

**THE IMPACT OF COVID-19 ON NON-ALCOHOLIC STEATOHEPATITIS(NASH):A
VIEW FROM ACE GASTROENTEROLOGIST****Akashdeep Sikdar***

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NASH and Covid19

(SARS-CoV-2) pandemic highlighted the importance of an effective host immune response. COVID-19, which can involve a number of diverse symptoms, including immune dysregulation and cytokine storm. Ongoing worldwide obesity pandemic that has led to insulin resistance, diabetes, and chronic liver disease (CLD), becoming a major public health burden. CLD is most commonly caused by chronic hepatitis B and C, alcohol-associated liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD). CLD can further lead to inflammation (nonalcoholic steatohepatitis [NASH]), fibrosis, and finally cirrhosis and hepatocellular carcinoma (HCC) as end-stage diseases. Cirrhosis, viral hepatitis, and HCC are responsible for approximately 2million deaths per year worldwide. Covid-19 have caused significant morbidity and mortality through increase inflammation and thrombosis. Non-alcoholic fatty liver disease and non- alcoholic steatohepatitis are states of chronic inflammation and indicate advanced metabolic disease. Hospitalizations for Covid-19 have disrupted thousands of lives. Obesity and metabolic disease appear to be the most significant modifiable risk factors for poor outcomes from Covid-19. Given Covid-19's pathophysiology through inflammation, NAFLD/NASH patients are at higher risk of poor outcomes from Covid-19. Here we discuss these serious healthcare burden with ace gastroenterologist Dr. Pardha Devaki. He received his medical education from Gandhi Medical College in Hyderabad, India. Dr. Pardha completed his Medicine Residency at Wayne State University/Detroit Medical Center in Detroit, Michigan, United States. He also completed his Gastroenterology and Hepatology Fellowship at Cleveland Clinic Foundation in Cleveland, Ohio. Currently Dr. Pardha is affiliated with Mercy Hospital Rogers. Below are excerpts from the discussion with Dr. Pardha.

How does obesity cause long term morbid affect in the time of COVID-19 pandemic?

The SARS-CoV-2 pandemic has proven a challenge to healthcare systems after its appearance in 2019. COVID-19 spread globally with devastating effects on patients and have resulted in many studies on risk factors and disease progression. Overweight and obesity remains one of the major risk factors for developing severe COVID-19. According to World Health Organization global prevalence of obesity has increased 3-fold between 1975 and 2016, the data shows that 13% of adults are obese and 39% are overweight in 2016. If this upward graph continues, it is estimated that by 2030, 38% of the population worldwide will be overweight and 20% will be obese. Now with COVID 19, it has probably changed the prediction, and impacted highly in the obesity of general population.

Excess energy from the diet is usually stored as fat in the white adipose tissue (WAT), which is widely distributed throughout the body. WAT can be subdivided in two major types: visceral fat depots (around abdominal viscera in mesentery and omentum) and subcutaneous fat

deposits (under the skin). In addition, to fat-storing adipocytes, WAT contains immune cells, which affect whole-body together, homeostasis through metabolic, endocrine, and immune functions. Chronic over nutrition results in obesity which can cause severe derangements in these functions, associated with increased leptin secretion, local inflammation, and release of inflammatory mediators can negatively affect the function of other tissues. This low-grade inflammatory state has major risk factor for developing diseases like diabetes mellitus type 2, hypertension, cardiovascular diseases, and fatty liver disease. Fatty liver disease can be classified into two types. When there is fat but no damage is done to liver, the disease is called nonalcoholic fatty liver disease (NAFLD). When there is fat in your liver and signs of inflammation, liver cell damage, the disease is called nonalcoholic steatohepatitis (NASH). 10% to 20% of Americans have NAFLD and 2% to 5% have NASH. Obesity is the most common cause of NASH. Obesity in the U.S. has doubled in the last decade, and we are seeing a steady rise in fatty liver disease. Although children and young adults can get fatty liver disease, it is most common in middle age. During

the time of pandemic, there are global food insecurity has developed among general population. There has been more consumption of fast food, processed food and high calorie food in most household. On top of that restriction in mobility has added the obesity and eventually lot of another metabolic syndrome. Patient have restricted there visit also for routine checkup and lab work. These all culminated into more into mild to severe NAFLD.

How global pandemic intertwined with COVID19, obesity and NAFLD?

It is a known fact that obesity and impaired metabolic health establishes risk factors for the non-communicable diseases (NCDs) like type 2 diabetes mellitus, cardiovascular disease, neurodegenerative diseases, cancer and nonalcoholic fatty liver disease, which is also known as metabolic associated fatty liver disease (MAFLD). With increasing global spread of SARS-CoV-2, obesity and impaired metabolic health also emerged as important determinants of COVID-19. Also, novel findings indicated that specifically visceral obesity and characteristics of impaired metabolic health such as hyperglycaemia, hypertension and subclinical inflammation which increases the high risk of severe COVID-19. Obesity is a strong and independent determinant of severe coronavirus COVID-19 and novel studies also suggest that visceral obesity increases the risk of complications. Liver dysfunction, specifically nonalcoholic fatty liver disease (NAFLD), is now accepted as a cause of impaired glucose and lipid metabolism, and as a consequence of obesity and impaired metabolic health. A close relationship of NAFLD with impaired glucose and lipid metabolism resulted in experts advocating a new definition for NAFLD, which is known as metabolic associated fatty liver disease (MAFLD) and it more strongly supports hepatic steatosis being an important non-communicable disease.

Is COVID-19 also causing gastrointestinal disease?

The gut has a well-defined and important role in the regulation of adipose tissue mass and of glucose and lipid metabolism. A Western diet induces dysregulation of the intestinal microbiome composition, which results in disruption of the intestinal barrier and translocation of gut microbiota, metabolites and activated immune cells into the circulation. Predominantly via such a leaky gut, bacteria-derived products are considered to contribute to the pathogenesis of metabolic diseases, inducing adipose tissue inflammation, hepatic steatosis, and hepatic inflammation.

COVID-19 pandemic is caused by the SARS-CoV-2. Angiotensin-converting enzyme 2 (ACE2) is not only an enzyme but it is also a functional receptor on cell surfaces through which SARS-CoV-2 enters the host cells and is expressed in the heart, kidneys, and lungs and shed into the plasma. ACE2 is a key regulator of the renin-angiotensin-aldosterone system (RAAS). SARS-CoV-2 causes ACE/ACE2 balance disruption and RAAS

activation, which leads ultimately to COVID-19 progression, especially in patients with comorbidities, such as hypertension, diabetes mellitus, and cardiovascular disease. Comparing with many other human tissues, the highest expression of ACE2 was found in the small intestine, followed by the colon and the duodenum. Furthermore, in small intestinal organoids, enterocytes were readily infected by SARS-CoV-2, and these enterocytes produced infectious viral particles. In addition, gastrointestinal symptoms are observed in a subset of patients with COVID-19.

What is your thought on COVID 19 and NAFLD.

My understanding of COVID-19 in people with NAFLD is evolving. People affected with cirrhosis of the liver, including cirrhosis caused by NAFLD, have potential risk of developing severe COVID-19 illness with prolonged hospitalization and increased mortality. These patients need to take careful precautions to avoid COVID-19 infection which may affect the processes and procedures for screening, diagnosis, and management of NAFLD. NAFLD, itself, is strongly associated with metabolic syndrome, and features of metabolic syndrome (obesity, diabetes mellitus, and hypertension) are well-established risk factors for severe illness from COVID-19. Elderly people over 65 years of age or those who are affected with kidney disease or chronic lung disease are also at a higher risk for severe illness from COVID-19. Also, COVID-19 infection and some of the medications for treatment may be associated with liver injury. The effect of NAFLD in these cases is not well understood. The COVID-19 pandemic has increased stress and anxiety for many people—around health, family, economic security, and other issues. Particularly, rates of alcohol use and abuse have increased. Reaching out for mental health and substance abuse support and maintaining healthy habits, such as exercising regularly, getting fresh air, eating wholesome foods, and getting regular sleep, remain very important during the pandemic.

Does alcohol consumption affect the risk of developing NASH or NAFLD in the general population?

Moderate or heavy alcohol use can cause additional damage and fat accumulation in the liver in people with NAFLD. Therefore, patients with NAFLD should avoid alcohol entirely if possible. The psychological stress and social distancing needed for initial control of the pandemic have resulted in significantly increased alcohol use and alcohol use disorders. Additionally, alcohol also adds to the caloric load. The increased food consumption that often occurs while drinking alcohol increases calories can also contribute to liver fat. So the risk of developing NASH/NAFLD has increased.

What are your suggestions to combat with this emerging issue?

Controlling obesity in pandemic and consequently other metabolic syndrome requires strong measures in the

public health sector, to reduce adipose tissue mass and improve metabolic health in the population. In this aspect, it is important for healthcare professionals to promote the health benefits of physical activity and support efforts to implement programs and policies to facilitate increased physical activity. These measures may include support of sports federations, sports clubs, schools, and employers to implement safety measures during the COVID-19 pandemic. Encouraging organizations that provide physical activity programs and schools to find new ways to ensure that physical activity levels can be maintained and increased. It is important for governments to supply incentives to support an active lifestyle. Importantly, the prevalence of obesity and impaired metabolic health is particularly high in people with low socioeconomic status and also in some ethnic groups. Large studies data investigated that those relationships of comorbidities with the course of COVID-19 using multivariate adjustment, obesity emerged as a strong and independent determinant of increased risk of morbidity and mortality in patients infected with SARS-CoV-2. In my opinion taking care of fundamental issue like healthy food habits and obesity can profoundly decrease the severity and comorbidity of COVID-19 infection. Reducing obesity not only helps to fight with infection, also helps to increase the effectiveness of vaccination.

