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Diabetes mellitus Gastrointestinal Complications

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Introduction :

Diabetes mellitus has already reached epidemic proportions in both industrialized and developing countries, affecting about 366 million people globally. Because of an ageing global population, urbanization, rising obesity rates, and sedentary lifestyles, this number is expected to rise in the future years. Diabetes affects nearly every organ system in the body, and the severity and duration of the disease may have a direct impact on organ involvement. Though gastrointestinal (GI) issues are common in people with long-term diabetes, doctors are often unaware of them. Early detection and management of GI problems are critical for improving both diabetic care and the affected patient's quality of life. (Krishnan,2013)

Diabetes mellitus (DM) is a disease that is affecting an increasing number of people. Around 415 million individuals are anticipated to be impacted globally, with the number of patients expected to reach 642 million by 2040. Chronic micro- and macropathy consequences are the main risk for the patient associated to the disease: they cause significant organic dysfunctions and can lead to the patient's unexpected death. (Atlas,2015) Alimentary disturbances are troublesome, even if they are rarely linked to a direct risk of death. They used to appear in people who had long-term diabetes, which was often untreated and physiologically imbalanced for years. The disorders can affect almost any part of the digestive system. Nausea, vomiting, difficulty swallowing, abdominal pain, disrupted absorption, diarrhea, and obstipation may be prodromes of another, concurrent disease or occur as a result of metabolically uncontrolled diabetes mellitus. Diabetes mellitus is also linked to an increased risk of getting infections, functional and organic problems, and some cancers. Furthermore,

poorly controlled diabetes can cause lesions in central and peripheral nerve fibres, making relevant indications and symptoms varied and making diagnosis difficult for physicians and practitioners. (Zawada,2018)

Gastroparesis, intestinal enteropathy (which can cause diarrhoea, constipation, and faecal incontinence), and nonalcoholic fatty liver disease are all gastrointestinal consequences of diabetes. Early satiety, nausea, vomiting, bloating, postprandial fullness, or upper abdominal pain are all symptoms of gastroparesis.

When all other reasons have been ruled out and postprandial gastric stasis has been verified by gastric emptying scintigraphy, the diagnosis of diabetic gastroparesis is made. Patients should avoid drugs that worsen gastric dysmotility, control blood glucose levels, increase the liquid content of their diet, eat smaller meals more frequently, quit smoking, and limit their intake of insoluble dietary fibre, high-fat foods, and alcohol whenever possible. Prokinetic drugs (e.g., metoclopramide, erythromycin) may aid in the management of gastroparesis symptoms. Supportive therapies and symptom control are used to treat diabetes-related constipation and diarrhoea. Obese and diabetic people are more likely to develop nonalcoholic fatty liver disease. It's critical to look for other causes of liver illness, such as hepatitis and hemochromatosis, in diabetics with increased hepatic transaminase levels. Gradual weight loss, blood glucose control, and the use of drugs (e.g., pioglitazone, metformin) may normalise hepatic transaminase levels, although the therapeutic value of aggressively treating nonalcoholic fatty liver disease is uncertain.(Krishnan,2013)

Oral diseases as a marker of metabolically imbalanced diabetic mellitus:

Diabetes mellitus causes issues to arise in the early stages of the digestive tract. Fungal infections and periodontal pathology are the most common mouth disorders. Inconveniences such as a dry oral cavity, reddening and hyperemia of the neck, and atrophic lesions on the tongue are all prodromes of such disorders. Candida infection is the most common oral cavity infection, accounting for 40–60% of all oral cavity infections. Shenoy et al. found that patients with diabetes type 1 (DM1) had 30 percent or diabetes type 2 (DM2) had 33 percent Candida infections, compared to diabetes-free people who had just 7% infections. The CFU/mL values in the DM1 and DM2 groups were similarly considerably higher than in healthy people. The study also discovered a strong positive association between CFU/mL and fasting glycemia and HbA1c level on the one hand, and fasting glycemia and HbA1c level on the other. (Shenoy,2014)

The severity of carbohydrate metabolism abnormalities is reflected in the course and intensity of candidiasis. Candidaiasis took a statistically more severe course in patients with a pre-diabetic condition (as measured by established laboratory procedures and tooth abnormalities) than in healthy people. Periodontitis is another oral ailment that used to be associated with diabetic individuals.(Javed,2014) It occurs 2.6 times more frequently in diabetic patients than in the general population, and the prevalence continues to rise in those with metabolically imbalanced diabetes (up to 2.9-fold higher one). (Tsai,2002) In parallel, the relationship can be concluded to be bilateral: diabetes aggravates periodontitis and makes it more difficult to treat, while the chronic inflammatory process exacerbates carbohydrate metabolism problems.(Al-Khabbaz,2014) In a metaanalysis conducted by Wang et al. on the basis of studies

including 1,135 people, it was proven that after 3 months of intensive periodontal disease therapy, lower HbA1c levels were identified. Bialecka et al. found a substantial reduction in HbA1c 1 year after tonsillectomy, and Bialecka et al. found a significant reduction in HbA1c 1 year after tonsillectomy. In order to gain metabolic control of diabetes mellitus, the investigations confirmed the requirement for thorough dental control and intensive treatment of any inflammatory foci in the mouth cavity. (Białecka,2013)

ESOPHAGEAL COMPLICATIONS :

Smooth muscle fibres in the thoracic oesophagus and lower esophageal sphincter (LES) are innervated by the myenteric plexus, and diabetic neuropathy can impair these autonomic nerves in patients with long-term diabetes. Diabetes causes aberrant peristalsis, spontaneous contractions, and decreased LES tone due to autonomic neuropathy and structural remodelling of the esophageal musculature.(Frøkjær,2007) In animal models of diabetes, morphological and biomechanical features of the oesophagus have been discovered to be drastically altered. (Yang,2006)

For many years, esophageal pH monitoring and conventional manometry have been used to diagnose reflux and dysmotility. The use of the wireless Bravo pH capsule, which permits catheter-free monitoring, and impedance-pH measurement, a catheter-based approach that detects acid and non-acid reflux, have both been big advances in the diagnostic sector recently (Wilson,2008). High resolution manometry, which uses many pressure sensors to generate spatiotemporal plots of esophageal pressure changes, and impedance manometry, a test that directly detects bolus transit and offers

traditional manometric data, are two innovative approaches for assessing esophageal motility. (Wilson,2008)

Glycemic control was found to be inversely associated to gastroesophageal reflux disease, and better glycemic control may reduce esophageal dysmotility and reflux. Prokinetic medicines like metoclopramide and proton pump inhibitors are used to treat reflux disease. In type 2 diabetics, a two-week course of erythromycin has been demonstrated to lower mean esophageal transit time and stomach emptying time. To avoid pill-induced esophagitis, patients should drink fluids right after taking their prescriptions.(Lauffer,2011)

GASTROPARESIS :

In the absence of physical obstruction, gastroparesis, one of the most prevalent GI consequences of diabetes mellitus, causes symptoms of gastric retention. Gastroparesis is believed to be uncommon among diabetics (5.2 % over 10 years in type 1 diabetes and 1% in type 2 diabetes), yet it is more common than in the general population (0.2 %). Delayed stomach emptying can be seen in 27 % to 65 % of type 1 diabetes patients and roughly 30 % of type 2 diabetes patients. Women are more likely than men to develop gastroparesis. Obesity is a strong independent predictor of symptoms suggestive of gastroparesis in people with type 2 diabetes mellitus (T2DM) and neuropathy, according to a recent study. (Boaz,,2011)

Pathogenesis :

Diabetic gastroparesis has a complex pathophysiology that is currently unknown. In diabetics, delayed stomach emptying may be the initial sign of gastroparesis. The

existence of macro- and microvascular problems, as well as an elevated glycated haemoglobin level, are all recognised risk factors for the development of diabetic gastroparesis. Delayed stomach emptying adds to poor glycemic control and could be the first sign of gastroparesis in the patient. Diabetes causes loss of normal Migrating Motor Complexes, muted antral contractions, pylorus and small intestine spasms, and poor meal accommodation in the stomach. Impaired inhibitory nitric oxide-containing neurons, missing or dysmorphic interstitial cells of Cajal, smooth muscle fibrosis, and aberrant macrophage-containing immunological infiltrates are all possible contributors to the pathophysiology.(Grover,2011)

In some people, bezoar formation can lead to the development of gastroparesis. Endoscopic biopsies from diabetic gastroparesis show aberrant mucosal nerve density and morphology, indicating the possibility of endoscopic enteric neuropathy diagnosis. Gastroparesis can be caused by neurohumoral variables such as glucagon-like peptide-1 (GLP-1), and the GLP-1 agonists Exenatide and Liraglutide can cause gastroparesis symptoms. In an animal model, apolipoprotein E deficiency was found to be a risk factor for diabetic gastroparesis in a recent study. Extrinsic factors like pharmaceuticals, as well as co-occurring illnesses like anxiety and depression, might lead to an increase in symptom reporting.(Ravella,2012)

Clinical features

Nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain are all symptoms of gastroparesis. Increased glycemic control, frequent hypoglycemic episodes, or unexplained alternating hyper- and hypoglycemia due to a mismatch between insulin action and carbohydrate absorption might alert the clinician

to consider diabetic gastroparesis. Weight loss is possible in 53 percent of patients, although weight gain is possible in 18 percent to 24 percent. More than half of those who are affected develop symptoms quickly, whereas the rest develop symptoms gradually. Persistent symptoms with occasional exacerbations affect one-third of cases, while chronic deteriorating symptoms affect the other third. Some patients may have epigastric distention and succussion splash, although physical examination is not always useful. (Parkman,2011)

Treatment

Gastroparesis treatments include general measures, dietary modifications, medications that enhance emptying or lessen vomiting, non-medication interventions, psychological therapies and consideration of more invasive surgical treatment. (Krishnan,2013)

Gastric disturbances in the course of diabetes mellitus :

Gastroparesis is one of the most common diabetic consequences. It is characterised by a set of signs and symptoms that are related to the upper portion of the alimentary canal and represent problems with stomach emptying. According to epidemiological data, the problem (which refers to autonomic system disruptions) occurs in 5–12% of diabetic patients, and it occurs substantially more frequently in people who have already had other difficulties. In a research by Bharucha et al.(Bharucha,2015) 47 percent of patients who were already suffering from other problems showed delayed stomach emptying. Nausea is the earliest and most common symptom of gastroparesis, which affects 90 percent of patients. Other symptoms, such as early post-meal satiety, vomiting, flatulence, and a feeling of gastric distension, can cause problems with

digestion and absorption of food components, as well as difficulty achieving metabolic control in people with diabetes. Often, there is no correlation between the severity of symptoms and the function of stomach emptying.

Nonetheless, the growing resistance of the pylorus in diabetic patients was observed to correspond with the intensity of symptoms and quality of life, as measured by the gastrointestinal quality of life (GIQLI) questionnaire, in a study by Gourcerol et al (Gourcerol,2015) In patients with type 1 diabetes, the severity of gastroparesis is linked to the absence of metabolic balance, albeit this has yet to be shown in patients with type 2 diabetes. Aside from vagus nerve neuropathy, abnormal stomach emptying can be caused by acute hyper- and hypoglycemia, hypo- or hyperinsulinemia, disrupted hormone production in the alimentary tract, and the more common *H. pylori* colonisation in this group. (Bahadoran,2015) Histopathological examinations revealed that patients with gastroparesis have a lower number of interstitial Cajal cells (ICCs), a lower number of NO-secreting neurons, and atrophy of smooth muscles with lymphocyte infiltrates leading to a persistent chronic inflammatory process (Grover,2012) . Choi et al research, 's on the other hand, confirmed the presence of CD206+ macrophages, which protected against gastroparesis. The number of these macrophages was related to the number of ICCs.(Choi,2010)

Celiac disease and alterations in intestinal microbiota are disorders that coexist with diabetes mellitus in the small intestine:

Patients with type 1 diabetes are increasingly being affected by the presence of absorption difficulties. According to sources, celiac disease and diabetes coexist in 6 to

15% of people. It is diagnosed in the majority of individuals within 5 years after their diabetes diagnosis (in 79 percent patients, celiac disease is diagnosed within the first 5 years, in 55 percent within 2 years and in 40 percent within a year after developing diabetes).(Unal, 2021)

However, it is noteworthy that only 10% of patients exhibit classic clinical signs and symptoms of the condition. Recurrent hypoglycemias and poor metabolic balancing of diabetes may be the only signs of the condition. Coeliac disease that develops in people with diabetes has a different path than it does in those who do not have diabetes. In diabetes, men and women had nearly identical rates of celiac disease, despite the fact that women have a 3-fold higher rate than men in the overall population. Anti-TTG antibodies and genetic investigations are used to rule out celiac disease, allowing the identification of the HLA-DQ2 antigen, which is present in 90 percent of celiac disease patients and 55 percent of diabetes type 1 patients. Aside from celiac disease, diabetic people are more likely to have a disruption in the motoric activity of the gastrointestinal tract in the form of periodic diarrheas that usually go away on their own. Previously, diarrhoea only appeared at night. Diabetic individuals, particularly those with type 2 diabetes, usually experience bacterial overgrowth in the small intestine (SIBO). However, data on the subject is mixed: some studies found a lower frequency of the syndrome in diabetic patients than in the general population, and the authors related this to dietary modifications. (Adamska,2015)

Large intestine disorders linked to diabetes :

A high-fat, high-carbohydrate diet, which leads to overweight and obesity, carbohydrate metabolic abnormalities, and hyperinsulinemia, are the main factors that

promote the development of colorectal cancer. Several scientific studies have also highlighted the function of diabetes as a separate risk factor for colorectal cancer.(Suh,2011) Furthermore, a link was discovered between the HbA1c level and the occurrence of intestinal polyps. Metformin, as a first-line treatment for type 2 diabetes, causes hyperinsulinemia to decrease and insulin resistance to decrease. Apart from its anti-hyperglycemic properties, it also has other metabolically beneficial effects. Metformin reduces aberrant crypt foci (ACF), a colorectal cancer marker, through the AMP kinase activation pathway (CRC). Choe et al. discovered a much lower frequency of colorectal polyps, their significantly smaller size, a lower number of hyperplastic and villiform polyps ($p = 0.01$), and less advanced instances of CRC in the metformin group (Cho,2014). It is important to note, however, that long-term use of metformin lowers vitamin B12 levels. Proton pump inhibitors (PPIs), which are often used in gastritis, have a similar impact, therefore monitoring vitamin B12 levels and maybe supplementing with the vitamin is an important part of coordinating pharmacological treatment. (Purchiaroni,2015)

Tumors in alimentary tract versus type of diabetes :

It has long been recognised that diabetic patients have a significantly increased risk of acquiring a gastrointestinal tumour than healthy people. The link is predicated on the presence of overweight and obesity, hyperinsulinemia, and insulin resistance (in the case of those with type 2 diabetes). Increased levels of IGF-1 result from the phenomenon, which stimulates uncontrolled cell growth while suppressing the process of apoptosis. Exogenous hyperinsulinemia can also cause pathological hypertrophy of cells and tissues in people with type 1 diabetes. The teratogenic impact of large doses

of exogenous insulin was established in experiments by Mannucci et al. Patients with type 2 diabetes are more likely to develop liver, pancreatic, oesophagus, and large intestine tumours (in the female population, rectal tumours are seen particularly frequently). (Mannucci,2010) They used to involve adenomas, as opposed to myomas, which have a prevalence that is equivalent to the overall population. Patic and pancreatic cancer, as well as any malignancies in their in situ forms, are more frequently seen in persons with type 1 diabetes.

The appearance of pancreatic cancer in people who have recently been diagnosed with diabetes is a big challenge for doctors. Diabetes is typically a primary symptom of a hidden disease in such circumstances. Such a risk primarily affects lean, adult persons with no evident insulin resistance, whose clinical pattern is not typical for type 1 diabetes, and whose signs/symptoms arise suddenly and with a high intensity. (Zawada, 2018)

However, imaging investigations in this group of patients are limited to those who are at high risk of developing a pancreatic tumour. People with type 3 diabetes are at an increased risk of getting a pancreatic tumour. The existence of cysts exceeding 3 cm in diameter, a dilatation of the pancreatic duct, and the presence of solid structures attached to the cyst wall or in its lumen in people with chronic pancreatitis is an indication for oncological control. In 2009, studies published by the European Association for the Study of Diabetes (EASD) raised the possibility that using a long-acting glargine analogue could increase the risk of breast cancer.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) research, released in 2014, did not support these findings. The main medicine used to treat type 2

diabetes, metformin, was discovered to block the neoplastic process. (Bordeleau,2014)
The medicine has a proven anti-proliferative action and acts as a neoplastic suppressor due to its involvement in the LKB1 kinase signalling pathway (a controller of AMPactivated protein kinase – AMPK). The ability of AMPK to sustain low levels of cell energy is also linked to metformin's impact, while phosphorylation of p27KIP and tuberous sclerosis complex 2 (TSC2) proteins inhibits signalling network proliferation. The administration of metformin from the start of the disease was observed to be associated with a decreased mortality of patients owing to tumours in the Zwolle Outpatient Diabetes Project Integrating Available Care investigations (ZODIAC16), and the impact seemed to be dose dependant.(Landman,2010)

General approaches and dietary modifications

Ensure sufficient hydration, rectify electrolyte imbalances, manage glycemic control, and reduce symptoms with pharmacotherapeutic drugs are all general approaches to gastroparesis therapy. If at all feasible, stop taking any medications that can cause a delay in stomach emptying. Increasing liquid-based meals (because the rate of emptying liquid from the stomach is usually the same in diabetic gastroparesis), reducing fat and non-digestible fibre intake, avoiding large meals with high calorie contents, and ensuring small frequent meals spread throughout the day are just a few of the dietary changes that can be made.

One of the fundamental objectives of diabetic gastroparesis management has been to maintain euglycemia. Patients with diabetic gastroparesis have been found to have longer postprandial hyperglycemia than those with normal stomach emptying. Another

study found that starting insulin pump therapy reduced haemoglobin A1C by 1.8 percent. The number and length of hospitalizations for diabetic gastroparetics were eventually reduced as a result of this.(Sharma,2011)

Endoscopic and surgical treatments

Pyloric spasmodic contractions were proposed by Mearin et al as one of the causes delaying stomach emptying. In the treatment of gastroparesis, endoscopic pyloric injections of botulinum toxin have been explored. This neurotoxic prevents acetylcholine from being released at the neuromuscular junction, producing pylorus paralysis. pyloric botulinum toxin injections improved symptoms and hastened stomach emptying for up to 3-6 months, notably in women and individuals with idiopathic gastroparesis. It was also found to be more effective in older males who had vomited. Botulinum toxins, on the other hand, did not show a greater response to placebo in tiny, underpowered placebo-controlled trials.(Mearin,1986)

Gastric electrical stimulator implantations have also been demonstrated to have long-term benefits, with up to 80% decreases in nausea and vomiting. Improvements in nutritional and metabolic status, quality of life, and health-care utilisation have also been observed. Despite this, the majority of research suggest that there is no effect on measured stomach emptying. Stomach stimulators relieved symptoms in gastroparetics due to lower gastric retention in diabetic patients, according to a recent study. The use of small wireless gastric stimulators placed during endoscopy is another novel technology in this field. More research is needed to compare the efficacy of this technique to that of other methods.(McCallum,2011)

Surgical procedures are rarely used and are usually reserved for patients who have refractory gastroparetic symptoms that have not responded to previous treatments. A recent study found that after Heineke-Mikulicz pyloroplasty, gastroparetic symptoms were reduced by 83 percent. Although data on patients with diabetic gastroparesis has been limited, completion gastrectomy has been proven to provide long-term symptom alleviation in certain patients with postsurgical gastroparesis. Pancreatic transplants for diabetic gastroparesis have not been proven to be beneficial. (Laufer, 2011)

Jejunostomy feeding and complete parenteral nutrition are two other options. In diabetic gastroparesis, jejunostomy feeding improves overall health and shows signs of lower healthcare consumption. In refractory idiopathic gastroparesis, the role of vented percutaneous gastrostomy is debatable. In patients with idiopathic gastroparesis, one research found symptom improvement as well as improvements in nutritional and functional status. Total parenteral nutrition, which is generally administered in patients with concomitant intestinal dysmotility, can reverse rapid weight loss and assure enough nourishment. (Kim, 1998)

ENTEROPATHY

In patients with long-term diabetes, small intestinal and colorectal dysfunctions are widespread, especially in those who have gastroparesis. Diarrhea, constipation, or faecal incontinence are all symptoms of diabetes-related enteropathy. The mechanism of enteropathy development is similar to that of diabetes-related upper GI involvement. In diabetes, advanced glycation end products (AGEs) destroy cellular DNA and tissues. In diabetic jejunum and ileum ganglia, crypt, and brush border, as well as the ganglia of diabetic colon, AGEs and their receptors are elevated. Stasis of the intestinal

contents is caused by damage to the myenteric nerve plexus caused by autonomic neuropathy and fibrosis of the intestinal muscular layers. Constipation is caused by decreased intestinal motility, which can sometimes lead to overflow incontinence. Intestinal stasis is the most common cause of small intestinal bacterial overgrowth (SIBO), which can cause diarrhoea. (Chen,2012)

One of the most prevalent symptoms of diabetic enteropathy is constipation followed by diarrhoea. The diarrhoea is usually painless, and it might be coupled with faecal incontinence. It can happen at any time of day, but it happens more frequently at night. It is most commonly found in diabetic patients with peripheral and autonomic neuropathy who are poorly managed. Diabetic diarrhoea can also be caused by pancreatic insufficiency, bile salt malabsorption, steatorrhea, and medications (Metformin). Before a diagnosis of diabetic enteropathy is made, suitable investigations should be performed to rule out these possibilities. (Lysy,1999)

Constipation is a common condition that affects up to 60% of diabetic people with long-term diabetes. Rarely, severe constipation might develop to a megacolon or colonic intestinal pseudo-obstruction. The occurrence of a stercoral ulcer, perforation, and overflow diarrhoea is uncommon.

Fecal incontinence, especially nocturnal incontinence, is a bothersome condition caused by internal and external sphincter dysfunction as a result of autonomic neuropathy. Acute hyperglycemia has been reported to reduce rectal compliance and block external anal sphincter activity, potentially raising the risk of faecal incontinence. (Russo,2004)

To rule out alternative possibilities, patients should have an endoscopic examination, ultrasonography, or computed tomography. Many people consider aspiration and direct culture of jejunal contents to be the gold standards for diagnosing SIBO. However, these methods have several drawbacks, including the risk of contamination by oropharyngeal bacteria during intubation and the fact that bacterial overgrowth can be patchy and missed by a single aspiration. Non-invasive SIBO diagnostic methods rely on the excretion of hydrogen in exhaled breath as a result of carbohydrate metabolism by luminal bacteria. These tests have an 80% specificity but a 40% sensitivity and have their own set of limitations. A radio opaque marker test can be used to rule out delayed transit constipation. Endoanal ultrasonography and anorectal manometry are two tests for faecal incontinence.(Ghoshal,2011)

Symptom relief, correction of fluid and electrolyte deficiencies, improvement of nutrition and glycemic control, and management of underlying causes are the mainstays of diabetic diarrhoea treatment. Anti-diarrheal medications should be taken with caution because toxic megacolon can occur. Rifaximin is a low-risk oral antibacterial drug that is concentrated in the gastrointestinal system and exhibits broad spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic bacteria. In up to 84 percent of patients, it has been demonstrated to eliminate bacterial overgrowth. Amoxicillin-clavulanic acid, doxycycline, ciprofloxacin, metronidazole, neomycin, and norfloxacin are some of the other antibiotics used to treat this illness. Anecdotal reports exist of somatostatin analogues successfully treating otherwise intractable secretory diarrhoea in diabetic patients with autonomic neuropathy. (Pimentel,2009)

In cases of faecal incontinence, loperamide may be helpful. Constipation can be relieved by drinking plenty of water, exercising regularly, and eating more fibre. In more severe situations, lactulose and osmotic laxatives may be required. Prucalopride, a selective 5-HT₄ receptor agonist that improves colonic transit, and lubiprostone, which promotes colonic water and electrolyte secretion by activating type 2 chloride channels in enterocytes, are two newer medications for chronic constipation treatment. They may be effective in the future for the treatment of persistent constipation caused by autonomic neuropathy and sluggish transit in people with diabetes. (Pimentel,2009)

NONALCOHOLIC FATTY LIVER DISEASE :

The presence of hepatic steatosis, either by imaging or histology, and the absence of secondary hepatic fat buildup, such as heavy alcohol intake, use of steatogenic medications, or genetic diseases, are required for the diagnosis of nonalcoholic fatty liver disease (NAFLD). The hepatic form of metabolic syndrome is known as NAFLD. The clinical tetrad of hyperinsulinemia with insulin resistance, visceral obesity, dyslipidemia, and hypertension is known as the metabolic syndrome. NAFLD is linked to metabolic risk factors such as obesity (60 percent-95 percent), diabetes mellitus (28 percent-55 percent), dyslipidemia (27 percent-92 percent), and, less clearly, increased arterial pressure in the majority of patients. NAFLD is further separated histologically into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) (NASH). (Falck-Ytter ,2001)

Clinical features

Although most people with NAFLD are asymptomatic, some may experience nonspecific symptoms like as lethargy and soreness in the right upper quadrant. The clinical manifestations of NAFLD range from moderate elevations in liver enzymes to severe fibrosis and nodular degeneration. According to a recent study, roughly 30% of NAFLD cases with isolated steatosis would proceed to NASH, with approximately 20% of them developing cirrhosis. Decompensated liver disease affects about 40% of these cirrhotic patients.

Hepatocellular carcinoma (HCC) is a well-known consequence of NAFLD-induced cirrhosis. In patients with NAFLD, diabetes, obesity, and cirrhosis-associated carcinogenic variables may all have a role in the development of HCC. Diabetes, a high BMI, and liver fibrosis have all been recognised as risk factors for HCC advancement in NAFLD patients. Animal models have recently revealed that metabolic syndrome is a high-risk state for the development of NASH and HCC.(Nishida,2013)

Pathogenesis

The link between T2DM and NAFLD is presented, and the development of NAFLD involves numerous pathways. The development of NAFLD is connected to obesity, insulin resistance, and metabolic syndrome. The development of steatohepatitis is currently thought to be caused by a combination of "multi hits." This theory has taken the place of the previous two hit theories. NASH, insulin resistance, and elevated levels of free fatty acids in the liver all have a strong link. Several variables are thought to have a role in the aetiology of NAFLD and NASH, including tumour necrosis factor

alpha, oxidative stress, adiponectin, leptin, apoptosis, and hereditary factors.
(Miele,2009)

Evaluation

According to the American Association for the Study of Liver Diseases (AASLD), hepatic steatosis must be visible on imaging or histology, there must be no significant alcohol consumption, there must be no competing etiologies for hepatic steatosis, and there must be no co-existing causes for chronic liver disease.

Nutritional causes (e.g., total parenteral nutrition and rapid weight loss), metabolic disorders (glycogen storage disorders), chronic hepatitis C (particularly genotype 3), other chronic liver diseases (autoimmune liver disease, Wilson's disease, and hemochromatosis), and endocrine disorders such as polycystic ovary syndrome, hypopituitarism, and hypothyroidism) should all be ruled out. Glucocorticoids, synthetic estrogens, amiodarone, methotrexate, and highly active antiretroviral medicines are all examples of pharmaceuticals that can cause steatosis. NAFL is a non-cancerous condition, but NASH can lead to cirrhosis, liver failure, and malignancy.(Kang,2009)

The most reliable method for detecting steatohepatitis and fibrosis in patients with NAFLD is liver biopsy, but it has drawbacks such as expense, sample inaccuracy, and procedure-related morbidity and mortality. In patients with NAFLD, features of the metabolic syndrome can predict the occurrence of steatohepatitis. As a result, in patients with NAFLD who also have the metabolic syndrome, a liver biopsy is indicated. There is a growing interest in finding non-invasive approaches for detecting fibrosis in NAFLD patients. The NAFLD Fibrosis Score is a clinically effective

measure for determining which NAFLD patients are more likely to have bridging fibrosis and/or cirrhosis. The NAFLD Fibrosis Score offers a 90 percent sensitivity and 60 percent specificity for excluding advanced fibrosis and a 67 percent sensitivity and 97 percent specificity for identifying the presence of advanced fibrosis, according to a meta-analysis of 13 trials including 3064 participants. The NAFLD Fibrosis Score is derived using the published formula and is based on six factors [age, BMI, hyperglycemia, platelet count, albumin, aspartate aminotransferase/alanine aminotransferase ratio]. (Kang,2009)

Patients with NAFLD are treated for liver disease as well as metabolic co-morbidities such obesity, hyperlipidemia, insulin resistance, and type 2 diabetes.

Modifications in food and lifestyle, as well as weight loss and exercise, are the cornerstones of NAFLD treatment, as it is a condition associated with excess weight and a sedentary lifestyle. When assessed by ultrasound or MR imaging and spectroscopy, many studies have demonstrated that changing one's lifestyle can lower aminotransferase levels and improve hepatic steatosis. In a randomised trial of 31 obese people with NASH who underwent intensive lifestyle changes (diet, behaviour modification, and 200 minutes of moderate physical activity per week for 48 weeks) vs. structured basic education alone, the obese group showed significant improvements in steatosis, necrosis, and inflammation, and participants who lost 7% of their body weight showed significant improvements in steatosis, lobular inflammation, ballooning, and NAFLD Activity Score.

Insulin sensitizers: Insulin resistance is a critical factor in the development of NAFLD. Biguanides (metformin) and thiazolidinediones are the two primary kinds of insulin-

sensitizing medications utilised in the treatment of NAFLD/NASH patients (pioglitazone). (Musso,2012)

Metformin improves insulin sensitivity by lowering triglyceride synthesis and decreasing hepatic gluconeogenesis. In limited, open-label investigations, insulin resistance and serum aminotransferase levels were reduced, but liver histology did not improve significantly. Metformin did not demonstrate a substantial advantage in NAFLD in a recent meta-analysis investigating the effects of medical treatment and/or lifestyle intervention. Metformin had no effect on liver histology and is not indicated as a treatment for persons with NASH who had liver damage.

For the treatment of T2DM, pioglitazone has been available for over a decade. It works by boosting circulating levels of adiponectin and improving peripheral and hepatic insulin sensitivity. In patients with NAFLD, pioglitazone reduced histological disease activity, glucose, lipid, and inflammatory factors, as well as delaying fibrosis progression, according to a recent meta-analysis. The American Association for the Study of Liver Diseases' current recommendation is that pioglitazone be used to treat steatohepatitis in individuals with biopsy-proven NASH, though the long-term safety and efficacy of pioglitazone in NASH patients remains uncertain.(Belfort,2006)

Vitamin E and betaine, both antioxidants, have been studied as potential therapeutic agents in NASH[103,104]. Vitamin E improved liver histology but raised insulin resistance and plasma triacylglycerols when given for two years[101]. As a result, the AASLD's current guideline is that vitamin E (-tocopherol) at an 800 IU/d daily dose be regarded first-line pharmacotherapy for non-diabetic persons with biopsy-proven

NASH. Due to a lack of evidence, vitamin E is not suggested to treat NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

Incretin mimetics: Incretins are a series of gastrointestinal hormones released after a meal that stimulate pancreatic beta cell insulin secretion. GLP-1 is the most researched of these hormones. The GLP-1 analogues exenatide and liraglutide have a well-established role in the therapy of T2DM in obesity. Because of comparable pathways in the aetiology of NAFLD, these medicines may provide new choices for treatment.

Inhibitors of dipeptidyl-peptidase IV (DPP4) were offered as a new way to boost GLP-1 activity. In patients with NASH, serum DPP4 activity is higher, and this correlates with the histological grade and degree of liver steatosis. DPP4 inhibitors are already well-known oral therapies for type 2 diabetes, and preliminary research suggests that they may also help to lower liver inflammation and steatosis. Incretin mimetics could be a new therapeutic option for decreasing the course of NAFLD in the future. (Balaban,2010)

GLYCOGENIC HEPATOPATHY :

Glycogenic hepatopathy is described as the pathological overloading of hepatocytes with glycogen, resulting in hepatic hypertrophy and/or liver enzyme abnormalities. It is most commonly seen in people with poorly managed type 1 diabetes (T1DM). Glycogen storage in the liver was originally identified in Mauriac's Syndrome in 1930. Stable hyperglycemia, hepatomegaly, hyperlipidemia, dwarfism, cushingoid characteristics, and a delay in sexual maturity were all symptoms of this illness. Glycogen buildup in hepatocytes can occur without all of the symptoms of Mauriac's Syndrome, according to recent research. Inadequate T1DM regulation leads to the

accumulation of insulin and excess glucose, which causes the liver to store more glycogen. Insulin activates the enzyme glycogen synthase phosphatase, which dephosphorylates and activates glycogen synthase, another enzyme essential for glycogen formation from glucose-1-phosphate. Glycogen accumulation in the liver increases as a result, and glycogenolysis is inhibited. Pale hepatocytes with sinusoids compressed, glycogenated nuclei, and large mitochondria characterise the histological image. Steatosis can be present or absent, with the latter being the most common. PAS-diastase staining demonstrates glycogen buildup, which is a characteristic of this disease. (Torbenson,2006)

Abdominal pain, nausea, vomiting, and abnormal liver function tests are common symptoms of the disease, which is under-recognized. While NAFLD is the most common cause of hepatic dysfunction in T2DM, glycogenic hepatopathy is the most common cause of liver dysfunction in T1DM. Clinically or by ultrasound, it cannot be separated from NAFLD, and confirmation requires a liver biopsy. When liver impairment occurs in T1DM patients, the illness should be investigated, especially if viral, autoimmune, and metabolic liver diseases are ruled out by laboratory tests. This condition is characterised by its reversibility when glycemic management is improved. Glycogen overload, unlike hepatic steatosis, is not known to develop to fibrosis separate from fatty liver disease. (Abaci,2008)

Conclusion :

It is estimated that up to 75 percent of diabetic people will develop gastrointestinal issues. The pathophysiology of gastrointestinal problems is complicated, and it is

mostly linked to gastrointestinal autonomic dysfunction, hyperglycemia, and diabetes duration.

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