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Review Article

The human microbiomes as a dynamic process: Old and new ideas

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Abstract

Probiotics, microbiota, and microbiomes play a great role in influencing immunological reactions and general health. Islam greatly influenced the early preventive medicine through different practices but mainly by Tahnik in early infancy through parent's saliva ingestion. It has been proved that microbiomes could change through multiple actions like taking prebiotics and foods, drugs, and direct skin contacts between individuals of different ages. Sex life and different sexual practices could have great contributing action on different aspects of micro-biomes in different systems thus improving the immunological functions and general health; hence new researches in this field might carry enormous benefits in this forgotten area.

Key words
Microbiome, tahnik, microbiota, probiotics, sex.

Introduction

The microbiome

Populated by trillions of commensal bacteria, collectively called the microbiota, the human body provides a perfect environment for these bacteria to flourish as they are essential for human health. The microbiota encodes for thousands of metabolic functions and is known as a whole as the microbiome. Bacteria are able to inhabit almost every organ of the body, including the vagina and skin,[1] although the majority of bacterial biomass is found in the small and large intestines.

Some of the microbiome’s functions involve immunity, metabolism, and epithelial development. Chronic illnesses like obesity,[2] inflammatory bowel disease,[3] diabetes mellitus,[4] allergic rhinitis,[5] and atopic dermatitis[6] are known to be associated with the human microbiome. It was once thought that childbirth was the first time at which babies are exposed to microbes; however, recent studies have challenged this idea. There is growing evidence of low biomass communities of microbes within the intrauterine cavity in a number of mammals. Both preterm and full-term neonates have distinct microbial communities in the meconium immediately postpartum, and these populations increase in size dramatically in the first days to weeks of life before even the infant changes its diet or engages fully with the wider world.[1]

The microbiome of a newborn is determined by its environment and differs significantly from the intestinal micro-ecology of adults. During vaginal delivery of a newborn, there is contact between the baby and the mother's intestinal and vaginal flora which has been shown to be a source of the Prevotella, Lactobacillus and

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Bifidobacterium colonies in newborns. This has been demonstrated by contrast with births by caesarian section in which the same contact does not occur between the baby and the mother's flora. As such, children born by caesarian section have an intestinal microbiome which much more closely resembles the bacterial colonies found on the surface of the skin, with a pre-dominance of Staphylococcus.[7]

In the neonate, alterations in the microbiome can lead to dysbiosis, the disturbance of the microbiome, and as a result lead to diseases not just in early but in later childhood. Intestinal bacteria are involved in the early development of the mucosal immune system of the gut at both a physical and functional level. Bacteria in the gut stimulate lymphoid tissue leading to the production of antibodies against pathogens,[8] and in turn there is no host reaction against these 'helpful' bacteria. There is also some evidence that bacteria in the intestinal microbiome are responsible for an increase in the expression of Toll-like receptors (TLRs) which allow the gut epithelium to distinguish between commensal and pathogenic bacteria.[9]

The intestinal microbiome of newborns and adults can be influenced by agents who interact with the gut flora in different ways like antibiotics, probiotics and prebiotics. Antibiotics, especially broad-spectrum antibiotics, cause a decrease in the total size and diversity of the intestinal microbiome. Prebiotics, including non-digestible substances such as oligosaccharides, can cause changes in the microbiome composition which are beneficial to the newborn, although the mechanism is unclear. Probiotics, in contrast, are live colonies of microbes which are ingested in order to directly introduce microbes and change the balance of the existing flora.[10]

Microbiome in relation to skin

Immediately following birth, our skin is colonized with microbiota, and delivery mode may in part contribute to differences in colonization. Analysis of neonatal skin microbiota indicates that those babies delivered via vaginal birth had skin microbiota similar to their mother's vaginal microbiota, and babies delivered via Caesarean section had skin microbiota similar their mother's skin microbiota. It is unclear how long these colonization differences persist, as most vaginal bacteria are not typically found on the skin and whether the associated differences translate into functional consequences and/or disease risk. Generally, the four dominant phyla of bacteria residing on the skin are the *Actinobacteria, Proteobacteria, Firmicutes*, and *Bacteroidetes*. The dominant types of bacteria, primarily *Staphylococcus*, *Propionibacterium,* and *Corynebacterium*, are differentially abundant depending on the skin site. Differentially distributed hair follicles, eccrine and apocrine glands, and sebaceous glands contribute to the variable cutaneous microenvironments and likely select for subsets of bacteria that can thrive in those specialized conditions.[11]

The skin microbiome might be transmitted from maternal skin into neonatal skin as a result of direct skin contact between mother and infant, suggesting breastfeeding and hugging infants may influence the microbiome among infants. A bidirectional relationship between the gut and skin has also been demonstrated. Gastrointestinal illnesses are commonly associated with cutaneous manifestations, and the gut microbiome, in particular, seems to be involved in the pathophysiology of many inflammatory disorders such as atopic dermatitis, acne and psoriasis. The mechanisms by which intestinal microbiota exert their influence on skin homeostasis is still not fully understood; however, they appear to be related to the modulatory effect of gut commensals on systemic immunity. Skin allostasis, the restoration of homeostasis after a disturbance or stressor, appears to be influenced by the intestinal microbiome through gut microbiota-mediated effects on both innate and adaptive immunity. There is also increasing evidence to demonstrate that gut bacteria can positively impact the response to disturbed skin barrier function.[12]

Effect of diet, drugs, and sex on the microbiome

It has been shown that dietary macronutrients can stimulate certain species within the gut microbiota, for example in vegetarian and vegan diets which are typically higher in carbohydrates and lower in fat and protein. The microbiota of vegans and vegetarians are therefore enriched for high carbohydrate-fermenting species such as *Prevotella, Clostridium clostridioforme* and *Faecalibacterium prausnitzii*. Vegetarians also show an increase in the *Clostridium* cluster XVIII (*Lachnospiraceae* and *Clostridium ramosum* group), and vegans show lower levels of *Bacteroides*, *Bifidobacteria, Enterobacteriaceae* species. In contrast, animal-based and omnivorous diets are typically lower in carbohydrate content with higher protein and fat consumption, and so in such cases, the gut shows a comparative increase in bile-tolerant bacteria, including *Bacteroides*, *Alistipes* and *Bilophila*, and butyrate-producing bacteria, specifically the *Clostridium* cluster XVIa.[13]

In addition to diet, drugs may also affect the human gut microbiome, whilst gut bacteria may also, conversely, modulate the efficacy and toxicity of drugs.[14] Numerous studies have found that antibiotics disrupt the human microbiota: vital processes such as defence against pathogens, nutrient supply and vitamin production may become less effective, which may lead to a dysbiotic microbiome. Dysbiosis of the microbiome has itself been associated with a large number of health problems, including susceptibility to infectious diseases, metabolic, developmental and immunological disorders.[15] In recent years the effect of drugs targeting human rather than microbial cells, including anti-diabetic medications, atypical antipsychotics, proton pump inhibitors and non-steroidal anti-inflammatories have been associated with changes to the composition of the microbiome.[16] For example, systemic antibiotic treatment of acne has been linked to changes in the composition and diversity of skin microbiota, specifically with regards to varying recovery rates between individual patients and parallel changes in specific populations of bacteria.[17]

In addition, many associations have been found between the composition of the vaginal microbiome and symptoms of bacterial vaginosis, and demographic factors including sexual and menstrual practices. The vaginal microbiome may be affected by hormone-based forms of birth control, or by the use of chemical or physical barriers. Intrauterine devices (IUDs), have been found to directly impact the presence of two types of bacteria, specifically *Lactobacillus gasseri* and *Sneathia*. The use of an IUD decreases the likelihood of finding these species within the vaginal microbiome.[18] The vaginal microbiota is formed of a dynamic structure of communities, with certain communities associated with poor reproductive outcomes or sexually transmitted diseases. In contrast, the presence of *Lactobacillus* species, particularly *Lactobacillus crispatus*, are mostly associated with good vaginal health. Community composition had been associated with many modifiable and nonmodifiable factors, including hygiene practice, behaviour, race and ethnicity.[19]

The Role of the Microbiome in Immunity

The microbiome is crucial to immunity, human development and nutrition. Firstly, the material supports the immune system through its role as a beneficial colonizer; the microbiota promotes protective responses to harmful pathogens. A majority of memory and activated T-cells are located in tissues where commensals are colonized, such as the gastrointestinal tract and skin, and cultivate from microbiota-derived signals.[20] This suggests that the microbiota contributes to a functioning immune system by playing a direct role in the development of key immune markers and, consequently, triggering the immune response. Similarly, in the absence of lung microbiota, one study observed significantly higher levels of infiltrating Th2 lymphocytes and eosinophils and activation of lung dendritic cells, which can cause airway inflammation.[21] This further indicates the correlation between immune markers and microbiota. However, Belkaid and Hamd[22] remark that, while the microbiome is important from a homeostatic immune perspective, pathogenesis is more fundamentally associated with active responses against flora. Similarly, the microbiome would not be able to support immunity without the appropriate conditions which allow microbiota to thrive. Thus, the immune system has evolved as a means of sustaining a symbiotic relationship between the host and a highly diverse spectrum of microbes.[22] This highlights the balance and alliances which exist to support both systems in the immune response.

Further evidence of the relationship between the microbiome and the immune system has been observed in the oral cavity. The oral cavity harbors a multitude of complex microbes that reside on both soft and hard tissues in sessile biofilms.[23] The oral microbiome contributes to the immune system by promoting inflammasome activity, which, in turn, causes a local increase in the inflammatory cytokine interleukin (IL)-1.[24] IL-1 promotes the expression of adhesion factors on endothelial cells, which permits transmigration, diapedesis, of immunocompetent cells to infection sites.[25] Likewise, IL-1 influences the thermoregulatory centre of the hypothalamus, contributing to the manifestation of a fever in the immune response.[26] Thus, the oral microbiome contributes to immunity through the propagation of immune factors relating to diapedesis and thermoregulation.

However, there is evidence to suggest that the microbiome can exacerbate certain rare physiological disorders. For example, the condition gastroparesis occurs due to the partial or complete paralysis of the digestive system, which can render nutrition through normal traditional oral means challenging. In this state, the digestive system has reduced activity and this can alter the microbiota; resultant increased Lactobacillus in the microbiota of Gastroparesis patients has been shown to lead to dysregulation of lipid metabolism via bile salt signaling.[27] This can not only impair gastric emptying further but induce physiological stress, which may render the individual more prone to the effects of invading microbes.[27] Similar findings are shown in the higher prevalence of Prevotella in colorectal cancer[28] and the altered microbiome in allergenic conditions, such as asthma and diabetes.[29] This demonstrates how the microbiome contributes to immunity under healthy and stable conditions, but, in cases of a strained environment, the absence or overactivation of microbiota can hinder health.

In review research, Kamada and Nunez[30] disseminated the role that guts microbiota plays in the regulation of the intestinal immune system. Their work highlights the beneficial role of vitamin A, a component that actively protects the microbiome from an overactive immune response; this mediator of the immune system-microbiome relationship could contribute to novel new therapies in autoimmune conditions, such as Crohn's disease.[30] This is backed up in further evidence, which shows that gut microbiome, in fact, modifies the concentration of retinol dehydrogenase,[25] the protein responsible for the conversion of vitamin A into its active form in the gastrointestinal tract.[31] This suggests that, in addition to research that shows that the microbiome contributes to the expression of key immune system compounds, the commensals also limit system activation to prevent overexpression and the ultimate breakdown of the microbiota associated with this. This fragile balance shines a light on the homeostatic equilibrium of the role of microbiota in the immune response.

Comparatively, Mezouar *et al*.[29] investigated drivers of the immune system and concluded that, although there is a strong and evidencable relationship between the microbiome and the immune system, both are similarly heavily influenced by environmental, dietary, genetic and host phenology factors. For example, exposome factors such as exposure to silica dust may weaken the immune system and account for higher rates of autoimmune rheumatic disease.[32] This is due to a complex physiological response, which ultimately destructs fibroblasts with the end formation of fibro-hyaline tissue.[32] This weakening of the immune system can occur regardless of the internal microbiome. This suggests that the relationship between the immune system and the microbiota is far from a secure inevitability and can be subject to variation and modification across the lifespan.

To conclude, this subject has reviewed the role and effects that the microbiota has upon human immunity. The microbiome plays a crucial function in the activation of various immune markers; these include activated T-cells and IL-1. These compounds contribute to the homeostatic regulatory management of the immune system response to pathogen invasion and thus promote immunity in the healthy individual. Likewise, on the contrasting side of this, the microbiota is able to influence the expression of vitamin A and, as a result, prevent over activation of the immune response. Ultimately, the relationship between microbiota and the immune system is complex and dependent upon a stable external and internal environment. Through stability, the relationship comes with lucrative physiological benefits and, by studying the devastating effects that consequent when this process is compromised, the scientific community may harbor the knowledge necessary to take positive strides towards treatments in debilitating autoimmune disorders.

Islamic preventive medicine

With a long history dating back centuries; The Islamic preventive medicine was formed as early as the time of the Holy Prophet Mohammad in Medina.[33] In the Quran and hadiths (words of the Prophet and Imams), many suggestions on the prevention of diseases have been coined. Among these suggestions, there are several recommendations on nutrition, hygiene, and health.[34]

The Prophet emphasized the importance of preventive medicine because worshipping cannot be concentrically performed without good health and well-being, and since health is the most prized, precious, and generous gift; preventive medicine should be given the same degree of attention as diagnosis and treatment of disease, because maintaining good health is something for which Muslims are accountable to God.[35]

Prophetic medicine includes multidisciplinary acts and practices, vivid examples are the practice of ablution, purification after urination or defecation (Istinja), fasting, performing prayers, which is of marked health benefits.[36] It was only later that the sayings related to dietary recommendations and restrictions, general health and hygiene, first aid measures, treatment and prescriptions, were grouped together in one chapter dealing with health matters, which were then studied in much greater details by Islamic jurists and scholars who wrote elaborate commentaries on them and made them available to Muslim populace as "Prophetic Medicine or al-Ṭibb al-Nabawi.[37] Muslim practices like praying play significant role in decreasing pathogens in many parts of the body; particularly nostrils and perineum and it has been found that there is a statistically significant decrease in frequency of pathogenic bacteria among Muslim prayers compared to non-prayers mainly due to ablution.[38]

The concept of Tahnik

Tahnik is a ritual in Islam in which the chewed fruit of the date palm, honey, or fruit juice is rubbed onto the palate of a newborn baby as its first food following childbirth.[39] As well as having a religious ritual function, it has been suggested that Tahnik may provide health benefits to neonates including protection from hypoglycaemia and the promotion of the immune response.[40] It is not clear what the mechanism of action of Tahnik would be in producing these effects, but one possibility is that the neonatal microbiome, consisting of microbial colonies in the gut and on the skin, may be altered by this first sweet food that mixed with parent's saliva. It is well-established that the microbiome is very influential in promoting the health of the human body including both sugar control and immunity,[41] so any changes caused by Tahnik could potentially lead to these benefits. In this essay, the nature of the Tahnik ritual will be discussed followed by a critical discussion of the potential health benefits and mechanism of action of this ritual.

Tahnik in relation to microbiome

There is currently no study which has investigated the effect of Tahnik on the infant microbiome, but there is evidence for the effect of Tahnik or sweet food on the newborn gut. Indrayani and Mudarris, in their discussion of the results of their study, described above, argue that Tahnik is not just a religious ritual but has health benefits for the newborn child. In their view, Tahnik has a number of potential benefits as a preventative medicine, including the prevention of infant hypoglycaemia, antibacterial and antifungal action, preparing the gut for digestion and the encouragement of the gut microbiome.[40] They also argue that the process of Tahnik allows the passing of amylase and other enzymes to the newborn from the person who has chewed the date. Finally, they hypothesize that micro RNA (miRNA) of 18-25 nucleotides in length from the same person could lead to an improved immune response in the newborn. The authors suggest these hypotheses but it should be noted that they are not investigated in the study itself so other evidence must be analyzed to determine if there is any worth in these suggestions.

Dates contain the sugar dextrose[42] and studies have shown that neonates with hypoglycaemia given dextrose respond better to treatment than those who are not given dextrose.[43] As such, it is plausible that Tahnik can provide benefits for babies with hypoglycaemia, but it is not clear whether this is mediated by the microbiome in any way. Some studies have shown that the use of infant formula milk to combat hypoglycaemia has the disadvantage of disrupting the neonatal microbiome in a way that is not true of dextrose,[44] suggesting that Tahnik may be beneficial for the microbiome when compared with this treatment.

Some researchers have attempted to explain the proposed immunity-boosting effects of Tahnik in greater detail. A literature review by Nurutstsany and Fujiyanti[45] analysed the Javanese Tahnik ritual in detail and attempted to reach conclusions regarding the potential mode of action of Tahnik in promoting the neonate immune response. They suggest that the adult saliva which comes from Tahnik through the mastication of the date contains substances which activate the neonate antibody response, though the authors are unclear about the exact molecules which might be involved in this process. This suggestion also implies that the use of honey or fruit juice, which are not chewed in an adult's mouth before application to the newborn, would not be effective at promoting the neonate immune response.

Premastication in non-Islamic cultures

Although there are currently no research investigating changes in the microbiome as a result of Tahnik, some studies have investigated the use of premastication in non-Islamic cultures and its interaction with infant health. Han *et al*.[46] investigated the use of premastication among the indigenous Tsimane population in the Bolivian Amazon. There are high levels of premastication among the Tsimane, not just ritually following birth. More than 80% of Tsimane mothers in a previous piece of research reported having ever premasticated food, and 54% reported doing so on the previous day.[47] Han *et al*. collected samples both of premasticated food and saliva from Tsimane mothers and infants, to determine whether there was evidence of the maternal salivary microbiome influencing that of the infant (children aged 9-24 months were studied). The authors found more than 400 genera of bacteria in the samples of premasticated food and saliva, but there was a distinct separation between the cultures taken from maternal and infant pairs, when analysed using a non-metric multidimensional scaling ordination (NMDS) plot. In general, infant saliva contained more Firmicutes and fewer Proteobacteria. However, the finding that there is no close relation between in the salivary microbiomes of infants and premasticating mothers is based on a very small sample of only 12 mother-infant dyads and only two samples of premasticated food.

Premastication of food for infants is also commonly carried out in some parts of China, and Pelto, Zhang and Habicht[48] conducted a three-part study into the use of premastication in China. The authors did not conduct a quantitative study, as with Han *et al*.[46] but instead conducted a qualitative study and a review of literature to determine the potential of premastication to provide health benefits for infants. The conclusion of the three parts of the study is that premastication should be considered as "second arm of infant and young child feeding for health and survival", with breastfeeding being the 'first arm'. The basis of this argument is that humans give birth to children who develop erupted teeth relatively late compared with other primates, and so premastication provides a way of providing children with nutrients which are not available from breastfeeding alone. The second section of their study demonstrates that levels of premastication in China remain high, with 63% of university students responding to the study reporting that they received premasticated food as infants.[48] The authors argue that the low prevalence of premastication in other studies suggests that there is underreporting of premastication in non-Western societies, but that this premastication is essential for effective weaning and the promotion of infant health in developing countries.

The potential for premastication to cause ill health has also been investigated. Gaur *et al*.[49] conducted a study to investigate whether premastication presented a risk of infant HIV infection. The authors examined three cases of HIV infection in children between 9 and 39 months of age at diagnosis. In two of the cases, the mothers had known they were infected with HIV and had avoided breastfeeding for this reason and in the third case a great aunt who had helped look after the child was infected with HIV, but the mother was not. In all three cases, the children had been fed food on multiple occasions which had been premasticated by the infected adults. The authors used phylogenetic analysis of the HIV strains in the children to determine whether it was likely that the infection had come from the infected adults and in two out of the three cases it was determined that the adults were the cause. The evidence provided by this study is comparatively weak as it relies on an extremely small sample of cases. However, the study does appear to offer compelling evidence that it is possible that premastication can lead to viral transmission of HIV.[49]

Sexual life and microbiomes

The sexual practice in adult life seems to have great impact on microbiota and microbiomes. Oral sex as mouth to mouth contact with saliva mixing and swallowing, in addition to orogenital contact will have great contributing influence on microbiota and microbiome, thus changing the behavior of immunological factors in a positive way as well as could be a negative way. While ordinary vaginal sex will change the microbiota and microbiome of the genital areas including the vulvar, vaginal and penile areas. In addition, direct skin contact between two partners during sex will change the dermatological microbiota and microbiome.[50,51] Hence extensive researches are mandatory required before and after marriages especially in conservative communities with one sexual partner to show any changes in microbiome and its influence on immunity and general health. As such, the general health and immunological functions can be tested in single individuals with no previous sexual contact and to be compared with persons that have single or multiple sexual partners.

Conclusion

Microbiome is an essential part of human lives; daily practices like handling currency, travelling, working in crowded environment, swimming in pools, children mingling in nurseries and schools, even a simple hand shake might influence a microbiome. Thus, interchanging microbiomes among individuals with frequent contact (whether through skin or body fluids) is a possible outcome. All these new speculations can open new avenues for future studies.

Islam has tried the early preventive medicine by Tahnik in early infancy, thus enhancing early microbiome formation by parent's saliva transmission. Similarly, sexual practices could have great impact on microbiomes, thus influencing the immunological functions and general health.

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