Review Article

Nonalcoholic Fatty Liver Disease and Risk of Diabetes and Cardiovascular Disease: What Is Important for Primary Care Physicians?

Mohamed H. Ahmed, Nazik Elmalaika OS. Husain[1], Ahmed O. Almobarak[2]

Department of Medicine, Milton Keynes Hospital NHS Foundation Trust, Eaglestone, Milton Keynes, Buckinghamshire, UK, [1]Department of Pathology, Faculty of Medicine and Health Sciences, Omdurman Islamic University, Khartoum, Sudan, [2]Department of Pathology, Faculty of Medicine, University of Medical Sciences and Technology, Khartoum, Sudan

Abstract

Nonalcoholic fatty liver disease (NAFLD) is emerging as the most common chronic liver condition in Western World and across the globe. NAFLD prevalence is estimated to be around one-third of the total population. There are no published data that project the future prevalence of NAFLD, but with an increase in epidemic of diabetes and obesity, it is possible to suggest an increase in a number of individuals with NAFLD. NAFLD is associated with insulin resistance and occurs with an increase in cluster of features of metabolic syndrome and type 2 diabetes. Therefore, it is important to exclude the possibility of diabetes in those individuals with evidence of fatty liver. The global diabetes epidemic continues to grow, and it is estimated that the number of people with diabetes will double by year 2030. NAFLD is also a risk factor for an increase in cardiovascular incidence independent of age, sex, low-density lipoprotein-cholesterol, smoking, and cluster of metabolic syndromes. It is expected that NAFLD will be an important challenge for health providers in the near future. Taking all these factors into consideration, we believe that increasing awareness of metabolic and cardiovascular impact of NAFLD among general practitioners and health authorities may decrease the serious consequences of late diagnosis of NAFLD. Importantly, the collaboration between medical specialties is vital in decreasing the impact of the epidemic of NAFLD. The focus of this review is in the role of primary care physician in diagnosis, treatment and prevention of NAFLD and patients education.

Keywords: Cardiovascular disease, insulin resistance, nonalcoholic fatty liver disease, primary care physician, type 2 diabetes mellitus

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease across the globe and become an increasingly important health issue. NAFLD is a condition given to the spectrum of liver disorders associated with hepatic steatosis that is not due to significant alcohol intake and other secondary causes of liver diseases.[1] The histological spectrum of NAFLD ranges from steatosis to steatosis with evidence of hepatocellular inflammation and damage [nonalcoholic steatohepatitis (NASH) Figure 1].[2] NAFLD is emerging as a common cause of liver disease, and most of the individuals thought to have cryptogenic cirrhosis are now believed to have cirrhosis due to NASH.[3] There is an invariable association between NAFLD and insulin resistance and its estimated that more than 90% of NAFLD patients have insulin resistance or feature of metabolic syndrome.[4] Importantly, in the view of the increase in the prevalence of diabetes, it is projected that NAFLD will be the leading cause of liver cirrhosis in the near future.[5]

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Epidemiology and Natural History

The prevalence of NAFLD in USA was found to be around 34% and 90% of these cases of NAFLD were attributed to nonalcoholic causes.[6] In addition, the prevalence in an ethnically diverse community in USA was estimated to be around 33.6%.[7] While in Europe, the prevalence of NAFLD was ~ 25% and 35% was associated with most features of the metabolic syndrome.[8] In Japan and China, the prevalence of NAFLD is estimated to be around 25%.[9-12] The prevalence of NAFLD in the far East

Address for correspondence: Dr. Mohamed H. Ahmed, Department of Medicine, Milton Keynes Hospital NHS Foundation Trust, Eaglestone, Milton Keynes, Buckinghamshire, UK.
E-mail: elziber@yahoo.com

and Asian population has been estimated to vary between 5% and 40%.[13] The increase in the epidemics of obesity and diabetes in the Middle-East may have a significant impact in the increase in the prevalence of the epidemic of NAFLD in that region. In a study by El-Hassan *et al.* in 1992, the prevalence of NAFLD was ~ 10%[14] and increased to 33.3% in 2012.

The prevalence of NAFLD in Africa is similar to Asia. For instance Almobarak et al showed that the prevalence of NAFLD in sudan is around 20%.[15] The synergistic effect of alcohol and obesity may worsen the NAFLD phenotype and may lead to an increase in risk of cirrhosis.[16,17] NAFLD *per se* is associated with high mortality.[18] NAFLD is also associated with worsening lipid profile in individuals with metabolic syndrome especially, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and high plasma triglyceride.[19]

Hyperglycemia is also significant risk factor for the development of NAFLD. For instance, the prevalence of NAFLD in the Japanese population rises with increasing degrees of hyperglycemia, being around 27% in people with normal fasting glucose levels, increasing to 43% among those with impaired fasting glycemia, and 62% among newly diagnosed diabetes.[20] Importantly, features of metabolic syndrome such as waist circumference, triglyceride level, and insulin resistance were independently associated with NAFLD in the normal-weight group.[21] Alarmingly, obese children are also at risk of developing NAFLD and this risk increases with features of the metabolic syndrome. NAFLD in children is also associated with risk of liver cirrhosis and transplantation and overall increase in mortality.[22-24]

There is growing the body of evidence from the natural history of NAFLD, which suggests that NAFLD has a benign course without excess mortality.[25,26] However, a recent large study by Adams *et al.*, concluded that the overall death rate is higher than expected in individuals with NAFLD, and this increase in mortality was associated with age, impaired fasting glucose/diabetes and cirrhosis.[27] Furthermore, the natural history of NASH is associated with the possibility of progression to cirrhosis, fibrosis, and in small number of patients hepatocellulars carcinoma[28,29] and once cirrhosis develops in patients with NAFLD, the prognosis is poor.[27,29-32]

Nonalcoholic Fatty Liver Disease, Metabolic Syndrome, and Diabetes

Nonalcoholic fatty liver disease is associated with insulin resistance and is regarded as hepatic component of the metabolic syndrome.[33,34] This due to the fact that most of the features of metabolic syndrome are commonly present in subjects with NAFLD, with 67–71% being obese, 12–37% having impaired fasting glycemia, 57–68% having disturbed lipid profiles, and 36–70% being hypertensive.[27] Metabolic syndrome can be diagnosed in the presence of three of the five criteria–including high waist circumference, high triglycerides, LDL, HDL-C levels, high blood pressure, and high fasting-glucose levels. Waist circumference is just one of five criteria that physicians can use when diagnosing the metabolic syndrome (Population- and country-specific definitions).[35] Insulin resistance is an important shared unique feature between metabolic syndrome, NAFLD and type 2 diabetes. Importantly, the increase in the features of the metabolic syndrome is associated with a parallel increase in the degree of insulin resistance.[33,36,37] Therefore, it is not surprising that NAFLD can be a manifestation of type 2 diabetes mellitus (T2DM) and present in up to 30% of patients with type 2 diabetes or impaired glucose tolerance[25,38] [Figure 1]. Several studies have showed a high prevalence of NAFLD among type 2 diabetes individuals. For instance, the prevalence of NAFLD among type 2 diabetes individuals in Brazil, Malaysia, and China were estimated to be 42%, 49.6%, and 61%, respectively.[39-41] In UK, the estimated prevalence of NAFLD among type 2 diabetes people was found to be around 42.6%, while in Italy, the prevalence of NAFLD among type 2 diabetes was ~ 70%.[42] Furthermore, a recent small study in diabetic Saudi individuals has suggested the prevalence of NAFLD is ~ 55%.[43]

Brinks *et al.* showed that the number of people with type 2 diabetes (age from 55 to 74 years old) in Germany will increase from 2.4 to 3.9 million by year 2030.[44] Honeycutt *et al.* showed that the projected number of people with diagnosed diabetes in USA will increase from 12 million to 39 million in 2050 (form 4.4% to 9.7%).[45] Boyle *et al.* showed that annual diagnosed diabetes incidence (new cases) will increase from about 8 cases/1,000 in 2008 to about 15 in 2050. The authors suggested that in case of low incidence and relatively high diabetes mortality, total diabetes prevalence (diagnosed and undiagnosed cases)

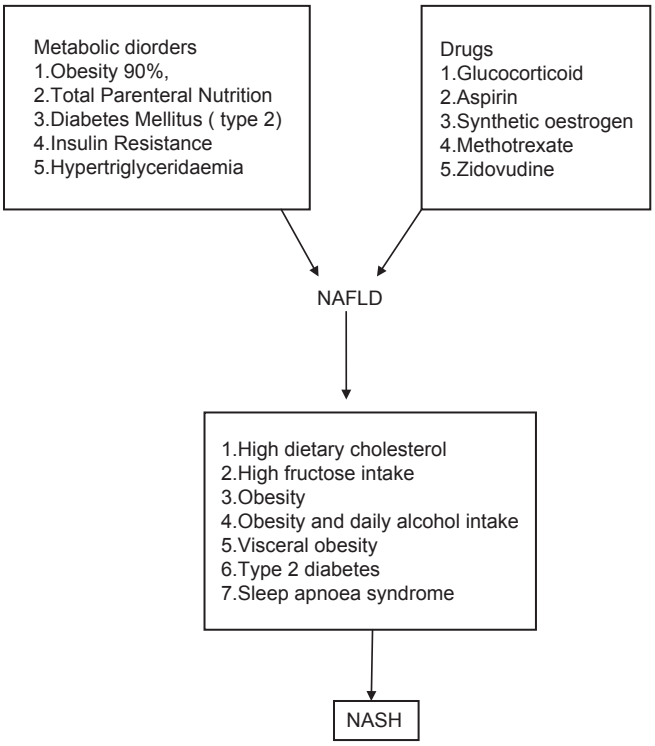

Figure 1: Conditions associated with nonalcoholic fatty liver disease (NAFLD) and factors that lead to nonalcoholic steatohepatits

is projected to increase from 14% in 2010 to 21% of the US adult population by 2050. Furthermore, it is projected that the prevalence of diabetes will increase to 33% by 2050 if diabetes mortality remained low and no decreased in incidence of diabetes is reported. Their projection is that the middle-ground scenario projects a prevalence of 25% to 28% by 2050.[46] Importantly, in 10 countries, it is estimated that the number of people with diabetes will increase from 366 million people to 552 million people by 2030.[47] The impact of the epidemic of diabetes not only in increasing the prevalence of NAFLD but also in how primary care resources will be able to cope is not yet established.

Nonalcoholic Fatty Liver Disease and Obesity and Dyslipidemia

Obesity and dyslipidemia are important risk factors for NAFLD. In a population-based studies in Japan and Korea, showed that obesity, dyslipidemia, and hypertension were independent risk factors for NAFLD.[48,49] Interestingly, visceral fat accumulation and insulin resistance were found to correlate with the severity of NAFLD in obese and nonobese individuals.[50] Therefore, it is not surprising that 50% of individuals with dyslipidemia have NAFLD.[51] Obesity is regarded as inflammatory condition and inflammation are crucial part of the pathogenesis of NAFLD.[52-54] Interestingly, around 70–100% of NASH patients are obese. In addition, steatosis is a common observation in obesity and may be associated with inflammatory signs of the nonspecific hepatitis.[55-57] In one large study of 528 patients with an average BMI of 42 kg/m^2, 74% of liver biopsies showed fatty deposition[56] and in another study, 12% of autopsies in cirrhotic patients obesity was the only recognized risk factor.[58] Therefore, it is important in obese individuals with long-standing obesity to exclude diabetes and fatty liver/cirrhosis.

Nonalcoholic Fatty Liver Disease and Cardiovascular Disease

Recent data suggest that NAFLD may be linked to increased cardiovascular disease (CVD) risk in both nondiabetic and type 2 diabetes. Interestingly, studies have reported associations between increased liver enzymes (particularly serum γ-GGT levels), as surrogate markers of NAFLD, with the occurrence of CVD events in both nondiabetic subjects and people with type 2 diabetes. The following table is summary of studies linking NAFLD and CVD [Table 1].[59-69]

Pathogenesis

A full understanding of the pathogenesis of NAFLD is not yet established and involves complex factors that alter different metabolic events [Figure 2]. Insulin resistance is one of the unique features of the pathogenesis of NAFLD and reported in the majority of individuals with obesity and visceral obesity. Insulin resistance leads to an increase in supply of free fatty acids to the liver.[70-74] Furthermore, insulin resistance is associated with impaired suppression of lipolysis by insulin leading to increased nonesterified fatty acid delivery to the liver. There is also reduced glucose uptake in the fed state by adipose tissue and skeletal muscle resulting in hyperglycemia and diversion of glucose to the hepatic *de novo* pathway. In addition, fatty food may also precipitate NASH. Excessive consumption of glucose or sucrose is also shown to promote NAFLD due increase *de novo* lipogenesis.[75-79]

There is a strong link between insulin resistance and excessive deposition of triglyceride in the hepatocytes, which is the unique features for diagnosis of NAFLD.[80-82] Different factors lead to more accumulation of fat in the liver. For instance, increased dietary fat, decreased mitochondrial β oxidation, and decreased clearance of very low-density lipoprotein (VLDL). Other important factors are increased fatty acid delivery from adipose tissue, increased synthesis of fatty acid via the *de novo* pathway.[83]

At cellular level, different factors are thought to induce different impacts. For instance, inflammation and oxidative stress are associated different metabolic changes that lead to insulin resistance and excess hepatic fat accumulation through increased triglyceride synthesis in the liver. Furthermore, because mitochondrial fat oxidation and export of VLDL particles are not able to match triglyceride synthesis, this will lead to further deposition of fat in the liver and worsening of insulin resistance. Inflammation is the link between obesity and insulin resistance and may have an

Table 1: Summary of studies showing the association of NAFLD with CVD

Study references	Main outcomes
Jousilahti *et al.*[59]	In a study of 14,874 middle-aged Finnish men and women, mildly increased GGT levels were independently associated with an increased risk of ischemic stroke in both sexes
Wannamethee *et al.*[60]	Among 7613 middle-aged British men followed for 11.5 years, increased GGT levels were independently associated with a significant increase in mortality from all causes and from CHD[30]
The Valpolicella heart diabetes study[61]	This study has demonstrated that NAFLD is associated with an increased risk of CVD events among people with type 2 diabetes and independent of classical risk factors, liver enzymes, and the metabolic syndrome[29]
The Hoorn study[62]	ALT predicts cardiovascular events independently of traditional risk factors and features of the metabolic syndrome
FIBAR study[63]	GGT or AST independent predictor of cardiovascular disease
Targher *et al.*, Volzke *et al.*, Fracanzani *et al.*[64-66]	The severity of NAFLD is associated with carotid atherosclerosis
Targher *et al.*,[67-69]	Different studies showed increased CVD with NAFLD

CVD: Cardiovascular disease; NAFLD: Nonalcoholic fatty liver disease; GGT: Gamma glutamyl transferase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CHD: Coronary heart disease; FIBAR: Firenze Bagno A Ripoli

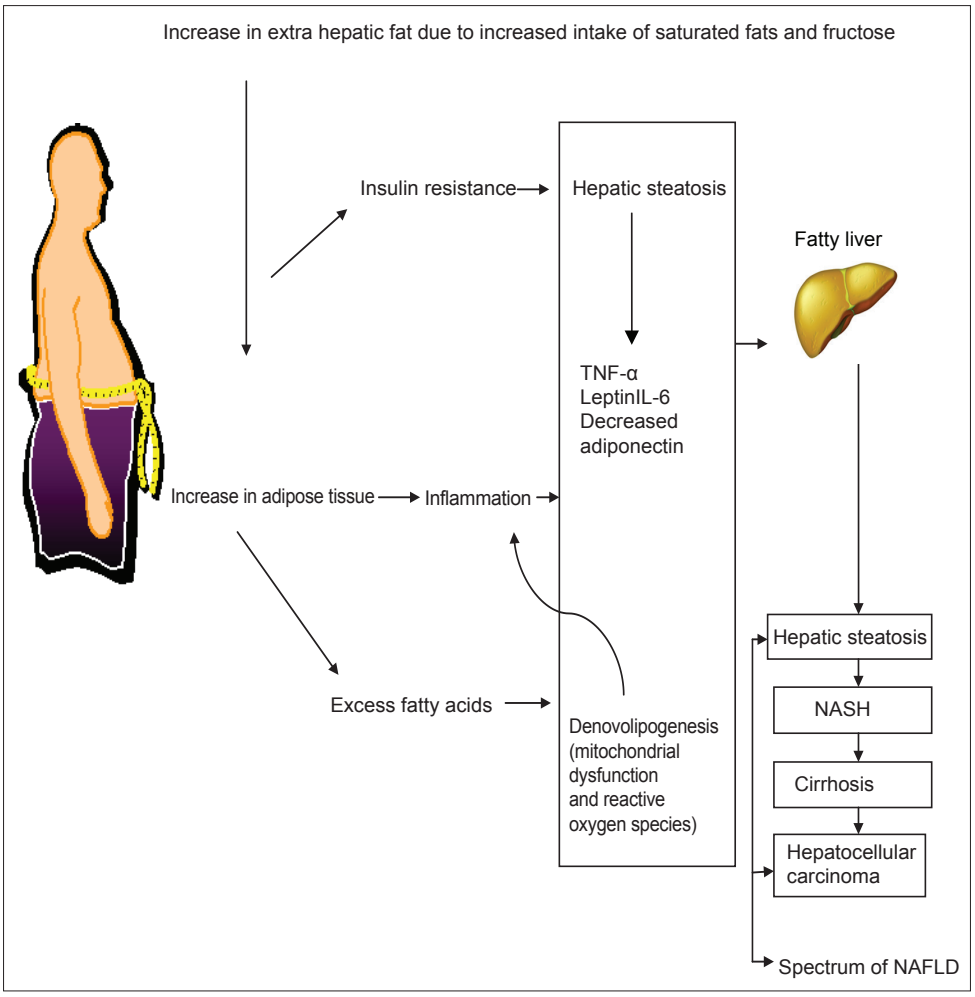

Figure 2: Schematic figure showing possible pathways involved in the pathogenesis of nonalcoholic fatty liver disease

important role in the pathogenesis of hepatic and systemic insulin resistance and CVD.[84,85] Adiponectin has been shown to decrease *de novo* fatty acid synthesis and enhance fat oxidation and improved insulin sensitivity.[86] Low levels of adiponectin are associated with NAFLD independent of the components of the metabolic syndrome, and low adiponectin is associated with CVD.[87-89]

Primary Care Physician and Nonalcoholic Fatty Liver Disease-What to Do?

It is good practice to exclude NAFLD in obese individuals and those with features of metabolic syndrome [summary of features of metabolic syndrome and patients at risk of developing NAFLD are shown in Figures 2 and 3]. The role of primary care physician is to diagnose and treat NAFLD and promote weight loss through lifestyle changes.

Diagnosis

There are no biochemical markers for NAFLD. A combination of laboratory tests, imaging, and histology can provide a diagnosis. Laboratory test results may show mild to moderate increase in liver enzymes e.g. of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)[1,3] [Figure 3]. Ultrasound commonly used in the diagnosis of NAFLD. Ultrasound has a sensitivity of 90% and specificity of 80%, for diagnosing hepatic steatosis but ultrasound cannot detect hepatic inflammation or mild fibrosis. Confusion between a diagnosis of NAFLD or malignancy arising from a computed tomography scan may be resolved using magnetic resonance imaging[1,3] [Figure 3]. Liver biopsy is requested by liver specialist in patients with persistent increased liver enzymes despite attempts to reverse known risk factors or those with possible risk of developing fibrosis. This is especially important in patients with clinical conditions associated with insulin resistance such as T2DM, hyperlipidemia, and obesity.[1,3,90]

Treatment

Currently, there is no definitive treatment for NAFLD. The aim of management should be to reverse the progression of NAFLD and to prevent liver-related illness and death.

Weight loss

Both weight loss and exercise improve insulin sensitivity. The current evidence suggests that gradual weight loss should be

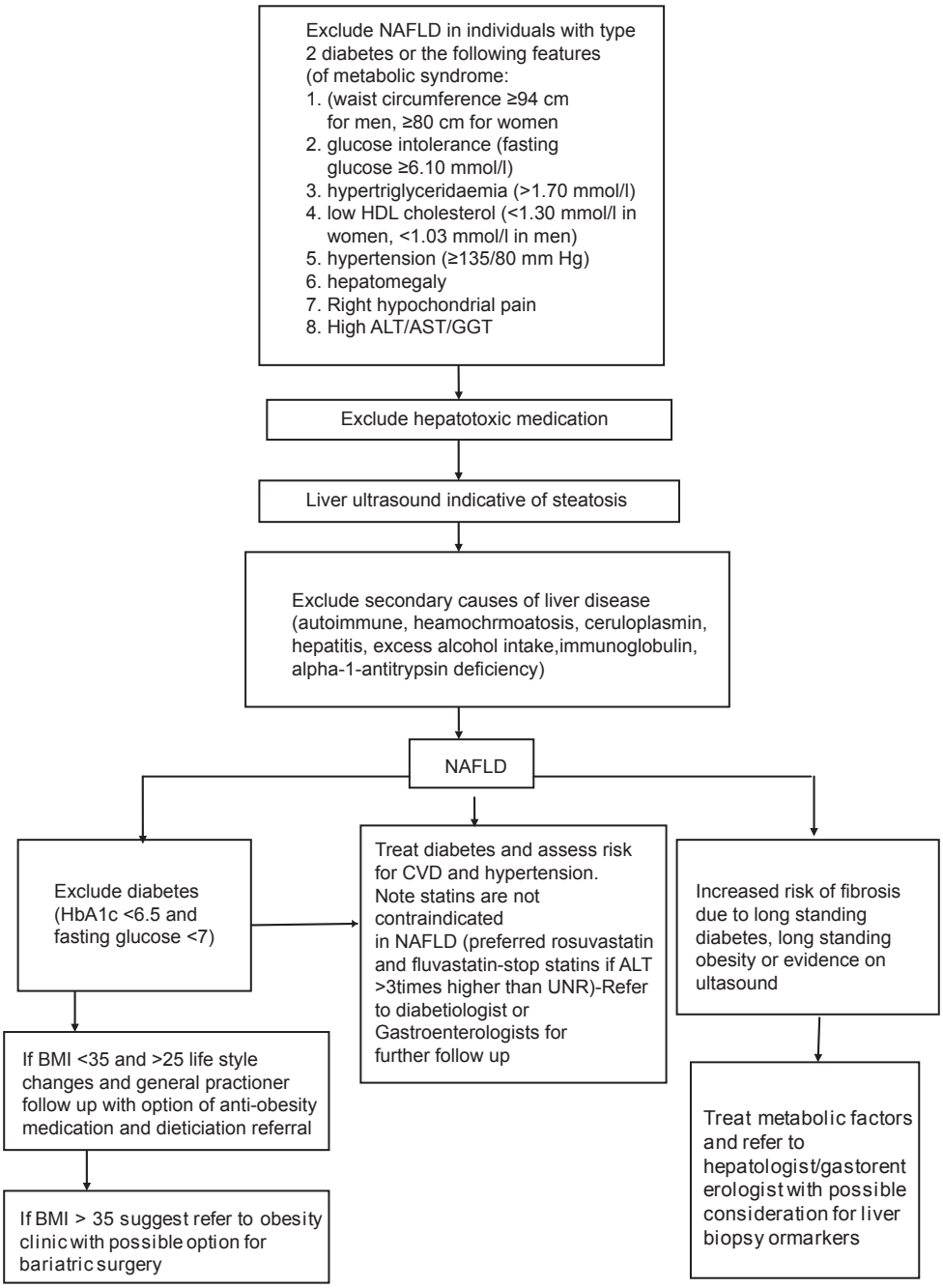

Figure 3: Possible algorithm for management of nonalcoholic fatty liver disease in primary health care

advocated in all patients with NAFLD as the majority of subjects are overweight. Importantly, a reasonable target is the loss of 10% of body weight over 6 months [Figure 3].[25]

Therapeutic agents shown potential benefit in treating nonalcoholic fatty liver disease

Antiobesity medication like orlistat showed significant improvement in histology, ultrasound and reduced ALT. Anidiabetic medication has role in NAFLD treatment. For instance, metformin can be useful in treating insulin resistance but is contraindicated in advanced liver failure. Thiazolidinediones, pioglitazone decreased ALT, hepatic fat content, glucose and free fatty acid concentration, and associated with both improvements in insulin sensitivity and liver histology. Statins, all statins, are safe in NAFLD, there is a theoretical benefit from using statins not metabolized by the liver, i.e. Rosuvastatin, fluvastatin, and pravastatin. Rarely, statins cause irreversible liver damage. Some statins (pravastatin, rosuvastatin, and pravastatin) showed decrease in ALT, GGT, and AST, while pravastatin and atrovastatin showed histological improvement. Long-term administration of satins (10–16 years) showed a significant reduction in steatosis. Increase in ALT > 3 times upper reference range may warrant need to stop statin treatment.[25]

Conclusion

NAFLD is emerging as a common liver disease and is associated with obesity and insulin resistance. Insulin resistance is associated with increased intrahepatic production of free fatty acids from glucose not taken up by peripheral adipocytes and myocytes. Therefore, it is important to exclude diabetes in individuals with abnormal liver enzymes and features of the metabolic syndrome. NAFLD had an insidious course of action and associated with high prevalence of obesity and diabetes. It is possible to postulate, in view of expected high prevalence of undiagnosed NAFLD, an increase in prevalence of liver cirrhosis. In addition, large proportions of patients are regularly reviewed by primary care physicians will also receive liver function test. In the view of absence of sensitive and specific biochemical markers that will allow easy and rapid mass screening of NAFLD, we recommend that using current criteria for diagnosis and management of NAFLD may assist in early diagnosis of both diabetes and liver fibrosis and direct patient to receive appropriate treatment from diabetologists, gastroenterologists, hepatologist, and bariatric surgeons. Ultimately, this may assist in early diagnosis of NAFLD and associated metabolic disturbances and in part in decreasing the epidemic of type 2 diabetes.

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