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NEW INSIGHTS INTO THE GUT MICROBIOME RESEARCH TO UNDERSTAND THE MICROBIAL DIVERSITY OF INDIAN AND WESTERN POPULATIONS WITH TYPE II DIABETES MELLITUS: A SHORT REVIEW

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ABSTRACT

Gut flora comprises ecologically beneficial indigenous microbial community that reside in the digestive tract of humans and inferred as gut microbiota. The aggregation of the genomes of all these gut microbiota is designated as gut meta-genome which play a pivotal role in most of the gut-associated diseases. Diabetes is an autoimmune disease whose incidence has rapidly surged through out all over the globe over the last two decades. Accruing evidence suggests that microbiota plays a key role in the biological mechanism of diabetes and other diseases. Establishment of microbes in the colon begins at birth, however, the succession and composition of the intestinal microbial community depend upon several factors, however not restricted to, the ageing, dietary, genetic variability, gender, geographic region, and health status of an individual. Therefore, the inclusion of diverse study population in the study of the gut microbiome is indispensable in case of Indian population which is unique in terms of ethnicity, food habits and geographic location. This review is intended to provide an association between gut microbiota and diabetes, which concisely explain the significance of the intestinal microbes and its present status in between Indian and western population. Further, this review has also explored the possible role and cause for the development of diabetes influenced by the gut microbiota. In conclusion, it can be suggested that Indian population could be the signatures required to promote the human health status by the clinicians.

KEYWORDS: Diabetes Mellitus; Health Status; Life Style; Gastrointestinal Tract.

Diabetes Mellitus

Diabetes is a complex metabolic disorder which can affect the whole body, may need self-care upon development of complications. It has a direct impact on quality of life and health status of an individual along with a high risk of survivability.[1] The growing burden of type II diabetes (T2D) in the current scenario is of notable relevance for public health in developing nations than developed nations. It is expected by World Health Organisation (WHO) that Type 2 diabetes would be the causal agent resulting in death by 2030 (WHO, 2016). The human enteric tract is an inimitable ecosystem that harbors a wide spectrum of microorganisms. The symbiotic relationship between intestinal microbes and host is major factor that denotes overall health status of the host. The relationship between the host and gut microbiome is a very complex process; which started from birth, several factors outline the composition of the intestinal microbiota of an individual. Mother of the host plays a key role to colonize microbes at birth.[2] Colonization of the intestinal microbiota depends on the type of delivery procedure. Vaginally delivered infants gut microbiota dominated with Lactobacillus *and Prevotella* spp. compared with infants delivered by cesarean section dominated with *Staphylococcus, Corynebacterium* and *Propionibacterium* spp.[47] Breastfed infants dominated with *Actinobacteria* and Bifidobacterium in gut during early childhood changing dietary habits (introducing of solid foods) also alters the intestinal microbiota ratio.[48] Subsequent to colonization, the composition of intestinal microbiota depends on several factors including the host genetic composition, diet, age, gender, geographic location, climatic condition, environmental factor and host immunity/defense mechanism.[3,4] Development of the indigenous microbiota depends upon above-mentioned factors. Recent studies implies that lifestyle directly associated with dysbiosis of the gut microbiota, which further leads to the development of several metabolic diseases including diabetes, adiposity and cardiovascular diseases.[5] The western/modern lifestyle influences the Indian population over last few years. Existing reports state less significance in incidence of developing metabolic diseases like adiposity and diabetes that rarely linked with the western lifestyle. Though, the current variations in a socio-economic situation have led to a transformation of

Indian lifestyle. Lifestyle modification in Indian population has resulted in the development of several metabolic diseases such as coronary heart disease, diabetes and adiposity.[6]

Current studies on European women's comprised of normal and insulin resistant individuals have revealed a significant difference in the metagenomic biomarkers than those of Chinese individuals.[5] Human microbiome studies showed a unique difference in Indian population. Indian population has attracted most of the anthropologists and geneticists for decades due to the vast distinctiveness in genetic composition, food habits and ethnicity. Indian population classified into four substructure, which is represented by four groups:1) Paleolithic people (indigenous tribals); 2) early farmers from the Fertile Crescent region; 3) the Indo-European speakers (from central Asia); and 4) the Austro-Asiatic and Tibeto-Burman speakers.[7]

Autosomal loci imply an influence of West Eurasians in the genetic configuration of Indians, Narrated from the studies on mitochondrial DNA, Y-chromosome.[8,9,10] Additionally, there is a divergence in the nature and origin of Indian population in response with western populations; The YY-paradox suggests a similar body mass index (BMI) in Indians that have nearly three times elevated fat percent as compared with the western population.[11]

Population Subgroup and genetic melange

The Indian populace is divided into four Sub-group: Australoid, Negrito, Mongoloid and Caucasoid. The Caucasoid group spread throughout the country, with maximum quantity in the northern region of India, while the Australoid clustered mostly in the western and southern states. The Negrito subgroup is found mostly in the Andaman Islands. Siddis, an immigrant, cluster from the Africa, inhabit in Karnataka, Gujarat and Andhra Pradesh. In addition, from the primeval times, Indian subcontinent is believed to have migrated with the Austro-Asiatic tribal clusters like Korkus, Mundas, Santhals, Khasis, Nicobarese and Oraon.[12] Huge genetic admixture has been developed due to migration by humans and hence most of the modern population has mixed genetic make-up. Indian population has been occupying the world's largest surviving social hierarchies, whereas the caste system has been more prevalent for a long time.[13,14] Marriages within the same caste have promoted the practice of marrying within a specific social group nature of different groups. For instance, the Parsi community in India is one of the genetically homogeneous community. It is believed that this community is more concomitant with the European population. Whole genome sequencing of this individual was helpful in discovering all the polymorphisms in this distinctive population that potentially bridge the eastern and western populations.[15] This study will be helpful to know the common genetic variations of western Asian individuals and that helps to provide analyzing natural human variation and human migration. One of the major dubiety in gut microbiota research is to understand the appropriate reason for the differences in the microbiome of western and the non-western populations.

Role of Geographic location

Lifestyle and dietary habits of individuals are closely associated with the Geographic location. This is due to the major foods mostly comprise the crops and vegetables which are easily cultivated under certain climatic conditions. India is known as the seventh largest country in the world in terms of area, having huge geographical diversity with the Himalayas on the north, the desert in the west, the northern Ganges plateau, the Deccan plateau of the south and other coastal areas and islands.[16,17] People residing in these different diverse geographical areas have adapted to specific dietary habits with reference to specific environmental condition. A comparative study of intestinal microbiota between individuals of United States, Japan and China have revealed a distinct microbiome composition when compared with Korean individuals.[18] Many studies reported that high abundances of *Firmicutes, Actinobacteria* and *Bacteroidetes,* respectively were found in the gut microbiota of American, Japanese, Korean and Chinese community.[59] Japanese population manifested with elevated *Bifidobacterium* and Clostridium at genus levels,[60], In American and Jamaican population's genus *Bacteroides* is most dominated while genus *Prevotella* is most dominated in the Indian population.[61] Studies on Netherlands healthy individuals showed that *Ruminococcus, Roseburia, Veillonellaceae* are most dominated gut microbiome.[62]

Diversity in dietary habits

The diversity in diet composition of Indians population generally depends on various factors including their socio-economic status (SES), caste and religious affiliation.[19,20] For instances, a group of the population belonging to Hindu religion, particularly the Brahmins and Jains follow a strict vegetarian diet which doesn't include egg, fish and meat. Kabeerdoss et al. (2011)[65] performed a study on gut microbiota of South Indian women who followed either a vegetarian or omnivorous diets. The study showed that fecal microbiome of the omnivorous group was comprising abundantly *Clostridium* cluster XIVa and *Roseburia-E. rectale* bacteria.[21] The Indian population which practices a strict vegetarian diet since ancient times makes themselves a unique group which differs from the rest of the world. These groups of the population are ideal choice to explore the role of diet on gut microbiome evolution as when compared with the population consuming non-vegetarian diet including meat. The comparative analysis of gut microbiome will be very useful to reconnoiter whether the wide spectrum of gut microbial populations is elevated in vegetarians as compared to non-vegetarians.

Occurrence of diseases possibilities in Indian Population

India accounts for 66.84 million diabetics and stands second to China which accounts for 96.28 million. Ineffective insulin use and lifestyle changes lead to systemic complications and mortality in diabetics.[63] Studies by Pushpanathan et al., 2016 on Indian (Chennai) population reported that *Firmicutes* is the most dominated phylum in both T2DM (50%) and healthy population (53%) which is followed by Proteobacteria (28%) and Bacteroidetes (19%), correspondingly. *Lactobacillus* is the most studied bacterial genera for its probiotic features. This genus of bacteria possesses varied specificity towards human intestinal epithelial cell lines.[22] Henceforth, the gut bacteria from the western population may not be effective in colonization of gut in Indians. For example; *Lactobacillus Plantarum* Lp9, which possess antibacterial activities, high resistance to low pH, anti-oxidative and cholesterol-lowering properties with beneficial probiotic features against human host is an ideal choice for Indian population[23] needs more clinical validation. The microbiome analysis of Indians may helpful for the development of novel indigenous probiotics.

Composition of gut microbiota

Gut microbiota comprises of microorganisms which live in the enteric tracts of humans and act as the largest pool of human flora with the concentration of 10^{14} cells/ml and approximate weight of 1.5 kg. The human body, consisting of about 10 trillion cells which comprise of 300 to 1000 different types species in the intestines.[7] The metabolic activities performed by these microorganisms resemble those of an organ, leading some to liken gut bacteria to a "forgotten" organ.[39,40,41]

The microbiota of gut helpful to the host by preventing the growth of pathogenic bacteria, modulating the immune system, fermentation of unused energy substrates, responsible for the good nourishment of the gut, helpful for producing vitamins (such as biotin, cobalamin and vitamin K) and helpful in stimulating certain hormones that regulate satiety. The human gut microbiota comprised of 6 types of phyla – *Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria, and Verucomicrobia*. During birth, the gut is inhabited by more than 100 species of bacteria which finally reaches adult like microbiome i.e., more than

1000 species within the first 3 yrs. Two important major phyla of intestinal microbiota *(Bacteroidetes* and Firmicutes) which occupy >90% of the total gut microbiota. Studies reported that, with increasing age, the percentage of *Firmicutes* increase and *Bacteroides* decrease. For better health, a symbiotic relationship is necessary between gut microbiota and human host.[11]

Inappropriate use of antibiotics

We often do see any implausible use of antibiotics in the Western population. Recent studies have hypothesized that the core intestinal microbiota of Indian population may have evolved to be resistant to a wide spectrum of antibiotics as compared to the western gut microbiome. The misuse of antibiotics may have developed antibiotic resistance against selective microbes. To assess the diversity in the consortia of gut microbiota a comparative study was undertaken in healthy Indian and western populations. The study highlighted that population of Indian origin is more diverse with incomparable features and divergent identities which distinguishes themselves unique from rest of the world. The distinct and unique identities of Indians call for gut microbiome studies associated with various aspects of health and these studies helpful in developing an idea about ‘Indian population’ at the focal point.[24]

Role of diet in gut microbiota

Gut microbiota has played a crucial job in the regulation of host genes and nutrient absorption. The intestinal microbial load influences more rapidly by shifting in nutritional load and when 20% rise in *Firmicutes* with the corresponding decrease in *Bacteroides* hikes the energy harvest by 150 kcal.[43] It is reported that when high-fat diet given to mice that resulted in reduced numbers of *Bifidobacteria* in the gut with increased endotoxemia developed.[25] When these mice were treated with prebiotic the enhancement of beneficial microbes restore the levels of *Bifidobacteria* and also reduced endotoxemia.[26] Individuals consuming animal products rich diets, *Bacteroides* were more prime and those population taking plant-rich diet, *Prevotella* was the more prime species among gut microbiota. Individuals on plant material rich diet were produced higher amounts Short-Chain Fatty Acids (SCFAs) and these were beneficial for sustaining a symbiotic environment of the gut.[26] These individuals were represented by enzymes for anabolism of metabolites like glutamate synthesis, riboflavin synthesis, and amylase, whereas, in individuals predominantly with animal source diet, the microbiota was represented by enzymes for catabolism of metabolites like enzymes for degradation of amino acids and glycan degradation.[27]

Comparative studies of gut microbiota the world population as compared with Indian Population

The prevalence of diabetes in India explained by factors such as differences in socio-economic status (SES), physical activity, dietary patterns, adiposity prevalence and possibly genetic variation. The overall prevalence of diabetes was higher on the mainland than in the northeast states. Studies reported that prevalence diabetes was higher in the more economically developed states and even within states diabetes was more common in individuals of medium or high SES than in individuals of low SES. The main factors influencing the diabetes epidemic in both urban and rural regions of India are adiposity, age, and family history of diabetes.[42,43]

Indian diet includes vast verity of spices and some spices consumed in daily diet have proven antimicrobial activity.[28] For instances, cinnamon, clove, and mustard are spices used in daily diets and these spices have tremendous antimicrobial activity against clinical isolates was found.[29] The role of these spices (if any) in modifying the intestinal microbiota is largely unexplored. Study needed to explore the role of microbiome linked to diet have not been studied within Indian population. These include possible role of genetic predisposition (Ramachandran et al., 2012)[30], intrauterine under nutrition (thrifty phenotype) leading to epigenetic predisposition, diabetes at an earlier age with lower body mass index (BMI) compared to white Caucasians (Yajnik, 2004). Cani et al. (2007) reported the gut microbiota in the context of type 2 diabetes in Indian population for the first time.[5] A search of keywords using logical operators ‘type 2 diabetes (or hyperglycemia) and gut microbiota (or gut microbiome)’ in PubMed (www.ncbi.nlm.nih.gov/pubmed/) yielded an around 612 research article, of which almost 50% are review articles (accessed on 09-November-2017).[31] Some other recent study reported on insulin resistance in between the intestinal microbiome and the fasting serum metabolome of Danish individuals without diabetes to look into whether the gut microbiome has any role in insulin resistance-associated metabolic diseases. A prominent increase in branched-chain amino acid (BCAA) biosynthesis and reduced potential for BCAA transport into bacterial cells was observed by analyzing the serum metabolome of insulin-resistance individuals.[32] Further, the study also advocated that BCAAs stalwartly co-varied with fasting serum metabolites of microbial origin where BCAA synthesis controlled by specific bacterial species (*Prevotella copri* and *Bacteroides vulgatus* often termed as top producers’ of BCAA. This signifies that intestinal microbiota plays a key role in the increase of BCAAs in insulin resistance.[32,33]

Adiposity is a growing burden in India. A study conducted by Patil et al. (2012) on the association of intestinal microbiota with adiposity within Indian population and reported that surgically treated and non-treated obese Indian individuals were dominated with *Bacteroidetes* phylum.[34] The majority of the studies in India about gut microbiota have employed sequencing techniques or alternative molecular techniques like qPCR Pandey et al. 2012.[35]

Dehingia et al. (2017)[37] reported that Prevotella belonging to the Prevotellaceae is the dominant genus found within Indian tribes. A similar study by Asian Microbiome Project reported that genus *Prevotella* is also dominated in Indonesia, KhonKaen and Thailand. It was reported that *Prevotella* became one of the dominant genera within the Malawian, Amerindian and Mongolian populations. Thus findings of these tribes clustered closely with Indian tribes which could be due to their carbohydrate-rich diet. As in the case of Yanomami, the uncontacted Amerindians, the GBP of the Indian tribes were composed of elevated *Prevotella* and low *Bacteroides* which may be due to their traditional lifestyle untouched by modernization.[36]

Bhute et al. (2017)[38] reported about Indian diabetic subjects. Indian diabetic subjects showing unique characteristics. Known- DMs subjects represented with elevated Firmicutes and OTUs belonging to genus *Lactobacillus.* A progressive decline in butyrate-producing bacteria was observed in Diabetes Mellitus individuals (Bhutto et al. 2017).

Modulation of Gut Microbiota

The composition of human gut microbiota influenced by diet. All these aspects emphasize that we are at the beginning of understanding these complex issues and that more intervention studies are needed. Every year new findings help to the scientific society to better understand this small world of microbiota within our belly. Studies reported that microbial community plays a key role in the development of adipogenesis, low-grade inflammation, and insulin resistance which characterizes adiposity.[44]

Probiotics containing live microorganisms, which, when given suitable amounts, confer a health benefit on the host". Probiotics are specially added active live cultures and some consumable food products; such as in soy yogurt, yogurt and dietary supplements which causes numerous beneficial effects to host organisms. The pathogenesis of diabetes mellitus depends upon several factors such as oxidative stress and inflammation. Studies reported that probiotic has a role in reducing the oxidative stress and to restrain the effector functions of CD4+ T cells, accompanied by decreasing the pro-inflammatory molecules.[45] Recent studies shown that probiotics have an antioxidant, immune-modulatory and antidiabetic effects. Probiotics have a lot of beneficial effects on health and disease by modulating the immune system. Current reviews suggested that regular intake of probiotic helpful get a sustained functional benefit. Future improvement microbiota-associated therapies will depend upon partnerships scientific community and pharma industries. It is necessary to know the variation of intestinal microbes in healthy populations as well as in diseased population for the development of personalized therapies.[46] That targeted therapies require small-molecule-based drugs and the sponsoring of clinical trials. Thus, bioinformatics will also serve as a key role to create a bridge between this scientific community and pharma industries to exploit the human microbiota for the benefit of the human.

CONCLUSION

Diabetes is one of the major health concern around the globe. The review argued here provides vital possibilities and role of the gut microbiota and its composition within Indian population. Considering the diversity of Indian population, defining the core gut microbiome with reference to type 2 DM in Indians remains a distant achievement. Unless the research society makes proper efforts to investigate and understand the microbiota dynamics within the gut environment, elucidating its role played by these intestinal microbes in the health status of Indian individuals will be complicated. Tribal populations of India follow a primitive lifestyle which harbors with that as of now. This signifies that the focal features of microbiome prior to a complete change to a modernized society can also be retained. A study involving both Indian populations and western populations in a comparative mode can help in elucidating a closer representation of gut microbiome prior to transformation in these populations. The rapid swing in socio-economic status creates a great havoc that requires a huge effort to conduct these researches as soon as possible before we lose this key information. However, the Indian population conjointly presents its own distinctive challenges that got to be self-addressed once gut microbiome studies are being conducted. It would be more interesting to find out what extent these gut microbiota patterns occur in other geographic regions of India and another part of the world. The beneficial microbes are directly proportional to the healthiness of an individual hence, rectification of dysbiosis in microbiota within diabetic population may prevent the Indian population from being the diabetic hub of the world.

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