41].

The fatty acid taken up by liver is oxidized and excess is esterified and accumulated or secreted. Esterification is most

efficient with mono-unsaturated lipids as monounsaturated fatty acyl-CoAs are the preferred substrates for the synthesis of triacylglycerol (TAG) in the endoplasmic reticulum (ER)[42]. This is possibly one reason why loss of members of desaturation enzyme family, stearoyl-CoA desaturase which catalyses the rate-limiting step in the synthesis of monounsaturated fatty acids, particularly oleate (18:1) and palmitoleate (16:1), protects mice against fatty liver in mice[43].

The decreased outflow

The increased hepatic uptake and biosynthesis of FAs are compensated through increased removal of lipids from the liver. In this process, VLDL plays a central role. The principal apoprotein for this particle is apoB100, but apoE and apoC-Ⅰ, C-Ⅱ, and C-Ⅲ are incorporated as well[44]. Lipid homeostasis in mammalian cells is regulated by a family of membrane-bound transcription factors designated sterol regulatory element-binding proteins (SREBPs). In the liver, three SREBPs regulate the production of lipids for export into the plasma as lipoproteins and into the bile as micelles. nSREBP-1a transgenic mice develop a massive fatty liver engorged with both cholesterol and triglycerides[45].

The bile acid receptor farnesoid X receptor (FXR; NR1H4) is a central regulator of bile acid and lipid metabolism. FXR protects the liver from the deleterious effect of bile acid overloading by inhibiting their biosynthesis and stimulating their excretion. FXR regulates the expression of several apolipoproteins involved in the transport and metabolism of lipids[46,47] (Figure 5).

Bile acid reduces the secretion of VLDL by repressing microsomal triglyceride transfer protein (MTTP) which mediates lipidation of apoB100 to form VLDL[48]. This effect is possibly mediated through FXR. Pharmacologic agents that induce hepatic steatosis like amiodarone, tetracycline, pirprofen, tianepine inhibited MTTP activity[49]. However it is still unclear whether FXR mediated decrease in triglyceride rich VLDL secretion and consequent decrease in lipid out flow from liver is important in the pathogenesis of fatty liver.

Abetalipoproteinemia, a genetic disease which is associated with fatty liver is caused by mutations in the MTTP gene resulting in blockage of VLDL assembly and secretion[48]. MTTP-493 G/T polymorphism may influence NASH by modulating postprandial lipemia and lipoprotein metabolism; homozygous GG carriers have a more atherogenic postprandial lipid profile than the other genotypes, independently of adipokines and insulin resistance[50]. Fatty acid level is sensed in liver by PPAR-α and genes which promote lipid secretion like FABP, MTTP and apoB100 are upregulated[51-53]. Indeed this could be one mechanism by which fibrates which are PPAR-α agonists used in the treatment of NAFLD exerts its effect. Since lipid synthesis should go hand in hand with lipid secretion; as lipogenesis is increased by activation of the liver X receptor, hepatic VLDL production is also increased. Selective modulators of nuclear receptors involved in lipid homeostasis could thus revolutionize the treatment of NAFLD, Gall Stone disease, obesity and type 2 diabetes mellitus.

HDL particles participate in reverse cholesterol transport, the mechanism by which cholesterol from extrahepatic tissues returns to the liver for excretion as biliary cholesterol[44]. Low HDL-cholesterol is associated with metabolic syndrome and NAFLD[28]. ABCA1 is a lipid binding protein which increases reverse cholesterol transport to pre-beta HDL. Patients with low HDL-cholesterol and abnormal cellular lipid efflux due to ABCA1 gene defects (Tangier disease) also have elevated plasma triglycerides[44,54] and fatty liver.

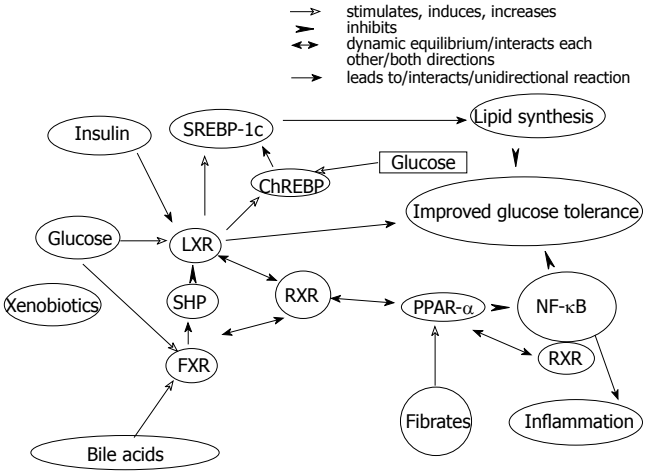

Figure 5 The complex interactions between various nuclear receptors involved in lipid-carbohydrate-bile acid homeostasis determines fat accumulation in liver. SREBP-Sterol regulatory element-binding proteins LXR-liver xenobiotic receptor, FXR-farnesoid xenobiotic receptor, SHP-short heterodimer partner, RXR-retinoid xenobiotic receptor, PPAR-peroxisome proliferator-activated receptor, ChREBP-carbohydrate responsive element binding protein. NF-κB-nuclear factor κB.

The increased synthesis

The synthesis of lipid and lipoproteins is important to metabolic disorders. In NAFLD nearly a quarter of the accumulated fat comes from *de novo* lipid (DNL) synthesis[17] and hepatic lipid synthesis is markedly increased in NAFLD[55]. Acetyl coenzyme A (acetyl CoA) is a crucial metabolic intermediate in carbohydrate and protein catabolism towards lipid synthesis. Acetyl CoA carboxylase (ACC) and Fatty Acid synthetase are two major enzymes that drive DNL in the liver[3]. Inhibitors of ACC decreases lipid accumulation by hepatocytes and might prove useful in the development of novel therapeutic agents to combat fatty liver[56].

Synthetic pathways for triacylglycerol (TAG), cholesterol and its esters, and phospholipids are separate, but transcriptionally co-regulated[57]. In insulin sensitive tissues and particularly in the liver, the transcription factor SREBP-1c transduces the insulin signaling regulating lipid synthesis. Overexpression of nSREBP-1c in the liver of transgenic mice bypasses insulin requirement and activates the same genes stimulated by insulin and produces a triglyceride-enriched fatty liver with no increase in cholesterol. The mRNAs for fatty acid synthetic enzymes and rates of fatty acid synthesis are elevated fourfold in liver[57,58]. Alcohol induces fatty liver partly by impairing PPAR-α and PPAR-γ activity and activation of SREBP-1[59]. Overexpression of nSREBP-2 in liver increases the mRNAs encoding all cholesterol biosynthetic enzymes[57,60].

Under physiological conditions, SREBP-1c is transiently

induced in the liver by insulin through activation of IRS-2; this causes a switch from glycogen synthesis to lipid synthesis. To complete a feedback loop, SREBP-1c then suppresses IRS-2 transcription. Under certain pathogenic conditions, expression of SREBP-1c in the liver remains elevated, and this increases lipid synthesis with resultant accumulation of fat[61].

Hepatitis B virus (HBV) infection is associated with fatty liver in a significant proportion of patients. HBV encoded protein HBx causes lipid accumulation in hepatic cells which is mediated through SREBP1 and PPAR-γ[62].

Obesity and insulin resistance is a pro-inflammatory state characterized by increased levels of pro-inflammatory cytokines[27,63]. Cytokines like IL-6 and TNF-α further promotes insulin resistance by increasing hepatic suppressors of cytokine signaling (SOCS) expression[3,63,64]. Over expression of SOCS-1 and SOCS-3 in liver causes insulin resistance and an increase in the key regulator of fatty acid synthesis in liver, SREBP-1c. In obesity, increased SOCS proteins enhance SREBP-1c expression by antagonizing STAT3-mediated inhibition of SREBP-1c promoter activity[64]. Interestingly n-3 PUFAs downregulate SREBP 1-c, which increases transcription of genes responsible for fatty acid synthesis such as fatty acid synthase and stearoyl Co-A desaturase[65].

The liver has a central role in glucose homeostasis. On feeding, glucose influx triggers gene expression changes in hepatocytes to suppress endogenous glucose production and convert excess glucose into glycogen or fatty acids to be stored in adipose tissue. This process is controlled by insulin, although debate exists as to whether insulin acts directly or indirectly on the liver. Transcriptional activation of glycolytic and lipogenic genes requires the presence of both insulin and glucose, neither of which is active alone. Recently, carbohydrate responsive element binding protein (ChREBP) emerged as a pivotal transcription factor implicated in the regulation of lipogenic genes by glucose[66].

Liver xenobiotic receptor (LXR) is another glucose sensor which is activated by glucose and switches on several genes involved in fatty acid synthesis[67]. An LXR-binding site in the *SREBP-1c* promoter activates SREBP-1c transcription in the presence of LXR agonists. When lipogenesis is increased by pharmacological activation of the liver X receptor, hepatic VLDL production is increased 2.5-fold, and the liver produces large TG-rich VLDL particles[68]. Interestingly, glucose induces expression of LXR target genes involved in cholesterol homeostasis like ABCA1 which is defective in Tangier disease[67].

A common feature of many metabolic pathways is their control by retinoid xenobiotic receptor (RXR) heterodimers. It is interesting to note that LXR heterodimerizes with RXR. Promiscuous RXR also heterodimerizes with PPAR members. PPAR-α plays a pivotal role in fatty acid catabolism in liver by upregulating the expression of numerous genes involved in mitochondrial fatty acid oxidation. Thus RXR is a common partner of two nuclear receptors acting in opposite directions with regard to fatty acid metabolism. So both LXR and PPAR-α compete for the limited pool of RXR and this dynamic equilibrium determines the direction of lipid metabolism[69].

FXR also plays a key regulatory role in glucose homeostasis. FXR-null mice developed severe fatty liver and elevated circulating FFAs, which was associated with elevated serum glucose and impaired glucose and insulin tolerance[70]. Activation of FXR lowers plasma glucose levels in fasted, fed, diabetic mice. Bile acids, by activating FXR, induce the expression of short heterodimer partner (SHP)[71]. SHP then interferes with SREBP-1c expression by inhibiting the activity of LXR and eventually other transcription factors that stimulate SREBP-1c expression[47].

An increase in serum triglyceride concentrations and fatty liver have been observed in patients with malabsorption of bile acid as found in chronic inflammatory bowel disease[72], ileal resection and cholestyramine treatment. This could be due to loss of bile salt mediated inhibitory effect on fatty acid synthesis mediated through FXR and further research is required in this area.

It may be noted that NAFLD is classically associated with gall stone disease and hypertriglyceridemia[30,73]. The increased incidence of gall stones at least partly is due to decreased secretion of bile salts, which are potent emulsifiers, and the consequent instability of bile pigments resulting in precipitation and stone formation. It would be logical to hypothesize that defective FXR expression or signaling and consequent deficiency in bile inhibition of fatty acid synthesis might play a role in certain cases of hepatic steatosis associated with biliary stones.

Hepatocyte nuclear factor-4α (HNF-4α) is a transcription factor which is mutated in monogenic autosomal dominant non-insulin-dependent diabetes mellitus type 1 (MODY-1), controls the expression of several genes, including hepatocyte nuclear factor 1α (HNF-1α), a transcription factor which regulates the expression of several hepatic genes and the human CYP7A1 gene in bile acid synthesis and phosphoenolpyruvate carboxykinase (PEPCK) gene in gluconeogenesis[74]. Long-chain fatty acids, including palmitic acid, have been identified as endogenous HNF-4α ligands and this allows the transcriptional control of gluconeogenesis during active lipid synthesis. It is interesting to note that glucose and fructose induces lipogenesis reduces hepatic HNF-4α levels, which in turn attenuates the expression of sex hormone binding globulin (*SHBG)*, a biomarker of metabolic syndrome[75]. Thus HNF-4α is another major protein at the cross roads of sex hormones, diabetes, fatty liver, dyslipidemia and gall stone disease.

Nuclear receptors are notoriously promiscuous. They are known to be activated, inhibited or otherwise modulated by numerous xenobiotic compounds which include alcohol, drugs, insecticides, dietary contaminants and numerous other chemicals acquired from environment[76]. This could explain the association of certain drugs as well as environmental toxins with fatty liver[77,78]. It may be noted that many of the *de novo* lipid synthesis pathways described above are shared by both alcoholic and nonalcoholic fatty liver disease.

The decreased oxidation

Fatty acid oxidation is compartmentalized in eukaryotic organisms into three subcellular organelles, with beta-oxidation confined to mitochondria and peroxisomes

and CYP4A-catalyzed omega oxidation occurring in the endoplasmic reticulum. Beta oxidation is primarily involved in the oxidation of fatty acids with carbon chains not longer than twenty while peroxisomal oxidization predominantly deals relatively complex and toxic fatty acids containing twenty or more carbon atoms and C27-bile acid intermediates[79]. Microsomal omega oxidation system hydroxylates saturated and unsaturated fatty acids which will eventually be oxidized by the other two oxidation systems[79]. Some of the key enzymes of these three fatty acid oxidation systems in liver are regulated by PPAR-α. When mice fed on a methionine-choline deficient (MCD) diet-a dietary model of fibrosing steatohepatitis-were treated with the PPAR-α agonist, Wy-14643, developed significantly less steatohepatitis, markedly lower ALT levels and less lipid peroxidation compared to controls. This occurred despite a marked increase of the liver P-450 enzymes which are oxidant stress inducers[80]. Mice lacking PPAR-α (PPARα-/-) fail to respond to the inductive effects of peroxisome proliferators, whereas those lacking fatty acyl-CoA oxidase (AOX-/-), the first enzyme of the peroxisomal beta-oxidation system, exhibit extensive microvesicular steatohepatitis, leading to hepatocellular regeneration and massive peroxisome proliferation, implying sustained activation of PPAR-α by natural ligands[79]. Ethanol a common cause of fatty liver interferes with DNA binding and transcription-activating properties of PPAR-α, as demonstrated with cultured cells and in ethanol-fed mice. Treatment of ethanol-fed mice with a PPAR-α agonist can reverse fatty liver even in the face of continued ethanol consumption[81].

Mitochondrial beta oxidation results in shortening of fatty acids and FA are oxidized carbon by carbon into acetyl-CoA subunits, which either condenses into ketone bodies that serve as oxidizable energy substrates for extrahepatic tissues, especially during starvation, or enter into the tricarboxylic acid cycle. Mitochondrial beta oxidation is regulated by carnitine palmitoyl transferase-1 (CPT-1), the carnitine concentration and malonyl-CoA, which inhibits CPT1. Fatty acids, fatty acyl-CoAs and several structurally different chemicals known as peroxisome proliferators, which activate PPAR-α, regulate CPT1 levels in the liver[82]. Inhibition of fatty acid oxidation in the liver is a intrahepatic cause of the development of liver steatosis. For instance, etomoxir, a CPT-1inhibitor, inhibits fatty acid oxidation and induces steatosis[83].

Thioredoxin (TRX) is an important redox regulator protein that has a redox-active dithiol/disulfide in its active site[84]. TRX binding protein-2 (TBP-2) was identified as a TRX binding protein from a yeast two-hybrid system study, and as a negative regulator of TRX through direct interaction. TBP-2 null mice are viable and fertile, but under fasting conditions, their survival rate was sharply reduced, concomitant with fatty liver, hypoglycemia, dyslipidemia, severe bleeding and hepatic and renal dysfunction. This mouse has been proposed as an animal model for Reye's syndrome an acute illness which is encountered exclusively in children below 15 years of age characterized clinically by vomiting and signs of progressive central nervous system damage, hypoglycemia and extensive fatty liver and liver damage[84]. TBP-2 is also reported to be a causative gene for familial combined hyperlipidemia (FCHL) in mice. Individuals with genetic deficiencies in fatty acid transport and mitochondrial oxidation show a similar pathology to Reye syndrome, which is defined as a Reye-like syndrome, such as CPT-I deficiency[85]. Defects in different enzymes involved in fatty acid utilization give rise to different disorders. A defect in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) is associated with acute fatty liver of pregnancy (AFLP) while medium-chain acyl-CoA dehydrogenase (MCAD) defect is involved in sudden infant death syndrome (SIDS)[86].

Less is understood about the role of mitochondrial beta oxidation in development of NAFLD. Mitochondrial trifunctional protein (MTP) catalyzes long-chain fatty acid oxidation. Chronic alcoholism is known to cause mitochondrial damage[87]. Megamitochondrion with crystalline inclusions is a feature of NAFLD underscoring its importance in pathogenesis[88]. A mouse model for MTP deficiency reported that homozygous (*MTPa*-/-) mice suffer neonatal death. Heterozygosity for fatty acid oxidation defects predisposes to NAFLD and insulin resistance in aging mice. Thus impaired mitochondrial oxidation may play an important role in pathogenesis of NAFLD[89]. Primary or age-related defects in mitochondrial beta oxidation could play a role in development of NAFLD[90]. MTP defects in man are recessively inherited and children with defects of any of the three enzymatic functions exhibit mostly microvesicular hepatic steatosis[91].

A diet that provides 2%-5% of energy from (n-3) and (n-6) PUFA leads to a coordinate suppression of glycolytic and lipogenic genes and to an induction of genes involved in fatty acid oxidation. This metabolic balance in liver leads to a 'partitioning' of fatty acids away from triglyceride synthesis toward fatty acid oxidation[92]. Long-chain n-3 PUFAs upregulate PPAR-α, increases transcription of genes responsible for fatty acid oxidation, such as mitochondrial CPT 1 and peroxisomal acyl-CoA oxidase[65]. Thus PUFA intake could be beneficial in treatment of NAFLD.

Epigenetic factors

The thrifty phenotype hypothesis (Barker's hypothesis) postulates epigenetic memory of the fetal/neonatal environment[93]. Feeding rats a high-carbohydrate diet during suckling rapidly leads to hyperinsulinism. Moreover, when these female rats become pregnant, hyperinsulinism also rapidly appears in their offspring even though they are fed a normal diet, suckling milk from their mothers[94]. Epigenetic regulation of gene expression involves chemical modification of chromatin by enzymes such as sirtuins (SIR2-related proteins), whose activities are linked to cellular energy stores and in lower organisms, sirtuin signaling interface with insulin signaling pathways[95,96] and SIR2 orthologues could possibly be involved in the pathogenesis of fatty liver disease.

Timers of fatty liver disease

Many biological processes are timed and there is a biological clock which keeps the time at the molecular level. Recent

studies have revealed that endogenous rhythms are generated at the cellular level by circadian core oscillators, which are composed of transcriptional/translational feedback loops involving a set of *CLOCK* genes. Obese diabetes attenuated this rhythmic expression in most of the clock and adipocytokine genes in adipose tissue. There was impairment in the rhythmic expression of the *CLOCK* genes in the liver as well. Interestingly, pioglitazone treatment improved the attenuated rhythmicity in the liver but not the adipose tissue[97]. A recent human study suggests a potential role of the *CLOCK* gene variants and their related haplotypes increased susceptibility to NAFLD and disease progression[98].

FATTY LIVER: THE MANY FACES IN CLINICS

The classic 'metabolic syndrome associated NAFLD'

The 'classical NAFLD' which is the 'fatty liver of affluence' is the commonest form and is associated with metabolic syndrome and can be viewed as a special class of adipose tissue malfunction and disordered lipid homeostasis. MS can be consider MS as inappropriate expression of 'thrifty genes' resulting in obesity, abnormal fat deposition, dyslipidemia, diabetes, pro-inflammatory (and pro-neoplastic?) states[99]. NAFLD, which is characterized by abnormal fat deposition in liver and chronic pro-inflammatory state, has been considered as a liver manifestation of MS[100]. This is substantiated by the epidemiological data where 50%-80% of the NAFLD has associated MS depending on the area studied and methods adopted. The association of NAFLD with MS and IR has been extensively reviewed by Marchesini *et al* and Cortez-Pinto *et al*[4,100].

Metabolic Syndrome is a tool for identifying individuals who are at the cardiovascular risk rather than a single disease. NAFLD is gaining importance in this context. Recent studies have reported the association of NAFLD with multiple classical and non-classical risk factors for cardiovascular disease (CVD). Moreover, there is a strong association between the severity of liver histopathology in NAFLD patients and greater carotid artery intima-media thickness and plaque, and lower endothelial flow-mediated vasodilation (as markers of subclinical atherosclerosis) independent of obesity and other MS components[28-30,101,102].

Identification of MS is very useful not only as a tool to identify people with cardiovascular and diabetic risk but also NAFLD but much confusion exists in the criteria of MS[103]. Criteria for MS should be convenient but flexible to the regional and ethnic differences is important in establishing its association with NAFLD, a disease which progress asymptomatically to cirrhosis[104]. There exists significant genetic environmental and life style diversity in population across different continents and cultures. For example Asian Indians are prone to central obesity and for same degree of weight gain are more insulin resistant[105-107].

In case of other well known syndromes, a single or a few well defined genetic defects results in the clustering of a host of strongly associated phenotypic features. But in MS, a host of poorly defined genetic defects results in loosely associated clustering of phenotypic features. The primary underlying causes of the metabolic syndrome are thought to be insulin resistance. Central obesity almost certainly is a major cause of insulin resistance[103]. There is considerable doubt whether all patients with the metabolic syndrome are indeed insulin resistant[103]. Many nondiabetic adults with a wide range of age and body mass are hyperinsulinemic and insulin resistant (about 50%), approximate 25% are insulin resistant but without hyperinsulinemia and the same proportion are hyperinsulinemic but without insulin resistance[103,107]. Thus the lack of consensus regarding MS criteria, insulin resistance cut off value together with the complex pathogenesis of hepatic steatosis makes it difficult to evaluate their association.

The lean nonalcoholic fatty liver disease

It became clear that Non-alcoholic steato hepatitis (NASH) has an equal sex distribution and that many, perhaps even the majority of patients according to some reports are neither obese nor diabetic[108].

We already described the importance of adipose tissue in fatty acid buffering. Several congenital forms of lipodystrophy are associated with fatty liver. Berardinelli-Seip syndrome caused by mutation of *BSCL2* gene is characterized by a near-total lack of body fat from birth. Interestingly *BSCL2* gene is highly expressed in the brain but only modestly in adipocytes, suggesting a role for the central nervous system in the pathogenesis[109]. MRI studies also reveal a near-complete absence of metabolically active adipose tissue from most subcutaneous areas, intraabdominal and intrathoracic regions and bone marrow. Fatty liver has been noted during infancy and can lead to cirrhosis and its complications. They show extreme insulin resistance[110].

Dunnigan variety of familial partial lipodystrophy and Mandibuloacral dysplasia (type-A lipodystrophy) are associated with laminin gene mutation, causes fatty liver and IR. PPAR-γ mutations result in a dominant form of lipodystrophy and fatty liver. Similarly in acquired lipodystrophies like Lawrence syndrome; hepatomegaly due to fat infiltration is a consistent finding[110].

In patients who undergo liposuction or other forms of obesity reduction surgery, fatty liver is a common finding. Highly active antiretroviral therapy (HAART) therapy for HIV, a combination that includes HIV-1 protease inhibitors, is associated with the development of lipodystrophy in the majority of patients after 18 mo to 2 years of treatment. It is characterized by fatty liver following marked reduction in subcutaneous fat from the face, trunk and limbs, resulting in an appearance of "increased muscularity". These patients are prone to develop insulin resistance, hypertriglyceridemia and fatty liver[111]. In animal models of lipodystrophy IR and fatty liver are corrected by infusion of adipokines[112]. This underscores the role of adipokines in modulating the response of adipose tissue and as messengers to other organs in response to changing energy environment and adaptive mechanisms like IR. Removal of adipose tissue causes IR and fatty liver in hamsters[113]. It is well known that patients who undergo liposuction as a treatment for

obesity do not show metabolic benefits[21]. It won't be surprising if liposuction worsens insulin resistance and fatty liver as this procedure removes active adipocytes from subcutaneous spaces. Thus, any defect that prevents adipose tissue from acting as an 'energy rich substrate sink' would result in fatty liver.

The fatty liver associated with infectious and immunological disorders

Fatty liver is associated with many chronic inflammatory conditions. Hepatitis C especially type 3 genotype is associated with fatty liver in nearly 50% of the patients. In patients with chronic liver disease due to hepatitis C virus, the major adipokine adiponectin was positively correlated with hepatic inflammation and adiponectin receptors were differentially regulated in the setting of hepatic insulin resistance[114]. It has been shown, that HCV internalization is facilitated *via* LDL (low density lipoprotein) receptors and the virus enters into the cell via endocytosis. More recently, a broadly expressed lipoprotein binding receptor, the human scavenger receptor class B type 1 was shown to serve as a receptor for HCV[115]. According to Younossi the HCV genotype 3 core protein inhibits very low-density lipoprotein (VLDL) secretion, leading to hepatic steatosis. Several studies demonstrate that steatosis disappears after patients with hepatitis C genotype 3 achieve a sustained response. The resolution of steatosis after treatment strongly supports the association between hepatic steatosis and HCV genotype 3[116].

Though less frequently, Hepatitis B is also associated with fatty liver. The hepatitis B virus encoded protein, HBx causes lipid accumulation in hepatic cells which mediated is by SREBP1 and PPARγ[117].

Fatty liver has been reported with certain bacterial infections like Q fever[118].

Autoimmune diseases like systemic lupus erythematosis (SLE) and rheumatoid arthritis *etc* are also associated with fatty liver[119].

There are reports that NAFLD is characterized by a low-grade systemic inflammation[120]. This could be partly because of the association of NAFLD with obesity which is a pro-inflammatory state. Conditions that induce inflammatory state in liver might in long term stimulate adipocytes and macrophages because they have a common ancestry and hence they share many cytokines, growth factors and signaling pathways[8-11,13]. There are many ways by which fat is deposited in liver but it is the body's response to fat and its derivatives which determines the progress of the disease from simple fatty liver to steatohepatitis and cirrhosis.

The xenobiotic fatty liver

NASH features are also encountered as an adverse reaction to a few drugs-for example, amiodarone and perhexiline. Drug like methotrexate, aspirin, vitamin A, glucocorticoids, amiodarone and synthetic estrogen causes macrovescicular steatosis while microvesicular is caused by valproic acid, tetracycline, nucleoside analogues etc. Chronic alcoholism causes predominantly macrovescicular steatosis[121,122]. However some hepatocytes in these livers with microvesicular steatosis may also reveal a macrovesicular fatty change, implying that with the progression of disease some of these small lipid vacuoles may fuse to become a large droplet.

The metabolism of ethanol enhances the level of NADH in the liver which, in turn, stimulates the synthesis of fatty acids and their incorporation into triglycerides. Ethanol mediated impairment or inhibition of PPAR-α and PPAR-γ and stimulation of SREBP, the receptor molecules that control the enzymes responsible for the oxidation and synthesis of fatty acids, respectively, appear to contribute to the overall lipid load in the alcoholic liver[59].

These xenobiotics cause steatosis by a host of mechanisms. Drugs like tetracycline, aspirin etc do so predominantly by inhibiting hepatic fatty acid oxidation[49]. Jamaican vomiting syndrome which is caused by hypoglycin-A present in unripened ackee fruit[121,123] is an example for natural toxins inducing fatty liver. Estrogen, various pesticides etc probably induces various nuclear receptors like FXR, PXR, CXR, LXR, PPARs *etc.* involved in lipid homeostasis as these nuclear receptors are promiscuous[76,77]. There is a paucity of literature and much research has to be done in this field.

Reye's syndrome and Reye like syndrome associated fatty liver

This acute illness is encountered exclusively in children below 15 years of age classically following a viral infection and the use of aspirin. It is characterized clinically by vomiting and signs of progressive central nervous system damage, signs of hepatic injury and hypoglycemia. Morphologically, there is extensive fatty vacuolization of the liver and renal tubules. There is mitochondrial dysfunction with decreased activity of hepatic mitochondrial enzymes. There are reports linking Thioredoxin Binding Protein-2, a protein that interacts with thiredoxin which is an important redox regulator protein and Rye's syndrome. Individuals with genetic deficiencies in fatty acid transport and mitochondrial oxidation show a similar pathology to Reye syndrome, which is defined as a Reye-like syndrome, such as CPT deficiency[84,85].

The fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a syndrome that occurs late in pregnancy and is often associated with jaundice and hepatic failure. AFLP has an incidence of 1 per 13000 deliveries. It affects women of all ages and races. The liver is typically small. AFLP is more common when the mother is carrying a male fetus and associated with a deficiency of long-chain-3-hydroxy acyl COA dehydrogenase (LCHAD). Preeclampsia or the HELLP syndrome, which may complicate eclampsia, presents in a similar fashion and progresses to severe liver dysfunction, though typically with a normal size liver. Aminotransferase elevations are typically modest in all of these conditions[124].

An association between recurrent maternal acute fatty liver of pregnancy with a fetal fatty acid oxidation disorder was reported first in two siblings who both died at 6 mo of age[125]. In another study involving 11 pregnancies in 5 mothers where 6 babies had confirmed deficiency of LCHAD, by enzymatic analysis of cultured skin fibroblasts. The mothers had either AFLP or HELLP

Table 1 Fatty liver: the many faces in clinics

Classification of fatty liver	
Classic metabolic syndrome associated fatty liver	'Fatty liver of the affluent': commonest form of fatty liver; associated with metabolic syndrome
The lean nonalcoholic fatty liver	Includes lipodystrophies, known and unknown adipose tissue defects of various origin resulting in lean phenotypes, liposuction (?)
Fatty liver of infection/ chronic inflammatory diseases	HCV, HBV, Q fever (?) autoimmune diseases
Xenobiotic fatty liver	Drugs like tetracycline, amiodarone, alcohol, environmental industrial toxins
Fatty liver of defective fatty acid catabolism	Reyes syndrome, reye like syndrome, sudden infant death syndrome, fatty liver of pregnancy
Malnourishment associated fatty liver	'Fatty liver of the deprived' : kwashiorkor
Transient fatty liver	Fatty liver which develops transiently following short excess calorie intake

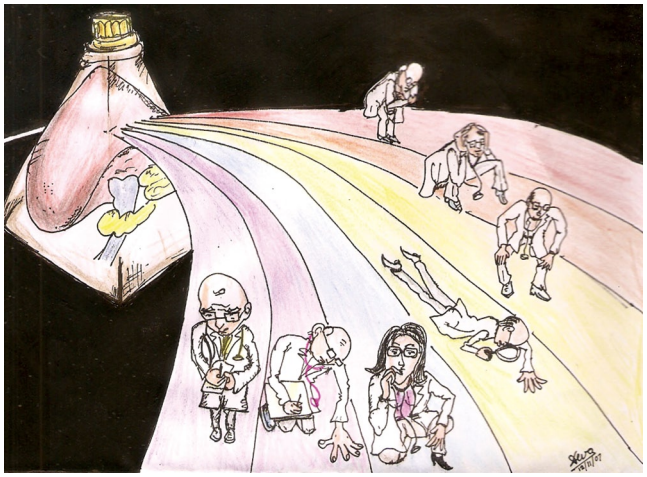

Figure 6 With the progress of medicine at molecular level diseases like type 2 diabetes and 'NAFLD' which results from a spectrum of genetic defects would split into hundreds if not thousands of diseases with 'individual' identity providing patients' accurate diagnosis of the disease and accurate treatment with minimum 'side effects' which is unavoidable in today's 'blind clinical practice'.

syndrome in all six pregnancies with the LCHAD deficient fetuses[126]. However how fetal defects induce acute fatty liver in mothers is still not clear.

Fatty liver in malnutrition

Protein malnutrition, especially in infancy and early childhood, accounts for most cases of severe fatty liver in the tropical zones of Africa, South America, and Asia. The hepatic changes may be associated with other clinical and pathologic features of Kwashiorkor. High plasma levels of free fatty acids are generally regarded as a key biochemical feature of the condition. Glucose intolerance is another characteristic feature. Interestingly in marasmus, a form of protein-calorie malnutrition, fatty liver is not part of the clinical picture[127].

The benign fatty liver-the non-progressive fatty liver

Kagansky *et al* evaluated 91 octogenarians (mean age, 85.56 ± 3.76 years) to determine the prevalence and the clinical presentation of NAFLD in the elderly. Among these patients, who had been admitted to a geriatric hospital, about 50% were diagnosed with NAFLD. An association of NAFLD with the metabolic syndrome or advanced liver disease was not observed in this older patient population. These data indicate that NAFLD is a common and relatively benign finding in the elderly[128]. Another study, examined sequential liver biopsies obtained from 103 NAFLD patients. The mean interval between biopsies was about 3 years and found that the stage of fibrosis slowly progressed in 37% of patients but remained stable in 34%[129]. The observation that NAFLD patients without NASH have a benign prognosis confirmed in several other studies as well[130].

Transient fatty liver

It is possible that fatty liver is physiological than pathological under certain circumstances for example after a fat carbohydrate rich diet for a short period. Increase in hepatic TG content can occur within 10 d after starting the high-fat diet in mice[131]. Overnight fasting increases plasma FFA to such an extent that liver TG content increases in dogs[132]. It is logical to assume that as in laboratory animals transient fatty liver follows a short term calorie rich diet in man as well. Unfortunately there is no diet related guide line for ultrasonological determination for fatty liver in the diagnosis of NAFLD. Ideally the subject should be on 'normal' and balanced diet at least for a week prior to ultrasonological evaluation for NAFLD. In a large population based study involving 4401 subjects it was observed that fatty liver regressed in a significant number of participants; fatty liver regressed in 14% of men and 25% of women[133]. In another follow up study involving sequential liver biopsies from 103 NAFLD patients it was observed that disease regressed in 29% of the cases[129]. In another recent study fatty liver regressed in nearly 1 of every 2 cases and had a substantially benign course[134]. A carbohydrate rich but fat deficient diet may predispose to fatty liver as surplus carbohydrate induce adipogenic genes[135]. This could well explain the fatty liver, which follows total parenteral nutrition[136].

The classification of fatty liver is summarized in Table 1.

NEED FOR PERSONALIZED MANAGEMENT OF NAFLD: NO TWO PEOPLE ARE THE SAME!

The advances in science would soon empower us to understand subtle differences between two individual patients at genotypic and phenotypic levels. It seems likely that a major focus of medicine over the next two decades will be within the arenas of 'pathogenomics', molecular diagnostics and 'pharmacogenomics' as a prelude to personalized molecular medicine. All polygenic

diseases like type 2 diabetes and 'NAFLD' would split into hundreds if not thousands of diseases with 'individual' identity providing patient' accurate diagnosis and accurate and effective treatment with minimum 'side effects' which is unavoidable in today's 'blind clinical practice' (Figure 6).

The difference in genotype and environment could explain the differences in the results observed even between drug well controlled drug trials and why certain drug therapies are effective only in certain individuals.

Above all, molecular level diagnosis and personalized treatment is more important because of difference in life style and environmental factors which are detrimental in the disease progress and treatment options. As mentioned before interactions between the genotype, phenotype and environment determines the disease process.

CONCLUSION

Currently the term NAFLD is loose to incorporate a host of diseases presenting with fatty liver in the absence alcohol abuse. 'Insulin resistance associated fatty liver' is the commonest type which could result from a variety of genetic, epigenetic defects and environmental factors. Clinically fatty liver is an important sign in predicting the risk of diabetes, cardiovascular accidents, stroke, cirrhosis and cancer. Individual variability in evaluating alcoholism and histopathological specimens, the variety of genetic defects presenting as fatty liver, together with the absence of reliable disease markers makes the accurate diagnosis of NAFLD difficult. Fat accumulation results from imbalance between feeding and physical activity, inflow and out flow, synthesis and oxidation. At molecular level defects in nuclear receptor signaling involving lipid sensing, synthesis and oxidation, defects in the lipid influx-efflux channels, proteins involved in insulin signaling, fatty acid catabolism, molecular defects in adipose tissue development, maturation and function and neural signaling can cause steatosis.

Bundling of several genetic defects under same diagnosis can result in inefficient patient management. With the advances in molecular medicine and diagnostics, diseases like NAFLD and Diabetes Mellitus Type-2 which are currently considered and managed as single entities would split into several distinct entities which might differ in management. Thus exploration of the molecular and genetic basis of NAFLD will allow us to segregate and manage them appropriately.

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