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Review Article

Microbiology Section

Exploring the Profile of the Gut Microbiome in Differentiating Type 2 Diabetes Mellitus and Non Alcoholic Fatty Liver Disease

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and Non Alcoholic Fatty Liver Disease (NAFLD) are emerging global pandemics and carry a significant burden of co-morbidity and mortality. Asian Indians have the highest prevalence of T2DM, leading to 2.54 million deaths yearly. In India, it is 11.6%, and 30-50% of patients with NAFLD have diabetes. Patients with worsening T2DM tend to have increased progression of NAFLD to cirrhosis. NAFLD leads to end-stage liver disease causing 2.59 million deaths annually. Therefore, the relationship between T2DM and NAFLD needs to be disclosed, and the gut microbiome shows significant characteristics for the same. The gut microbiome is a collection of trillions of bacteria, archaea and fungi that resides in the digestive tract of humans. It plays a significant role in health by helping control digestion and benefits our immune system. Progression of metabolic health disorders shows changes in the quality and heterogeneity of the gut microbiome. It has been established that metabolic and immunological disorders are mainly influenced by the gut microbiome and not by the type of diet. Butyrate-producing bacteria benefit insulin resistance leading to more chances of T2DM. Since, the liver is close to the gut microbiome, the influence of the gut microbiome and its metabolites affecting liver function is great. But, gut microbiome being specific in both cases can assist in exploring the relationship and differentiating one from the other. Therefore, further analysis and studies are required to understand the role of the gut microbiome and its significance in better diagnosis.

Keywords: Archaea and Fungi, Bacteria, Diabetes, Dysbiosis, Gut flora, Gut-liver axis, Obesity

INTRODUCTION

The Type 2 diabetes mellitus (T2DM) and non alcoholic fatty liver disease are emerging as a global pandemic and carry a significant burden of comorbidity and mortality. The worldwide prevalence of T2DM is 1 out of 10 people. In India, prevalence of NAFLD is 11.6% and 30-50% of patients with NAFLD are diabetic. Asian Indians have the highest prevalence of T2DM leading to 2.54 million deaths every year. NAFLD leads to end-stage liver disease causing 2.59 million deaths annually [1]. The prevalence of NAFLD is 59.67% in T2DM [2]. Patients with worsening T2DM tend to have increased progression of NAFLD to cirrhosis. Heart disease in NAFLD increases 1.87 times in cases with T2DM. Since, the liver is in a close affinity with the gut microbiome, the influence of the gut microbiome and its metabolites affecting liver function is high [3]. The gut microbiome is a collection of trillions of bacteria, archaea and fungi that resides in the digestive tract of humans. It plays a significant role in health by helping control digestion and is beneficial to our immune system. Progression of metabolic health disorders shows changes in the quality and heterogeneity of the gut microbiome. It has been established that metabolic and immunological disorders are mainly influenced by the gut microbiome and not by the type of diet. Butyrate-producing bacteria benefits insulin resistance leading to more chances of T2DM [4]. But, gut microbiome being specific in both cases can assist in exploring the relationship or differentiating one from the other. Thereby, this review aims to further analyse and understand the role of gut microbiome and its relationship between T2DM and NAFLD for better diagnosis.

PRESENTATION OF T2DM AND NAFLD

The human gastrointestinal tract is an important site for organism residing in mutualism. According to the recent data trillions of organisms are found in human gut [5]. There, presence is highly fluctuating depending on different factors responsible for the aetiology and development of diseases [6,7]. The recent studies have exposed vital role of gut microbiome as an important factor responsible for metabolic comorbidities such as diabetes [8,9], obesity [10-13], cardiovascular diseases [14-16], and NAFLD [17]. The ongoing pandemic obesity is creating a havoc worldwide causing huge number of T2DM cases. Obesity is a risk factor leading to metabolic disorder, since its causes increased insulin resistance, hypertension, etc., [18,19]. Exploring gut microbiome is essential as said by Hippocrates-'All diseases begins in the gut'. According to the recent studies in 55% cases of T2DM, showed presence of NAFLD and other way round [1,20,21]. In addition, its association has a poorer prognosis and high mortality rate [22]. Ongoing research has revealed that changes in gut microbiome are characteristic features of these two metabolic diseases [23,24]. In this review article, we explored the profile of gut microbiome in differentiating T2DM & NAFLD on the basis of specific microbiome presence.

GUT MICROBIOME AND ITS SIGNIFICANCE

Gut microbiome is a collection of trillions of bacteria, archaea, and fungi that resides in mutualism in the digestive tract of human. It has an important role in our health by controlling digestion and is also beneficial for our immune system. As a metabolic disorder develops in our body, it shows changes in the diversity of gut microbe. The essential fuel for this gut microbiome is probiotics it helps the gut microbe to become strong and healthy. This fact has been proven by necessary intake of probiotic supplement for middle aged or old age people as their gut flora becomes weak with increased age. It has also proven to be effective during stress thus preventing from stress related co-morbidities. When a pathogen enters our body, through contaminated food or water pathogen fights with microbe present in gut for nutrient and space, thus gut microbes weaken the pathogen. Also, when toxic food consumes, gut microbe breaks it into amino acid and vitamin which can serve as an essential biomarker. Since, immune system is challenged regularly by favourable organism through pathogens and gut microbe evolved mutually so intelligently that, they play a major role in immunological

well-being [12]. Growth of microbes starts soon after the birth of baby depending on factors like: type of delivery [25,26], feeding pattern [27], then it remains constant till adulthood [28,29]. When person changes diet, use of medication [30], diabetic drug [31,32], and proton pump inhibitor [33] causes change in gut flora. Obesity is referred to as intake of excessive calories then burned by normal daily activity [34]. These imbalance is recognised by hypothalamus in brain which causes behavioural and metabolic responses in order to balance the variation [35,36]. This two-way connection of central nervous system with enteric nervous system and its regulation is called as gut-brain axis. This accounts for its creditability with all other organs, such as brain and endocrine organ and its metabolites and hormones acts as key messenger [37].

Gut Microbiome in NAFLD

The major cause of metabolic disorder is linked to obese individual. An essential role is played by the gut flora in causing metabolic disorders related to obese individual [38], this is done by production of Short Chain Fatty Acids (SCFA) that induces energy scavenging [39,40]. The microbes present in gut induces the absorption of simple carbohydrates like glucose, fructose and galactose from intestine, leading to the production of fatty acids from acetyl-CoA through this carbohydrate metabolism causing accumulation of triglycerides in adipocytes. Insulin resistance fastens adipocyte cumulation and leads to inflammation in liver [41]. This increases with time causing the development of NAFLD. These deleterious bacteria are transported into circulation but a natural barrier that is our gut epithelium prevents its translocation.

The gut-liver axis is defined as a two-way co-relation with gut, and its microbiome and liver. On the contrary, dysbiosis is defined as imbalance in the gut microbial number that is associated with disease. This leads to gut barrier damage causing translocation of metabolites from gut wall to portal vein. This causes release of bile acids and Farnesoid X Receptor (FXR) causing lipotoxicity that leads to mitochondrial dysfunction causing lipid accumulation in hepatocytes that is development of NAFLD. On the other hand, dysbiosis also causes release of Lipopolysaccharides (LPS), pathogen associated molecular pattern that acts on Kupffer cells causing inflammation in liver that further progression of NAFLD. This upsurge of LPS level in circulation is referred to as "metabolic endotexemia" generally observed in metabolic diseases [42]. This LPS integrates with LPS binding protein and next to it themenocyte differentiate antigen (CD-14)-TLR-4-complex mediating inflammatory reaction and insulin and activates inflammation [43].

Broad range of physiological activity produces bile acids from cholesterol. This bile acids help in digestion, absorption of fat containing foods and conserves the gut membrane putting a stop to metabolic translocation [44,45]. In cases of NAFLD, the disparity in the gut microbial association is primarily explained by age. It has been hypothesised that the presence of *megamonas* and *ruminococcus* is seen in case of NAFLD only [24]. *Enterobacter* [46] and clostridium [47] has shown to associated with NAFLD. While *Rombustia* over existed in slim patients of NAFLD [48]. Influence of medication on gut microbiome has been comprehensively observed. NAFLD deals with need of specified medical treatment by means of drugs that is distinct pharmacotherapy. It indicates change in the ongoing sedentary lifestyle in addition to alteration in diet pattern is beholden as far as finest treatment strategy for control and prevention of further development of the disease.

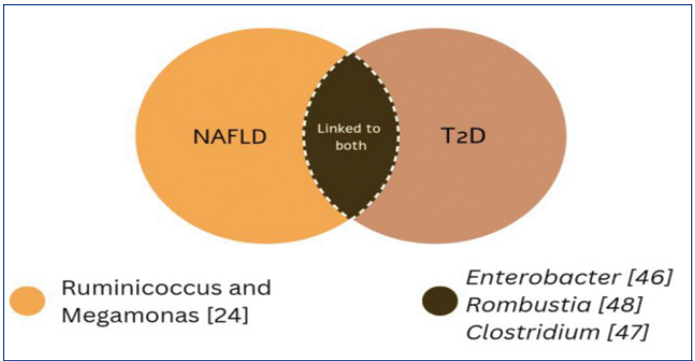
Gut Microbiome in T2DM and its Effect on Cardio Metabolism

Dietary regimen is a regulator of the make-up and the ramification of the gut microbiome [49]. Clinical trials have disclosed few characteristic feature in which dietary regimen can make alteration to the gut microbiome [50]. Initially, the microbiome makes changes instantly, when disclosed to substantial and quick variation in feeding pattern. Military diet that is short-term diet variation that includes chop and changes in between vegetarian diet and non-vegetarian diet or including an additional 40 gm fibre per day to the dietary regimen. Subsequently a diet with varying fat-containing food or fibre driven food can alter human gut microbiome in the ramification and make-up of the gut microbiome that is noteworthy in 48 hours [50,51]. High-fibre diet has revealed to ameliorate insulin resistance in slim and in overweight subject with T2DM. And important point to note here is that only regular, constant, long-term, dietary regimen are significant to all intent and purposed in stating the health of the gut microbe ramification. Military dietary regimen ceases to function the alteration of the major makeup and categorisation of the gut flora. It is believed that metabolites that are developed from the gut flora in response to metabolisation of diet consumed are key factors impacting human biology, contrarily the effect to nutrients are impacted by microbe present in gut. Two such micronutrients that influence the gut flora are Choline and Trimethyl Amine N-Oxide (TMAO). It has been studied that inadequate choline intake in human regulates the gut flora with varied levels of *Grammaproteobacteria* and *Erysipelotrichi* and this are in a straight line associated with NAFLD progression [52]. In some studies, on animal models it has been observed that obesity is directly associated with gut microbiome [53]. This is demonstrated in a study on genetically obese mice which has half and half cut back of *Bacteroidetes* and rise of *Firmicutes* in contrast to their slim brothers and sisters [53]. This variation influences consumption level of microbes and these obese mice shows expanded function in deriving nutrition from digested food.

Gut-Microbe derived Short Chain Fatty Acids (SCFA)

The main source of energy for human beings is derived from the food intake. This food intake in regular terms is referred to as dietary regimen. When food enters into human body it is broken down into small molecule by the gut microbes. These molecules are then absorbed through different mechanism. These have a direct effect on various cells of human organ like hepatocytes through the absorption of metabolites by the portal vein. In the liver these metabolites run away from the first pass metabolism and enters into the circulation leading to various consequences on human biology [54]. In a balance diet human body receives varied substrate like carbohydrates, lipids, amino acids and iron which are broken down in the lumen of the small intestine, where the gut microbes convert it into specific metabolites. Few carbohydrates are indigestible and therefore they are roasted by the gut microbiome leading to formation of SCFA, in which the most essential ones are acetate, butyrate, lactate and propionate [55]. Now the response of our human body on these metabolites are reciprocated on the basis of synthesis of SCFA and relative liver clearance, leading to the production of fatty acids from acetyl-CoA during carbohydrate metabolism and subsequent other procedure goes hand in hand, while a small amount enters into the circulation [53]. It is of key importance here that all the SCFA doesn't have similar effect. This effect of gut microbiota in the synthesis of SCFA has been shown using oral antibiotic treatment that causes extreme outcome on the synthesis of maximum number of metabolites [56].

In this article, the profile of gut microbiome was reviewed in case of T2DM and NAFLD. The gut microbiome has a different profile in terms of taxon found in T2DM and NAFLD. Specific taxon for NAFLD was recognised that is *Ruminococcus and Megamonas* [24]. While *Enterobacter* [46], *Rombustia* [48], and *Clostridium* [47] linked to both NAFLD and T2DM these were also linked to diabetes marker like Hb1Ac and fasting blood glucose as shown in [Table/Fig-1].



[Table/Fig-1]: The profile of gut microbiome for Type-2 Diabetes (T2DM) and Non-Alcoholic Fatty Liver Desease (NAFLD).

CONCLUSION(S)

To conclude, helped us by identifying the gut microbiome establish relationship with host parameters that are specific for diabetes mellitus and liver disease; and a further approach to analyse and validate the results by cohort study. The recent studies have exposed vital role of gut microbiome as an important factor responsible for metabolic comorbidities. The reliability of gut-brain axis on all the other organs plays a vital role as a messenger. Further research that aims at enhancing the detection, cure and therapeutic treatment of these metabolic disorders is required to establish the role of using the gut microbiome for diagnostic purposes. Also, primary research needs to be done in order to further analyse these gut microbiomes in anticipation of the advancement and evolving nature of this metabolic disorder.

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