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RESEARCH ARTICLE

SCREENING AND MANAGEMENT OF NON-ALCOHOL FATTY LIVER DISEASES IN TYPE 2 DIABETIC PATIENTS

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NAFLD (Non-alcohol fatty liver diseases),
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FGF 21 Fibroblast growth factor 21,
Type 2DM Diabetes mellitus,
DPP-4 Dipeptidyl peptidase-4 inhibitor.

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) has a high prevalence in type 2 diabetes mellitus (T2DM) patients; most likely cause is the frequent occurrence of obesity and insulin resistance in T2DM. Weight reduction by diet and exercise is effective in preventing and treating NAFLD in diabetics. Bariatric surgery is recommended in obese patients to reverse NAFLD. There is evidence that drugs used as hypoglycemic agents for T2DM thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) analogs, and dipeptidylpeptidase-4 (DPP-4) inhibitors and also preventing or can even treat NAFLD. Screening for progression in fatty liver diseases by LFT and ultrasound is now recommended. Fibroblast growth factor (FGF21)

Conclusion: From the literature search done on pubmed, Medline it was found that Non-Alcohol fatty liver diseases are one of the common complications of type 2 Diabetes mellitus. Early diagnosis and screening can prevent serious complications such as cirrhosis and liver failure or hepatocellular carcinoma. Effective management by weight loss, exercise and use of the oral hypoglycemic agents such as Sitagliptin has shown to improve NAFLD. FGF21 levels correlate with hepatic and peripheral insulin resistance and is markedly increased in obesity and type II diabetes.

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INTRODUCTION

Type-2 diabetic patients have a high prevalence of NAFLD and it is associated with obesity, (mainly abdominal), hypertriglyceridaemia and raised ALT levels. Non-alcoholic fatty liver disease in diabetic patients may develop and progress independent of the diabetes progression itself (Leite *et al*., 2009). NAFLD in the general population is approximately 20–30%, but reaches nearly 70% in patients with T2DM. It causes increase in liver enzyme levels and one of the common of liver type of disease in the world. NAFLD is more common in men than women and is increasing not only in Western countries, but also in Asian populations (Jian-Gao Fan and Geoffrey C. Farrell, 2009). Diabetes is one of the most common non-communicable disorders throughout the world. It poses a great economical and medical burden on the world by both the lifetime cost of medicines required to keep it in control and the numerous medical professionals required to deal with complications which involve cardiovascular diseases, diabetic nephropathy, NAFLD, nephropathy and diabetic retinopathy (WHO).

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Diabetes is a chronic metabolic diseases characterized by inability of the body to utilize glucose either due to total lack of insulin in TYPE 1 DM or increased insulin resistance ultimately leading to exhaustion of pancreatic β-cells and decreased insulin TYPE 2 DM.NAFLD, which is the most common chronic liver disease affecting up to one-third of the adult population in developed countries. (Organization, 2014; Firneisz, 2014).The prevalence of diabetes for all age-groups worldwide was predicted as 2.8% in 2000 upto 4.4% in 2030. The total number of people with diabetes has been estimated to rise from 171 million in 2000 to 366 million in 2030. (Alwan, 2010; Wild *et al*., 2004) Insulin is the hormone which regulates blood glucose levels, controls adipose tissue functions and keeps blood lipids in check. Deficiency of insulin causes hyperglycemia and hyperlipidemia. Diabetic complications include multiple disorders such as atherosclerosis, neuropathy, nephropathy, retinopathy and NAFLD (Forbes and Cooper, 2013; Jia *et al*., 2015). Non-alcoholic fatty liver disease (NAFLD) is closely associated with type 2 diabetes mellitus (T2DM). NAFLD (Non Alcoholic Fatty Liver Disease) commonly called Fatty Liver Diseases is a major problem arising in diabetic population which has been neglected till now. It was first described by Ludwig in 1980 (Ludwig *et al*., 1980). It is a disorder similar to alcoholic liver disease

histologically. NAFLD is recognized if patient is not suffering from alcoholism, viral hepatitis or congenital metabolic defects. It has been associated with obesity, hypercholesterolemia and diabetes. According to Niaz *et al*. (2011) 13.5% of healthy Pakistani population has NAFLD. This prevalence rises to 60.8% in diabetics in Pakistan (Westphal, 2008) 40% cases of NAFLD can progress to NASH (non alcoholic steatohepatitis) of whom 32% - 37% can progress to advanced fibrosis (Ozturk and Kadayifci, 2014) making it most common cause of cryptogenic cirrhosis which can lead to hepatocellular carcinoma (Bugianesi *et al*., 2002). Diagnosis of NAFLD is made by LFTs, Ultasonography, CT scan, MRI. The most common tests are ultrasound and LFTs. Ultasound has 80% specificity and 99% sensitivity (Sharavanan and Premalatha, 2015). NAFLD was classified on standard bases of ultrasound criteria as: Grade 1: (Mild steatosis) slightly increased liver echogenicity with normal vessels and absent posterior attenuation. Grade 2: (Moderate steatosis) moderate increase in liver echogenicity with partial dimming of vessels .Grade 3: (severe steatosis) diffuse increase in liver echogenicity with absence of visible vessels (Sharavanan and Premalatha, 2015). ALT level is raised and AST/ALT ratio ranges below 1, differentiating it from Alcoholic liver disease. But the normal LFTs do not mean absence of NAFLD, normal ALT levels have been recorded with biopsy proven fibrosis and cirrhosis (Westphal, 2008). So ALT levels do not necessarily correspond with severity of NAFLD. This ratio can reverse if NAFLD progresses to fibrosis (Westphal, 2008) NAFLD is usually a incidental finding when an abdominal scan is done for some other suspected pathology. It can be associated with abnormal LFTs (Liver function tests) but advanced cases may present with normal LFTs (Luxmi *et al*., 2008). The symptoms at presentation usually are anorexia, nausea, fatigue, malaise and sometimes right hypochondriac discomfort, but hepatomegaly is usually the consistent finding. NAFLD is characterized by accumulation of fat mostly triglycerides (Westphal, 2008). Nonalcoholic fatty liver disease has no definitive biochemical markers or peculiar clinical signs.

A simple and effective screening and diagnostic approach for NAFLD should include inquiry into other common causes of fatty liver (alcohol, drugs, hepatitis C virus–related chronic hepatitis, hemochromatosis), ultrasound scan of the liver, and assessment of serum transaminase levels. (Westphal, 2008) Approximately 1 in 200 cases of NASH leads to hepatocellular carcinoma (Bugianesi). Not only NAFLD causes increased liver related mortality but it also increases cardiovascular moratlity (Forbes and Cooper, 2013).

Type 2 DM, obesity and insulin resistance appear to be individual risk factors for NAFLD. Insulin resistance is known to be associated with NAFLD either as cause or effect (Westphal, 2008). Hepatic steatosis leads to insulin resistance by inhibiting insulin signaling at receptor level. Insulin resistance causes hepatic steatosis by altering plasma free fatty acid levels (Westphal, 2008). Two hit model has been proposed as the cause of NAFLD/NASH (Westphal, 2008; Ye Liu *et al*., 2014). First hit is increased hepatic steatosis due to insulin resistance. Second hit is increased oxidative stress characterized by increased reactive oxygen species (ROS), free radicals, lipid per-oxidation, cytochrome P450 activation and pro-inflammatory cytokines which leads to progression from NAFLD to NASH and further on (Forbes and Cooper, 2013).

Screening for NAFLD

The symptoms at presentation usually are anorexia, nausea, fatigue, malaise and right hypochondriac discomfort, although hepatomegaly is usually the most common finding (Sharavanan and Premalatha, 2015; Ahren, 2010). NAFLD is characterized by accumulation of fat in liver (Westphal, 2008). Diagnosis of NAFLD is made by LFTs, ultasonography, CT scan, MRI. The most common tests are Liver function test (LFTs) and ultrasound. Ultasound has 80% specificity and 99% sensitivity (Samson *et al*., 2011) NAFLD is usually an incidental finding when an abdominal scan is done for some other suspected pathology. It can be associated with abnormal LFTs but even advanced cases may present with normal LFTs (Grattagliano *et al*., 2007). Recently there has been a proposed role of subfamily of FGFs in liver metabolism, which includes FGF19 & FGF21. Unlike conventional FGFs, they lack heparin binding domain so they freely reach blood and act as hormones (Luxmi *et al*., 2008) and bind to its specific receptors. FGF19 regulates energy expenditure and FGF21 regulates glucose and lipid metabolism in liver (Schaap, 2012; Samson *et al*., 2011) FGF19 signaling regulates glucose homeostasis in mice. The pathophysiological role of FGF19 in glucose homeostasis in humans remains to be determined. Its specific insulin-mimetic actions, combined with the elimination of its mitogenic activity FGF19 may have a role for the managment of type 2 diabetes. FGF19 is produced in small intestine in response to food. FGF21 is produced in liver, pancreas and adipose tissue (Schaap, 2012). FGF21 increases mitochondrial fatty acid oxidation (Samson *et al*., 2011), stimulates adipocyte glucose uptake, increases insulin sensitivity and controls lipolysis in adipose tissue (Samson *et al*., 2011).

These effects appear to be mediated by activation of AMP-kinase activity. Administration of FGF21 to rats and monkeys caused marked reduction in weight, LDL, TGs and glucose and increase in HDL. FGF21 levels correlate with hepatic and peripheral insulin resistance and is markedly increased in obesity and type II diabetes suggesting "FGF21 resistance" state (Samson *et al*., 2011). Liver FGF21 levels and its mRNA expression is increased in steatosis and its serum levels are also markedly increased in NAFLD and correspond with its stage (Samson *et al*., 2011). FGF21 levels are regulated by PPAR-α not PPAR-γ. Recent studies showed no improvement in FGF21 levels with pioglitazone and rosiglitazone as both these drugs are PPAR- γ agonists (Ozturk and Kadayifci, 2014). DPP-4 (Dipeptidyl peptidase-4) levels are increased in liver in NAFLD patients and its serum and hepatic levels correlate with grades of steatosis (Forbes and Cooper, 2013; Jia *et al*., 2015). DPP-4 is an enzyme which is responsible for degradation of GLP-1. It is produced in liver, small intestine, pancreas, spleen and brain (Itou *et al*., 2013). DPP-4 is present in acinar zones 2 and 3 in human liver which also have γGT, cytochrome P450 and glutamine synthetase suggesting its role in hepatic metabolism. It has been seen that DPP-4 is related with pathology of NAFLD (Itou *et al*., 2013). GLP-1 (Glucagon like peptide-1) is a 30-amino acid peptide, secreted from intestinal langerhan cells in response to meal. GLP-1 increases the glucose mediated insulin response, decreases glucagon secretion, suppresses appetite and delays gastric emptying (Ye Liu *et al*., 2014). GLP-1 is rapidly degraded by DPP-4. This effect has been made to use in treatment of diabetes and various GLP-1 analogues and DPP-4 inhibitors have been developed. GLP-1 based therapies now are widely accepted worldwide for treatment of type 2 DM. Apart from its

hypoglycaemic effects, GLP-1 is shown to be involved in pathogenesis of NAFLD or NASH. There were decreased levels of GLP-1 in patients with NAFLD as compared to controls upon glucose administration (Ye Liu *et al*., 2014), although this could be due to increased DPP-4 expression in NAFLD patients in liver (Ozturk and Kadayifci, 2014) There appears to be direct effect of GLP-1 on liver as GLP-1 receptors have been found to be present on hepatocytes and are downregulated in patients with NASH or NAFLD (Ye Liu *et al*., 2014). When GLP-1Rs were blocked prior to administration with GLP-1 analogues, cAMP production in hepatocytes significantly decreased suggesting its role liver metabolism (Ye Liu *et al*., 2014). GLP-1 directed effects are induction of genes responsible for hepatic insulin sensitivity and fatty acid oxidation (Ozturk and Kadayifci, 2014).

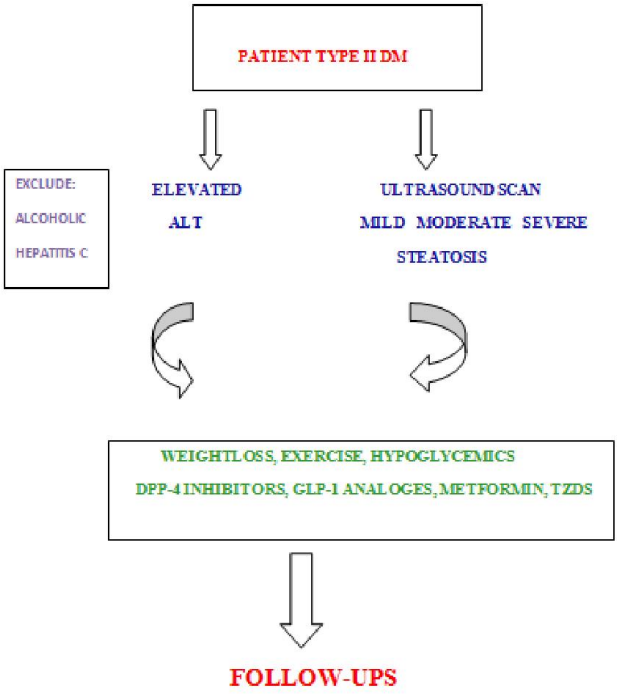

Figure 1. Screenig and management of NAFLD

Administration of GLP-1 analogue increased AMP kinase activity (Nilius *et al*., 1991) which is important signaling molecule in hepatic insulin sensitivity causing increased hepatic expression and activation of protein kinase C and insulin receptor substrate-1 (IRS-1). This resulted in decreased hepatic glucose production and fatty acid synthesis (Ye Liu *et al*., 2014). In a mice treated with GLP-1 analogues there was depressed JNK pathway which is a key mechanism in hepatic oxidative stress (Ahren, 2010). GLP-1 is protective as it attenuates oxidative stress a key factor in progression to NASH and fibrosis. In ob/ob mice, endogenously elevated GLP-1 levels resulted in increased hepatic expression of PPARα and acetyl-CoA oxidase, whereas there were decreased fatty acid synthase (FAS), stearoyl-CoA desaturase 1, sterol regulatory element binding protein 1 (SREBP-1) and acetyl-CoA carboxylase (ACC) hepatic expression (Ye Liu *et al*., 2014). Dipeptidyl peptidase-4 (DPP-4) is a membrane-associated peptidase. A representative target peptide is glucagon-like peptide-1 (GLP-1), and inactivation of GLP-1 results in the development of glucose intolerance, diabetes mellitus and hepatic steatosis. The liver has high expression of DPP-4, and studies suggest that DPP-4 is involved in the development of various chronic liver diseases such as hepatitis C virus infection, non-alcoholic fatty liver disease, and hepatocellular carcinoma. Also DPP-4 occurs in hepatic stem cells and plays a vital role in hepatic cellular regeneration (Itou *et al*., 2013). Serum level of DPP-4 is elevated in patients with liver cirrhosis (Nilius *et al*., 1991). This above background strongly suggests there is a likely role of GLP-1 analogues and DPP-4 inhibitors in treatment of NAFLD along with their role in treating diabetes. Multiple studies have shown beneficial effects in NAFLD animal models and human clinical studies. It has been usually neglected in the treatment of Diabetes Mellitus. Now, it has increased to such an alarming level that it demands prompt attention because it can progress to cirrhosis (Nilius *et al*., 1991) and hepatocellular cancer (Parkash and Hamid, 2016).

Management of NAFLD

Currently guidelines suggest weight loss as the primary and most effective treatment for NAFLD. Drugs such as insulin, statins and oral hypoglycemics (thiodozolidinones, sulfonylureas and metformin) showed promise in treating NAFLD. Study by Liu *et al* (Ye Liu *et al*., 2014) states that GLP-1 decreases insulin resistance, decreases oxidative stress and improved lipid metabolism. GLP-1 receptors reduces hepatic glucose output, glucagon release, gastric emptying, and appetite. This leads to decrease in weight (Greig *et al*., 1999; Nilius *et al*., 1991).

Glucagon-like peptide-1 (GLP-1) Analogs: Exentide

Exenatide reduces fasting and postprandial glucose concentrations in patients with type 2 diabetes. During fasting, glucose-dependent enhancement of insulin secretion and suppression of glucagon secretion are the predominant mechanisms and postprandial, slowing of gastric emptying is additional action of GLP-1 Analog. This antidiabetic effect should be further evaluation for exenatide (Kolterman *et al*., 2003; Ahren, 2010).

Dipeptidyl peptidase- 4 (DPP-4) inhibitors

Sitagliptin, (a dipeptidyl peptidase-4 (DPP-4 inhibitor) (Kolterman *et al*., 2003) is the prototype drug in this class. DPP-4 is responsible for the metabolism of active incretin (24). It is highly selective inhibitor of DPP-4, increasing GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulin-tropic polypeptide) levels 2-3 times. Adding Sitagliptin to multiple daily insulin injections significantly improved glycemic control and decreased the daily glucose fluctuation in subjects with type 2 diabetes inadequately controlled with multiple daily insulin injections only, without adverse effects of weight gain or an increase in the incidence of hypoglycemia (Ahren, 2010; Katsuno *et al*., 2013; Shimoda *et al*., 2013)

METFORMIN

Metformin is the most commonly prescribed and first line oral hypoglycemic agent in T2DM. Its primary actions include decreasing hepatic gluconeogenesis and hepatic glucose production and increasing glucose uptake in skeletal muscle (Angela Mazza *et al*., 2012). Due to the risk of lactic acidosis, there is a relative contraindication to the use of metformin in liver disease. Studies have shown that metformin is well tolerated in NAFLD and suggest that it can result in improved liver transaminases. Study of 20 subjects with NAFLD treated with metformin for four months showed improvement in liver

transaminase levels when compared to non-compliant individuals within the group (Angela Mazza *et al*., 2012).

THIAZOLIDINEDIONES (TZDS)

TZDs are second line oral hypoglycemic agents for T2DM that decrease insulin resistance by activating nuclear peroxisome proliferator-activated receptor. This results in enhanced insulin sensitivity and increased glucose uptake in peripheral tissues and reduced hepatic glucose production. Pioglitazone is the most prescribed TZD. Clinical trials involving subjects both with and without diabetes, TZDs were found to improve steatosis but not fibrosis. Pioglitazone has shown greater decrease in fibrosis compared to Rosiglitazone or placebo in the analysis (Yki-Järvinen H. 2004). Studies have shown that 40% of patients with NAFLD may go on to develop NASH is most common cause of cryptogenic cirrhosis, it may progresses to fibrosis in 32% to 37% of patients (Bugianesi *et al*., 2002). Takamasa *et al* study. (Ohki *et al*., 2012) demonstrated the improvement of liver inflammation and diabetes in NAFLD patients with type 2 DM treated by Liraglutide, Sitagliptin, and Pioglitazone. Additional studies are required to determine the appropriate therapy to prevent the progress of this diseases. Some studies suggest NAFLD can progress to NASH (Non-Alcoholic Steato-hepatitis). Approximately 3% to 5% patients of NAFLD can progress to NASH (takamasa *et al*., Ohki *et al*., 2012). Diabetes mellitus (DM) and Non Alcoholic fatty liver disease (NAFLD) studies as well as multiple systemic reviews had shown strong association of DM with Hepatocellular carcinoma. A systematic review that included a total of 49 case-control and cohort studies estimated that the risk was increased by approximately 2.2-fold. In Pakistan about 6% of the population is suffering from diabetes hence with increased number of diabetic patients there is also increase in prevalence of NAFLD/NASH thus increased threat of hepatocellular carcinoma (Parkash and Hamid, 2016)

Conclusion

In order to reduce the risk and complication of NASH and liver failure, early diagnosis and appropriate management of NAFLD is most required. Weight loss, exercise, appropriate hypoglycemic agent and follow-ups should be done in diabetic with non-alcohol liver diseases. Dipepidyl–peptidases 4 inhibitors (Sitaglaptin) have proved to have a protective role in such patient further studies should be carried out to find their benefits in long term use as single agent of combination to prevent progresses of this diseases.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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